



COMPENDIUM OF STEM CELL  
**RESEARCH**

# Compendium of Research: **STEM CELLS**

Research Topic  
**Stem Cells**

# Research Subtopics

STEM CELLS: GENERAL

STEM CELLS: SAFETY

STEM CELLS: ORTHOPEDIC CONDITIONS

STEM CELLS: ARTHRITIS

STEM CELLS: ANKLE

STEM CELLS: KNEE

STEM CELLS: HIP CONDITIONS

STEM CELLS: INTERVERTEBRAL DISC

STEM CELLS: SPINAL CORD INJURY

STEM CELLS: SHOULDER CONDITIONS

STEM CELLS: ELBOW

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STEM CELLS: PARKINSON'S DISEASE

STEM CELLS: DEMENTIA & ALZHEIMER'S

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STEM CELLS: MULTIPLE SCLEROSIS

STEM CELLS: AMYOTROPHIC LATERAL SCLEROSIS  
(ALS)

STEM CELLS: AUTISM

STEM CELLS: SICKLE CELL DISEASE

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STEM CELLS: REHABILITATION AND RECOVERY POST  
STEM CELL TREATMENT

STEM CELLS: CONCUSSION & HYPERBARIC OXYGEN  
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STEM CELLS: IMMUNOSUPPRESSIVE (ORGAN  
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# STEM CELLS: GENERAL

## Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement.

Horwitz et al.. (2005). *Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy, 7(5), 393-5.*

<https://doi.org/10.1080/14653240500319234>

### ABSTRACT

The plastic-adherent cells isolated from BM and other sources have come to be widely known as mesenchymal stem cells (MSC). However, the recognized biologic properties of the unfractionated population of cells do not seem to meet generally accepted criteria for stem cell activity, rendering the name scientifically inaccurate and potentially misleading to the lay public. Nonetheless, a bona fide MSC most certainly exists. To address this inconsistency between nomenclature and biologic properties, and to clarify the terminology, we suggest that the fibroblast-like plastic-adherent cells, regardless of the tissue from which they are isolated, be termed multipotent mesenchymal stromal cells, while the term mesenchymal stem cells is used only for cells that meet specified stem cell criteria. The widely recognized acronym, MSC, may be used for both cell populations, as is the current practice; thus, investigators must clearly define the more scientifically correct designation in their reports. The International Society for Cellular Therapy (ISCT) encourages the scientific community to adopt this uniform nomenclature in all written and oral communications.

# Mesenchymal Stem Cells

*Ding, D.C, Shyu, W.C & Lin, S.Z. (2011). Mesenchymal Stem Cells. Cell Transplantation, 20(1), 5-14.*  
<http://dx.doi.org/10.3727/096368910X>

## ABSTRACT

Stem cells have two features: the ability to differentiate along different lineages and the ability of self-renewal. Two major types of stem cells have been described, namely, embryonic stem cells and adult stem cells. Embryonic stem cells (ESC) are obtained from the inner cell mass of the blastocyst and are associated with tumorigenesis, and the use of human ESCs involves ethical and legal considerations. The use of adult mesenchymal stem cells is less problematic with regard to these issues. Mesenchymal stem cells (MSCs) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc. This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications. Recently, MSCs have been found in new sources, such as menstrual blood and endometrium. There are likely more sources of MSCs waiting to be discovered, and MSCs may be a good candidate for future experimental or clinical applications. One of the major challenges is to elucidate the mechanisms of differentiation, mobilization, and homing of MSCs, which are highly complex. The multipotent properties of MSCs make them an attractive choice for possible development of clinical applications. Future studies should explore the role of

MSCs in differentiation, transplantation, and immune response in various diseases.

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# **Human Infrapatellar Fat Pad-Derived Stromal Cells have more Potent Differentiation Capacity than other Mesenchymal Cells and can be Enhanced by Hyaluronan**

*Ding et al.. (2015). Human Infrapatellar Fat Pad-Derived Stromal Cells have more Potent Differentiation Capacity than other Mesenchymal Cells and can be Enhanced by Hyaluronan. Cell Transplantation, 24(7), 1221-1232.*  
<https://doi.org/10.3727/096368914X681937>

## **ABSTRACT**

The microenvironment plays an important role in the homing in and differentiation of stem cells to repair injured tissue. Infrapatellar fat pad stromal cells (IFPSCs) are a promising source of such cells for the repair of articular injury-induced degeneration. This study investigated the chemotaxis of IFPSCs to chondrocytes and the effect of hyaluronan (HA) on the biological and regenerative properties of IFPSCs. The IFPSCs were obtained from patients undergoing arthroscopy and cultured via a standard 2-week culture protocol that yielded more than 10 million cells on passage 3. The results showed that the IFPSCs had a higher capacity for

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chondrogenic differentiation than mesenchymal cells from body fat, bone marrow, and Wharton's jelly of the umbilical cord. The IFPSCs cultured on 25% or 50% HA showed better osteogenic and adipogenic capabilities than those without HA or with 75% HA ( $p < 0.001$ ). Cultures of the IFPSCs on 25% HA had a fourfold increase in chondrogenic differentiation compared to cultures without HA, which was better than with 50% and 75% HA ( $p < 0.05$ ). Cell proliferation was not affected by the presence of HA. In conclusion, IFPSCs have a strong potential for chondrogenic regeneration, which can even be augmented in a 25% HA microenvironment.

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### **Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement.**

Dominici et al.. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells The International Society for Cellular Therapy position statement. *Cytotherapy*, 8(4), 315-317. <https://doi.org/10.1080/14653240600855905>

#### **ABSTRACT**

The considerable therapeutic potential of human multipotent mesenchymal stromal cells (MSC) has generated markedly increasing interest in a wide variety of biomedical disciplines. However, investigators report studies of MSC using different

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methods of isolation and expansion, and different approaches to characterizing the cells. Thus it is increasingly difficult to compare and contrast study outcomes, which hinders progress in the field. To begin to address this issue, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposes minimal criteria to define human MSC. First, MSC must be plastic-adherent when maintained in standard culture conditions. Second, MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules. Third, MSC must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*. While these criteria will probably require modification as new knowledge unfolds, we believe this minimal set of standard criteria will foster a more uniform characterization of MSC and facilitate the exchange of data among investigators.

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## Multilineage Potential of Adult Human Mesenchymal Stem Cells.

Pittenger et al.. (1999). *Multilineage Potential of Adult Human Mesenchymal Stem Cells*. *Science*, 284(5411), 143-147. <http://dx.doi.org/10.1126/science.284.5411.143>

### ABSTRACT

Human mesenchymal stem cells are thought to be multipotent cells, which are present in adult marrow, that can replicate as undifferentiated cells and that have the potential

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to differentiate to lineages of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle, and marrow stroma. Cells that have the characteristics of human mesenchymal stem cells were isolated from marrow aspirates of volunteer donors. These cells displayed a stable phenotype and remained as a monolayer in vitro. These adult stem cells could be induced to differentiate exclusively into the adipocytic, chondrocytic, or osteocytic lineages. Individual stem cells were identified that, when expanded to colonies, retained their multilineage potential.

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## Mesenchymal stem cells in health and disease

*Uccelli, A, Moretta, L & Pistoia, V.I.T.O. (2008).*

*Mesenchymal stem cells in health and disease. Nature Reviews Immunology, 8, 726-736.*

<http://dx.doi.org/10.1038/nri2395>

### ABSTRACT

Mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells that can be isolated from many adult tissues. They can differentiate into cells of the mesodermal lineage, such as adipocytes, osteocytes and chondrocytes, as well as cells of other embryonic lineages. MSCs can interact with cells of both the innate and adaptive immune systems, leading to the modulation of several effector functions. After *in vivo* administration, MSCs induce

peripheral tolerance and migrate to injured tissues, where they can inhibit the release of pro-inflammatory cytokines and promote the survival of damaged cells. This Review discusses the targets and mechanisms of MSC-mediated immunomodulation and the possible translation of MSCs to new therapeutic approaches.

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## **Biology and clinical applications of mesenchymal stem cells**

*Barry, F. (2003). Biology and clinical applications of mesenchymal stem cells. Birth Defects Research, Part C: Embryo Today: Reviews, 69(3), 250-256.*

<http://dx.doi.org/10.1002/bdrc.10021>

### **ABSTRACT**

Stem cell populations are found in most adult tissues and, in general, their differentiation potential may reflect the local cell population. Hematopoietic, epidermal, mesenchymal, neural and hepatic stem cells have been described. It may be that, in the adult, these cells are the reservoirs of reparative cells that are mobilized following injury and migrate to the wound site where, in cooperation with local cells, they participate in the repair response. Mesenchymal stem cells, isolated from the bone marrow, have the capacity to differentiate into cells of connective tissues. Some striking examples of the therapeutic use of MSCs have been reported recently in applications such as coronary artery disease, spinal cord injury, Parkinson's Disease, and liver

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regeneration. In orthopaedic medicine, MSC therapy has been applied in bone and cartilage repair and in the treatment of osteoarthritis. The question of the host response to implanted MSCs is critical as these cells are being evaluated in clinical applications. There are several aspects to the implanted cell-host interaction that need to be addressed as we attempt to understand the mechanisms underlying stem cell therapies. These are (1) the host immune response to implanted cells, (2) the homing mechanisms that guide delivered cells to a site of injury, and (3) differentiation of implanted cells under the influence of local signals.

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## **Mesenchymal stem cells: clinical applications and biological characterization**

Barry, F & Murphy, J. .M. (2004). Mesenchymal stem cells: clinical applications and biological characterization. The International Journal of Biochemistry & Cell Biology, 36(4), 568-584. <https://doi.org/10.1016/j.biocel.2003.11.001>

### **ABSTRACT**

Mesenchymal stem cells (MSCs) have been isolated from bone marrow, periosteum, trabecular bone, adipose tissue, synovium, skeletal muscle and deciduous teeth. These cells have the capacity to differentiate into cells of connective tissue lineages, including bone, fat, cartilage and muscle. A great deal has been learned in recent years about the

isolation and characterization of MSCs, and control of their differentiation. These cells have generated a great deal of interest because of their potential use in regenerative medicine and tissue engineering and there are some dramatic examples, derived from both pre-clinical and clinical studies, that illustrate their therapeutic value. This review summarizes recent findings regarding the potential clinical use of MSCs in cardiovascular, neural and orthopaedic applications. As new methods are developed, there are several aspects to the implanted cell–host interaction that need to be addressed before we can fully understand the underlying mechanisms. These include the host immune response to implanted cells, the homing mechanisms that guide delivered cells to a site of injury and the differentiation *in vivo* of implanted cells under the influence of local signals.

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## **Why are MSCs therapeutic? New data: new insight**

*Caplan, A. I. (2008). Why are MSCs therapeutic? New data: new insight. The Journal of Pathology, 217(2), 318-324.*  
<http://dx.doi.org/10.1002/path.2469>

### **ABSTRACT**

Adult marrow-derived mesenchymal stem cells (MSCs) are able to differentiate into bone, cartilage, muscle, marrow stroma, tendon–ligament, fat and other connective tissues. The questions can be asked, what do MSCs do naturally and

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where is the MSC niche? New insight and clinical experience suggest that MSCs are naturally found as perivascular cells, summarily referred to as pericytes, which are released at sites of injury, where they secrete large quantities of bioactive factors that are both immunomodulatory and trophic. The trophic activity inhibits ischaemia-caused apoptosis and scarring while stimulating angiogenesis and the mitosis of tissue intrinsic progenitor cells. The immunomodulation inhibits lymphocyte surveillance of the injured tissue, thus preventing autoimmunity, and allows allogeneic MSCs to be used in a variety of clinical situations. Thus, a new, enlightened era of experimentation and clinical trials has been initiated with xenogenic and allogeneic MSCs.

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## The MSC: An Injury Drugstore

*Caplan, A.I & Correa, D. (2011). The MSC: An Injury Drugstore. Cell Stem Cell, 9(1), 11-15.*

<https://doi.org/10.1016/j.stem.2011.06.008>

### ABSTRACT

Now that mesenchymal stem cells (MSCs) have been shown to be perivascular *in vivo*, the existing traditional view that focuses on the multipotent differentiation capacity of these cells should be expanded to include their equally interesting role as cellular modulators that brings them into a broader therapeutic scenario. We discuss existing evidence that leads us to propose that during local injury, MSCs are

released from their perivascular location, become activated, and establish a regenerative microenvironment by secreting bioactive molecules and regulating the local immune response. These trophic and immunomodulatory activities suggest that MSCs may serve as site-regulated “drugstores” in vivo.

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## **Adult mesenchymal stem cells for tissue engineering versus regenerative medicine**

*Caplan, A.I. (2007). Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. Journal of Cellular Physiology, 213(2), 341-347.*

<http://dx.doi.org/10.1002/jcp.21200>

### **ABSTRACT**

Adult mesenchymal stem cells (MSCs) can be isolated from bone marrow or marrow aspirates and because they are culture-dish adherent, they can be expanded in culture while maintaining their multipotency. The MSCs have been used in preclinical models for tissue engineering of bone, cartilage, muscle, marrow stroma, tendon, fat, and other connective tissues. These tissue-engineered materials show considerable promise for use in rebuilding damaged or diseased mesenchymal tissues. Unanticipated is the realization that the MSCs secrete a large spectrum of bioactive molecules. These molecules are

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immunosuppressive, especially for T-cells and, thus, allogeneic MSCs can be considered for therapeutic use. In this context, the secreted bioactive molecules provide a regenerative microenvironment for a variety of injured adult tissues to limit the area of damage and to mount a self-regulated regenerative response. This regenerative microenvironment is referred to as trophic activity and, therefore, MSCs appear to be valuable mediators for tissue repair and regeneration. The natural titers of MSCs that are drawn to sites of tissue injury can be augmented by allogeneic MSCs delivered via the bloodstream. Indeed, human clinical trials are now under way to use allogeneic MSCs for treatment of myocardial infarcts, graft-versus-host disease, Crohn's Disease, cartilage and meniscus repair, stroke, and spinal cord injury. This review summarizes the biological basis for the *in vivo* functioning of MSCs through development and aging.

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### **Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Umbilical Cord Blood, or Adipose Tissue**

*Kern et al.. (2006). Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Umbilical Cord Blood, or Adipose Tissue. Stem Cells, 24(5), 1294-1301.*

<http://dx.doi.org/10.1634/stemcells.2005-0342>

## ABSTRACT

Mesenchymal stem cells (MSCs) represent a promising tool for new clinical concepts in supporting cellular therapy. Bone marrow (BM) was the first source reported to contain MSCs. However, for clinical use, BM may be detrimental due to the highly invasive donation procedure and the decline in MSC number and differentiation potential with increasing age. More recently, umbilical cord blood (UCB), attainable by a less invasive method, was introduced as an alternative source for MSCs. Another promising source is adipose tissue (AT). We compared MSCs derived from these sources regarding morphology, the success rate of isolating MSCs, colony frequency, expansion potential, multiple differentiation capacity, and immune phenotype. No significant differences concerning the morphology and immune phenotype of the MSCs derived from these sources were obvious. Differences could be observed concerning the success rate of isolating MSCs, which was 100% for BM and AT, but only 63% for UCB. The colony frequency was lowest in UCB, whereas it was highest in AT. However, UCB-MSCs could be cultured longest and showed the highest proliferation capacity, whereas BM-MSCs possessed the shortest culture period and the lowest proliferation capacity. Most strikingly, UCB-MSCs showed no adipogenic differentiation capacity, in contrast to BM- and AT-MSCs. Both UCB and AT are attractive alternatives to BM in isolating MSC: AT as it contains MSCs at the highest frequency and UCB as it seems to be expandable to higher numbers.

# **Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Cartilage, and Adipose Tissue**

*Peng et al.. (2008). Comparative Analysis of Mesenchymal Stem Cells from Bone Marrow, Cartilage, and Adipose Tissue. Stem Cells and Development, 17(4), 761-73.*  
<https://doi.org/10.1089/scd.2007.0217>

## **ABSTRACT**

Mesenchymal stem cells (MSCs) isolated from bone marrow (BM), cartilage, and adipose tissue (AT) possess the capacity for self-renewal and the potential for multilineage differentiation, and are therefore perceived as attractive sources of stem cells for cell therapy. However, MSCs from these different sources have different characteristics. We compared MSCs of adult Sprague Dawley rats derived from these three sources in terms of their immunophenotypic characterization, proliferation capacity, differentiation ability, expression of angiogenic cytokines, and anti-apoptotic ability. According to growth curve, cell cycle, and telomerase activity analyses, MSCs derived from adipose tissue (AT-MSCs) possess the highest proliferation potential, followed by MSCs derived from BM and cartilage (BM-MSCs and C-MSCs). In terms of multilineage differentiation, MSCs from all three sources displayed osteogenic, adipogenic, and chondrogenic differentiation potential. The result of realtime RT-PCR indicated that these cells all expressed angiogenic

cytokines, with some differences in expression level. Flow cytometry and MTT analysis showed that C-MSCs possess the highest resistance toward hydrogen peroxide -induced apoptosis, while AT-MSCs exhibited high tolerance to serum deprivation-induced apoptosis. Both AT and cartilage are attractive alternatives to BM as sources for isolating MSCs, but these differences must be considered when choosing a stem cell source for clinical application.

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## **Human Adipose Tissue Is a Source of Multipotent Stem Cells**

Zuk et al.. (2002). *Human Adipose Tissue Is a Source of Multipotent Stem Cells. Molecular Biology of the Cell*, 13(12), 4279-4295.

<http://www.molbiolcell.org/cgi/doi/10.1091/mbc.E02-02-0105>

### **ABSTRACT**

Much of the work conducted on adult stem cells has focused on mesenchymal stem cells (MSCs) found within the bone marrow stroma. Adipose tissue, like bone marrow, is derived from the embryonic mesenchyme and contains a stroma that is easily isolated. Preliminary studies have recently identified a putative stem cell population within the adipose stromal compartment. This cell population, termed processed lipoaspirate (PLA) cells, can be isolated from human lipoaspirates and, like MSCs, differentiate toward the osteogenic, adipogenic, myogenic, and chondrogenic

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lineages. To confirm whether adipose tissue contains stem cells, the PLA population and multiple clonal isolates were analyzed using several molecular and biochemical approaches. PLA cells expressed multiple CD marker antigens similar to those observed on MSCs. Mesodermal lineage induction of PLA cells and clones resulted in the expression of multiple lineage-specific genes and proteins. Furthermore, biochemical analysis also confirmed lineage-specific activity. In addition to mesodermal capacity, PLA cells and clones differentiated into putative neurogenic cells, exhibiting a neuronal-like morphology and expressing several proteins consistent with the neuronal phenotype. Finally, PLA cells exhibited unique characteristics distinct from those seen in MSCs, including differences in CD marker profile and gene expression.

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## **Human Umbilical Cord Mesenchymal Stem Cells: A New Era for Stem Cell Therapy**

*Ding et al.. (2015). Human Umbilical Cord Mesenchymal Stem Cells: A New Era for Stem Cell Therapy. Cell Transplantation, 24(3), 339-347.*  
<https://doi.org/10.3727/096368915X686841>

### **ABSTRACT**

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The human umbilical cord is a promising source of mesenchymal stem cells (HUCMSCs). Unlike bone marrow stem cells, HUCMSCs have a painless collection procedure and faster self-renewal properties. Different derivation protocols may provide different amounts and populations of stem cells. Stem cell populations have also been reported in other compartments of the umbilical cord, such as the cord lining, perivascular tissue, and Wharton's jelly. HUCMSCs are noncontroversial sources compared to embryonic stem cells. They can differentiate into the three germ layers that promote tissue repair and modulate immune responses and anticancer properties. Thus, they are attractive autologous or allogenic agents for the treatment of malignant and nonmalignant solid and soft cancers. HUCMCs also can be the feeder layer for embryonic stem cells or other pluripotent stem cells. Regarding their therapeutic value, storage banking system and protocols should be established immediately. This review critically evaluates their therapeutic value, challenges, and future directions for their clinical applications.

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# **Umbilical Cord Mesenchymal Stem Cells: The New Gold Standard for Mesenchymal Stem Cell-Based Therapies?**

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*Omar et al.. (2014). Umbilical Cord Mesenchymal Stem Cells: The New Gold Standard for Mesenchymal Stem Cell-Based Therapies?. Tissue Engineering Part B: Reviews, 20(5), 523-44. <http://dx.doi.org/10.1089/ten.TEB.2013.0664>*

### **ABSTRACT**

Due to their self-renewal capacity, multilineage differentiation potential, paracrine effects, and immunosuppressive properties, mesenchymal stromal cells (MSCs) are an attractive and promising tool for regenerative medicine. MSCs can be isolated from various tissues but despite their common immunophenotypic characteristics and functional properties, source-dependent differences in MSCs properties have recently emerged and lead to different clinical applications. Considered for a long time as a medical waste, umbilical cord appears these days as a promising source of MSCs. Several reports have shown that umbilical cord-derived MSCs are more primitive, proliferative, and immunosuppressive than their adult counterparts. In this review, we aim at synthesizing the differences between umbilical cord MSCs and MSCs from other sources (bone marrow, adipose tissue, periodontal ligament, dental pulp, ) with regard to their proliferation capacity, proteic and transcriptomic profiles, and their secretome involved in their regenerative, homing, and immunomodulatory capacities. Although umbilical cord MSCs are until now not particularly used as an MSC source in clinical practice, accumulating evidence shows that they may have a therapeutic advantage to treat several diseases, especially autoimmune and neurodegenerative diseases.

# **Therapeutic Potentials of Mesenchymal Stem Cells Derived from Human Umbilical Cord**

*Fan, C.G, Zhang, Q.J & Zhou, J.R. (2011). Therapeutic Potentials of Mesenchymal Stem Cells Derived from Human Umbilical Cord. Stem Cell Reviews and Reports, 7(1), 195-207. <https://doi.org/10.1007/s12015-010-9168-8>*

## **ABSTRACT**

Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs), isolated from discarded extra-embryonic tissue after birth, are promising candidate source of mesenchymal stem cells (MSCs). Apart from their prominent advantages in abundant supply, painless collection, and faster self-renewal, hUC-MSCs have shown the potencies to differentiate into a variety of cells of three germ layers (such as bone, cartilage, adipose, skeletal muscle, cardiomyocyte, endothelium, hepatocyte-like cluster, islet-like cluster, neuron, astrocyte and oligodendrocyte), to synthesize and secret a set of trophic factors and cytokines, to support the expansion and function of other cells (like hematopoietic stem cells, embryonic stem cells, natural killer cells, islet-like cell clusters, neurons and glial cells) , to migrate toward and home to pathological areas, and to be readily transfected with conventional methods. Two excellent previous reviews documenting the characteristics of this cell population with

special emphasis on its niche, isolation, surface markers and primitive properties have been published recently. In this review, we will firstly give a brief introduction of this cell population, and subsequently dwell on the findings of differential capacities with emphasis on its therapeutic potentials.

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## **Comparison of mesenchymal stem cells derived from arterial, venous, and Wharton's jelly explants of human umbilical cord**

*Ishige, I., Nagamura-Inoue, T., Honda, M.J. et al.  
International Journal of Hematology Hematol (2009) 90:  
261. <https://doi.org/10.1007/s12185-009-0377-3>*

### **ABSTRACT**

We isolated mesenchymal stem cells (MSC) from arteries (UCA), veins (UCV), and Wharton's jelly (UCWJ) of human umbilical cords (UC) and determined their relative capacities for sustained proliferation and multilineage differentiation. Individual UC components were dissected, diced into 1–2 mm<sup>3</sup> fragments, and aligned in explant cultures from which migrating cells were isolated using trypsinization. Preparations from 13 UCs produced 13 UCWJ, 11 UCV, and 10 UCA cultures of fibroblast-like, spindle-shaped cells

negative for CD31, CD34, CD45, CD271, and HLA-class II, but positive for CD13, CD29, CD44, CD73, CD90, CD105, and HLA-class I. UCV cells exhibited a significantly higher frequency of colony-forming units fibroblasts than did UCWJ and UCA cells. Individual MSCs could be selectively differentiated into osteoblasts, chondrocytes, and adipocytes. When compared for osteogenic potential, UCWJ cells were the least effective precursors, whereas UCA-derived cells developed alkaline phosphatase activity with or without an osteogenic stimulus. UC components, especially blood vessels, could provide a promising source of MSCs with important clinical applications.

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## **Isolation and Characterization of Mesenchymal Stem Cells From the Sub-Amniotic Human Umbilical Cord Lining Membrane**

*Kita et al.. (2010). Isolation and Characterization of Mesenchymal Stem Cells From the Sub-Amniotic Human Umbilical Cord Lining Membrane. Stem Cells and Development, 19(4), 491-502.*

<https://doi.org/10.1089/scd.2009.0192>

### **ABSTRACT**

The use of human stem cells (SCs) is a promising novel approach for the treatment of many diseases and injuries.

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Umbilical cord and amniotic membrane represent good sources for SCs, because they are abundant sources and there are less ethical issues unlike embryonic SCs. We aimed to isolate and characterize adult SCs from the subamnion region of the umbilical cord/amniotic membrane. Because mesenchymal stem cells (MSCs) are thought to show less immunogenicity, we first focused on the characterization of MSCs. Significant expression of typical SC-specific markers, such as SSEA-4, Oct-4, and Nanog was observed. Subamniotic MSCs did not lose the expression of Oct-4 and Nanog after freeze-thawing. Cell surface expression of MSC markers (CD73 and CD105) was confirmed by flow cytometry, and cells also differentiated into adipogenic, osteogenic, and chondrogenic lineages. On the other hand, typical embryonic SC-specific markers were not expressed and the cells also did not grow in soft agar. Thus, the subamniotic MSCs are distinct from embryonic SCs and do not show tumorigenicity in vitro. The cord lining membrane (subamniotic) MSCs isolated by our method maintain typical characteristics of MSCs in vitro, but also showed several specific features.

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# **Isolation and characterization of Oct-4+/HLA-G+mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers**

*La Rocca, G., Anzalone, R., Corrao, S. et al. Histochem Cell Biol (2009) 131: 267. <https://doi.org/10.1007/s00418-008-0519-3>*

## **ABSTRACT**

The presence of multipotent cells in several adult and embryo-related tissues opened new paths for their use in regenerative medicine. Extraembryonic tissues such as umbilical cord are considered a promising source of stem cells, potentially useful in therapy. The characterization of cells from the umbilical cord matrix (Wharton's Jelly) and amniotic membrane revealed the presence of a population of mesenchymal-like cells, sharing a set of core-markers expressed by "mesenchymal stem cells". Several reports enlightened the differentiation capabilities of these cells, even if at times the lack of an extensive characterization of surface markers and immune co-stimulators expression revealed hidden pitfalls when *in vivo* transplantation was performed. The present work describes a novel isolation protocol for obtaining mesenchymal stem cells from the umbilical cord matrix. These cells are clonogenic, retain long telomeres, can undergo several population doublings *in vitro*,

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and can be differentiated in mature mesenchymal tissues as bone and adipose. We describe for the first time that these cells, besides expressing all of the core-markers for mesenchymal stem cells, feature also the expression, at both protein and mRNA level, of tolerogenic molecules and markers of all the three main lineages, potentially important for both their differentiative potential as well as immunological features

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### **Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility**

*Nagamura-inoue, T & He, H. (2014). Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. World Journal of Stem Cells, 6(2), 195-202.*  
<http://dx.doi.org/10.4252/wjsc.v6.i2.195>

#### **ABSTRACT**

Human umbilical cord (UC) is a promising source of mesenchymal stem cells (MSCs). Apart from their prominent advantages, such as a painless collection procedure and faster self-renewal, UC-MSCs have shown the ability to differentiate into three germ layers, to accumulate in damaged tissue or inflamed regions, to promote tissue repair, and to modulate immune response. There are diverse

protocols and culture methods for the isolation of MSCs from the various compartments of UC, such as Wharton's jelly, vein, arteries, UC lining and subamnion and perivascular regions. In this review, we give a brief introduction to various compartments of UC as a source of MSCs and emphasize the potential clinical utility of UC-MSCs for regenerative medicine and immunotherapy.

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## **Comparison of immunomodulatory effects of placenta mesenchymal stem cells with bone marrow and adipose mesenchymal stem cells**

*Lee et al.. (2012). Comparison of immunomodulatory effects of placenta mesenchymal stem cells with bone marrow and adipose mesenchymal stem cells. International Immunopharmacology, 13(2), 219-224.*

<https://doi.org/10.1016/j.intimp.2012.03.024>

### **ABSTRACT**

Mesenchymal stem cells (MSCs) are powerful sources for cell therapy in regenerative medicine because they can be isolated from various tissues, expanded, and induced into multiple-lineages. Of note, their immunomodulatory effects maximize the therapeutic effects of stem cells engrafted on host, making them an especially attractive choice. Recently, several varieties of placenta-derived stem cells (PDSCs)

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including chorionic plate-derived MSCs (CP-MSCs) have been suggested as alternative sources of stem cells. However, comparative studies of immunomodulatory effects for CP-MSCs among various MSCs are largely lacking. We examined and compared immunomodulatory function of CP-MSCs with that of BM-MSCs and AD-MSCs using co-culture system with activated T-cells derived from human umbilical cord blood (UCB) exposed to anti-CD3 and anti-CD28 which are T-cell activating monoclonal antibodies. All MSCs expressed markers of stem cells and three germ layers by RT-PCR. These cells also exhibited comparable immunomodulatory effects when they were co-cultured with activated T-cells in dose-dependent manner. However, expression of HLA-ABC and HLA-G was highly positive in CP-MSCs compared to other MSCs, and higher levels of cytokines of IL-2, IL-4, IL-13, and GM-CSF were detected in dose-dependent manner in CP-MSCs. Taken together, the results of the present study suggest that while CP-MSCs, BM-MSCs, and AD-MSCs all have immunomodulatory effects, CP-MSCs may have additional advantage over the other MSCs in terms of immunomodulation. In conjunction with other previous studies, CP-MSCs are suggested to be a useful stem cell source in cell therapy.

### Highlights

- We compared immunomodulation of CP-MSCs with that of BM-MSCs and AD-MSCs. ► MSC exhibited immunomodulation in co-culture system with activated T-cells. ► Expressions of HLA-ABC and HLA-G in CP-MSCs were more increased than other MSCs. ► Higher levels of

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IL-2, IL-4, IL-13, and GM-CSF were detected in CP-MSCs.

►CP-MSCs are suggested to be a useful stem cell source in cell therapy.

# STEM CELLS: SAFETY

## Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials

Lalu et al.. (2012). *Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials*. PLoS ONE, 7(10), e47559.  
<https://doi.org/10.1371/journal.pone.0047559>

### ABSTRACT

#### Background

Mesenchymal stromal cells (MSCs, “adult stem cells”) have been widely used experimentally in a variety of clinical contexts. There is interest in using these cells in critical illness, however, the safety profile of these cells is not well known. We thus conducted a systematic review of clinical trials that examined the use of MSCs to evaluate their safety.

#### Methods and Findings

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (to June 2011), were searched. Prospective clinical trials that used intravascular delivery of MSCs (intravenously or intra-arterially) in adult populations or mixed adult and pediatric populations were identified. Studies using differentiated MSCs or additional cell types

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were excluded. The primary outcome adverse events were grouped according to immediate events (acute infusional toxicity, fever), organ system complications, infection, and longer term adverse events (death, malignancy). 2347 citations were reviewed and 36 studies met inclusion criteria. A total of 1012 participants with clinical conditions of ischemic stroke, Crohn's disease, cardiomyopathy, myocardial infarction, graft versus host disease, and healthy volunteers were included. Eight studies were randomized control trials (RCTs) and enrolled 321 participants. Meta-analysis of the RCTs did not detect an association between acute infusional toxicity, organ system complications, infection, death or malignancy. There was a significant association between MSCs and transient fever.

### **Conclusions**

Based on the current clinical trials, MSC therapy appears safe. However, further larger scale controlled clinical trials with rigorous reporting of adverse events are required to further define the safety profile of MSCs.

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## **Clarifying Stem-Cell Therapy's Benefits and Risks**

*Marks, P.W, Witten, C.M & Califf, R.M. (2017). Clarifying Stem-Cell Therapy's Benefits and Risks. The New England Journal of Medicine, 376(11), 1007-9.*

<https://medicinainternaelsalvador.com/wp->

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[content/uploads/2017/03/Clarificacion-del-tx-de-celulas-madres.pdf](#)

### **ABSTRACT**

To ensure that the emerging field of stem-cell therapy fulfills its promise to patients, we must first understand its risks and benefits and develop therapeutic approaches based on sound science. That requires a commitment to the principles of evidence generation. We at the Food and Drug Administration (FDA) share this excitement. However, to ensure that this emerging field fulfills its promise to patients, we must first understand its risks and benefits and develop therapeutic approaches based on sound science. Without a commitment to the principles of adequate evidence generation that have led to so much medical progress, we may never see stem-cell therapy reach its full potential.

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# **STEM CELLS: ORTHOPEDIC CONDITIONS**

## **Mesenchymal Stem Cells for Bone Repair: Preclinical Studies and Potential Orthopedic Applications**

*Arinze, T.L. (2005). Mesenchymal Stem Cells for Bone Repair: Preclinical Studies and Potential Orthopedic Applications. Foot and Ankle Clinics, 10(4), 651–665.*  
<https://doi.org/10.1016/j.fcl.2005.06.004>

### **ABSTRACT**

Mesenchymal stem cells (MSCs), derived from adult bone marrow, are multi-potent stem cells capable of differentiating along several lineage pathways. From a small bone marrow aspirate, MSCs can be readily isolated and easily expanded. Therefore, MSCs are thought to be a readily available source of cells for many tissue engineering and regenerative medicine applications. This review covers preclinical models that evaluate the efficacy of MSC-loaded scaffolds in large bone defects as a potential substitute for autologous and allogeneic bone grafts. This review also covers new approaches to clinical use of MSC technology.

## **Regenerative medicine through mesenchymal stem cells for bone and cartilage repair.**

Noël, D, Djouad, F & Jorgense, C. (2002). *Regenerative medicine through mesenchymal stem cells for bone and cartilage repair*. Current Opinion in Investigational Drugs, 3(7), 1000-1004.

<https://www.ncbi.nlm.nih.gov/pubmed/12186258>

### **ABSTRACT**

Bone and cartilage defects are common features of bone fracture and joint diseases, such as rheumatoid arthritis or osteoarthritis, that have great social and economic impact on the aging occidental population. Despite progress in orthopedic surgery, bone and cartilage repair is a major challenge as large defects will not spontaneously heal. Recent investigations on the stromal mesenchymal stem cell (MSC) offer a new perspective for bone and cartilage tissue engineering. However, the standard of full healing is extremely demanding and may be achieved through the engineering of MSCs combined with scaffolds and growth factors as recombinant proteins, or using a gene therapy approach.

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# Trophic Effects of Mesenchymal Stem Cells Increase Chondrocyte Proliferation and Matrix Formation

*Ling Wu, Jeroen C.H. Leijten, Nicole Georgi, Janine N. Post, Clemens A. van Blitterswijk, and Marcel Kuperien. Tissue Engineering Part A. February 2011, 17(9-10): 1425-1436.*  
<https://doi.org/10.1089/ten.tea.2010.0517>

## ABSTRACT

Previous studies showed that coculture of primary chondrocytes (PCs) with various sources of multipotent cells results in a higher relative amount of cartilage matrix formation than cultures containing only chondrocytes. The aim of this study was to investigate the mechanism underlying this observation. We used coculture pellet models of human mesenchymal stem cells (hMSCs) and human PCs or bovine PCs (bPCs) and studied the fate and the contribution to cartilage formation of the individual cell populations during coculture. Enhanced cartilage matrix deposition was confirmed by histology and quantification of total glycosaminoglycan deposition. Species-specific quantitative polymerase chain reaction demonstrated that cartilage matrix gene expression was mainly from bovine origin when bPCs were used. Short tandem repeat analysis and species-specific quantitative polymerase chain reaction analysis of genomic DNA demonstrated the near-complete loss of MSCs in coculture pellets after 4 weeks of culture. In coculture pellets of immortalized MSCs and bPCs,

chondrocyte proliferation was increased, which was partly mimicked using conditioned medium, and simultaneously preferential apoptosis of immortalized MSCs was induced. Taken together, our data clearly demonstrate that in pellet cocultures of MSCs and PCs, the former cells disappear over time. Increased cartilage formation in these cocultures is mainly due to a trophic role of the MSCs in stimulating chondrocyte proliferation and matrix deposition by chondrocytes rather than MSCs actively undergoing chondrogenic differentiation.

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## **Direct Cell–Cell Contact with Chondrocytes Is a Key Mechanism in Multipotent Mesenchymal Stromal Cell-Mediated Chondrogenesis**

*de Windt Tommy S., Saris Daniel B.F., Slaper-Cortenbach Ineke C.M., van Rijen Mattie H.P., Gawlitta Debby, Creemers Laura B., de Weger Roel A., Dhert Wouter J.A., and Vonk Lucienne A.. Tissue Engineering Part A. August 2015, 21(19-20): 2536-2547.*

<https://doi.org/10.1089/ten.tea.2014.0673>

### **ABSTRACT**

Using a combination of articular chondrocytes (ACs) and mesenchymal stromal cells (MSCs) has shown to be a viable option for a single-stage cell-based treatment of focal

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cartilage defects. However, there is still considerable debate whether MSCs differentiate or have a chondroinductive role through trophic factors. In addition, it remains unclear whether direct cell–cell contact is necessary for chondrogenesis. Therefore, the aim of this study was to investigate whether direct or indirect cell–cell contact between ACs and MSCs is essential for increased cartilage production in different cellular environments and elucidate the mechanisms behind these cellular interactions. Human ACs and MSCs were cultured in a 10:90 ratio in alginate beads, fibrin scaffolds, and pellets. Cells were mixed in direct cocultures, separated by a Transwell filter (indirect cocultures), or cultured with conditioned medium. Short tandem repeat analysis revealed that the percentages of ACs increased during culture, while those of MSCs decreased, with the biggest change in fibrin glue scaffolds. For alginate, where the lack of cell–cell contact could be confirmed by histological analysis, no difference was found in matrix production between direct and indirect cocultures. For fibrin scaffolds and pellet cultures, an increased glycosaminoglycan production and type II collagen deposition were found in direct cocultures compared with indirect cocultures and conditioned medium. Positive connexin 43 staining and transfer of cytosolic calcein indicated communication through gap junctions in direct cocultures. Taken together, these results suggest that MSCs stimulate cartilage formation when placed in close proximity to chondrocytes and that direct cell–cell contact and communication through gap junctions are essential in this chondroinductive interplay.

# **Repair of articular cartilage defect in non-weight bearing areas using adipose derived stem cells loaded polyglycolic acid mesh**

*Cui et al.. (2009). Repair of articular cartilage defect in non-weight bearing areas using adipose derived stem cells loaded polyglycolic acid mesh. Biomaterials, 30(14), 2683-2693. <https://doi.org/10.1016/j.biomaterials.2009.01.045>*

## **ABSTRACT**

The current study was designed to observe chondrogenic differentiation of adipose derived stem cells (ASCs) on fibrous polyglycolic acid (PGA) scaffold stabilized with polylactic acid (PLA), and to further explore the feasibility of using the resulting cell/scaffold constructs to repair full thickness articular cartilage defects in non-weight bearing area in porcine model within a follow-up of 6 months.

Autologous ASCs isolated from subcutaneous fat were expanded and seeded on the scaffold to fabricate ASCs/PGA constructs. Chondrogenic differentiation of ASCs in the constructs under chondrogenic induction was monitored with time by measuring the expression of collagen type II (COL II) and glycosaminoglycan (GAG). The constructs after being in vitro induced for 2 weeks were implanted to repair full thickness articular cartilage defects (8 mm in diameter, deep to subchondral bone) in femur trochlea (the experimental group), while scaffold alone was

implanted to serve as the control. Histologically, the generated neo-cartilage integrated well with its surrounding normal cartilage and subchondral bone in the defects of experimental group at 3 months post-implantation, whereas only fibrous tissue was filled in the defects of control group. Immunohistochemical and toluidine blue staining confirmed the similar distribution of COL II and GAG in the regenerated cartilage as the normal one. A vivid remolding process with post-operation time was also witnessed in the neo-cartilage as its compressive moduli increased significantly from 50.55% of the normal cartilage at 3 months to 88.05% at 6 months. The successful repair thus substantiates the potentiality of using chondrogenic induced ASCs and PGA/PLA scaffold for cartilage regeneration.

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## **Healing Full-Thickness Cartilage Defects Using Adipose-Derived Stem Cells**

*Jason L. Dragoo, Grace Carlson, Frank McCormick, Haumith Khan-Farooqi, Min Zhu, Patricia A. Zuk, and Prosper Benhaim. Tissue Engineering. July 2007, 13(7): 1615-1621. <https://doi.org/10.1089/ten.2006.0249>*

### **ABSTRACT**

The purpose of this study was to evaluate the use of adipose-derived stem cells (ADSCs) as a source for full-

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thickness cartilage repair in an animal model. Autologous ADSCs were isolated and induced with growth medium and placed in a fibrin glue scaffold and into 3-mm × 4-mm full-thickness chondral defects in rabbits with negative controls. Specimens were evaluated for early healing using immunostaining, Western blotting, reverse transcriptase polymerase chain reaction, transfection with the Lac Z gene, and quantitative assessment. Twelve of 12 (100%) articular surface defects containing tissue-engineered stem cell constructs healed with hyaline-like cartilage, versus 1 of 12 (8%) in the control group ( $p < .001$ ). There was complete healing to subchondral bone in 12 of 12 experimental defects (100%), and 10 of 12 (83%) had seamless annealing to the native cartilage. Aggrecan, superficial zone protein, collagen type II messenger ribonucleic acid, and Lac-Z gene products were identified in 12 of 12 experimental specimens, which exhibited a collagen type II:I protein ratio similar to that of normal rabbit cartilage. Quantitative histologic analysis revealed an average score of 18.2 of 21 in the experimental group, compared with 10.0 in the controls ( $p = .001$ ). Induced ADSCs supported in a fibrin glue matrix are a promising cell source for cartilage tissue engineering.

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# Mesenchymal Cell-Based Repair of Large, Full-Thickness Defects of Articular Cartilage.

*Wakitani et al.. (1994). Mesenchymal Cell-Based Repair of Large, Full-Thickness Defects of Articular Cartilage. The Journal of Bone & Joint Surgery, 76(4), 579–592.*

[https://journals.lww.com/jbjsjournal/Abstract/1994/04000/Mesenchymal\\_Cell\\_Based\\_Repair\\_of\\_Large..13.aspx](https://journals.lww.com/jbjsjournal/Abstract/1994/04000/Mesenchymal_Cell_Based_Repair_of_Large..13.aspx)

## ABSTRACT

Osteochondral progenitor cells were used to repair large, full-thickness defects of the articular cartilage that had been created in the knees of rabbits. Adherent cells from bone marrow, or cells from the periosteum that had been liberated from connective tissue by collagenase digestion, were grown in culture, dispersed in a type-I collagen gel, and transplanted into a large (three-by-six-millimeter), full-thickness (three-millimeter) defect in the weight-bearing surface of the medial femoral condyle. The contralateral knee served as a control: either the defect in that knee was left empty or a cell-free collagen gel was implanted.

The periosteal and the bone-marrow-derived cells showed similar patterns of differentiation into articular cartilage and subchondral bone. Specimens of reparative tissue were analyzed with use of a semiquantitative histological grading system and by mechanical testing with employment of a porous indenter to measure the compliance of the tissue at intervals until twenty-four weeks after the operation. There

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was no apparent difference between the results obtained with the cells from the bone marrow and those from the periosteum. As early as two weeks after transplantation, the autologous osteochondral progenitor cells had uniformly differentiated into chondrocytes throughout the defects. This repair cartilage was subsequently replaced with bone in a proximal-to-distal direction, until, at twenty-four weeks after transplantation, the subchondral bone was completely repaired, without loss of overlying articular cartilage. The mechanical testing data were a useful index of the quality of the long-term repair. Twenty-four weeks after transplantation, the reparative tissue of both the bone-marrow and the periosteal cells was stiffer and less compliant than the tissue derived from the empty defects but less stiff and more compliant than normal cartilage.

**CLINICAL RELEVANCE** The current modalities for the repair of defects of the articular cartilage have many disadvantages. The transplantation of progenitor cells that will form cartilage and bone offers a possible alternative to these methods. As demonstrated in this report, autologous, bone-marrow-derived, osteochondral progenitor cells can be isolated and grown in vitro without the loss of their capacity to differentiate into cartilage or bone. Sufficient autologous cells can be generated to initiate the repair of articular cartilage and the reformation of subchondral bone. The repair tissues appear to undergo the same developmental transitions that originally led to the formation of articular tissue in the embryo. This approach to the repair of defects of the articular cartilage may have useful applications in the repair of large, full-thickness defects of joint surfaces.

# **Osteochondral Defect Repair with Autologous Bone Marrow–Derived Mesenchymal Stem Cells in an Injectable, In Situ, Cross-Linked Synthetic Extracellular Matrix**

*Yanchun Liu, Xiao Zheng Shu, and Glenn D. Prestwich.*  
*Tissue Engineering. December 2006, 12(12): 3405-*  
*3416. <https://doi.org/10.1089/ten.2006.12.3405>*

## **ABSTRACT**

A co-cross-linked synthetic extracellular matrix (sECM) composed of chemically modified hyaluronic acid and gelatin was used as a cell delivery vehicle for osteochondral defect repair in a rabbit model. A full-thickness defect was created in the patellar groove of the femoral articular cartilage in each of 2 rabbit joints, and 4 experimental groups were assigned (12 rabbits/group): untreated control, autologous mesenchymal stem cells (MSCs) only, sECM only, and MSCs + sECM. The sECM hydrogels were allowed to cross-link in the defect *in situ*. Rabbits were sacrificed at 4, 8, and 12 weeks post-surgery, and cartilage repair was evaluated and scored. In the controls, defects were filled with fibrous tissue. In the MSC-only group, hyaline-like cartilage filled the peripheral area of the defect, but the center was filled with fibrous tissue. In the sECM-only group, hyaline cartilage with

zonal architecture filled the defect at 12 weeks, but an interface between repaired and adjacent host cartilage was evident. In the MSCs + sECM group, defects were completely filled with elastic, firm, translucent cartilage at 12 weeks and showed superior integration of the repair tissue with the normal cartilage. The sECM delivers and retains MSCs, and the injectable cell-seeded sECM could be delivered arthroscopically in the clinic.

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## **The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair**

*Mifune et al.. (2013). The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair. Osteoarthritis and Cartilage, 21(1), 175–185. [http://www.oarsijournal.com/article/S1063-4584\(12\)00993-4/fulltext](http://www.oarsijournal.com/article/S1063-4584(12)00993-4/fulltext)*

### **ABSTRACT**

#### **Objective**

Platelet-rich plasma (PRP) is reported to promote collagen synthesis and cell proliferation as well as enhance cartilage repair. Our previous study revealed that the intracapsular injection of muscle derived stem cells (MDSCs) expressing bone morphogenetic protein 4 (BMP-4) combined with

soluble Flt-1 (sFlt1) was effective for repairing articular cartilage (AC) after osteoarthritis (OA) induction. The current study was undertaken to investigate whether PRP could further enhance the therapeutic effect of MDSC therapy for the OA treatment.

## **Methods**

MDSCs expressing BMP-4 and sFlt1 were mixed with PRP and injected into the knees of immunodeficient rats with chemically induced OA. Histological assessments were performed 4 and 12 weeks after cell transplantation. Moreover, to elucidate the repair mechanisms, we performed in vitro assays to assess cell proliferation, adhesion, migration and mixed pellet co-culture of MDSCs and OA chondrocytes.

## **Results**

The addition of PRP to MDSCs expressing BMP-4 and sFlt1 significantly improved AC repair histologically at week 4 compared to MDSCs expressing BMP-4 and sFlt1 alone. Higher numbers of cells producing type II collagen and lower levels of chondrocyte apoptosis were observed by MDSCs expressing BMP-4 and sFlt1 and mixed with PRP. In the in vitro experiments, the addition of PRP promoted proliferation, adhesion and migration of the MDSCs. During chondrogenic pellet culture, PRP tended to increase the number of type II collagen producing cells and in contrast to the in vivo data, it increased cell apoptosis.

## Conclusions

Our findings indicate that PRP can promote the therapeutic potential of MDSCs expressing BMP-4 and sFlt1 for AC repair (4 weeks post-treatment) by promoting collagen synthesis, suppressing chondrocyte apoptosis and finally by enhancing the integration of the transplanted cells in the repair process.

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## **Comparative evaluation of MSCs from bone marrow and adipose tissue seeded in PRP-derived scaffold for cartilage regeneration**

Xie et al.. (2012). *Comparative evaluation of MSCs from bone marrow and adipose tissue seeded in PRP-derived scaffold for cartilage regeneration*. *Biomaterials*, 33(29), 7008-7018.

<https://doi.org/10.1016/j.biomaterials.2012.06.058>

### **ABSTRACT**

The aims of this study were to (1) determine whether platelet-rich plasma (PRP) could be prepared as a bioactive scaffold capable of endogenous growth factor release for cartilage repair; (2) compare the chondrogenic differentiation ability of mesenchymal stem cells (MSCs) from bone marrow (BMSC) and from adipose (ADSC) seeded within the PRP scaffold; and (3) test the efficacy of ADSC-PRP construct in cartilage regeneration *in vivo*. In vitro evaluation showed that

a 3-dimensional scaffold with a mesh-like microstructure was formed from PRP, with the capability of endogenous growth factor release and ready cell incorporation. Upon seeding in the PRP scaffold, BMSC showed higher proliferation rate, and higher expression of cartilage-specific genes and proteins than ADSC. In an osteochondral defect model in rabbits, implanted BMSC seeded within PRP scaffold also exhibited better gross appearance and histological and immunohistochemical characteristics, higher cartilage-specific gene and protein expression as well as subchondral bone regeneration. ADSC seeded constructs developed into functional chondrocytes secreting cartilaginous matrix in rabbits at 9 weeks post-implantation. Our findings suggest that PRP is a candidate bioactive scaffold capable of releasing endogenous growth factors and that BMSC and ADSC seeded within the PRP scaffold differentiate into chondrocytes and may be suitable for cell-based cartilage repair.

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## **Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review**

*Peeters et al.. (2013). Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic*

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*literature review. Osteoarthritis and Cartilage, 21(10), 1465–1473. <https://doi.org/10.1016/j.joca.2013.06.025>*

### **ABSTRACT**

#### **Background**

An important goal of stem cell research in orthopaedics is to develop clinically relevant techniques that could be applied to heal cartilage or joint pathology. Stem cell treatment in orthopaedics for joint pathology is promising since these cells have the ability to modulate different processes in the various tissues of the joint simultaneously. The non life-threatening nature of musculoskeletal system disorders makes safety of stem cell therapy a necessary prerequisite.

#### **Objective**

To systematically review the literature and provide an overview of reported adverse events (AEs) of intra-articular treatment with culture-expanded stem cells in humans.

#### **Design**

A systematic literature search was performed in Pubmed, EMBASE, Web of Science and CINAHL in February 2013. AEs were reported into three categories: local/systemic, serious adverse event or AE (SAE/AE), related/unrelated.

#### **Results**

3039 Potentially eligible articles were identified of which eventually eight fulfilled our inclusion criteria. In total, 844 procedures with a mean follow-up of 21 months were analysed. Autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) were used for cartilage repair and

osteoarthritis treatment in all included studies. Four SAEs were reported by the authors. One infection following bone marrow aspiration (BMA) was reported as probably related and resolved with antibiotics. One pulmonary embolism occurred 2 weeks after BMA and was reported as possibly related. Two tumours, both not at the site of injection, were reported as unrelated. Twenty-two other cases of possible procedure-related and seven of possible stem cell-product related adverse events (AEs) were documented. The main AEs related to the procedure were increased pain/swelling and dehydration after BMA. Increased pain and swelling was the only AE reported as related to the stem cell-product.

### **Conclusions**

Based on current literature review we conclude that application of cultured stem cells in joints appears to be safe. We believe that with continuous caution for potential side effects, it is reasonable to continue with the development of articular stem cell therapies.

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## **Stem cells in articular cartilage regeneration**

*Filardo et al.. (2016). Stem cells in articular cartilage regeneration. Journal of Orthopaedic Surgery and Research, 11(42). <https://doi.org/10.1186/s13018-016-0378-x>*

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## ABSTRACT

### Background

Mesenchymal stem cells (MSCs) have emerged as a promising option to treat articular chondral defects and early OA stages. However, their potential and limitations for clinical use remain controversial. Thus, the aim of this systematic review was to examine MSCs treatment strategies in order to summarize the current clinical evidence for the treatment of cartilage lesions and OA.

### Methods

A systematic review of the literature was performed on the PubMed database using the following string: “cartilage treatment” AND “mesenchymal stem cells”. The filters included publications on the clinical use of MSCs for cartilage defects and OA in English language up to 2015.

### Results

Our search identified 1639 papers: 60 were included in the analysis, with an increasing number of studies published on this topic over time. Seven were randomized, 13 comparative, 31 case series, and 9 case reports; 26 studies reported the results after injective administration, whereas 33 used surgical implantation. One study compared the 2 different modalities. With regard to the cell source, 20 studies concerned BMSCs, 17 ADSCs, 16 BMC, 5 PBSCs, 1 SDSCs, and 1 compared BMC vs PBSCs.

### Conclusions

The available studies allow to draw some indications. First, no major adverse events related to the treatment or to the

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cell harvest have been reported. Second, a clinical benefit of using MSCs therapies has been reported in most of the studies, regardless of cell-source, indication or administration method. Third, young age, lower BMI, smaller lesion size for focal lesions and earlier stages of OA joints, have been shown to correlate with better outcomes, even though the available data strength doesn't allow to define clear cutoff values.

# STEM CELLS: ARTHRITIS

## **Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy – a review**

*Freitag et al.. (2016). Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy – a review. BMC Musculoskeletal Disorders, 17(230). <https://doi.org/10.1186/s12891-016-1085-9>*

### **ABSTRACT**

Osteoarthritis is a leading cause of pain and disability across the world. With an aging population its prevalence is likely to further increase. Current accepted medical treatment strategies are aimed at symptom control rather than disease modification. Surgical options including joint replacement are not without possible significant complications. A growing interest in the area of regenerative medicine, led by an improved understanding of the role of mesenchymal stem cells in tissue homeostasis and repair, has seen recent focused efforts to explore the potential of stem cell therapies in the active management of symptomatic osteoarthritis. Encouragingly, results of pre-clinical and clinical trials have provided initial evidence of efficacy and indicated safety in the therapeutic use of mesenchymal stem cell therapies for the treatment of knee osteoarthritis. This paper explores the

pathogenesis of osteoarthritis and how mesenchymal stem cells may play a role in future management strategies of this disabling condition.

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## **Mesenchymal stem cell therapy in joint disease**

*Barry, F.P. (2003). Mesenchymal stem cell therapy in joint disease. Novartis Found Symp, 249, 86-96.*

<https://www.ncbi.nlm.nih.gov/pubmed/12708651>

### **ABSTRACT**

Mesenchymal stem cells have the capacity to differentiate into a variety of connective tissue cells including bone, cartilage, tendon, muscle and adipose tissue. These multipotent cells have been isolated from bone marrow and from other adult tissues including skeletal muscle, fat and synovium. Because of their multipotentiality and capacity for self renewal adult stem cells may represent units of active regeneration of tissues damaged as a result of trauma or disease. In certain degenerative diseases such as osteoarthritis (OA) stem cells are depleted, and have reduced proliferative capacity and reduced ability to differentiate. The delivery of stem cells to these individuals may therefore enhance repair or inhibit the progressive destruction of the joint. We have developed methods for the delivery of mesenchymal stem cell preparations taken from bone marrow to the injured knee joint. This treatment has the

potential to stimulate regeneration of cartilage and retard the progressive destruction of the joint that typically occurs following injury.

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## **Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells?**

*Im, G.I, Shin, Y.W & Lee, K.B. (2005). Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells?. Osteoarthritis and Cartilage, 13(10), 845–853.*

[http://www.oarsijournal.com/article/S1063-4584\(05\)00147-0/abstract](http://www.oarsijournal.com/article/S1063-4584(05)00147-0/abstract)

### **ABSTRACT**

#### **Objective**

Adipose tissue-derived mesenchymal stem cells (ATMSCs) have been shown to differentiate into bone, cartilage, fat or muscle. However, it is not certain that ATMSCs are equal to bone marrow-derived mesenchymal stem cells (BMMSC) for their bone and cartilage forming potential. The purpose of this study was to answer the question.

## Methods

BMMSCs were obtained from the medullary canal of femur and ATMSCs were isolated from the fat harvested during liposuction procedures. After cell expansion in culture media and two passages, the immunofluorescent studies for STRO-1 and CD34 were performed to characterize the BMMSCs and ATMSCs. Osteogenesis was induced on a monolayer culture with osteogenic medium containing dexamethasone,  $\beta$ -glycerophosphate and ascorbate. After 2–3 weeks, alkaline phosphatase (AP) and Von Kossa staining were done. To test for chondrogenesis, mesenchymal stem cells (MSCs) were cultured in a pellet culture and in a fibrin scaffold with a chondrogenic medium (CM) containing transforming growth factor- $\beta$ 2 and insulin-like growth factor-I. After 4 weeks, Safranin-O staining and immunohistochemical staining for type II collagen were done to evaluate the chondrogenic differentiation and the matrix production. A histological scale was used to semiquantitatively assess the degree of chondrogenesis.

## Results

Both BMMSCs and ATMSCs were STRO-1 positive and CD34 negative. On the test of osteogenesis, the osteoblastic differentiation of ATMSCs as demonstrated by AP staining was much less than that of the BMMSCs ( $P=0.002$ ). The amount of matrix mineralization shown by Von Kossa staining also showed statistical differences between the two MSCs ( $P=0.011$ ). On the test for chondrogenesis by the pellet culture ATMSCs showed much weaker presentation as chondrogenic cells in both cell morphology and the matrix production. The histological score was 6.5 (SD1.3) for the

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BMMSCs, and 4.3 (SD1.6) for the ATMSCs cultured in CM, which was statistically significant ( $P=0.023$ ). The results from fibrin gel paralleled those from the pellet culture in general.

### **Conclusion**

The results of our study suggest that the ATMSCs may have an inferior potential for both osteogenesis and chondrogenesis compared with the BMMSCs, and these cast doubts on the value of adipose tissue as a source of MSCs.

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## **Human osteoarthritic synovium impacts chondrogenic differentiation of mesenchymal stem cells via macrophage polarisation state**

*Fahy et al.. (2014). Human osteoarthritic synovium impacts chondrogenic differentiation of mesenchymal stem cells via macrophage polarisation state. Osteoarthritis and Cartilage, 22(8), 1167–1175. <https://doi.org/10.1016/j.joca.2014.05.021>*

### **ABSTRACT**

#### **Objective**

Mesenchymal stem cells (MSCs) are a promising cell type for the repair of damaged cartilage in osteoarthritis (OA). However, OA synovial fluid and factors secreted by synovium impede chondrogenic differentiation of MSCs, and

the mechanism responsible for this effect remains unclear. In this study, we sought to investigate whether M1 and M2 synovial macrophages can contribute to the inhibition of MSC chondrogenesis.

### **Design**

The constitution of synovial macrophage subsets was analysed by immunohistochemical staining of human OA synovium sections for CD86 (M1 marker) and CD206 (M2 marker). To assess the effect of synovial macrophages on chondrogenesis, collagen type II (COL2) and aggrecan (ACAN) gene expression were compared between MSCs undergoing chondrogenic differentiation in medium conditioned (CM) by human OA synovial explants, human synovial macrophages and fibroblasts, or peripheral blood derived primary human monocytes differentiated towards an M1 or M2 phenotype.

### **Results**

OA synovium contained both M1 and M2 macrophages. Medium conditioned by synovial macrophages (CD45 + plastic adherent cells) down-regulated chondrogenic gene expression by MSCs. Additionally, CM of M1 polarised monocytes significantly decreased COL2 and ACAN gene expression by MSCs; this effect was not observed for treatment with CM of M2 polarised monocytes.

### **Conclusion**

MSC chondrogenesis is inhibited by OA synovium CM through factors secreted by synovial macrophages and our findings suggest that M1 polarised subsets are potential

mediators of this anti-chondrogenic effect. Modulation of macrophage phenotype may serve as a beneficial strategy to maximise the potential of MSCs for efficient cartilage repair.

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## **Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis**

*Murphy et al.. (2002). Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. Arthritis & Rheumatology, 46, 704–713.*

<http://onlinelibrary.wiley.com/doi/10.1002/art.10118/full>

### **ABSTRACT**

#### **Objective**

Mesenchymal stem cells (MSCs) are resident in the bone marrow throughout normal adult life and have the capacity to differentiate along a number of connective tissue pathways, among them bone, cartilage, and fat. To determine whether functionally normal MSC populations may be isolated from patients with advanced osteoarthritis (OA), we have compared cells from patients undergoing joint replacement with cells from normal donors. Cell populations were

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compared in terms of yield, proliferation, and capacity to differentiate.

### Methods

MSCs were prepared from bone marrow aspirates obtained from the iliac crest or from the tibia/femur during joint surgery. In vitro chondrogenic activity was measured as glycosaminoglycan and type II collagen deposition in pellet cultures. Adipogenic activity was measured as the accumulation of Nile Red O-positive lipid vacuoles, and osteogenic activity was measured as calcium deposition and by von Kossa staining.

### Results

Patient-derived MSCs formed colonies in primary culture that were characteristically spindle-shaped with normal morphology. The primary cell yield in 36 of 38 cell cultures from OA donors fell within the range found in cultures from normal donors. However, the proliferative capacity of patient-derived MSCs was significantly reduced. There was a significant reduction in in vitro chondrogenic and adipogenic activity in cultures of patient-derived cells compared with that in normal cultures. There was no significant difference in in vitro osteogenic activity. There was no decline in chondrogenic potential with age in cells obtained from individuals with no evidence of OA.

### Conclusion

These results raise the possibility that the increase in bone density and loss of cartilage that are characteristic of OA may result from changes in the differentiation profile of the

progenitor cells that contribute to the homeostatic maintenance of these tissues.

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## **Mesenchymal stem cells in joint disease and repair**

*Barry, F & Murphy, M. (2013). Mesenchymal stem cells in joint disease and repair. Nature Reviews Rheumatology, 9(0), 584–594.*

<https://www.nature.com/articles/nrrheum.2013.109>

### **ABSTRACT**

Osteoarthritis (OA), a prevalent chronic condition with a striking impact on quality of life, represents an enormous societal burden that increases greatly as populations age. Yet no approved pharmacological intervention, biologic therapy or procedure prevents the progressive destruction of the OA joint. Mesenchymal stem cells (MSCs)—multipotent precursors of connective tissue cells that can be isolated from many adult tissues, including those of the diarthrodial joint—have emerged as a potential therapy. Endogenous MSCs contribute to maintenance of healthy tissues by acting as reservoirs of repair cells or as immunomodulatory sentinels to reduce inflammation. The onset of degenerative changes in the joint is associated with aberrant activity or depletion of these cell reservoirs, leading to loss of chondrogenic potential and preponderance of a fibrogenic phenotype. Local delivery of ex vivo cultures of MSCs has

produced promising outcomes in preclinical models of joint disease. Mechanistically, paracrine signalling by MSCs might be more important than differentiation in stimulating repair responses; thus, paracrine factors must be assessed as measures of MSC therapeutic potency, to replace traditional assays based on cell-surface markers and differentiation. Several early-stage clinical trials, initiated or underway in 2013, are testing the delivery of MSCs as an intra-articular injection into the knee, but optimal dose and vehicle are yet to be established.

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## **Chondrogenesis of Adult Stem Cells from Adipose Tissue and Bone Marrow: Induction by Growth Factors and Cartilage-Derived Matrix**

*Brian O. Diekman, Christopher R. Rowland, Donald P. Lennon, Arnold I. Caplan, and Farshid Guilak. Tissue Engineering Part A. October 2009, 16(2): 523-533.  
<https://doi.org/10.1089/ten.tea.2009.0398>*

### **ABSTRACT**

#### **Objectives**

Adipose-derived stem cells (ASCs) and bone marrow-derived mesenchymal stem cells (MSCs) are multipotent adult stem cells with potential for use in cartilage tissue engineering. We hypothesized that these cells show distinct

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responses to different chondrogenic culture conditions and extracellular matrices, illustrating important differences between cell types.

### Methods

Human ASCs and MSCs were chondrogenically differentiated in alginate beads or a novel scaffold of reconstituted native cartilage-derived matrix with a range of growth factors, including dexamethasone, transforming growth factor  $\beta$ 3, and bone morphogenetic protein 6. Constructs were analyzed for gene expression and matrix synthesis.

### Results

Chondrogenic growth factors induced a chondrocytic phenotype in both ASCs and MSCs in alginate beads or cartilage-derived matrix. MSCs demonstrated enhanced type II collagen gene expression and matrix synthesis as well as a greater propensity for the hypertrophic chondrocyte phenotype. ASCs had higher upregulation of aggrecan gene expression in response to bone morphogenetic protein 6 (857-fold), while MSCs responded more favorably to transforming growth factor  $\beta$ 3 (573-fold increase).

### Conclusions

ASCs and MSCs are distinct cell types as illustrated by their unique responses to growth factor-based chondrogenic induction. This chondrogenic induction is affected by the composition of the scaffold and the presence of serum.

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# **Mesenchymal stem cell therapy for osteoarthritis: current perspectives**

Wyles et al.. (2015). *Mesenchymal stem cell therapy for osteoarthritis: current perspectives*. *Stem Cells Cloning*, 8(0), 117–124.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4559256/>

## **ABSTRACT**

Osteoarthritis (OA) is a painful chronic condition with a significant impact on quality of life. The societal burden imposed by OA is increasing in parallel with the aging population; however, no therapies have demonstrated efficacy in preventing the progression of this degenerative joint disease. Current mainstays of therapy include activity modification, conservative pain management strategies, weight loss, and if necessary, replacement of the affected joint. Mesenchymal stem cells (MSCs) are a multipotent endogenous population of progenitors capable of differentiation to musculoskeletal tissues. MSCs have a well-documented immunomodulatory role, managing the inflammatory response primarily through paracrine signaling. Given these properties, MSCs have been proposed as a potential regenerative cell therapy source for patients with OA. Research efforts are focused on determining the ideal source for derivation, as MSCs are native to several tissues. Furthermore, optimizing the mode of delivery remains a challenge both for appropriate localization of MSCs and for directed guidance toward stemming the local inflammatory process and initiating a regenerative response. Scaffolds

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and matrices with growth factor adjuvants may prove critical in this effort. The purpose of this review is to summarize the current state of MSC-based therapeutics for OA and discuss potential barriers that must be overcome for successful implementation of cell-based therapy as a routine treatment strategy in orthopedics.

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# STEM CELLS: ANKLE

## Mesenchymal Stem Cells: Potential Role in the Treatment of Osteochondral Lesions of the Ankle

Tribe et al.. (2017). *Mesenchymal Stem Cells: Potential Role in the Treatment of Osteochondral Lesions of the Ankle.* *Biotechnology Journal*, 12(12),  
<http://dx.doi.org/10.1002/biot.201700070>

### ABSTRACT

Given articular cartilage has a limited repair potential, untreated osteochondral lesions of the ankle can lead to debilitating symptoms and joint deterioration necessitating joint replacement. While a wide range of reparative and restorative surgical techniques have been developed to treat osteochondral lesions of the ankle, there is no consensus in the literature regarding which is the ideal treatment. Tissue engineering strategies, encompassing stem cells, somatic cells, biomaterials, and stimulatory signals (biological and mechanical), have a potentially valuable role in the treatment of osteochondral lesions. Mesenchymal stem cells (MSCs) are an attractive resource for regenerative medicine approaches, given their ability to self-renew and differentiate into multiple stromal cell types, including chondrocytes. Although MSCs have demonstrated significant promise in in vitro and in vivo preclinical studies, their success in treating

osteochondral lesions of the ankle is inconsistent, necessitating further clinical trials to validate their application. This review highlights the role of MSCs in cartilage regeneration and how the application of biomaterials and stimulatory signals can enhance chondrogenesis. The current treatments for osteochondral lesions of the ankle using regenerative medicine strategies are reviewed to provide a clinical context. The challenges for cartilage regeneration, along with potential solutions and safety concerns are also discussed.

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## **Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis.**

*Emadedin et al.. (2015). Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Arch Iran Med, 18(6), 336-44. <http://dx.doi.org/015186/AIM.003>*

### **ABSTRACT**

### **BACKGROUND:**

Osteoarthritis (OA) is a debilitating disease that typically affects a large number of the middle-aged and elderly population. Current treatment strategies have had limited success in these patients. This study aims to investigate the

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safety of treatment with autologous bone marrow (BM)-derived mesenchymal stem cells(MSCs) transplanted in patients with OA of the knee, ankle, or hip.

### **METHODS:**

We enrolled 18 patients with different joint involvements (knee, ankle, or hip OA) and one was lost to follow-up. BM samples were taken from the patients, after which BM-derived MSCs were isolated and cultured. Each patient received one MSC injection. Patients were followed with clinical examinations, MRI and laboratory tests at 2, 6, 12, and 30 months post-transplantation.

### **RESULTS:**

We observed no severe adverse events such as pulmonary embolism, death, or systemic complications. A limited number of patients had very minor localized adverse effects such as rash and erythema. There were no changes in liver function, hematology, or biochemistry analyses before and after cell therapy. There was no evidence of tumor or neoplastic changes in the patients during the 30-month follow-up period. All patients exhibited therapeutic benefits such as increased walking distance, decreased visual analog scale (VAS), and total Western Ontario and McMaster Universities OA Index (WOMAC) scores which were confirmed by MRI.

### **CONCLUSIONS:**

Our study has shown that injection of MSCs in different OA affected joints is safe and therapeutically beneficial.

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However, further studies are needed with larger sample sizes and longer follow-up periods to confirm these findings.

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# STEM CELLS: KNEE

## **Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees**

*Wakitani et al.. (2002). Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis and Cartilage, 10(3), 199-206.*

<https://doi.org/10.1053/joca.2001.0504>

### **ABSTRACT**

#### **Objective:**

There is no widely accepted method to repair articular cartilage defects. Bone marrow mesenchymal cells have the potential to differentiate into bone, cartilage, fat and muscle. Bone marrow mesenchymal cell transplantation is easy to use clinically because cells can be easily obtained and can be multiplied without losing their capacity of differentiation. The objective of this study was to apply these cell transplantations to repair human articular cartilage defects in osteoarthritic knee joints.

#### **Design:**

Twenty-four knees of 24 patients with knee osteoarthritis (OA) who underwent a high tibial osteotomy comprised the study group. Adherent cells in bone marrow aspirates were

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culture expanded, embedded in collagen gel, transplanted into the articular cartilage defect in the medial femoral condyle and covered with autologous periosteum at the time of 12 high tibial osteotomies. The other 12 subjects served as cell-free controls.

### **Results:**

In the cell-transplanted group, as early as 6.3 weeks after transplantation the defects were covered with white to pink soft tissue, in which metachromasia was partially observed. Forty-two weeks after transplantation, the defects were covered with white soft tissue, in which metachromasia was observed in almost all areas of the sampled tissue and hyaline cartilage-like tissue was partially observed. Although the clinical improvement was not significantly different, the arthroscopic and histological grading score was better in the cell-transplanted group than in the cell-free control group.

### **Conclusions:**

This procedure highlights the availability of autologous culture expanded bone marrow mesenchymal cell transplantation for the repair of articular cartilage defects in humans.

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# **Autologous Bone Marrow–Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation**

*An Observational Cohort Study*

*Nejadnik et al.. (2010). Autologous Bone Marrow–Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation An Observational Cohort Study. The American Journal of Sports Medicine, 38(6), 1110-1116.*  
<https://doi.org/10.1177/0363546509359067>

## **ABSTRACT**

### **Background:**

First-generation autologous chondrocyte implantation has limitations, and introducing new effective cell sources can improve cartilage repair.

### **Purpose:**

This study was conducted to compare the clinical outcomes of patients treated with first-generation autologous chondrocyte implantation to patients treated with autologous bone marrow–derived mesenchymal stem cells (BMSCs).

Study Design: Cohort study; Level of evidence, 3.

### **Methods:**

Seventy-two matched (lesion site and age) patients underwent cartilage repair using chondrocytes ( $n = 36$ ) or BMSCs ( $n = 36$ ). Clinical outcomes were measured before

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operation and 3, 6, 9, 12, 18, and 24 months after operation using the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package, which included questions from the Short-Form Health Survey, International Knee Documentation Committee (IKDC) subjective knee evaluation form, Lysholm knee scale, and Tegner activity level scale.

### **Results:**

There was significant improvement in the patients' quality of life (physical and mental components of the Short Form-36 questionnaire included in the ICRS package) after cartilage repair in both groups (autologous chondrocyte implantation and BMSCs). However, there was no difference between the BMSC and the autologous chondrocyte implantation group in terms of clinical outcomes except for Physical Role Functioning, with a greater improvement over time in the BMSC group ( $P = .044$  for interaction effect). The IKDC subjective knee evaluation ( $P = .861$ ), Lysholm ( $P = .627$ ), and Tegner ( $P = .200$ ) scores did not show any significant difference between groups over time. However, in general, men showed significantly better improvements than women. Patients younger than 45 years of age scored significantly better than patients older than 45 years in the autologous chondrocyte implantation group, but age did not make a difference in outcomes in the BMSC group.

### **Conclusion:**

Using BMSCs in cartilage repair is as effective as chondrocytes for articular cartilage repair. In addition, it

required 1 less knee surgery, reduced costs, and minimized donor-site morbidity.

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## **Increased Knee Cartilage Volume in Degenerative Joint Disease using Percutaneously Implanted, Autologous Mesenchymal Stem Cells**

*Centeno et al.. (2008). Increased Knee Cartilage Volume in Degenerative Joint Disease using Percutaneously Implanted, Autologous Mesenchymal Stem Cells. Pain Physician, 11(3), 343-353.*

<https://www.ncbi.nlm.nih.gov/pubmed/18523506>

### **ABSTRACT**

### **BACKGROUND:**

The ability to repair tissue via percutaneous means may allow interventional pain physicians to manage a wide variety of diseases including peripheral joint injuries and osteoarthritis. This review will highlight the developments in cellular medicine that may soon permit interventional pain management physicians to treat a much wider variety of clinical conditions and highlight an interventional case study using these technologies

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### **OBJECTIVE:**

To determine if isolated and expanded human autologous mesenchymal stem cells could effectively regenerate cartilage and meniscal tissue when percutaneously injected into knees.

### **DESIGN:**

Case Study

### **SETTING:**

Private Interventional Pain Management practice.

### **METHODS:**

An IRB approved study with a consenting volunteer in which mesenchymal stem cells were isolated and cultured ex-vivo from bone marrow aspiration of the iliac crest. The mesenchymal stem cells were then percutaneously injected into the subject's knee with MRI proven degenerative joint disease. Pre- and post-treatment subjective visual analog pain scores, physical therapy assessments, and MRIs measured clinical and radiographic changes.

### **RESULTS:**

At 24 weeks post-injection, the patient had statistically significant cartilage and meniscus growth on MRI, as well as increased range of motion and decreased modified VAS pain scores.

### **CONCLUSION:**

The described process of autologous mesenchymal stem cell culture and percutaneous injection into a knee with

symptomatic and radiographic degenerative joint disease resulted in significant cartilage growth, decreased pain and increased joint mobility in this patient. This has significant future implications for minimally invasive treatment of osteoarthritis and meniscal injury.

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## **Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells**

*Kuroda et al.. (2007). Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells. Osteoarthritis and Cartilage, 15(2), 226-231.*

<https://doi.org/10.1016/j.joca.2006.08.008>

### **ABSTRACT**

#### **Objectives**

Human bone-marrow stromal cells are believed to be multipotent even in adults. This study assessed the effectiveness of autologous bone-marrow stromal cells, which were embedded within a collagen scaffold, to repair a full-thickness articular cartilage defect in the medial femoral condyle of an athlete.

## Patient and methods

A 31-year-old male judo player suffering from pain in the right knee was reviewed. A 20×30-mm full-thickness cartilage defect (International Cartilage Repair Society classification (ICRS) grade IV) was revealed in the weight-bearing area of the medial femoral condyle. With the informed consent of the patient, the defect was treated with autologous bone-marrow stromal cells. Bone marrow was aspirated from the iliac crest of the patient 4 weeks before surgery. After removing the erythrocytes, the remaining cells were expanded in culture. Adherent cells were collected and embedded within a collagen gel, which was transferred to the articular cartilage defect in the medial femoral condyle. The implant was covered with an autologous periosteal flap.

## Results

Seven months after surgery, arthroscopy revealed the defect to be covered with smooth tissues. Histologically, the defect was filled with a hyaline-like type of cartilage tissue which stained positively with Safranin-O. One year after surgery, the clinical symptoms had improved significantly. The patient had reattained his previous activity level and experienced neither pain nor other complications.

## Conclusions

Our findings indicate that the transplantation of autologous bone-marrow stromal cells can promote the repair of large focal articular cartilage defects in young, active patients.

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# Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis.

*Emadedin et al.. (2012). Intra-articular Injection of Autologous Mesenchymal Stem Cells in Six Patients with Knee Osteoarthritis. Arch Iran Med, 15(7), 422-8.*  
<http://dx.doi.org/012157/AIM.0010>

## ABSTRACT

### BACKGROUND:

Osteoarthritis (OA) is a progressive disorder of the joints caused by gradual loss of articular cartilage, which naturally possesses a limited regenerative capacity. In the present study, the potential of intra-articular injection of mesenchymal stem cells (MSCs) has been evaluated in six osteoarthritic patients.

### METHODS:

Six female volunteers, average age of 54.56 years, with radiologic evidence of knee OA that required joint replacement surgery were selected for this study. About 50 ml bone marrow was aspirated from each patient and taken to the cell laboratory, where MSCs were isolated and characterized in terms of some surface markers. About  $20-24 \times 10^6$  passaged-2 cells were prepared and tested for microbial contamination prior to intra-articular injection.

**RESULTS:** During a one-year follow-up period, we found no local or systemic adverse events. All patients were partly satisfied with the results of the study. Pain, functional status of

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the knee, and walking distance tended to be improved up to six months post-injection, after which pain appeared to be slightly increased and patients' walking abilities slightly decreased. Comparison of magnetic resonance images (MRI) at baseline and six months post-stem cell injection displayed an increase in cartilage thickness, extension of the repair tissue over the subchondral bone and a considerable decrease in the size of edematous subchondral patches in three out of six patients.

### **CONCLUSION:**

The results indicated satisfactory effects of intra-articular injection of MSCs in patients with knee OA.

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## **Articular Cartilage Regeneration With Autologous Peripheral Blood Stem Cells Versus Hyaluronic Acid: A Randomized Controlled Trial**

Saw et al.. (2013). *Articular Cartilage Regeneration With Autologous Peripheral Blood Stem Cells Versus Hyaluronic Acid: A Randomized Controlled Trial*. *Arthroscopy*, 29(4), 684-694. <https://doi.org/10.1016/j.arthro.2012.12.008>

### **ABSTRACT**

## Purpose

The purpose of this study was to compare histologic and magnetic resonance imaging (MRI) evaluation of articular cartilage regeneration in patients with chondral lesions treated by arthroscopic subchondral drilling followed by postoperative intra-articular injections of hyaluronic acid (HA) with and without peripheral blood stem cells (PBSC).

## Methods

Fifty patients aged 18 to 50 years with International Cartilage Repair Society (ICRS) grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling; 25 patients each were randomized to the control (HA) and the intervention (PBSC + HA) groups. Both groups received 5 weekly injections commencing 1 week after surgery. Three additional injections of either HA or PBSC + HA were given at weekly intervals 6 months after surgery. Subjective IKDC scores and MRI scans were obtained preoperatively and postoperatively at serial visits. We performed second-look arthroscopy and biopsy at 18 months on 16 patients in each group. We graded biopsy specimens using 14 components of the International Cartilage Repair Society Visual Assessment Scale II (ICRS II) and a total score was obtained. MRI scans at 18 months were assessed with a morphologic scoring system.

## Results

The total ICRS II histologic scores for the control group averaged 957 and they averaged 1,066 for the intervention group ( $P = .022$ ). On evaluation of the MRI morphologic scores, the control group averaged 8.5 and the intervention

group averaged 9.9 ( $P = .013$ ). The mean 24-month IKDC scores for the control and intervention groups were 71.1 and 74.8, respectively ( $P = .844$ ). One patient was lost to follow-up. There were no notable adverse events.

### **Conclusions**

After arthroscopic subchondral drilling into grade 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSC in combination with HA resulted in an improvement of the quality of articular cartilage repair over the same treatment without PBSC, as shown by histologic and MRI evaluation.

### **Level of Evidence**

Level II, randomized controlled trial (RCT).

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## **Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized, Double-Blind, Controlled Study**

*Vangsness et al.. (2014). Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized,*

*Double-Blind, Controlled Study. The Journal of Bone & Joint Surgery, 96(2), 90-98.*

<http://dx.doi.org/10.2106/JBJS.M.00058>

## **ABSTRACT**

### **Background:**

There are limited treatment options for tissue restoration and the prevention of degenerative changes in the knee. Stem cells have been a focus of intense preclinical research into tissue regeneration but limited clinical investigation. In a randomized, double-blind, controlled study, the safety of the intra-articular injection of human mesenchymal stem cells into the knee, the ability of mesenchymal stem cells to promote meniscus regeneration following partial meniscectomy, and the effects of mesenchymal stem cells on osteoarthritic changes in the knee were investigated.

### **Methods:**

A total of fifty-five patients at seven institutions underwent a partial medial meniscectomy. A single superolateral knee injection was given within seven to ten days after the meniscectomy. Patients were randomized to one of three treatment groups: Group A, in which patients received an injection of  $50 \times 10^6$  allogeneic mesenchymal stem cells; Group B,  $150 \times 10^6$  allogeneic mesenchymal stem cells; and the control group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control. Patients were followed to evaluate safety, meniscus regeneration, the overall condition of the knee joint, and clinical outcomes at intervals through two years. Evaluations included sequential magnetic resonance imaging (MRI).

**Results:**

No ectopic tissue formation or clinically important safety issues were identified. There was significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in Group A and 6% in Group B at twelve months post meniscectomy ( $p = 0.022$ ). No patients in the control group met the 15% threshold for increased meniscal volume. Patients with osteoarthritic changes who received mesenchymal stem cells experienced a significant reduction in pain compared with those who received the control, on the basis of visual analog scale assessments.

**Conclusions:**

There was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human mesenchymal stem cells. These results support the study of human mesenchymal stem cells for the apparent knee-tissue regeneration and protective effects.

**Level of Evidence:**

Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

**Peer Review:**

This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections

and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

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# **Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial**

Vega et al.. (2015). *Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial*. *Transplantation*, 99(8), 1681-1690. <http://dx.doi.org/10.1097/TP.0000000000000678>

## **ABSTRACT**

### **Background**

Osteoarthritis is the most prevalent joint disease and a common cause of joint pain, functional loss, and disability. Conventional treatments demonstrate only modest clinical benefits without lesion reversal. Autologous mesenchymal stromal cell (MSC) treatments have shown feasibility, safety, and strong indications for clinical efficacy. We performed a randomized, active control trial to assess the feasibility and safety of treating osteoarthritis with allogeneic MSCs, and we obtain information regarding the efficacy of this treatment.

## Methods

We randomized 30 patients with chronic knee pain unresponsive to conservative treatments and showing radiological evidence of osteoarthritis into 2 groups of 15 patients. The test group was treated with allogeneic bone marrow MSCs by intra-articular injection of  $40 \times 10^6$  cells. The control group received intra-articular hyaluronic acid (60 mg, single dose). Clinical outcomes were followed for 1 year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping.

## Results

Feasibility and safety were confirmed and indications of clinical efficacy were identified. The MSC-treated patients displayed significant improvement in algofunctional indices versus the active controls treated with hyaluronic acid.

Quantification of cartilage quality by T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.

## Conclusions

Allogeneic MSC therapy may be a valid alternative for the treatment of chronic knee osteoarthritis that is more logistically convenient than autologous MSC treatment. The intervention is simple, does not require surgery, provides pain relief, and significantly improves cartilage quality.

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# **Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients**

*Davatchi et al.. (2011). Mesenchymal stem cell therapy for knee osteoarthritis Preliminary report of four patients. International Journal of Rheumatic Diseases, 14(2), 211-215. <http://dx.doi.org/10.1111/j.1756-185X.2011.01599>.*

## **ABSTRACT**

### **Background:**

Osteoarthritis (OA) is a cartilage degenerative process, involving the immune system, producing local inflammatory reactions, with production of pro-inflammatory cytokines and metalloproteinases. No treatment is still available to improve or reverse the process. Stem cell therapy opened new horizons for treatment of many incurable diseases.

Mesenchymal stem cells (MSCs) due to their multi-lineage potential, immunosuppressive activities, limited immunogenicity and relative ease of growth in culture, have attracted attentions for clinical use.

### **Aim:**

The aim of this study was to examine whether MSC transplantation could reverse the OA process in the knee joint. The project was approved by the Tehran University of Medical Sciences Research Committee and Ethical Committee.

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**Patients and Methods:** Four patients with knee osteoarthritis were selected for the study. They were aged 55, 57, 65 and 54 years, and had moderate to severe knee OA. After their signed written consent, 30 mL of bone marrow were taken and cultured for MSC growth. After having enough MSCs in culture (4–5 weeks) and taking in consideration all safety measures, cells were injected in one knee of each patient.

### **Results:**

The walking time for the pain to appear improved for three patients and remained unchanged for one. The number of stairs they could climb and the pain on visual analog scale improved for all of them. On physical examination, the improvement was mainly for crepitus. It was minor for the improvement of the range of motion.

### **Conclusion:**

Results were encouraging, but not excellent. Improvement of the technique may improve the results.

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## **Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients**

*Davatchi et al.. (2015). Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients.*

*International Journal of Rheumatic Diseases, 19(3), 219-*

*225. <http://dx.doi.org/10.1111/1756-185X.12670>*

## **ABSTRACT**

### **Aim**

Osteoarthritis is a degenerative joint disease characterized by the destruction of joint cartilage. Mesenchymal stem cells (MSCs) are found in low numbers in normal cartilage, mainly in the superficial layer, acting as repairing agents. In OA, MSCs are seen in larger numbers, but act chaotic and are unable to repair the cartilage. The synovial membrane becomes inflamed and interacts with the cartilage.

Transplanted MSC have the ability to normalize them, redirecting them to their normal function. In a preliminary study, we showed that MSC could improve knee OA in four patients at 6 months. This report shows their long-term follow-up at 5 years.

### **Methods**

One patient was lost to follow-up at 2 years and three were followed for 5 years. They were aged 55, 57, 65 and 54 years, and had moderate to severe knee osteoarthritis. The worse knee of each patient was injected with  $8-9 \times 10^6$  MSC.

### **Results**

As previously reported, all parameters improved in transplant knees at 6 months (walking time, stair climbing, gelling pain, patella crepitus, flexion contracture and the visual analogue score on pain). Then, they started gradually to deteriorate, but at 5 years they were still better than at baseline. PGA (Patient Global Assessment) improved from baseline to 5 years. The better knee at baseline (no MSC), continued its

progression toward aggravation and at 5 years became the worse knee.

## **Conclusion**

Transplant knees were all in a rather advanced stage of OA. Earlier transplantation may give better results in long-term follow-up. This is what future studies have to demonstrate.

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# **Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis**

*Koh et al.. (2013). Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis. Arthroscopy, 29(4), 748-755. <https://doi.org/10.1016/j.arthro.2012.11.017>*

## **ABSTRACT**

### **Purpose**

The purpose of this study was to evaluate the clinical and imaging results of patients who received intra-articular injections of autologous mesenchymal stem cells for the treatment of knee osteoarthritis.

### **Methods**

The study group comprised 18 patients (6 men and 12 women), among whom the mean age was 54.6 years (range, 41 to 69 years). In each patient the adipose synovium was

harvested from the inner side of the infrapatellar fat pad by skin incision extension at the arthroscopic lateral portal site after the patient underwent arthroscopic debridement. After stem cells were isolated, a mean of  $1.18 \times 10^6$  stem cells (range,  $0.3 \times 10^6$  to  $2.7 \times 10^6$  stem cells) were prepared with approximately 3.0 mL of platelet-rich plasma (with a mean of  $1.28 \times 10^6$  platelets per microliter) and injected into the selected knees of patients. Clinical outcome was evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index, the Lysholm score, and the visual analog scale (VAS) for grading knee pain. We also compared magnetic resonance imaging (MRI) data collected both preoperatively and at the final follow-up.

## Results

Western Ontario and McMaster Universities Osteoarthritis Index scores decreased significantly ( $P < .001$ ) from 49.9 points preoperatively to 30.3 points at the final follow-up (mean follow-up, 24.3 months; range, 24 to 26 months). Lysholm scores also improved significantly ( $P < .001$ ) by the last follow-up visit, increasing from a mean preoperative value of 40.1 points to 73.4 points by the end of the study. Likewise, changes in VAS scores throughout the follow-up period were also significant ( $P = .005$ ); the mean VAS score decreased from 4.8 preoperatively to 2.0 at the last follow-up visit. Radiography showed that, at the final follow-up point, the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points ( $P < .001$ ). Particularly notable was the change in cartilage whole-organ MRI score, which improved from 28.3 points to 21.7 points ( $P < .001$ ). Further analysis showed that improvements in clinical and MRI

results were positively related to the number of stem cells injected.

## **Conclusions**

The results of our study are encouraging and show that intra-articular injection of infrapatellar fat pad-derived mesenchymal stem cells is effective for reducing pain and improving knee function in patients being treated for knee osteoarthritis.

## **Level of Evidence**

Level IV, therapeutic case series.

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# **Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis.**

*Emadedin et al.. (2015). Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Arch Iran Med, 18(6), 336-44. <http://dx.doi.org/10.15186/AIM.003>*

## **ABSTRACT**

## **BACKGROUND:**

Osteoarthritis (OA) is a debilitating disease that typically affects a large number of the middle-aged and elderly

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population. Current treatment strategies have had limited success in these patients. This study aims to investigate the safety of treatment with autologous bone marrow (BM)-derived mesenchymal stem cells(MSCs) transplanted in patients with OA of the knee, ankle, or hip.

### **METHODS:**

We enrolled 18 patients with different joint involvements (knee, ankle, or hip OA) and one was lost to follow-up. BM samples were taken from the patients, after which BM-derived MSCs were isolated and cultured. Each patient received one MSC injection. Patients were followed with clinical examinations, MRI and laboratory tests at 2, 6, 12, and 30 months post-transplantation.

### **RESULTS:**

We observed no severe adverse events such as pulmonary embolism, death, or systemic complications. A limited number of patients had very minor localized adverse effects such as rash and erythema. There were no changes in liver function, hematology, or biochemistry analyses before and after cell therapy. There was no evidence of tumor or neoplastic changes in the patients during the 30-month follow-up period. All patients exhibited therapeutic benefits such as increased walking distance, decreased visual analog scale (VAS), and total Western Ontario and McMaster Universities OA Index (WOMAC) scores which were confirmed by MRI.

### **CONCLUSIONS:**

Our study has shown that injection of MSCs in different OA affected joints is safe and therapeutically beneficial.

However, further studies are needed with larger sample sizes and longer follow-up periods to confirm these findings.

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## **Primary ACL Repair in Athletes with Mesenchymal Stem Cells and Platelet-Rich Plasma**

*Gobbi A., Lad D.G., Karnatzikos G., Sankineni S. (2013)*

*Primary ACL Repair in Athletes with Mesenchymal Stem Cells and Platelet-Rich Plasma. In: Doral M., Karlsson J. (eds) Sports Injuries. Springer, Berlin, Heidelberg*  
[https://doi.org/10.1007/978-3-642-36801-1\\_262-1](https://doi.org/10.1007/978-3-642-36801-1_262-1)

### **ABSTRACT**

Anterior cruciate ligament (ACL) injuries are very common, affecting a young, active population and shrouded in controversy regarding the appropriate treatment. New and alternative treatment options need to be investigated to address acute partial ACL tears. There are numerous advantages in repairing the ACL rather than reconstructing it. With bone marrow healing stimulation, introduction of platelet-rich plasma injections, and availability of synthetic and biologic scaffolds, repair of the ACL is no longer an impossible task. Current treatment strategy for ACL rupture, although satisfactory, can be improved in the case of partial tears.

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# STEM CELLS: HIP CONDITIONS

## Mesenchymal stem cell therapy in the treatment of hip osteoarthritis

*Mardones et al.. (2017). Mesenchymal stem cell therapy in the treatment of hip osteoarthritis. Journal of Hip Preservation Surgery, 4(2), 159–163.*

<https://doi.org/10.1093/jhps/hnx011>

### ABSTRACT

This study was performed to investigate the safety and efficacy of the intra-articular infusion of ex vivo expanded autologous bone marrow-derived mesenchymal stem cells (BM-MSC) to a cohort of patients with articular cartilage defects in the hip. The above rationale is sustained by the notion that MSCs express a chondrocyte differential potential and produce extracellular matrix molecules as well as regulatory signals, that may well contribute to cure the function of the damaged hip joint. A cohort of 10 patients with functional and radiological evidences of hip osteoarthritis, either in one or both legs, was included in the study. BM-MSC (the cell product) were prepared and infused into the damaged articulation(s) of each patient ( $60 \times 10^6$  cells in 3 weekly/doses). Before and after completion of the cell infusion scheme, patients were evaluated (hip scores for pain, stiffness, physical function, range of motion), to assess

whether the infusion of the respective cell product was beneficial. The intra-articular injection of three consecutive weekly doses of ex vivo expanded autologous BM-MSC to patients with articular cartilage defects in the hip and proved to be a safe and clinically effective treatment in the restoration of hip function and range of motion. In addition, the statistical significance of the above data is in line with the observation that the radiographic scores (Tönnis Classification of Osteoarthritis) of the damaged leg(s) remained without variation in 9 out of 10 patients, after the administration of the cell product.

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## **Stem Cell Therapy for the Treatment of Hip Osteonecrosis: A 30-Year Review of Progress**

*Hernigou et al.. (2016). Stem Cell Therapy for the Treatment of Hip Osteonecrosis: A 30-Year Review of Progress. Clinics in Orthopedic Surgery, 8(1), 1-8.*

<https://doi.org/10.4055/cios.2016.8.1.1>

### **ABSTRACT**

Avascular necrosis of the femoral head is caused by a multitude of etiologic factors and is associated with collapse with a risk of hip arthroplasty in younger populations. A focus on early disease management with the use of stem cells was proposed as early as 1985 by the senior author (PH). We undertook a systematic review of the medical literature to

examine the progress in cell therapy during the last 30 years for the treatment of early stage osteonecrosis.

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## **Stem cell treatment for avascular necrosis of the femoral head: current perspectives**

*Houdek et al.. (2014). Stem cell treatment for avascular necrosis of the femoral head: current perspectives. Stem Cells Cloning, 7, 65-70.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986287/>

### **ABSTRACT**

Avascular necrosis (AVN) of the femoral head is a progressive disease that predominantly affects younger patients. Although the exact pathophysiology of AVN has yet to be elucidated, the disease is characterized by a vascular insult to the blood supply of the femoral head, which can lead to collapse of the femoral head and subsequent degenerative changes. If AVN is diagnosed in the early stages of the disease, it may be possible to attempt surgical procedures which preserve the hip joint, including decompression of the femoral head augmented with concentrated bone marrow. The use of autologous stem cells has shown promise in halting the progression of AVN of the femoral head, and subsequently preventing young patients from undergoing total hip arthroplasty. The purpose

of this study was to review the current use of stem cells for the treatment of AVN of the femoral head.

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## **Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head.**

*Rackwitz et al.. (2012). Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head. Stem Cell Res Ther, 22(3), 7.*

[https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retri</u>e&list\\_uids=22356811](https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retrieve&list_uids=22356811)

### **ABSTRACT**

Avascular necrosis (AVN) of the femoral head is a debilitating disease of multifactorial genesis, predominately affects young patients, and often leads to the development of secondary osteoarthritis. The evolving field of regenerative medicine offers promising treatment strategies using cells, biomaterial scaffolds, and bioactive factors, which might improve clinical outcome. Early stages of AVN with preserved structural integrity of the subchondral plate are accessible to retrograde surgical procedures, such as core decompression to reduce the intraosseous pressure and to induce bone remodeling. The additive application of concentrated bone marrow aspirates, ex vivo expanded mesenchymalstem cells, and osteogenic or angiogenic growth factors (or both) holds great potential to improve

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bone regeneration. In contrast, advanced stages of AVN with collapsed subchondral bone require an osteochondral reconstruction to preserve the physiological joint function. Analogously to strategies for osteochondral reconstruction in the knee, anterograde surgical techniques, such as osteochondral transplantation (mosaicplasty), matrix-based autologous chondrocyte implantation, or the use of acellular scaffolds alone, might preserve jointfunction and reduce the need for hip replacement. This review summarizes recent experimental accomplishments and initial clinical findings in the field of regenerative medicine which apply cells, growth factors, and matrices to address the clinical problem of AVN.

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### **Treatment of avascular necrosis of the femoral head by hepatocyte growth factor-transgenic bone marrow stromal stem cells.**

*Wen et al.. (2008). Treatment of avascular necrosis of the femoral head by hepatocyte growth factor-transgenic bone marrow stromal stem cells. Gene Ther, 15(23), 1523-35.*

[https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retrieve&list\\_uids=18633448](https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retrieve&list_uids=18633448)

#### **ABSTRACT**

The treatment of hormone-induced early-stage avascular necrosis of the femoral head (ANFH) with transplantation of hepatocyte growth factor (HGF)-transgenic bone marrow

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stromal stem cells (BMSCs) was examined. A rabbit model of hormone-induced early ANFH was first established. BMSCs were transplanted by core decompression under the guidance of computed tomography (CT). A supportive fibrinogen drug delivery mixture (FG) was tested for mechanical enhancement of stem cell delivery. Therapeutic efficacy was evaluated by CT, magnetic resonance imaging (MRI), CT perfusion imaging, ink artery infusion angiography, hematoxylin-and-eosin staining and immunohistochemical staining for extracellular signal-regulated kinase-1/2 of pathological sections. A regular arrangement of trabeculae and obvious bone regeneration were observed in the animals receiving transplanted transgenic BMSCs with FG. Newly generated capillaries were visible on the bone plates of the trabeculae, and the bone marrow was rich in hematopoietic tissue. These results demonstrate that the combination of core decompression and transplantation of HGF transgenic autologous BMSCs enhanced blood vessel regeneration and bone reconstruction in the ANFH model. This study provides experimental data that motivate possible clinical use of this therapeutic strategy.

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# **Abnormal vascular endothelial growth factor expression in mesenchymal stem cells from both osteonecrotic and osteoarthritic hips.**

*Mwale et al.. (2011). Abnormal vascular endothelial growth factor expression in mesenchymal stem cells from both osteonecrotic and osteoarthritic hips. Bull NYU Hosp Jt Dis, 69(1), S56-61.*

<https://www.ncbi.nlm.nih.gov/pubmed/22035487>

## **ABSTRACT**

In osteonecrosis (ON) of the hip, interruption of angiogenesis is a pathological process that may lead to impairment of the nutrient supply, cell death, and the collapse of bone.

However, the process of angiogenesis in ON is not well understood. The purpose of this study was to investigate the expression of vascular endothelial growth factor (VEGF) in human mesenchymal stem cells (MSCs) in vitro. Cultured MSCs obtained from the hips of normal, ON, and osteoarthritic (OA) patients all expressed VEGF-A.

Furthermore, MSCs from normal stem cells also expressed VEGF-B, but its expression had a tendency to increase in those stem cells from ON and OA patients, while VEGF-C was absent in all of the stem cells. However, VEGF-D expression consistently decreased in MSCs from ON patients, but increased in stem cells from OA donors over that of control cells. In addition, placental growth factor (PGF), which has a similar function as VEGF, was

expressed in MSCs, and the levels were similar in MSCs from normal, ON, and OA donors. The results suggest that ON and OA are associated with aberrant VEGF-D expression.

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## **Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis.**

*Emadeddin et al.. (2015). Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Arch Iran Med, 18(6), 336-44. <http://dx.doi.org/10.15186/AIM.003>*

### **ABSTRACT**

### **BACKGROUND:**

Osteoarthritis (OA) is a debilitating disease that typically affects a large number of the middle-aged and elderly population. Current treatment strategies have had limited success in these patients. This study aims to investigate the safety of treatment with autologous bone marrow (BM)-derived mesenchymal stem cells(MSCs) transplanted in patients with OA of the knee, ankle, or hip.

### **METHODS:**

We enrolled 18 patients with different joint involvements (knee, ankle, or hip OA) and one was lost to follow-up. BM

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samples were taken from the patients, after which BM-derived MSCs were isolated and cultured. Each patient received one MSC injection. Patients were followed with clinical examinations, MRI and laboratory tests at 2, 6, 12, and 30 months post-transplantation.

### **RESULTS:**

We observed no severe adverse events such as pulmonary embolism, death, or systemic complications. A limited number of patients had very minor localized adverse effects such as rash and erythema. There were no changes in liver function, hematology, or biochemistry analyses before and after cell therapy. There was no evidence of tumor or neoplastic changes in the patients during the 30-month follow-up period. All patients exhibited therapeutic benefits such as increased walking distance, decreased visual analog scale (VAS), and total Western Ontario and McMaster Universities OA Index (WOMAC) scores which were confirmed by MRI.

### **CONCLUSIONS:**

Our study has shown that injection of MSCs in different OA affected joints is safe and therapeutically beneficial. However, further studies are needed with larger sample sizes and longer follow-up periods to confirm these findings.

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# **STEM CELLS: INTERVERTEBRAL DISC**

## **Stem cell therapy for intervertebral disc regeneration: obstacles and solutions**

*Sakai, D & Andersson, G.B.J. (2015). Stem cell therapy for intervertebral disc regeneration: obstacles and solutions. Nature Reviews Rheumatology, 1, 243–256.*

<https://www.nature.com/articles/nrrheum.2015.13>

### **ABSTRACT**

Intervertebral disc (IVD) degeneration is frequently associated with low back and neck pain, which accounts for disability worldwide. Despite the known outcomes of the IVD degeneration cascade, the treatment of IVD degeneration is limited in that available conservative and surgical treatments do not reverse the pathology or restore the IVD tissue.

Regenerative medicine for IVD degeneration, by injection of IVD cells, chondrocytes or stem cells, has been extensively studied in the past decade in various animal models of induced IVD degeneration, and has progressed to clinical trials in the treatment of various spinal conditions. Despite preliminary results showing positive effects of cell-injection

strategies for IVD regeneration, detailed basic research on IVD cells and their niche indicates that transplanted cells are unable to survive and adapt in the avascular niche of the IVD. For this therapeutic strategy to succeed, the indications for its use and the patients who would benefit need to be better defined. To surmount these obstacles, the solution will be identified only by focused research, both in the laboratory and in the clinic.

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## **Future perspectives of cell-based therapy for intervertebral disc disease**

*Sakai, D. (2008). Future perspectives of cell-based therapy for intervertebral disc disease. European Spine Journal, 17(4), 452–458.*

<https://link.springer.com/article/10.1007/s00586-008-0743-5>

### **ABSTRACT**

Intervertebral disc degeneration is a primary cause of low back pain and has a high societal cost. Research on cell-based therapies for intervertebral disc disease is emerging, along with the interest in biological therapy to treat disc disease without reducing the mobility of the spinal motion segment. Results from animal models have shown promising results under limited conditions; however, future studies are needed to optimise efficacy, methodology, and safety. To

advance research on cell-based therapy for intervertebral disc disease, a better understanding of the phenotype and differentiation of disc cells and of their microenvironment is essential. This article reviews current concepts in cell-based therapy for intervertebral disc disease, with updates on potential cell sources tested primarily using animal models, and discusses the hurdles to clinical application. Future perspectives for cell-based therapies for intervertebral disc disease are also discussed.

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## **Homing of Mesenchymal Stem Cells in Induced Degenerative Intervertebral Discs in a Whole Organ Culture System**

*Illien-jünger et al.. (2015). Homing of Mesenchymal Stem Cells in Induced Degenerative Intervertebral Discs in a Whole Organ Culture System. Spine, 37(22), 1865–1873.*  
[https://journals.lww.com/spinejournal/Abstract/2012/10150/Homing\\_of\\_Mesenchymal\\_Stem\\_Cells\\_in\\_Induced.4.aspx](https://journals.lww.com/spinejournal/Abstract/2012/10150/Homing_of_Mesenchymal_Stem_Cells_in_Induced.4.aspx)

### **ABSTRACT**

#### **Study Design.**

Homing of human bone marrow-derived mesenchymal stem cells (BMSCs) was studied using ex vivo cultured bovine caudal intervertebral discs (IVDs).

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### **Objective.**

To investigate in a whole organ culture whether metabolic and mechanical challenges can induce BMSC recruitment into the IVD.

### **Summary of Background Data.**

Cells from injured tissues release cytokines and mediators that enable the recruitment of progenitor cells. BMSCs have the ability to survive within the IVD.

### **Methods.**

Bovine IVDs with or without endplates were cultured for 1 week under simulated physiological or degenerative conditions; disc cells were analyzed for cell viability and gene expression, whereas media was analyzed for nitric oxide production and chemotaxis. Homing of BMSCs was investigated by supplying PKH-labeled human BMSCs onto cultured IVDs ( $1 \times 10^6$  cells/disc on d 8, 10, and 12 of culture); on day 14, the number of homed BMSCs was microscopically assessed. Moreover, a comparative study was performed between transduced BMSCs (transduced with an adenovirus encoding for insulin-like growth factor 1 [IGF-1]) and nontransduced BMSCs. Disc proteoglycan synthesis rate was quantified via  $^{35}\text{S}$  incorporation. The secretion of IGF-1 was evaluated by enzyme-linked immunosorbent assay on both simulated physiological and degenerative discs.

### **Results.**

Discs cultured under degenerative conditions showed reduced cell viability, upregulation of matrix degrading

enzymes, and increased nitric oxide production compared with simulated physiological discs. Greater homing occurred under degenerative compared with physiological conditions with or without endplate. Media of degenerative discs demonstrated a chemoattractive activity toward BMSCs. Finally, discs homed with IGF-1-transduced BMSCs showed increased IGF-1 secretion and significantly higher proteoglycan synthesis rate than discs supplied with nontransduced BMSCs.

### **Conclusion.**

We have demonstrated for the first time that degenerative conditions induce the release of factors promoting BMSC recruitment in an ex vivo organ culture. Moreover, IGF-1 transduction of BMSCs strongly increases the rate of proteoglycan synthesis within degenerative discs. This finding offers a new delivery system for BMSCs and treatment strategy for IVD regeneration.

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## **Isolation and Characterization of Mesenchymal Stromal Cells From Human Degenerated Nucleus Pulposus: Comparison With Bone Marrow Mesenchymal Stromal Cells From the Same Subjects**

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*Blanco et al.. (2010). Isolation and Characterization of Mesenchymal Stromal Cells From Human Degenerated Nucleus Pulposus: Comparison With Bone Marrow Mesenchymal Stromal Cells From the Same Subjects. Spine, 35(26), 2259-2265.*

[https://journals.lww.com/spinejournal/Abstract/2010/12150/Isolation\\_and\\_Characterization\\_of\\_Mesenchymal.2.aspx](https://journals.lww.com/spinejournal/Abstract/2010/12150/Isolation_and_Characterization_of_Mesenchymal.2.aspx)

### **ABSTRACT**

#### **Study Design.**

To identify mesenchymal stromal cells (MSC) from degenerate human nucleus pulposus (NP) and compare them with bone marrow (BM) MSC.

#### **Objective.**

To test whether MSC obtained from NP and BM from the same subjects share similar biologic characteristics.

#### **Summary of Background Data.**

Recent studies have proposed biologic strategies for the treatment of intervertebral disc degeneration, including cell therapy. Bone marrow (BM) MSC could be an attractive approach to restore disc function, and there is evidence that NP may contain MSC-like cells.

#### **Methods.**

Tissue samples were obtained from degenerate lumbar NP and from iliac crest of the same 16 patients with degenerative disc diseases, undergoing discectomy and fusion procedures. MSC isolated from both sources were compared regarding their expansion time,

immunophenotype, differentiation ability, and molecular analysis.

### **Results.**

In all cases, MSC from NP were isolated and expanded. They fulfil nearly all morphological, immunophenotypical, and differentiation criteria described by the International Society of Cell Therapy for MSC, with the exception that NP-MSC are not able to differentiate into adipocytes. Slight differences were observed with BM-MSC from the same subjects.

### **Conclusion.**

The NP contains mesenchymal stem cells. These cells were quite similar to mesenchymal stem cells from BM, with the exception of their adipogenic differentiation ability. These findings suggest that we may treat intervertebral disc degeneration by cell therapy (MSC from BM) and by stimulating endogenous MSC from NP.

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## **Characteristics of Stem Cells Derived from the Degenerated Human Intervertebral Disc Cartilage Endplate**

*Liu L-T, Huang B, Li C-Q, Zhuang Y, Wang J, Zhou Y (2011)  
Characteristics of Stem Cells Derived from the Degenerated*

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*Human Intervertebral Disc Cartilage Endplate. PLoS ONE*  
6(10): e26285. <https://doi.org/10.1371/journal.pone.0026285>

### **ABSTRACT**

Mesenchymal stem cells (MSCs) derived from adult tissues are an important candidate for cell-based therapies and regenerative medicine due to their multipotential differentiation capability. MSCs have been identified in many adult tissues but have not reported in the human intervertebral disc cartilage endplate (CEP). The initial purpose of this study was to determine whether MSCs exist in the degenerated human CEP. Next, the morphology, proliferation capacity, cell cycle, cell surface epitope profile and differentiation capacity of these CEP-derived stem cells (CESCs) were compared with bone-marrow MSCs (BM-MSCs). Lastly, whether CESCs are a suitable candidate for BM-MSCs was evaluated. Isolated cells from degenerated human CEP were seeded in an agarose suspension culture system to screen the proliferative cell clusters. Cell clusters were chosen and expanded in vitro and were compared with BM-MSCs derived from the same patient. The morphology, proliferation rate, cell cycle, immunophenotype and stem cell gene expression of the CESCs were similar to BM-MSCs. In addition, the CESCs could be induced into osteoblasts, adipocytes, chondrocytes, and are superior to BM-MSCs in terms of osteogenesis and chondrogenesis. This study is first to demonstrate the presence of stem cells in the human degenerated CEP. These results may improve our understanding of intervertebral disc (IVD) pathophysiology and the degeneration process, and could provide cell

candidates for cell-based regenerative medicine and tissue engineering.

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# **The Presence of Local Mesenchymal Progenitor Cells in Human Degenerated Intervertebral Discs and Possibilities to Influence These In Vitro: A Descriptive Study in Humans**

*Brisby et al.. (2012). The Presence of Local Mesenchymal Progenitor Cells in Human Degenerated Intervertebral Discs and Possibilities to Influence These In Vitro: A Descriptive Study in Humans. Stem Cells and Development, 22(5), 804-814. <https://doi.org/10.1089/scd.2012.0179>*

## **ABSTRACT**

Low back pain is common and degenerated discs (DDs) are believed to be a major cause. In non-degenerated intervertebral discs (IVDs) presence of stem/progenitor cells was recently reported in different mammals (rabbit, rat, pig). Understanding processes of disc degeneration and regenerative mechanisms within DDs is important. The aim of the study was to examine the presence of local stem/progenitor cells in human DDs and if these cell populations could respond to paracrine stimulation in vitro. Tissue biopsies from the IVD region (L3-S1) were collected from 15 patients, age 34-69 years, undergoing surgery

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(spinal fusion) and mesenchymal stem cells (MSCs) (iliac crest) from 2 donors. Non-DD cells were collected from 1 donor (scoliosis) and chordoma tissue was obtained from (positive control, stem cell markers) 2 donors. The IVD biopsies were investigated for gene and protein expression of: OCT3/4, CD105, CD90, STRO-1, and NOTCH1. DD cell cultures (pellet mass) were performed with conditioned media from MSCs and non-degenerated IVD cells. Pellets were investigated after 7, 14, 28 days for the same stem cell markers as above. Gene expression of OCT3/4 and STRO-1 was detected in 13/15 patient samples, CD105 in 14/15 samples, and CD90 and NOTCH1 were detected 15/15 samples. Immunohistochemistry analysis supported findings on the protein level, in cells sparsely distributed in DDs tissues. DDs cell cultures displayed more undifferentiated appearance with increased expression of CD105, CD90, STRO-1, OCT3/4, NOTCH1, and JAGGED1, which was observed when cultured in conditioned cell culture media from MSCs compared to cell cultures cultured with conditioned media from non-DD cells. Expression of OCT3/4 (multipotency marker) and NOTCH1 (regulator of cell fate), MSC-markers, CD105, CD90, and STRO-1, indicate that primitive cell populations are present within DDs. Furthermore, the possibility to influence cells from DDs by paracrine signaling /soluble factors from MSCs and from nondegenerated IVD cells was observed in vitro indicating that repair processes within human DDs may be stimulated.

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# **Viability, growth kinetics and stem cell markers of single and clustered cells in human intervertebral discs: implications for regenerative therapies**

*Turner et al.. (2014). Viability, growth kinetics and stem cell markers of single and clustered cells in human intervertebral discs: implications for regenerative therapies. European Spine Journal, 23(11), 2462–2472.*

<https://link.springer.com/article/10.1007/s00586-014-3500-y>

## **ABSTRACT**

### **Purpose**

There is much interest in the development of a cellular therapy for the repair or regeneration of degenerate intervertebral discs (IVDs) utilising autologous cells, with some trials already underway. Clusters of cells are commonly found in degenerate IVDs and are formed via cell proliferation, possibly as a repair response. We investigated whether these clusters may be more suitable as a source of cells for biological repair than the single cells in the IVD.

### **Methods**

Discs were obtained at surgery from 95 patients and used to assess the cell viability, growth kinetics and stem or progenitor cell markers in both the single and clustered cell populations.

## Results

Sixty-nine percent ( $\pm 15$ ) of cells in disc tissue were viable. The clustered cell population consistently proliferated more slowly in monolayer than single cells, although this difference was only significant at P0–1 and P3–4. Both populations exhibited progenitor or notochordal cell markers [chondroitin sulphate epitopes (3B3(–), 7D4, 4C3 and 6C3), Notch-1, cytokeratin 8 and 19] via immunohistochemical examination; stem cell markers assessed with flow cytometry (CD73, 90 and 105 positivity) were similar to those seen on bone marrow-derived mesenchymal stem cells.

## Conclusions

These results confirm those of previous studies indicating that progenitor or stem cells reside in adult human intervertebral discs. However, although the cell clusters have arisen via proliferation, there appear to be no greater incidence of these progenitor cells within clusters compared to single cells. Rather, since they proliferate more slowly in vitro than the single cell population, it may be beneficial to avoid the use of clustered cells when sourcing autologous cells for regenerative therapies.

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# A comparison of intravenous and intradiscal delivery of multipotential stem cells on the healing of injured intervertebral disk

*Tam et al.. (2014). A comparison of intravenous and intradiscal delivery of multipotential stem cells on the healing of injured intervertebral disk. Journal of Orthopaedic Research, 32(6), 819–825.*

<http://onlinelibrary.wiley.com/doi/10.1002/jor.22605/full>

## ABSTRACT

A major hurdle of cellular therapy for biological treatment of intervertebral disk (IVD) degeneration is the delivery method where current delivery methods are limited to intradiscal injection which can potentially cause further degeneration. Recent studies indicated that multipotential stem cells (MPSCs) from human umbilical cord blood home to injured sites and induce local therapeutic changes, thereby potentially addressing the drawbacks of direct delivery. We tested the effects of these cells on injured IVD using a mouse model of puncture-induced degeneration via two delivery methods. Caudal IVD underwent needle puncture, and MPSCs were injected indirectly (intravenously), or directly (intradiscally) into the nucleus pulposus. IVD were harvested for histological, gene and protein analysis after 14 weeks. Our finding showed limited homing ability of the MPSCs. However, regardless of delivery method, no engraftment or expansion of MPSCs was observed at the injured site. Contrasting to direct injection, intravenous

injection neither improved the degeneration status, nor preserve disk height, however, both delivery methods increased glycosaminoglycan (GAG) protein and Acan gene expression relative to controls, suggesting possible paracrine effects. Identifying the mechanisms by which MPSCs act on endogenous IVD cells would provide insights into the potential of these cells to treat IVD injuries and degeneration.

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## **Transplantation of mesenchymal stem cells embedded in Atelocollagen® gel to the intervertebral disc: a potential therapeutic model for disc degeneration**

Sakai et al.. (2003). *Transplantation of mesenchymal stem cells embedded in Atelocollagen® gel to the intervertebral disc: a potential therapeutic model for disc degeneration.* *Biomaterials*, 24(20), 3531-3541.

[https://doi.org/10.1016/S0142-9612\(03\)00222-9](https://doi.org/10.1016/S0142-9612(03)00222-9)

### **ABSTRACT**

Intervertebral disc degeneration is considered to be one of the major causes of low back pain. Despite this irreversible phenomenon, attempts to decelerate disc degeneration using various techniques have been reported. However, to date there has been no proven technique effective for broad

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clinical application. Based on previous studies, we hypothesize that maintenance of proteoglycan content in the disc is achieved by avoiding the depletion of nucleus pulposus and preserving the structure of the annulus is a primary factor in decelerating disc degeneration.

One novel approach to solve the dilemma of intervertebral disc degeneration is found at the stem cell level.

Mesenchymal stem cells (MSCs) are known to possess the ability to differentiate into various kinds of cells from mesenchymal origin. Although the majority of cells that contribute to disc formation are known to obtain chondrocyte-like phenotypes, no reported study has emphasized the correlation with mesenchymal stem cells.

To evaluate the possible potential of MSCs in disc cell research and treatment of degenerative disc disease, autologous MSCs embedded in Atelocollagen® gel were transplanted into the discs of rabbits which had undergone a procedure proven to induce degeneration.

The results suggest that MSC transplantation is effective in decelerating disc degeneration in experimental models and provided new hopes for treatment of degenerative disc disease in humans. Atelocollagen® gel served as an important carrier of MSCs in transplantation, permitting proliferation, matrix synthesis and differentiation of MSCs. This study strengthens the viable efficacy of practical application of MSCs in treatment of intervertebral disc disease.

## **Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc**

*Sakai et al.. (2006). Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. Biomaterials, 27(3), 335-345. <https://doi.org/10.1016/j.biomaterials.2005.06.038>*

### **ABSTRACT**

Intervertebral disc (IVD) degeneration, a common cause of low back pain in humans, is a relentlessly progressive phenomenon with no currently available effective treatment. In an attempt to solve this dilemma, we transplanted autologous mesenchymal stem cells (MSCs) from bone marrow into a rabbit model of disc degeneration to determine if stem cells could repair degenerated IVDs. LacZ expressing MSCs were transplanted to rabbit L2–L3, L3–L4 and L4–L5 IVDs 2 weeks after induction of degeneration. Changes in disc height by plain radiograph, T2-weighted signal intensity in magnetic resonance imaging (MRI), histology, immunohistochemistry and matrix associated gene expressions were evaluated between normal controls (NC) without operations, sham operated with only disc degeneration being induced, and MSC-transplanted animals for a 24-week period.

Results showed that after 24 weeks post-MSC transplantation, degenerated discs of MSC-transplanted group animals regained a disc height value of about 91%, MRI signal intensity of about 81%, compared to NC group discs. On the other hand, sham-operated group discs demonstrated the disc height value of about 67% and MRI signal intensity of about 60%. Macroscopic and histological evaluations confirmed relatively preserved nucleus with circular annulus structure in MSC-transplanted discs compared to indistinct structure seen in sham. Restoration of proteoglycan accumulation in MSC-transplanted discs was suggested from immunohistochemistry and gene expression analysis. These data indicate that transplantation of MSCs effectively led to regeneration of IVDs in a rabbit model of disc degeneration as suggested in our previous pilot study. MSCs may serve as a valuable resource in cell transplantation therapy for degenerative disc disease.

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## **Effect of Severity of Intervertebral Disc Injury on Mesenchymal Stem Cell-Based Regeneration**

*Ho et al.. (2008). Effect of Severity of Intervertebral Disc Injury on Mesenchymal Stem Cell-Based Regeneration. Connective Tissue Research, 49(1), 15-21.*  
<https://doi.org/10.1080/03008200701818595>

## ABSTRACT

Mesenchymal stem cell (MSC) implantation has been shown previously to arrest disc degeneration. This study aims to assess the effect of severity of disc degeneration on the ability of MSCs to arrest the degeneration. Disc degeneration was induced in New Zealand white rabbits at lumbar levels by annular puncture. The degeneration was allowed to progress for 1 month (early group) or 7 months (late group), followed by intradiscal injection of autologous MSCs. For disc levels that received MSCs treatment, 1 × 105 BrdU-labeled MSCs were injected per disc level. For the early group, MSC-injection had no significant effects on disc height or the progression of disc degeneration. For the late group, although the MSC-injected discs displayed lower disc heights than the control discs, they were significantly less degenerated together with near normal level of proteoglycan in localized areas. This is the first pilot study to demonstrate that severity of degeneration can influence the therapeutic effect of MSCs. Future studies of cell-based intervertebral disc regeneration should be carefully controlled in the context of stage of disc degeneration.

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## Feasibility of a stem cell therapy for intervertebral disc degeneration

Sobajima et al.. (2008). *Feasibility of a stem cell therapy for intervertebral disc degeneration. The Spine Journal, 8(6), 888–896.* <https://doi.org/10.1016/j.spinee.2007.09.011>

## **ABSTRACT**

### **Background context**

Different strategies to supplement/replenish the disc cell population have been proposed. Recently, adult stem cells have shown promise as a cell source for a variety of tissue engineering and cell therapy applications. A stem cell can renew itself through cell division and can be induced to develop into many different specialized cell types. Moreover, stem cells have shown ability to migrate and engraft within various tissues, as well as to exert stimulatory effects on other cell types through various mechanisms (eg, paracrine effects, cell-cell interactions). These characteristics make stem cells worthy of investigation as a source of cells for intervertebral disc (IVD) tissue engineering and cell therapy.

### **Purpose**

To determine feasibility of a stem cell therapy of IVD degeneration.

### **Study design**

In vitro studies of adult human cells to examine interactions between nucleus pulposus cells (NPCs) and mesenchymal stem cells (MSCs) at different ratios in 3-D pellet culture. In vivo studies of healthy adult rabbit discs injected with allogenic adult rabbit MSCs to examine stem cell survival and engraftment in living disc tissue.

### **Methods**

In vitro study: Human NPCs were cocultured with human MSCs in different ratios (75:25, 50:50, 25:75) for 2 weeks in pellet culture, for comparison with pure NPC (100:0) and

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pure MSC (0:100) pellet cultures. Proteoglycan synthesis rate and glycosaminoglycan (GAG) content were measured by radioactive sulfate incorporation and dimethylmethylen blue assay, respectively. In vivo study: MSCs were isolated from the bone marrow of a New Zealand White (NZW) rabbit, retrovirally transduced with the lacZ marker gene, and injected into the nucleus pulposi of the L2–3, L3–4, and L4–5 lumbar discs of 12 other NZW rabbits. Three rabbits each were sacrificed at 3, 6, 12, or 24 weeks after cell implantation, and X-Gal staining was done to assess survival and localization of MSCs in the disc tissues.

### Results

In vitro study: the 75:25 and 50:50 NPC:MSC cocultures yielded the greatest increases in extracellular matrix (ECM) production. In vivo study: MSCs were detected in histological sections of rabbit discs up to 24 weeks after allogenic stem cell implantation, without evidence of systemic illness in the recipient rabbits. The 24-week results in particular suggested the possibility of stem cell migration and engraftment into the inner annulus fibrosus.

### Conclusions

These encouraging results support feasibility of a stem cell therapy approach toward supplementation/replenishment of IVD cells and synthesis/maintenance of a more functional ECM in a degenerated disc. Moreover, the in vivo results demonstrate that transplanted MSCs survive and successfully engraft into the IVD tissue, and are effective vehicles for exogenous gene delivery to the IVD—thus there appear to be multiple mechanisms whereby stem cells might

able to confer therapeutic effects in a stem cell therapy of IVD degeneration.

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## **In vivo intervertebral disc regeneration using stem cell-derived chondroprogenitors Laboratory investigation**

*Sheikh et al.. (2009). In vivo intervertebral disc regeneration using stem cell-derived chondroprogenitors Laboratory investigation. Journal of Neurosurgery, 10(3), 265-272.  
<http://thejns.org/doi/abs/10.3171/2008.12.SPINE0835>*

### **ABSTRACT**

### **OBJECT**

There is currently no biologic therapy to repair or restore a degenerated intervertebral disc. A potential solution may rest with embryonic stem cells (ESCs), which have a potential to grow indefinitely and differentiate into a variety of cell types in vitro. Prior studies have shown that ESCs can be encouraged to differentiate toward specific cell lineages by culture in selective media and specific growth environment. Among these lineages, there are cells capable of potentially producing nucleus pulposus (NP) in vivo. In this investigation, the authors studied ESCderived chondroprogenitors implanted into a degenerated disc in a

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rabbit. For this purpose, a rabbit model of disc degeneration was developed.

### METHODS

A percutaneous animal model of disc degeneration was developed by needle puncture of healthy intact discs in 16 New Zealand white rabbits. Series of spine MR imaging studies were obtained before disc puncture and after 2, 6, and 8 weeks. Prior to implantation, murine ESCs were cultured with cis-retinoic acid, transforming growth factor  $\beta$ , ascorbic acid, and insulin-like growth factor to induce differentiation toward a chondrocyte lineage. After confirmation by MR imaging, degenerated disc levels were injected with chondrogenic derivatives of ESCs expressing green fluorescent protein. At 8 weeks post-ESC implantation, the animals were killed and the intervertebral discs were harvested and analyzed using H & E staining, confocal fluorescent microscopy, and immunohistochemical analysis. Three intervertebral disc groups were analyzed in 16 rabbits, as follows: 1) Group A, control: naïve, nonpunctured discs (32 discs, levels L4–5 and L5–6); 2) Group B, experimental control: punctured disc (16 discs, level L2–3); and 3) Group C, experimental: punctured disc followed by implantation of chondroprogenitor cells (16 discs, level L3–4).

### RESULTS

The MR imaging studies confirmed intervertebral disc degeneration at needle-punctured segments starting at  $\sim$  2 weeks. Postmortem H & E histological analysis of Group A discs showed mature chondrocytes and no notochordal

cells. Group B discs displayed an intact anulus fibrosus and generalized disorganization within fibrous tissue of NP. Group C discs showed islands of notochordal cell growth. Immunofluorescent staining for notochordal cells was negative for Groups A and B but revealed viable notochordal-type cells within experimental Group C discs, which had been implanted with ESC derivatives. Notably, no inflammatory response was noted in Group C discs.

## **CONCLUSIONS**

This study illustrates a reproducible percutaneous model for studying disc degeneration. New notochordal cell populations were seen in degenerated discs injected with ESCs. The lack of immune response to a xenograft of mouse cells in an immunocompetent rabbit model may suggest an as yet unrecognized immunoprivileged site within the intervertebral disc space.

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## **Effects of implantation of bone marrow mesenchymal stem cells, disc distraction and combined therapy on reversing degeneration of the intervertebral disc**

*Hee et al.. (2010). Effects of implantation of bone marrow mesenchymal stem cells, disc distraction and combined*

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*therapy on reversing degeneration of the intervertebral disc.*  
*The Journal of Bone and Joint Surgery, 92(B), 726-36.*  
<https://www.ncbi.nlm.nih.gov/pubmed/20436013>

### **ABSTRACT**

Although success has been achieved with implantation of bone marrow mesenchymal stem cells (bMSCs) in degenerative discs, its full potential may not be achieved if the harsh environment of the degenerative disc remains. Axial distraction has been shown to increase hydration and nutrition. Combining both therapies may have a synergistic effect in reversing degenerative disc disease. In order to evaluate the effect of bMSC implantation, axial distraction and combination therapy in stimulating regeneration and retarding degeneration in degenerative discs, we first induced disc degeneration by axial loading in a rabbit model. The rabbits in the intervention groups performed better with respect to disc height, morphological grading, histological scoring and average dead cell count. The groups with distraction performed better than those without on all criteria except the average dead cell count. Our findings suggest that bMSC implantation and distraction stimulate regenerative changes in degenerative discs in a rabbit model.

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# **Autologous Stem Cell Therapy Maintains Vertebral Blood Flow and Contrast Diffusion Through the Endplate in Experimental Intervertebral Disc Degeneration**

*Bendtsen et al.. (2011). Autologous Stem Cell Therapy Maintains Vertebral Blood Flow and Contrast Diffusion Through the Endplate in Experimental Intervertebral Disc Degeneration. Spine, 36(6), E373–E379.*

[https://journals.lww.com/spinejournal/Abstract/2011/03150/Prolonged\\_and\\_Repeated\\_Upright\\_Posture\\_Promotes.16.aspx](https://journals.lww.com/spinejournal/Abstract/2011/03150/Prolonged_and_Repeated_Upright_Posture_Promotes.16.aspx)

## **ABSTRACT**

### **Study Design.**

Experimental, controlled, randomized, and paired study.

### **Objective.**

To evaluate regenerative effect of stem cell therapy on the vertebral endplate and introduce dynamic contrast-enhanced magnetic resonance imaging (MRI) as a tool in the investigation of endplate function.

### **Summary of Background Data.**

The vertebral endplate plays a crucial role in nutritional supply to the intervertebral disc. Estimation of endplate

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function is an important parameter in future biologic therapy of intervertebral disc degeneration (IDD).

### **Methods.**

Four-level IDD was induced in each of 15 Gottingen minipigs. Percutaneous intradiscal injection of two hydrogels (Zimmer Biologics Inc, Austin, TX) and one loaded with stem cells was used as single interventions after 12 weeks. Total observation time was 24 weeks. MRI was performed before the initiation of treatment and killing of animals.

### **Results.**

Three animals were excluded because of spondylodiscitis. Stem cell and hydrogel treatment had significantly higher T2 values, relative vertebral blood flow and volume, as well as lower Pfirrmann scores when compared with degenerative controls. No statistical differences were found compared to normal controls.

### **Conclusion.**

Stem cell and hydrogel therapy is able to partly regenerate IDD and maintain perfusion and permeability of the vertebral endplate and subchondral bone. Dynamic contrast-enhanced MRI may become an important tool in future investigation of the vertebral endplate.

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# **STEM CELLS: SPINAL CORD INJURY**

## **The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications.**

*Forostyak, S, jendelova, P & Sykova, E. (2013). The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications. Biochimie, 95(12), 2257-70.*

<https://www.ncbi.nlm.nih.gov/pubmed/23994163>

### **ABSTRACT**

Diseases of the central nervous system still remain among the most challenging pathologies known to mankind, having no or limited therapeutic possibilities and a very pessimistic prognosis. Advances in stem cell biology in the last decade have shown that stem cells might provide an inexhaustible source of neurons and glia as well as exerting a neuroprotective effect on the host tissue, thus opening new horizons for tissue engineering and regenerative medicine. Here, we discuss the progress made in the cell-based therapy of spinal cord injury. An emphasis has been placed on the application of adult mesenchymal stromal cells (MSCs). We then review the latest and most significant

results from in vitro and in vivo research focusing on the regenerative/neuroprotective properties of MSCs. We also attempt to correlate the effect of MSCs with the pathological events that are taking place in the nervous tissue after SCI. Finally, we discuss the results from preclinical and clinical trials involving different routes of MSC application into patients with neurological disorders of the spinal cord.

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## **HPMA-RGD hydrogels seeded with mesenchymal stem cells improve functional outcome in chronic spinal cord injury.**

*Hejcl et al.. (2010). HPMA-RGD hydrogels seeded with mesenchymal stem cells improve functional outcome in chronic spinal cord injury. Stem Cells Dev, 19(10), 1535-46.*  
<https://www.ncbi.nlm.nih.gov/pubmed/20053128>

### **ABSTRACT**

Chronic spinal cord injury (SCI) is characterized by tissue loss and a stable functional deficit. While several experimental therapies have proven to be partly successful for the treatment of acute SCI, treatment of chronic SCI is still challenging. We studied whether we can bridge a chronic spinal cord lesion by implantation of our newly developed hydrogel based on 2-hydroxypropyl methacrylamide, either alone or seeded with mesenchymal stem cells (MSCs), and whether this treatment leads to functional improvement. A balloon-induced compression

lesion was performed in adult 2-month-old male Wistar rats. Five weeks after injury, HPMA-RGD hydrogels [N-(2-hydroxypropyl)-methacrylamide with attached amino acid sequences--Arg-Gly-Asp] were implanted into the lesion, either with or without seeded MSCs. Animals with chronic SCI served as controls. The animals were behaviorally tested using the Basso–Beattie-Bresnahan (BBB) (motor) and plantar (sensory) tests once a week for 6 months. Behavioral analysis showed a statistically significant improvement in rats with combined treatment, hydrogel and MSCs, compared with the control group ( $P < 0.05$ ). Although a tendency toward improvement was found in rats treated with hydrogel only, this was not significant. Subsequently, the animals were sacrificed 6 months after SCI, and the spinal cord lesions evaluated histologically. The combined therapy (hydrogel with MSCs) prevented tissue atrophy ( $P < 0.05$ ), and the hydrogels were infiltrated with axons myelinated with Schwann cells. Blood vessels and astrocytes also grew inside the implant. MSCs were present in the hydrogels even 5 months after implantation. We conclude that 5 weeks after injury, HPMA-RGD hydrogels seeded with MSCs can successfully bridge a spinal cord cavity and provide a scaffold for tissue regeneration. This treatment leads to functional improvement even in chronic SCI.

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# **Transplantation of bone marrow mesenchymal stem cells reduces lesion volume and induces axonal regrowth of injured spinal cord.**

*Gu et al.. (2010). Transplantation of bone marrow mesenchymal stem cells reduces lesion volume and induces axonal regrowth of injured spinal cord. Neuropathology, 20(3), 205-17.*

<https://www.ncbi.nlm.nih.gov/pubmed/19845866>

## **ABSTRACT**

It has been demonstrated that transplantation of bone marrow mesenchymal stem cells (BMSCs) improves recovery of injured spinal cord in animal models. However, the mechanism of how BMSCs promote repair of injured spinal cord remains under investigation. The present study investigated the neural differentiation of BMSCs, the lesion volume and axonal regrowth of injured spinal cord after transplantation. Seven days after spinal cord injury,  $3 \times 10^5$  BMSCs or PBS (control) was delivered into the injury epicenter of the spinal cord. At 8 weeks after spinal cord injury, transplantation of BMSCs reduced the volume of cavity and increased spared white matter as compared to the control. BMSCs did not express the cell marker of neurons, astrocytes and oligodendrocytes in injured spinal cord. Transmission electron microscopic examination displayed an increase in the number of axons in BMSC rats.

The effect of BMSCs on growth of neuronal process was further investigated by using a coculture system. The length and the number of neurites from spinal neurons significantly increased when they cocultured with BMSCs. PCR and immunochemical analysis showed that BMSCs expressed brain-derived neurotrophic factor (BDNF) and glia cell line-derived neurotrophic factor (GDNF). These findings demonstrate that transplantation of BMSCs reduces lesion volume and promotes axonal regrowth of injured spinal cord.

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## **Physical activity-mediated functional recovery after spinal cord injury: potential roles of neural stem cells**

*Teng et al.. (2006). Physical activity-mediated functional recovery after spinal cord injury: potential roles of neural stem cells. REGENERATIVE MEDICINE, 1(6).*

<https://doi.org/10.2217/17460751.1.6.763>

### **ABSTRACT**

As data elucidating the complexity of spinal cord injury pathophysiology emerge, it is increasingly being recognized that successful repair will probably require a multifaceted approach that combines tactics from various biomedical disciplines, including pharmacology, cell transplantation, gene therapy and material sciences. Recently, new evidence highlighting the benefit of physical activity and rehabilitation

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interventions during the post-injury phase has provided novel possibilities in realizing effective repair after spinal cord injury. However, before a comprehensive therapeutic strategy that optimally utilizes the benefits of each of these disciplines can be designed, the basic mechanisms by which these various interventions act must be thoroughly explored and important synergistic and antagonistic interactions identified. In examining the mechanisms by which physical activity-based functional recovery after spinal cord injury is effected, endogenous neural stem cells, in our opinion, engender a potentially key role. Multipotent neural stem cells possess many faculties that abet recovery, including the ability to assess the local microenvironment and deliver biofactors that promote neuroplasticity and regeneration, as well as the potential to replenish damaged or eradicated cellular elements. Encouragingly, the functional recovery owing to physical activity-based therapies appears relatively robust, even when therapy is initiated in the chronic stage of spinal cord injury. In this article, we review experimental outcomes related to our hypothesis that endogenous neural stem cells mediate the functional recovery noted in spinal cord injury following physical activity-based treatments. Overall, the data advocates the incorporation of increased physical activity as a component of the multidimensional treatment of spinal cord injury and underscores the critical need to employ research-based mechanistic approaches for developing future advances in the rehabilitation of neurological injury and disorders.

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# STEM CELLS: SHOULDER CONDITIONS

## Stem cell therapy in the management of shoulder rotator cuff disorders

Mora et al.. (2015). *Stem cell therapy in the management of shoulder rotator cuff disorders*. *World Journal of Stem Cells*, 7(4), 691–699.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444610/>

### ABSTRACT

Rotator cuff tears are frequent shoulder problems that are usually dealt with surgical repair. Despite improved surgical techniques, the tendon-to-bone healing rate is unsatisfactory due to difficulties in restoring the delicate transitional tissue between bone and tendon. It is essential to understand the molecular mechanisms that determine this failure. The study of the molecular environment during embryogenesis and during normal healing after injury is key in devising strategies to get a successful repair. Mesenchymal stem cells (MSC) can differentiate into different mesodermal tissues and have a strong paracrine, anti-inflammatory, immunoregulatory and angiogenic potential. Stem cell therapy is thus a potentially effective therapy to enhance rotator cuff healing. Promising results have been reported with the use of autologous MSC of different origins in animal

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studies: they have shown to have better healing properties, increasing the amount of fibrocartilage formation and improving the orientation of fibrocartilage fibers with less immunologic response and reduced lymphocyte infiltration. All these changes lead to an increase in biomechanical strength. However, animal research is still inconclusive and more experimental studies are needed before human application. Future directions include expanded stem cell therapy in combination with growth factors or different scaffolds as well as new stem cell types and gene therapy.

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### **Isolation of mesenchymal stem cells from shoulder rotator cuff: a potential source for muscle and tendon repair.**

*Tsai et al.. (2013). Isolation of mesenchymal stem cells from shoulder rotator cuff: a potential source for muscle and tendon repair. Cell Transplant, 22(3), 413-22.*

<https://www.ncbi.nlm.nih.gov/pubmed/23006509>

#### **ABSTRACT**

The self-healing potential of each tissue belongs to endogenous stem cells residing in the tissue; however, there are currently no reports mentioned for the isolation of human rotator cuff-derived mesenchymal stem cells (RC-MSCs) since. To isolate RC-MSCs, minced rotator cuff samples were first digested with enzymes and the single cell suspensions were seeded in plastic culture dishes. Twenty-

four hours later, nonadherent cells were removed and the adherent cells were further cultured. The RC-MSCs had fibroblast-like morphology and were positive for the putative surface markers of MSCs, such as CD44, CD73, CD90, CD105, and CD166, and negative for the putative markers of hematopoietic cells, such as CD34, CD45, and CD133. Similar to BM-MSCs, RC-MSCs were demonstrated to have the potential to undergo osteogenic, adipogenic, and chondrogenic differentiation. Upon induction in the defined media, RC-MSCs also expressed lineage-specific genes, such as Runx 2 and osteocalcin in osteogenic induction, PPAR- $\gamma$  and LPL in adipogenic differentiation, and aggrecan and Col2a1 in chondrogenic differentiation. The multipotent feature of RC-MSCs in the myogenic injury model was further strengthened by the increase in myogenic potential both *in vitro* and *in vivo* when compared with BM-MSCs. These results demonstrate the successful isolation of MSCs from human rotator cuffs and encourage the application of RC-MSCs in myogenic regeneration.

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## **Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears.**

*Utsunomiya et al.. (2013). Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears. American Journal of*

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*Sports Medicine*, 41(3), 657-68.

<https://www.ncbi.nlm.nih.gov/pubmed/23371475>

### **ABSTRACT**

#### **BACKGROUND:**

Recent studies report a relatively high failure rate for tendon-bone healing after rotator cuff repair. Several studies have investigated biologically augmented rotator cuff repair; however, none has shown the application of synovial mesenchymal stem cells for such repair.

#### **PURPOSE:**

To demonstrate whether cells derived from shoulder tissues have mesenchymal stem cell properties and to identify which tissue is the best source of the mesenchymal stem cells.

#### **STUDY DESIGN:**

Controlled laboratory study.

#### **METHODS:**

Forty-two patients with a diagnosed rotator cuff tear preoperatively were enrolled in this study. Human mesenchymal tissues were obtained during arthroscopic surgery for rotator cuff tears from 19 donors who met the inclusion criteria and had investigable amounts of tissue. Colony-forming units, yield obtained, expandability, differentiation potential, epitope profile, and gene expression were compared among the cells from 4 shoulder tissues: synovium of the glenohumeral joint, subacromial bursa, margin of the ruptured supraspinatus tendon, and residual tendon stump on the greater tuberosity (enthesis).

## **RESULTS:**

The number of live passage 0 cells from whole tissue was significantly higher in cells derived from the subacromial bursa ( $P < .05$ ). Subacromial bursa-derived cells retained their expandability even at passage 10. In adipogenesis experiments, the frequency of Oil Red O-positive colonies was significantly higher for synovium- and subacromial bursa-derived cells than for tendon- and enthesis-derived cells ( $P < .0001$ ). In studies of osteogenesis, the rate of von Kossa- and alkaline phosphatase-positive colonies was highest in subacromial bursa-derived cells ( $P < .0001$ ). The chondrogenic potential was highest in cells derived from the enthesis. For epitope profiling, 11 surface antigens were measured, and most had similar epitope profiles, irrespective of cell source.

## **CONCLUSION:**

The findings indicate that the subacromial bursa is a good candidate for the source of mesenchymal stem cells in rotator cuff tears.

## **CLINICAL RELEVANCE:**

Synovial cells from the subacromial bursa in patients with rotator cuff tears are a superior cell source *in vitro*, suggesting that mesenchymal stem cells from this tissue could be good candidates for biological augmentation of rotator cuff repair.

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# **Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study**

*Hernigou et al.. (2014). Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study. International Orthopaedics, 38(9), 1811–1818. <https://link.springer.com/article/10.1007/s00264-014-2391-1>*

## **ABSTRACT**

### **Purpose**

The purpose of this study was to evaluate the efficiency of biologic augmentation of rotator cuff repair with iliac crest bone marrow-derived mesenchymal stem cells (MSCs). The prevalence of healing and prevention of re-tears were correlated with the number of MSCs received at the tendon-to-bone interface.

### **Methods**

Forty-five patients in the study group received concentrated bone marrow-derived MSCs as an adjunct to single-row rotator cuff repair at the time of arthroscopy. The average number of MSCs returned to the patient was  $51,000 \pm 25,000$ . Outcomes of patients receiving MSCs

during their repair were compared to those of a matched control group of 45 patients who did not receive MSCs. All patients underwent imaging studies of the shoulder with iterative ultrasound performed every month from the first postoperative month to the 24th month. The rotator cuff healing or re-tear was confirmed with MRI postoperatively at three and six months, one and two years and at the most recent follow up MRI (minimum ten-year follow-up).

## **Results**

Bone marrow-derived MSC injection as an adjunctive therapy during rotator cuff repair enhanced the healing rate and improved the quality of the repaired surface as determined by ultrasound and MRI. Forty-five (100 %) of the 45 repairs with MSC augmentation had healed by six months, versus 30 (67 %) of the 45 repairs without MSC treatment by six months. Bone marrow concentrate (BMC) injection also prevented further ruptures during the next ten years. At the most recent follow-up of ten years, intact rotator cuffs were found in 39 (87 %) of the 45 patients in the MSC-treated group, but just 20 (44 %) of the 45 patients in the control group. The number of transplanted MSCs was determined to be the most relevant to the outcome in the study group, since patients with a loss of tendon integrity at any time up to the ten-year follow-up milestone received fewer MSCs as compared with those who had maintained a successful repair during the same interval.

## **Conclusion**

This study showed that significant improvement in healing outcomes could be achieved by the use of BMC containing

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MSC as an adjunct therapy in standard of care rotator cuff repair. Furthermore, our study showed a substantial improvement in the level of tendon integrity present at the ten-year milestone between the MSC-treated group and the control patients. These results support the use of bone marrow-derived MSC augmentation in rotator cuff repair, especially due to the enhanced rate of healing and the reduced number of re-tears observed over time in the MSC-treated patients.

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# STEM CELLS: ELBOW

## **Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs.**

*Black et al.. (2008). Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Vet Ther, 9(3), 192-200.*

<https://www.ncbi.nlm.nih.gov/pubmed/19003780>

### **ABSTRACT**

Autologous adipose-derived mesenchymal stem cell (AD-MSC) therapy involves harvesting fat from the patient, isolating the stem and regenerative cells, and administering the cells back to the patient. Autologous AD-MSC therapy in veterinary regenerative medicine has been commercially available since 2003. Previously reported results from a blinded, controlled trial in dogs with chronic osteoarthritis of the coxofemoral (hip) joint demonstrated efficacy of a single intraarticular injection of autologous AD-MSC therapy. The

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primary objective of the current study was to evaluate the effectiveness of this therapy in dogs with chronic osteoarthritis of the humeroradial (elbow) joints and to determine the duration of effect. Fourteen dogs were recruited. Veterinarians assessed each dog for lameness, pain on manipulation, range of motion, and functional disability using a numeric rating scale at baseline and specified intervals up to 180 days after treatment. Statistically significant improvement in outcome measures was demonstrated.

# STEM CELLS: JOINT REPLACEMENT

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## Anatomic Mesenchymal Stem Cell-Based Engineered Cartilage Constructs for Biologic Total Joint Replacement

Saxena et al.. (2016). *Anatomic Mesenchymal Stem Cell-Based Engineered Cartilage Constructs for Biologic Total Joint Replacement. Tissue Engineering Part A*, 22(3-4), 386-395. <https://doi.org/10.1089/ten.tea.2015.0384>

### ABSTRACT

Cartilage has a poor healing response, and few viable options exist for repair of extensive damage. Hyaluronic acid (HA) hydrogels seeded with mesenchymal stem cells (MSCs) polymerized through UV crosslinking can generate functional tissue, but this crosslinking is not compatible with indirect rapid prototyping utilizing opaque anatomic molds. Methacrylate-modified polymers can also be chemically crosslinked in a cytocompatible manner using ammonium persulfate (APS) and N,N,N',N'-tetramethylethylenediamine (TEMED). The objectives of this study were to (1) compare

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APS/TEMED crosslinking with UV crosslinking in terms of functional maturation of MSC-seeded HA hydrogels; (2) generate an anatomic mold of a complex joint surface through rapid prototyping; and (3) grow anatomic MSC-seeded HA hydrogel constructs using this alternative crosslinking method. Juvenile bovine MSCs were suspended in methacrylated HA (MeHA) and crosslinked either through UV polymerization or chemically with APS/TEMED to generate cylindrical constructs. Minipig porcine femoral heads were imaged using microCT, and anatomic negative molds were generated by three-dimensional printing using fused deposition modeling. Molded HA constructs were produced using the APS/TEMED method. All constructs were cultured for up to 12 weeks in a chemically defined medium supplemented with TGF- $\beta$ 3 and characterized by mechanical testing, biochemical assays, and histologic analysis. Both UV- and APS/TEMED-polymerized constructs showed increasing mechanical properties and robust proteoglycan and collagen deposition over time. At 12 weeks, APS/TEMED-polymerized constructs had higher equilibrium and dynamic moduli than UV-polymerized constructs, with no differences in proteoglycan or collagen content. Molded HA constructs retained their hemispherical shape in culture and demonstrated increasing mechanical properties and proteoglycan and collagen deposition, especially at the edges compared to the center of these larger constructs. Immunohistochemistry showed abundant collagen type II staining and little collagen type I staining. APS/TEMED crosslinking can be used to produce MSC-seeded HA-based neocartilage and can be used in combination with rapid prototyping techniques to generate

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anatomic MSC-seeded HA constructs for use in filling large and anatomically complex chondral defects or for biologic joint replacement.

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# STEM CELLS: RHEUMATIC DISEASE

## Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases

Djouad et al.. (2009). *Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases*. *Nat Rev Rheumatol*, 5(7), 392-9.

<http://dx.doi.org/10.1038/nrrheum.2009.104>

### ABSTRACT

Mesenchymal stem cells (MSCs), or multipotent mesenchymal stromal cells as they are also known, have been identified in bone marrow as well as in other tissues of the joint, including adipose, synovium, periosteum, perichondrium, and cartilage. These cells are characterized by their phenotype and their ability to differentiate into three lineages: chondrocytes, osteoblasts and adipocytes.

Importantly, MSCs also potently modulate immune responses, exhibit healing capacities, improve angiogenesis and prevent fibrosis. These properties might be explained at least in part by the trophic effects of MSCs through the secretion of a number of cytokines and growth factors. However, the mechanisms involved in the differentiation potential of MSCs, and their immunomodulatory and paracrine properties, are currently being extensively studied. These unique

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properties of MSCs confer on them the potential to be used for therapeutic applications in rheumatic diseases, including rheumatoid arthritis, osteoarthritis, genetic bone and cartilage disorders as well as bone metastasis.

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# **STEM CELLS: NEUROLOGICAL**

## **Transformation of human umbilical mesenchymal cells into neurons in vitro**

*Fu, Y.S, Shih, Y.T & Cheng, Y.C. (2004). Transformation of human umbilical mesenchymal cells into neurons in vitro. Journal of Biomedical Science, 11(5), 652-660.*  
<https://doi.org/10.1007/BF02256131>

### **ABSTRACT**

Neuronal transplantation has provided a promising approach for treating neurodegenerative diseases. Recently, efforts have been directed at in vitro induction of various stem cells to transform into neurons. We report the first successful quantities in an in vitro attempt at directing the transformation into neurons of human umbilical mesenchymal cells, which are capable of rapid proliferation in vitro and are easily available. When cultured in neuronal conditioned medium, human umbilical mesenchymal cells started to express neuron-specific proteins such as NeuN and neurofilament (NF) on the 3rd day and exhibited retraction of the cell body, elaboration of processes, clustering of cells and expression of functional mRNA responsible for the synthesis of subunits of the kainate

receptor and glutamate decarboxylase on the 6th day. Between the 9th and 12th days, the percentage of human umbilical mesenchymal cells expressing NF was as high as 87%, while functionality was demonstrated by glutamate invoking an inward current. At this stage, cells were differentiated into mature neurons in the postmitosis phase.

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## **Human umbilical cord Wharton's Jelly-derived mesenchymal stem cells differentiation into nerve-like cells.**

*Ma et al.. (2005). Human umbilical cord Wharton's Jelly-derived mesenchymal stem cells differentiation into nerve-like cells. Chin Med J, 118(23), 1987-93.*

<https://www.ncbi.nlm.nih.gov/pubmed/16336835>

### **ABSTRACT**

### **BACKGROUND:**

The two most basic properties of mesenchymal stem cells (MSCs) are the capacities to self-renew indefinitely and differentiate into multiple cells and tissue types. The cells from human umbilical cord Wharton's Jelly have properties of MSCs and represent a rich source of primitive cells. This study was conducted to explore the possibility of inducing human umbilical cord Wharton's Jelly-derived MSCs to differentiate into nerve-like cells.

### **METHODS:**

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MSCs were cultured from the Wharton's Jelly taken from human umbilical cord of babies delivered after full-term normal labor. *Salvia miltiorrhiza* and beta-mercaptoethanol were used to induce the human umbilical cord-derived MSCs to differentiate. The expression of neural protein markers was shown by immunocytochemistry. The induction process was monitored by phase contrast microscopy, electron microscopy (EM), and laser scanning confocal microscopy (LSCM). The pleiotrophin and nestin genes were measured by reverse transcription-polymerase chain reaction (RT-PCR).

### **RESULTS:**

MSCs in the Wharton's Jelly were easily attainable and could be maintained and expanded in culture. They were positive for markers of MSCs, but negative for markers of hematopoietic cells and graft-versus-host disease (GVHD)-related cells. Treatment with *Salvia miltiorrhiza* caused Wharton's Jelly cells to undergo profound morphological changes. The induced MSCs developed rounded cell bodies with multiple neurite-like extensions. Eventually they developed processes that formed networks reminiscent of primary cultures of neurons. *Salvia miltiorrhiza* and beta-mercaptoethanol also induced MSCs to express nestin, beta-tubulinIII, neurofilament (NF) and glial fibrillary acidic protein (GFAP). It was confirmed by RT-PCR that MSCs could express pleiotrophin both before and after induction by *Salvia miltiorrhiza*. The expression was markedly enhanced after induction and the nestin gene was also expressed.

## **CONCLUSIONS:**

MSCs could be isolated from human umbilical cord Wharton's Jelly. They were capable of differentiating into nerve-like cells using Salvia miltorrhiza or beta-mercaptoethanol. The induced MSCs not only underwent morphologic changes, but also expressed the neuron-related genes and neuronal cell markers. They may represent an alternative source of stem cells for central nervous system cell transplantation.

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## **Matrix cells from Wharton's jelly form neurons and glia.**

*Mitchell et al.. (2003). Matrix cells from Wharton's jelly form neurons and glia. Stem Cells, 21(1), 50-60.*

<http://dx.doi.org/10.1634/stemcells.21-1-50>

## **ABSTRACT**

We have identified an easily attainable source of primitive, potentially multipotent stem cells from Wharton's jelly, the matrix of umbilical cord. Wharton's jelly cells have been propagated in culture for more than 80 population doublings. Several markers for stem cells, including c-kit (CD117), and telomerase activity are expressed in these cells. Treatment with basic fibroblast growth factor overnight and low-serum media plus butylated hydroxyanisole and dimethylsulfoxide induced Wharton's jelly cells to express a neural phenotype.

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Within several hours of this treatment, Wharton's jelly cells developed rounded cell bodies with multiple neurite-like extensions, similar to the morphology of neural stem cells. Neuron-specific enolase (NSE), a neural stem cell marker, was expressed in these cells, as shown by immunocytochemistry. Immunoblot analysis showed similar levels of NSE expression in both untreated and induced Wharton's jelly cells. After 3 days, the induced Wharton's jelly cells resembled bipolar or multipolar neurons, with processes that formed networks reminiscent of primary cultures of neurons. The neuron-like cells in these cultures stained positively for several neuronal proteins, including neuron-specific class III beta-tubulin, neurofilament M, an axonal growth-cone-associated protein, and tyrosine hydroxylase. Immunoblot analysis showed increasing levels of protein markers for mature neurons over time post induction. Markers for oligodendrocytes and astrocytes were also detected in Wharton's jelly cells. These exciting findings show that cells from the matrix of umbilical cord have properties of stem cells and may, thus, be a rich source of primitive cells. This study shows their capacity to differentiate into a neural phenotype in vitro.

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# Progress of mesenchymal stem cell therapy for neural and retinal diseases

*Ng et al.. (2014). Progress of mesenchymal stem cell therapy for neural and retinal diseases. World Journal of Stem Cells, 6(2), 111-119.*

<http://dx.doi.org/10.4252/wjsc.v6.i2.111>

## ABSTRACT

Complex circuitry and limited regenerative power make central nervous system (CNS) disorders the most challenging and difficult for functional repair. With elusive disease mechanisms, traditional surgical and medical interventions merely slow down the progression of the neurodegenerative diseases. However, the number of neurons still diminishes in many patients. Recently, stem cell therapy has been proposed as a viable option. Mesenchymal stem cells (MSCs), a widely-studied human adult stem cell population, have been discovered for more than 20 years. MSCs have been found all over the body and can be conveniently obtained from different accessible tissues: bone marrow, blood, and adipose and dental tissue. MSCs have high proliferative and differentiation abilities, providing an inexhaustible source of neurons and glia for cell replacement therapy. Moreover, MSCs also show neuroprotective effects without any genetic modification or reprogramming. In addition, the extraordinary immunomodulatory properties of MSCs enable autologous and heterologous transplantation.

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These qualities heighten the clinical applicability of MSCs when dealing with the pathologies of CNS disorders. Here, we summarize the latest progress of MSC experimental research as well as human clinical trials for neural and retinal diseases. This review article will focus on multiple sclerosis, spinal cord injury, autism, glaucoma, retinitis pigmentosa and age-related macular degeneration.

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### **Enhancement of neuroplasticity through upregulation of $\beta 1$ -integrin in human umbilical cord-derived stromal cell implanted stroke model**

*Ding et al.. (2007). Enhancement of neuroplasticity through upregulation of  $\beta 1$ -integrin in human umbilical cord-derived stromal cell implanted stroke model. Neurobiology of Disease, 27(3), 339-353.*

<https://doi.org/10.1016/j.nbd.2007.06.010>

#### **ABSTRACT**

Neuroplasticity subsequent to functional angiogenesis is an important goal for cell-based therapy of ischemic neural tissues. At present, the cellular and molecular mechanisms involved are still not well understood. In this study, we isolated mesenchymal stem cells (MSCs) from Wharton's jelly (WJ) to obtain clonally expanded human umbilical cord-derived mesenchymal stem cells (HUCMSCs) with multilineage differentiation potential. Experimental rats

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receiving intracerebral HUCMSC transplantation showed significantly improved neurological function compared to vehicle-treated control rats. Cortical neuronal activity, as evaluated by proton MR spectroscopy (<sup>1</sup>H-MRS), also increased considerably in the transplantation group. Transplanted HUCMSCs migrated towards the ischemic boundary zone and differentiated into glial, neuronal, doublecortin+, CXCR4+, and vascular endothelial cells to enhance neuroplasticity in the ischemic brain. In addition, HUCMSC transplantation promoted the formation of new vessels to increase local cortical blood flow in the ischemic hemisphere. Modulation by stem cell-derived macrophage/microglial interactions, and increased  $\beta$ 1-integrin expression, might enhance this angiogenic architecture within the ischemic brain. Inhibition of  $\beta$ 1-integrin expression blocked local angiogenesis and reduced recovery from neurological deficit. In addition, significantly increased modulation of neurotrophic factor expression was also found in the HUCMSC transplantation group. In summary, regulation of  $\beta$ 1-integrin expression plays a critical role in the plasticity of the ischemic brain after the implantation of HUCMSCs.

## **Stem cell therapy for human neurodegenerative disorders-how to make it work.**

*Lindvall, O, Kokaia, Z & Martinez-serrano, A. (2004). Stem cell therapy for human neurodegenerative disorders-how to make it work. Nat Med, 10(Suppl), 42-50.*

<http://dx.doi.org/10.1038/nm1064>

Recent progress shows that neurons suitable for transplantation can be generated from stem cells in culture, and that the adult brain produces new neurons from its own stem cells in response to injury. These findings raise hope for the development of stem cell therapies in human neurodegenerative disorders. Before clinical trials are initiated, we need to know much more about how to control stem cell proliferation and differentiation into specific phenotypes, induce their integration into existing neural and synaptic circuits, and optimize functional recovery in animal models closely resembling the human disease.

# **Application of neural stem cells in tissue-engineered artificial nerve.**

*Guo, B.F & Dong, M.M. (2009). Application of neural stem cells in tissue-engineered artificial nerve. Otolaryngol Head Neck Surg, 140(2), 159-64.*

<http://dx.doi.org/10.1016/j.otohns.2008.10.039>

## **OBJECTIVE:**

To observe the curative effect of neural stem cells (NSCs), which are used in tissue-engineered artificial nerve, on repairing rabbit 10-mm facial nerve defects.

## **METHODS:**

Thirty-six Oryctolagus cuniculi were randomly divided into three groups (each group with 12 Oryctolagus cuniculi). In group A, chitosan conduit, collagen protein sponge, nerve growth factor (NGF), and NSCs were used. In group B, chitosan conduit, collagen sponge, and NGF were used. In group C, nerve autograft was performed. Electrophysiologic detection, histologic observation, and BrdU and S100 immunohistochemical examination were performed 12 weeks after operation.

## **RESULTS:**

All observation items in group A were better than those in group B ( $P < 0.01$ ), and there were no significant differences between group A and group C ( $P > 0.05$ ).

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### **CONCLUSION:**

NSCs may be served as seed cells of peripheral nerve tissue engineering and be used in artificial nerve to repair facial nerve defects.

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# STEM CELLS: STROKE

## Current Concepts in Adult Stem Cell Therapy for Stroke

*Ding et al.. (2006). Current Concepts in Adult Stem Cell Therapy for Stroke. Current Medical Chemistry, 13(29), 3565-3574. <https://doi.org/10.2174/092986706779026237>*

### ABSTRACT

Acute ischemic stroke causes a disturbance of neuronal circuitry and disruption of the blood-brain barrier that can lead to functional disabilities. At present, thrombolytic therapy inducing recanalization of the occluded vessels in the cerebral infarcted area is a commonly used therapeutic strategy. However, only a minority of patients have timely access to this kind of therapy. Therefore, finding other techniques to effectively treat stroke patients is an important research goal. Stem cell therapies, such as adult stem cell transplantation, are promising strategies for the treatment of stroke. Preclinical experimental studies have included the application of human stem cells from various sources including the brain, bone marrow, umbilical cord, and adipose tissue. This review provides an update on current preclinical cell-therapies for stroke, focusing on stem cells derived from adult sources.

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# **Intravenous Autologous Bone Marrow Mononuclear Stem Cell Therapy for Ischemic Stroke**

*Prasad et al.. (2014). Intravenous Autologous Bone Marrow Mononuclear Stem Cell Therapy for Ischemic Stroke. Stroke, 42(12), 3618-3624.*

<http://stroke.ahajournals.org/content/45/12/3618.short>

## **ABSTRACT**

### **Background and Purpose**

Pilot studies have suggested benefit from intravenous administration of bone marrow mononuclear stem cells (BMSCs) in stroke. We explored the efficacy and safety of autologous BMSCs in subacute ischemic stroke.

### **Methods**

This was a phase II, multicenter, parallel group, randomized trial with blinded outcome assessment that included 120 patients. Patients with subacute ischemic stroke were randomly assigned to the arm that received intravenous infusion of autologous BMSCs or to control arm. Coprimary clinical efficacy outcomes were Barthel Index score and modified Rankin scale at day 180. Secondary outcomes were change in infarct volume, National Institute of Health Stroke Scale (NIHSS) at day 90 and 180. Main safety outcomes were adverse events, any new area of 18fluorodeoxyglucose positron emission tomography uptake in any body part over 365 days.

## Results

Fifty-eight patients received a mean of 280.75 million BMSCs at median of 18.5 days after stroke onset. There was no significant difference between BMSCs arm and control arm in the Barthel Index score (63.1 versus 63.6; P=0.92), modified Rankin scale shift analysis (P=0.53) or score >3 (47.5% versus 49.2%; P=0.85), NIHSS score (6.3 versus 7.0; P=0.53), change in infarct volume (-11.1 versus -7.36; P=0.63) at day 180. Adverse events were also similar in the 2 arms, and no patient showed any new area of 18fluorodeoxyglucose uptake.

## Conclusions

With the methods used, results of this hitherto first randomized controlled trial indicate that intravenous infusion of BMSCs is safe, but there is no beneficial effect of treatment on stroke outcome.

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# **Spontaneous Recovery of Upper Extremity Motor Impairment After Ischemic Stroke: Implications for Stem Cell-Based Therapeutic Approaches**

*Delavaran et al.. (2017). Spontaneous Recovery of Upper Extremity Motor Impairment After Ischemic Stroke: Implications for Stem Cell-Based Therapeutic Approaches. Translational Stroke Research, 8(4), 351–361.*

<https://link.springer.com/article/10.1007/s12975-017-0523-9>

## **ABSTRACT**

Preclinical studies suggest that stem cell therapy (SCT) may improve sensorimotor recovery after stroke. Upper extremity motor impairment (UEMI) is common after stroke, often entailing substantial disability. To evaluate the feasibility of post-stroke UEMI as a target for SCT, we examined a selected sample of stroke patients potentially suitable for SCT, aiming to assess the frequency and recovery of UEMI, as well as its relation to activity limitations and participation restrictions. Patients aged 20–75 years with first-ever ischemic stroke, and National Institutes of Health Stroke

Scale (NIHSS) scores 1–18, underwent brain diffusion-weighted MRI within 4 days of stroke onset (n = 108). Survivors were followed up after 3–5 years, including assessment with NIHSS, Fugl-Meyer assessment of upper extremity (FMA-UE), modified Rankin Scale (mRS), and Stroke Impact Scale (SIS). UEMI was defined as NIHSS arm/hand score ≥1. UEMI recovery was evaluated with change in NIHSS arm/hand scores between baseline and follow-up. Of 97 survivors, 84 were available to follow-up. Among 76 subjects (of 84) without recurrent stroke, 41 had UEMI at baseline of which 10 had residual UEMI at follow-up. The FMA-UE showed moderate-severe impairment in seven of 10 survivors with residual UEMI. UEMI was correlated to mRS ( $r_s = 0.49$ ,  $p < 0.001$ ) and the SIS social participation domain ( $r_s = -0.38$ ,  $p = 0.001$ ). Nearly 25% of the subjects with UEMI at baseline had residual impairment after 3–5 years, whereas about 75% showed complete recovery. Most of the subjects with residual UEMI had moderate-severe impairment, which correlated strongly to dependency in daily activities and social participation

restrictions. Our findings suggest that SCT targeting post-stroke UEMI may be clinically valuable with significant meaningful benefits for patients but also emphasize the need of early prognostication to detect patients that will have residual impairment in order to optimize patient selection for SCT.

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## **The future of stem cell therapy for stroke rehabilitation**

*Borlongan, C.V, Jolkkonen, J & Detante, O. (2015). The future of stem cell therapy for stroke rehabilitation. Future Neurology, 10(4), 313-319. <https://doi.org/10.2217/fnl.15.27>*

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## **Enhancement of neuroplasticity through upregulation of $\beta$ 1-integrin in human umbilical cord-derived stromal cell implanted stroke model**

*Ding et al.. (2007). Enhancement of neuroplasticity through upregulation of  $\beta$ 1-integrin in human umbilical cord-derived stromal cell implanted stroke model. Neurobiology of*

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*Disease*, 27(3), 339-353.

<https://doi.org/10.1016/j.nbd.2007.06.010>

### ABSTRACT

Neuroplasticity subsequent to functional angiogenesis is an important goal for cell-based therapy of ischemic neural tissues. At present, the cellular and molecular mechanisms involved are still not well understood. In this study, we isolated mesenchymal stem cells (MSCs) from Wharton's jelly (WJ) to obtain clonally expanded human umbilical cord-derived mesenchymal stem cells (HUCMSCs) with multilineage differentiation potential. Experimental rats receiving intracerebral HUCMSC transplantation showed significantly improved neurological function compared to vehicle-treated control rats. Cortical neuronal activity, as evaluated by proton MR spectroscopy (<sup>1</sup>H-MRS), also increased considerably in the transplantation group.

Transplanted HUCMSCs migrated towards the ischemic boundary zone and differentiated into glial, neuronal, doublecortin+, CXCR4+, and vascular endothelial cells to enhance neuroplasticity in the ischemic brain. In addition, HUCMSC transplantation promoted the formation of new vessels to increase local cortical blood flow in the ischemic hemisphere. Modulation by stem cell-derived macrophage/microglial interactions, and increased  $\beta$ 1-integrin expression, might enhance this angiogenic architecture within the ischemic brain. Inhibition of  $\beta$ 1-integrin expression blocked local angiogenesis and reduced recovery from neurological deficit. In addition, significantly increased modulation of neurotrophic factor expression was also found in the HUCMSC transplantation group. In

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summary, regulation of  $\beta 1$ -integrin expression plays a critical role in the plasticity of the ischemic brain after the implantation of HUCMSCs.

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# STEM CELLS: CARDIAC HEALTH

## Effect of Aging on Human Mesenchymal Stem Cell Therapy in Ischemic Cardiomyopathy Patients

Golpanian et al.. (2015). *Effect of Aging on Human Mesenchymal Stem Cell Therapy in Ischemic Cardiomyopathy Patients*. *Journal of the American College of Cardiology*, 65(2), 125-132.

<https://doi.org/10.1016/j.jacc.2014.10.040>

### ABSTRACT

#### Background

The role of patient age in the efficacy of mesenchymal stem cell (MSC) therapy in ischemic cardiomyopathy (ICM) is controversial.

#### Objectives

This study sought to determine whether the therapeutic effect of culture-expanded MSCs persists, even in older subjects.

#### Methods

Patients with ICM who received MSCs via transendocardial stem cell injection (TESI) as part of the TAC-HFT (Transendocardial Autologous Cells in Ischemic Heart

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Failure) ( $n = 19$ ) and POSEIDON (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis) ( $n = 30$ ) clinical trials were divided into 2 age groups: younger than 60 and 60 years of age and older. Functional capacity was measured by 6-min walk distance (6MWD) and quality of life using the Minnesota Living With Heart Failure Questionnaire (MLHFQ) score, measured at baseline, 6 months, and 1 year post-TESI. Various cardiac imaging parameters, including absolute scar size, were compared at baseline and 1 year post-TESI.

### Results

The mean 6MWD was similar at baseline and increased at 1 year post-TESI in both groups:  $48.5 \pm 14.6$  m ( $p = 0.001$ ) for the younger and  $35.9 \pm 18.3$  m ( $p = 0.038$ ) for the older participants ( $p = \text{NS}$  between groups). The older group exhibited a significant reduction in MLHFQ score ( $-7.04 \pm 3.54$ ;  $p = 0.022$ ), whereas the younger than 60 age group had a borderline significant reduction ( $-11.22 \pm 5.24$ ;  $p = 0.058$ ) from baseline ( $p = \text{NS}$  between groups). Although there were significant reductions in absolute scar size from baseline to 1 year post-TESI, the effect did not differ by age.

### Conclusions

MSC therapy with TESI in ICM patients improves 6MWD and MLHFQ score and reduces myocardial infarction size.

Importantly, older individuals did not have an impaired response to MSC therapy.

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## **A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction**

*Hare et al.. (2009). A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction. Journal of the American College of Cardiology, 54(24), 2277-2286.*

<https://doi.org/10.1016/j.jacc.2009.06.055>

### **ABSTRACT**

#### **Objectives**

Our aim was to investigate the safety and efficacy of intravenous allogeneic human mesenchymal stem cells (hMSCs) in patients with myocardial infarction (MI).

#### **Background**

Bone marrow-derived hMSCs may ameliorate consequences of MI, and have the advantages of preparation ease, allogeneic use due to immunoprivilege, capacity to home to injured tissue, and extensive pre-clinical support.

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### Methods

We performed a double-blind, placebo-controlled, dose-ranging (0.5, 1.6, and 5 million cells/kg) safety trial of intravenous allogeneic hMSCs (Prochymal, Osiris Therapeutics, Inc., Baltimore, Maryland) in reperfused MI patients ( $n = 53$ ). The primary end point was incidence of treatment-emergent adverse events within 6 months. Ejection fraction and left ventricular volumes determined by echocardiography and magnetic resonance imaging were exploratory efficacy end points.

### Results

Adverse event rates were similar between the hMSC-treated (5.3 per patient) and placebo-treated (7.0 per patient) groups, and renal, hepatic, and hematologic laboratory indexes were not different. Ambulatory electrocardiogram monitoring demonstrated reduced ventricular tachycardia episodes ( $p = 0.025$ ), and pulmonary function testing demonstrated improved forced expiratory volume in 1 s ( $p = 0.003$ ) in the hMSC-treated patients. Global symptom score in all patients ( $p = 0.027$ ) and ejection fraction in the important subset of anterior MI patients were both significantly better in hMSCs versus placebo subjects. In the cardiac magnetic resonance imaging substudy, hMSC treatment, but not placebo, increased left ventricular ejection fraction and led to reverse remodeling.

### Conclusions

Intravenous allogeneic hMSCs are safe in patients after acute MI. This trial provides pivotal safety and provisional

efficacy data for an allogeneic bone marrow-derived stem cell in post-infarction patients.

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## **A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF)**

*Perin et al.. (2011). A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF). American Heart Journal, 161(6), 1078-1087.e3.*

<https://doi.org/10.1016/j.ahj.2011.01.028>

### **ABSTRACT**

#### **Background**

Autologous bone marrow mononuclear cell (ABMMNC) therapy has shown promise in patients with heart failure (HF). Cell function analysis may be important in interpreting trial results.

#### **Methods**

In this prospective study, we evaluated the safety and efficacy of the transendocardial delivery of ABMMNCs in no-option patients with chronic HF. Efficacy was assessed by maximal myocardial oxygen consumption, single photon emission computed tomography, 2-dimensional

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echocardiography, and quality-of-life assessment (Minnesota Living with Heart Failure and Short Form 36). We also characterized patients' bone marrow cells by flow cytometry, colony-forming unit, and proliferative assays.

### Results

Cell-treated ( $n = 20$ ) and control patients ( $n = 10$ ) were similar at baseline. The procedure was safe; adverse events were similar in both groups. Canadian Cardiovascular Society angina score improved significantly ( $P = .001$ ) in cell-treated patients, but function was not affected. Quality-of-life scores improved significantly at 6 months ( $P = .009$  Minnesota Living with Heart Failure and  $P = .002$  physical component of Short Form 36) over baseline in cell-treated but not control patients. Single photon emission computed tomography data suggested a trend toward improved perfusion in cell-treated patients. The proportion of fixed defects significantly increased in control ( $P = .02$ ) but not in treated patients ( $P = .16$ ). Function of patients' bone marrow mononuclear cells was severely impaired. Stratifying cell results by age showed that younger patients ( $\leq 60$  years) had significantly more mesenchymal progenitor cells (colony-

forming unit fibroblasts) than patients >60 years ( $20.16 \pm 14.6$  vs  $10.92 \pm 7.8$ ,  $P = .04$ ). Furthermore, cell-treated younger patients had significantly improved maximal myocardial oxygen consumption ( $15 \pm 5.8$ ,  $18.6 \pm 2.7$ , and  $17 \pm 3.7$  mL/kg per minute at baseline, 3 months, and 6 months, respectively) compared with similarly aged control patients ( $14.3 \pm 2.5$ ,  $13.7 \pm 3.7$ , and  $14.6 \pm 4.7$  mL/kg per minute,  $P = .04$ ).

### **Conclusions**

ABMMNC therapy is safe and improves symptoms, quality of life, and possibly perfusion in patients with chronic HF.

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## **Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction**

*Amando et al.. (2009). Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. Proc Natl Acad Sci U S A, 102(32), 11474–11479.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1183573/>

### **ABSTRACT**

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Although clinical trials of autologous whole bone marrow for cardiac repair demonstrate promising results, many practical and mechanistic issues regarding this therapy remain highly controversial. Here, we report the results of a randomized study of bone-marrow-derived mesenchymal stem cells, administered to pigs, which offer several new insights regarding cellular cardiomyoplasty. First, cells were safely injected by using a percutaneous-injection catheter 3 d after myocardial infarction. Second, cellular transplantation resulted in long-term engraftment, profound reduction in scar formation, and near-normalization of cardiac function. Third, transplanted cells were preprepared from an allogeneic donor and were not rejected, a major practical advance for widespread application of this therapy. Together, these findings demonstrate that the direct injection of cellular grafts into damaged myocardium is safe and effective in the periinfarct period. The direct delivery of cells to necrotic myocardium offers a valuable alternative to intracoronary cell injections, and the use of allogeneic mesenchymal stem cells provides a valuable strategy for cardiac regenerative therapy that avoids the need for preparing autologous cells from the recipient.

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# **Concise review: mesenchymal stromal cells: potential for cardiovascular repair.**

*Psaltis et al.. (2008). Concise review: mesenchymal stromal cells: potential for cardiovascular repair. Stem Cells, 26(9), 2201-10. <https://www.ncbi.nlm.nih.gov/pubmed/18599808>*

## **ABSTRACT**

Cellular therapy for cardiovascular disease heralds an exciting frontier of research. Mesenchymal stromal cells (MSCs) are present in adult tissues, including bone marrow and adipose, from which they can be easily isolated and cultured ex vivo. Although traditional isolation of these cells by plastic adherence results in a heterogeneous composite of mature and immature cell types, MSCs do possess plasticity of differentiation and under appropriate in vitro culture conditions can be modified to adopt cardiomyocyte and vascular cell phenotypic characteristics. In vivo preclinical studies have demonstrated their capacity to facilitate both myocardial repair and neovascularization in models of cardiac injury. The mechanisms underlying these effects appear to be mediated predominantly through indirect paracrine actions, rather than direct regeneration of endogenous cells by transdifferentiation, especially because current transplantation strategies achieve only modest engraftment of cells in the host myocardium. Currently, published clinical trial experience of MSCs as cardiac therapy is limited, and the outcomes of ongoing studies are

keenly anticipated. Of relevance to clinical application is the fact that MSCs are relatively immunoprivileged, potentially enabling their allogeneic therapeutic use, although this too requires further investigation. Overall, MSCs are an attractive adult-derived cell population for cardiovascular repair; however, research is still required at both basic and clinical levels to resolve critical areas of uncertainty and to ensure continued development in cell culture engineering and cell transplantation technology.

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## **Transplantation of marrow-derived mesenchymal stem cells and platelet-rich plasma during distraction osteogenesis—a preliminary result of three cases**

*Kitoh et al.. (2004). Transplantation of marrow-derived mesenchymal stem cells and platelet-rich plasma during distraction osteogenesis—a preliminary result of three cases. Bone, 35(4), 892–898.*

<https://doi.org/10.1016/j.bone.2004.06.013>

### **ABSTRACT**

Clinical results of distraction osteogenesis with transplantation of marrow-derived mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) were reviewed in three femora and two tibiae of the two patients with achondroplasia and one patient with congenital

pseudarthrosis of the tibia. MSCs derived from the iliac crest were cultured with osteogenic supplements and differentiated into osteoblast-like cells. PRP, which is known to contain several growth factors and coagulate immediately by a minute introduction of thrombin and calcium, was prepared just before transplantation. Culture-expanded osteoblast-like cells and autologous PRP were injected into the distracted callus with the thrombin–calcium mixture so that the PRP gel might develop within the injected site. Transplantation of MSCs and PRP was done at the lengthening and consolidation period in each patient. The target lengths were obtained in every leg without major complications and the average healing index was 23.0 days/cm (18.8–26.9 days/cm). Although these results are still preliminary, transplantation of osteoblast-like cells and PRP, which seemed to be a safe and minimally invasive cell therapy, could shorten the treatment period by acceleration of bone regeneration during distraction osteogenesis.

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## **Adipose Tissue-Derived Stromal Cells as a Novel Option for Regenerative Cell Therapy**

*Nakagami et al.. (2006). Adipose Tissue-Derived Stromal Cells as a Novel Option for Regenerative Cell Therapy. Journal of Atherosclerosis and Thrombosis, 13(2), 77-81.*  
<https://doi.org/10.5551/jat.13.77>

## **ABSTRACT**

Adult stem cells hold great promise for use in tissue repair and regeneration, and the delivery of autologous progenitor cells into ischemic tissue is emerging as a novel therapeutic option. We and others have recently demonstrated the potential impact of adipose tissue-derived stromal cells (ADSC) on regenerative cell therapy for ischemic diseases. The main benefit of ADSC is that they can be easily harvested from patients by a simple, minimally invasive method and also easily cultured. Cultured ADSC can be induced to differentiate into not only adipocytes, but also bone, neurons or endothelial cells in certain conditions. Interestingly, they secrete a number of angiogenesis-related cytokines, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which might be suitable for regenerative cell therapy for ischemic diseases. In the ischemic mouse hindlimb, the angiogenic score was improved in the ADSC-treated group. Moreover, recent reports demonstrated that these ADSC can also be induced to differentiate into cardiac myocytes. These adipose tissue-derived cells have potential in angiogenic cell therapy for ischemic disease, and might be applied for regenerative cell therapy instead of bone marrow cells in the near future

# STEM CELLS: EYE CONDITIONS

## Progress of mesenchymal stem cell therapy for neural and retinal diseases

*Ng et al.. (2014). Progress of mesenchymal stem cell therapy for neural and retinal diseases. World Journal of Stem Cells, 6(2), 111-119.*

<http://dx.doi.org/10.4252/wjsc.v6.i2.111>

### ABSTRACT

Complex circuitry and limited regenerative power make central nervous system (CNS) disorders the most challenging and difficult for functional repair. With elusive disease mechanisms, traditional surgical and medical interventions merely slow down the progression of the neurodegenerative diseases. However, the number of neurons still diminishes in many patients. Recently, stem cell therapy has been proposed as a viable option. Mesenchymal stem cells (MSCs), a widely-studied human adult stem cell population, have been discovered for more than 20 years. MSCs have been found all over the body and can be conveniently obtained from different accessible tissues: bone marrow, blood, and adipose and dental tissue. MSCs have

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high proliferative and differentiation abilities, providing an inexhaustible source of neurons and glia for cell replacement therapy. Moreover, MSCs also show neuroprotective effects without any genetic modification or reprogramming. In addition, the extraordinary immunomodulatory properties of MSCs enable autologous and heterologous transplantation. These qualities heighten the clinical applicability of MSCs when dealing with the pathologies of CNS disorders. Here, we summarize the latest progress of MSC experimental research as well as human clinical trials for neural and retinal diseases. This review article will focus on multiple sclerosis, spinal cord injury, autism, glaucoma, retinitis pigmentosa and age-related macular degeneration.

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## **Umbilical Cord Lining Stem Cells as a Novel and Promising Source for Ocular Surface Regeneration**

Reza et al.. (2011). *Umbilical Cord Lining Stem Cells as a Novel and Promising Source for Ocular Surface Regeneration*. *Stem Cell Reviews and Reports*, 7(4), 935–947. <https://link.springer.com/article/10.1007/s12015-011-9245-7>

### **ABSTRACT**

The stem cells involved in renewal of the corneal epithelium are located in the basal region of the limbus, a narrow

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transition zone surrounding the cornea. In many ocular surface disorders loss of these stem cells results in partial or complete vision loss. Conventional corneal transplant in these patients is associated with dismal results. Stem cell transplantation offers new hope to such patients. The umbilical cord is emerging as an important source of stem cells that may have potential clinical applications. There are advantages to the use of umbilical cord stem cells as these cells are less immunogenic, non-tumorigenic, highly proliferative and ethically acceptable. In this study, we have confirmed the expression of several putative limbal stem cell markers such as HES1, ABCG2, BMI1, CK15 as well as cell adhesion-associated molecules INTEGRIN- $\alpha$ 6, - $\alpha$ 9, - $\beta$ 1, COLLAGEN-IV and LAMININ in our recently characterized CLEC-muc population derived from human umbilical cord. Ex vivo expansion of these cells on a human amniotic membrane substrate formed a stratified cell sheet that similarly expresses some of these molecules as well as cornea-specific cytokeratins, CK3 and CK12.

Transplantation of a bioengineered CLEC-muc sheet in limbal stem cell-deficient rabbit eyes resulted in regeneration of a smooth, clear corneal surface with phenotypic expression of the normal corneal-specific epithelial markers CK3, CK12 but not CK4 or CK1/10. Our results suggest that CLEC-muc is a novel stem cell that can be ex vivo expanded for corneal epithelial regeneration in the treatment of various eye diseases.

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# **Effects of bone marrow stromal cell injection in an experimental glaucoma model.**

*Yu et al.. (2006). Effects of bone marrow stromal cell injection in an experimental glaucoma model. Biochem Biophys Res Commun, 344(4), 1071-9.*

<https://www.ncbi.nlm.nih.gov/pubmed/16643846>

## **ABSTRACT**

We investigated if bone marrow stromal cells (BMSCs) transplanted into the vitreous body of a glaucoma model eye could be integrated in the host retina and also whether they could rescue the retinal ganglion cells (RGCs) from death induced by the elevated intraocular pressure. Glaucoma was induced in the right eye of adult Wistar rats by ligating the episcleral veins. The GFP-expressing BMSCs (GFP-BMSCs) were injected into the vitreous body of both the control and the glaucomatous eyes. After transplantation, GFP-BMSCs were mostly present along with the inner limiting membrane and only a few cells were integrated into the ganglion cell layer. At 2 or 4 weeks after transplantation, GFP-BMSCs were observed to express various trophic factors. The BMSCs injected glaucoma model eyes showed less reduction in the number of RGCs compared to the glaucomatous eyes with PBS injection. This study suggests that BMSC transplantation may be worthy as a neuroprotective tool to treat glaucoma.

# **Neuroprotective Effects of Intravitreal Mesenchymal Stem Cell Transplantation in Experimental Glaucoma**

*Johnson et al.. (2010). Neuroprotective Effects of Intravitreal Mesenchymal Stem Cell Transplantation in Experimental Glaucoma. Invest Ophthalmol Vis Sci, 51(4), 2051–2059.*  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868400/>

## **ABSTRACT**

### **Purpose.**

Retrograde neurotrophic factor transport blockade has been implicated in the pathophysiology of glaucoma. Stem cell transplantation appears to ameliorate some neurodegenerative conditions in the brain and spinal cord, in part by neurotrophic factor secretion. The present study was conducted to determine whether local or systemic bone marrow-derived mesenchymal stem cell (MSC) transplantation can confer neuroprotection in a rat model of laser-induced ocular hypertensive glaucoma.

### **Methods.**

MSCs were isolated from the bone marrow of adult wild-type and transgenic rats that ubiquitously express green fluorescent protein. MSCs were transplanted intravitreally 1 week before, or intravenously on the day of, ocular hypertension induction by laser photocoagulation of the

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trabecular meshwork. Ocular MSC localization and integration were determined by immunohistochemistry. Optic nerve damage was quantified by counting axons within optic nerve cross-sections 4 weeks after laser treatment.

### **Results.**

After intravitreal transplantation, MSCs survived for at least 5 weeks. Cells were found mainly in the vitreous cavity, though a small proportion of discrete cells migrated into the host retina. Intravitreal MSC transplantation resulted in a statistically significant increase in overall RGC axon survival and a significant decrease in the rate of RGC axon loss normalized to cumulative intraocular pressure exposure.

After intravenous transplantation, MSCs did not migrate to the injured eye. Intravenous transplantation had no effect on optic nerve damage.

### **Conclusions.**

Local, but not systemic, transplantation of MSCs was neuroprotective in a rat glaucoma model. Autologous intravitreal transplantation of MSCs should be investigated further as a potential neuroprotective therapy for glaucoma.

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# **Mesenchymal stem cells from trabecular meshwork become photoreceptor-like cells on amniotic membrane.**

*Nadri et al.. (2013). Mesenchymal stem cells from trabecular meshwork become photoreceptor-like cells on amniotic membrane. Neurosci Lett, 541, 43-8.*

<https://www.ncbi.nlm.nih.gov/pubmed/23403103>

## **ABSTRACT**

Stem cell therapy is a promising approach for treatment of degenerative retinal disorders such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). In this study, human mesenchymal stem cells (MSCs) were isolated from the trabecular meshwork (TM), the major functional tissue of the anterior chamber angle in the eye, were characterized and differentiated into photoreceptor cells on amniotic membrane (AM). After isolation of trabecular meshwork and culture of the stromal segment of this tissue, fibroblast-like cells (CD105(+), CD90(+), CD44(+), CD166(+)) capable of differentiation toward mesenchymal and photoreceptor lineages were obtained. The isolated cells were seeded on amniotic membrane and were treated with induction medium. Immunocytochemistry and quantitative real time RT-PCR (qPCR) were used to detect expression of photoreceptor genes such as rhodopsin, recoverin, CRX, and peripherin; and the bipolar cell marker protein kinase C alpha (PKC-alpha). As a result,

immunocytochemistry revealed that the differentiated TMMSCs expressed rhodopsin, CRX and PKC proteins. qPCR showed the expression of rhodopsin (rod like photoreceptor-specific marker), and CRX genes were significantly higher in TMMSCs differentiated on AM than those differentiated on tissue culture polystyrene (TCPS). In conclusion, our findings suggested that a combination of TMMSCs (as a new source) and basement membrane support from AM might be a suitable source of cells for subretinal transplantation in regenerative therapy for retinal disorders such as AMD and RP.

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## **High yield of cells committed to the photoreceptor-like cells from conjunctiva mesenchymal stem cells on nanofibrous scaffolds.**

*Nadri et al.. (2013). High yield of cells committed to the photoreceptor-like cells from conjunctiva mesenchymal stem cells on nanofibrous scaffolds. Mol Biol Rep, 40(6), 3883-90.*  
<https://www.ncbi.nlm.nih.gov/pubmed/23588957>

### **ABSTRACT**

Transplantation of stem cells using biodegradable and biocompatible nanofibrous scaffolds is a promising therapeutic approach for treating inherited retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration. In this study, conjunctiva

## Compendium of Research: STEM CELLS

mesenchymal stem cells (CJMSCs) were seeded onto poly-L-lactic acid (PLLA) nanofibrous scaffolds and were induced to differentiate toward photoreceptor cell lineages. Furthermore, the effects of orientation of scaffold on photoreceptor differentiation were examined. Scanning electron microscopy (SEM) imaging, quantitative real time RT-PCR (qPCR) and immunocytochemistry were used to analyze differentiated cells and their expression of photoreceptor-specific genes. Our observations demonstrated the differentiation of CJMSCs to photoreceptor cells on nanofibrous scaffolds and suggested their potential application in retinal regeneration. SEM imaging showed that CJMSCs were spindle shaped and well oriented on the aligned nanofiber scaffolds. The expression of rod photoreceptor-specific genes was significantly higher in CJMSCs differentiated on randomly-oriented nanofibers compared to those on aligned nanofibers. According to our results we may conclude that the nanofibrous PLLA scaffold reported herein could be used as a potential cell carrier for retinal tissue engineering and a combination of electrospun nanofiber scaffolds and MSC-derived conjunctiva stromal cells may have potential application in retinal regenerative therapy.

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# Differentiation of mesenchymal stem cell in the microenvironment of retinitis pigmentosa

Hou et al.. (2010). *Differentiation of mesenchymal stem cell in the microenvironment of retinitis pigmentosa. International Journal of Ophthalmology*, 3(3), 216–219.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340632/>

## ABSTRACT

### AIM

To access the differentiation of rat mesenchymal stem cell (MSC) in the microenvironment of retinal degeneration induced by the administration of sodium iodate.

## METHODS

In-vitro cultured Lewis rat MSC were injected into the sub-retinal space of NaIO<sub>3</sub> induced retinal degeneration rat eyes (30g/L NaIO<sub>3</sub> 100mg/kg). To observe the trace and differentiation of MSC by immuno-fluorescent method successively in 5 weeks after the surgery.

## RESULTS

The majority of the transplanted cells stay in retinal pigment epithelium layer and cones & rods layer. From the 2nd week after transplantation, the engrafted MSC express PCK and rhodopsin under fluorescent microscope.

## CONCLUSION

## Compendium of Research: STEM CELLS

MSC can survive mainly in the outer layer of retina in the microenvironment of retinal degeneration and differentiate forward the RPE cell and photoreceptor.

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# STEM CELLS: CANCER

## Human umbilical cord mesenchymal stem cells support nontumorigenic expansion of human embryonic stem cells.

*Ding et al.. (2012). Human Umbilical Cord Mesenchymal Stem Cells Support Nontumorigenic Expansion of Human Embryonic Stem Cells. Cell Transplantation, 21(7), 1515-27.*  
<http://dx.doi.org/10.3727/096368912X647199>

### ABSTRACT

The expansion of pluripotent human embryonic stem cells (hESCs) requires a culture on feeder layers of mouse embryonic fibroblasts (MEFs). The culture model often causes immunogenic contaminations such as xenocarbohydrate, and inevitably forms teratoma in vivo. This study tested human umbilical cord-derived mesenchymal stem cells (HUCMSCs) as the feeder for hESCs. Wharton's jelly-derived HUCMSCs showed characteristics of MSCs and were easily maintained in a culture for over 20 passages. Under the mitomycin-inhibited HUCMSC feeder, hESCs maintained the features of embryonic stem cells (pluripotency and maintenance of normal karyotypes) after a prolonged culture of more than 20 passages. Notably, in extensive trials, no teratoma was formed in xenograft in NOD/SCID mice, but subsequent

resumption of teratoma formation was noted upon transient coculturing with MEFs. Interestingly, among the four pluripotency-conferring genes, MYC and OCT4 were found to be downregulated in hESCs cocultured with HUCMSCs. Results of this study supported a nontumorigenic sustained culture of hESCs and did not form teratoma *in vivo*.

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## **Human umbilical cord Wharton's jelly stem cell (hWJSC) extracts inhibit cancer cell growth *in vitro*.**

*Guathaman et al.. (2012). Human umbilical cord Wharton's jelly stem cell (hWJSC) extracts inhibit cancer cell growth *in vitro*. Journal Cell Biochem, 113(6), 2027-39.*

<http://dx.doi.org/10.1002/jcb.24073>

### **ABSTRACT**

Umbilical cord mesenchymal stem cells (MSCs) have been shown to inhibit breast cancer cell growth but it is not known whether this effect is specific to only breast cancer cells. We compared the effects of human Wharton's jelly stem cell (hWJSC) extracts [conditioned medium (hWJSC-CM) and cell lysate (hWJSC-CL)] on breast adenocarcinoma (MDA-MB-231), ovarian carcinoma (TOV-112D), and osteosarcoma (MG-63) cells. The cells were treated with either hWJSC-CM (50%) or hWJSC-CL (15 µg/ml) for 48-72 h and changes in cell morphology, proliferation, cycle, gene expression, migration, and cell death studied. All three

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cancer cell lines showed cell shrinkage, blebbing, and vacuolations with hWJSC-CL and hWJSC-CM compared to controls. MTT and BrdU assays showed inhibition of cell growth by 2-6% and 30-60%, while Transwell migration assay showed inhibition by 20-26% and 31-46% for hWJSC-CM and hWJSC-CL, respectively, for all three cancer cell lines. Cell cycle assays showed increases in sub-G1 and G2/M phases for all three cancer cell lines suggestive of apoptosis and metaphase arrest. AnnexinV-FITC and TUNEL positive cells seen in TOV-112D and MDA-MB-231 suggested that inhibition was via apoptosis while the presence of anti-BECLIN1 and anti-LC3B antibodies seen with MG-63 indicated autophagy. Upregulation of pro-apoptotic BAX and downregulation of anti-apoptotic BCL2 and SURVIVIN genes were observed in all three cancer cell lines and additionally the autophagy genes (ATG5, ATG7, and BECLIN1) were upregulated in MG-63 cells. hWJSCs possess tumor inhibitory properties that are not specific to breast cancer cells alone and these effects are mediated via agents in its extracts.

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## **Human umbilical cord blood mesenchymal stem cell-derived extracellular matrix prohibits metastatic cancer cell MDA-MB-231 proliferation**

*Sun et al.. (2010). Human umbilical cord blood mesenchymal stem cell-derived extracellular matrix prohibits metastatic cancer cell MDA-MB-231 proliferation. Cancer Lett, 296(2), 178-85.*

<http://dx.doi.org/10.1016/j.canlet.2010.04.007>

## **ABSTRACT**

It is not clear whether adult stem cell extracellular matrix (ECM) can regulate cancer cells. We demonstrated that the ECM produced by UCB-MSCs was able to arrest the growth of metastatic tumor cells by upregulating levels of PTEN in aggressive cancer cells. Human UCB-MSCs produced dickkopf (DKK1) are capable of inhibiting cancer cell proliferation but has no contribution to the tumor inhibition effect of UCB-MSC ECM. This study also provides an innovative approach to specifically examine the effect of stem cell microenvironments on cancer cells without the complexity of cell-cell interactions. In conclusion, human UCB-MSC ECM prohibits cancer cell proliferation.

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## **A role for cancer stem cells in therapy resistance: Cellular and molecular mechanisms**

*Cojoc et al.. (2015). A role for cancer stem cells in therapy resistance: Cellular and molecular mechanisms. Seminars in Cancer Biology, 31(0), 16-27.*

<http://dx.doi.org/10.1016/j.semcan.2014.06.004>

## ABSTRACT

Similar to normal tissue, many tumors have a hierarchical organization where tumorigenic cancer stem cells (CSCs) differentiate into non-tumorigenic progenies. A host of studies have demonstrated that although CSCs and their non-tumorigenic progenies within the same clone can share common genotype, they display different epigenetic profiles that results in changes of multiple signaling pathways. Many of these pathways confer cell adaptation to the microenvironmental stresses including inflammation, hypoxia, low pH, shortage in nutrients and anti-cancer therapies. Treatment strategies based on combination of conventional therapies targeting bulk tumor cells and CSC-specific pathway inhibition bear a promise to improve cancer cure compared to monotherapies. In this review we describe the mechanisms of CSC-related therapy resistance including drug efflux by ABC transporters, activation of aldehyde dehydrogenase and developmental pathways, enhanced DNA damage response, autophagy and microenvironmental conditions, and discuss possible therapeutic strategies for improving cancer treatment.

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## **Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma.**

*Khakoo et al.. (2006). Human mesenchymal stem cells exert*

*potent antitumorigenic effects in a model of Kaposi's sarcoma.* *J Exp Med,* 203(5), 1235-47.

<http://dx.doi.org/10.1084/jem.20051921>

## ABSTRACT

Emerging evidence suggests that both human stem cells and mature stromal cells can play an important role in the development and growth of human malignancies. In contrast to these tumor-promoting properties, we observed that in an *in vivo* model of Kaposi's sarcoma (KS), intravenously (i.v.) injected human mesenchymal stem cells (MSCs) home to sites of tumorigenesis and potently inhibit tumor growth. We further show that human MSCs can inhibit the *in vitro* activation of the Akt protein kinase within some but not all tumor and primary cell lines. The inhibition of Akt activity requires the MSCs to make direct cell-cell contact and can be inhibited by a neutralizing antibody against E-cadherin. We further demonstrate that *in vivo*, Akt activation within KS cells is potently down-regulated in areas adjacent to MSC infiltration. Finally, the *in vivo* tumor-suppressive effects of MSCs correlates with their ability to inhibit target cell Akt activity, and KS tumors engineered to express a constitutively activated Akt construct are no longer sensitive to i.v. MSC administration. These results suggest that in contrast to other stem cells or normal stromal cells, MSCs possess intrinsic antineoplastic properties and that this stem cell population might be of particular utility for treating those human malignancies characterized by dysregulated Akt.

# **Cytotoxicity of human umbilical cord blood-derived mesenchymal stem cells against human malignant glioma cells.**

*Kang et al.. (2008). Cytotoxicity of human umbilical cord blood-derived mesenchymal stem cells against human malignant glioma cells. Childs Nerv Syst, 24(3), 293-302.  
<http://dx.doi.org/10.1007/s00381-007-0515-2>*

## **ABSTRACT**

### **BACKGROUND:**

Mesenchymal stem cells (MSCs) represent a potential useful source for cell-based glioma therapies because these cells evidence both orthodox and unorthodox plasticity and also show tropism for cancer. In this study, the authors attempted to assess the cytotoxicity of human umbilical cord blood (hUCB)-derived MSCs, with or without cytokine activations against malignant glioma cells.

### **MATERIALS AND METHODS:**

hUCB-derived MSCs were activated by interleukin-2, interleukin-15, granulocyte macrophage colony-stimulating factor, and combinations. The hUCB-derived MSCs and activated hUCB-derived MSCs were effector cells. The cytotoxicity of the unactivated hUCB-derived MSCs and activated hUCB-derived MSCs against the target cells (human malignant glioma cells) was estimated via visual survival cell

assays and transwell inserts. Phenotypic changes occurring in these hUCB-derived MSCs before and after cytokine activation were determined via flow cytometry. The secreted proteins from these effector cells were estimated via enzyme-linked immunosorbent assays.

## **RESULTS:**

We noted a significant cytotoxicity of hUCB-derived MSCs against malignant glioma cells. In addition, the hUCB-derived MSCs activated with cytokines evidenced significantly higher cytotoxicity than that observed with unactivated hUCB-derived MSCs. Differentiated immune effectors cells from the hUCB-derived MSCs after cytokine activation were not shown to have increased in number. However, the activated hUCB-derived MSCs secreted more immune response-related proteins (interleukin 4, interferon-gamma) than did the unactivated hUCB-derived MSCs.

## **CONCLUSION:**

The data collected herein confirm for the first time that hUCB-derived MSCs, with or without activation, evidence significant cytotoxicity against human malignant glioma cells, and the immune response-related proteins secreted in this process may perform relevant functions.

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# Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors.

*Studeny et al.. (2002). Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors. Cancer Res, 62(13), 3603-8.*

<https://www.ncbi.nlm.nih.gov/pubmed/12097260?dopt=Abstract>

## ABSTRACT

Molecules that physiologically control cell proliferation are often produced locally in tissues and are rapidly destroyed when they enter circulation. This allows local effects while avoiding interference with other systems. Unfortunately, it also limits the therapeutic use of these molecules via systemic delivery. We here demonstrate that, for the purpose of anticancer therapy, bone marrow-derived mesenchymal stem cells (MSCs) can produce biological agents locally at tumor sites. We show that the tumor microenvironment preferentially promotes the engraftment of MSCs as compared with other tissues. MSCs with forced expression of IFN-beta inhibited the growth of malignant cells *in vivo*. Importantly, this effect required the integration of MSCs into the tumors and could not be achieved by systemically delivered IFN-beta or by IFN-beta produced by MSCs at a site distant from the tumors. Our results indicate

that MSCs may serve as a platform for delivery of biological agents in tumors.

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## **Mesenchymal stem cells: potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents.**

*Studeny et al.. (2004). Mesenchymal stem cells: potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents. J Natl Cancer Inst, 96(21), 1593-603.*

<http://dx.doi.org/10.1093/jnci/djh299>

### **ABSTRACT**

#### **BACKGROUND:**

High concentrations of interferon beta (IFN-beta) inhibit malignant cell growth in vitro. However, the therapeutic utility of IFN-beta in vivo is limited by its excessive toxicity when administered systemically at high doses. Mesenchymal stem cells (MSC) can be used to target delivery of agents to tumor cells. We tested whether MSC can deliver IFN-beta to tumors, reducing toxicity.

#### **METHODS:**

Human MSC were transduced with an adenoviral expression vector carrying the human IFN-beta gene (MSC-IFN-beta cells). Flow cytometry was used to measure tumor cell proliferation among in vitro co-cultures of MSC-IFN-beta cells

## Compendium of Research: STEM CELLS

and human MDA 231 breast carcinoma cells or A375SM melanoma cells. We used a severe combined immunodeficiency mouse xenograft model (4-10 mice per group) to examine the effects of injected MSC-IFN-beta cells and human recombinant IFN-beta on the growth of MDA 231- and A375SM-derived pulmonary metastases in vivo and on survival. All statistical tests were two-sided.

### **RESULTS:**

Co-culture of MSC-IFN-beta cells with A375SM cells or MDA 231 cells inhibited tumor cell growth as compared with growth of the tumor cells cultured alone (differences in mean percentage of control cell growth: -94.0% [95% confidence interval [CI] = -81.2% to -106.8%; P<.001] and -104.8% [95% CI = -82.1% to -127.5%; P<.001], respectively). Intravenous injection of MSC-IFN-beta cells into mice with established MDA 231 or A375SM pulmonary metastases led to incorporation of MSC in the tumor architecture and, compared with untreated control mice, to prolonged mouse survival (median survival for MDA 231-injected mice: 60 and 37 days for MSC-injected and control mice, respectively [difference = 23.0 days (95% CI = 14.5 to 34.0 days; P<.001]; median survival for A375SM-injected mice: 73.5 and 30.0 days for MSC-injected and control mice, respectively [difference = 43.5 days (95% CI = 37.0 to 57.5 days; P<.001]). By contrast, intravenous injection of recombinant IFN-beta did not prolong survival in the same models (median survival for MDA 231-injected mice: 41.0 and 37.0 days for IFN-beta-injected and control mice, respectively [difference = 4 days, 95% CI = -5 to 10 days; P = .308]; median survival for A375SM-injected mice: 32.0 and 30.0 days for IFN-beta-injected and control mice, respectively [difference = 2 days, 95% CI = 0 to 4.5 days; P = .059]).

**CONCLUSIONS:**

Injected MSC-IFN-beta cells suppressed the growth of pulmonary metastases, presumably through the local production of IFN-beta in the tumor microenvironment. MSC may be an effective platform for the targeted delivery of therapeutic proteins to cancer sites.

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# STEM CELLS: BREAST CANCER

## Naïve human umbilical cord matrix derived stem cells significantly attenuate growth of human breast cancer cells in vitro and in vivo

Ayuzawa et al.. (2009). *Naïve human umbilical cord matrix derived stem cells significantly attenuate growth of human breast cancer cells in vitro and in vivo*. *Cancer Lett.*, 280(1), 31-37. <http://dx.doi.org/10.1016/j.canlet.2009.02.011>

### ABSTRACT

The effect of un-engineered (naïve) human umbilical cord matrix stem cells (hUCMSC) on the metastatic growth of MDA 231 xenografts in SCID mouse lung was examined. Three weekly IV injections of  $5 \times 10^5$  hUCMSC significantly attenuated MDA 231 tumor growth as compared to the saline-injected control. IV injected hUCMSC were detected only within tumors or in close proximity to the tumors. This in vivo result was corroborated by multiple in vitro studies such as colony assay in soft agar and [<sup>3</sup>H]-thymidine uptake. These results suggest that naïve hUCMSC may be a useful tool for cancer cytotherapy.

# **Human umbilical cord mesenchymal stem cells suppress breast cancer tumourigenesis through direct cell–cell contact and internalization**

*Chao, K.C, Yang, H.T & Chen, M.W. (2012). Human umbilical cord mesenchymal stem cells suppress breast cancer tumourigenesis through direct cell–cell contact and internalization. Journal of Cellular and Molecular Medicine, 16(8), 1803-1815. <http://dx.doi.org/10.1111/j.1582-4934.2011.01459.x>*

## **ABSTRACT**

The purpose of this study was to investigate how human umbilical cord mesenchymal stem cells (HUMSCs) affect breast cancer tumourigenesis. To observe the influence of HUMSCs on tumourigenesis in vitro, we performed a co-culture of MDA MB-231 breast cancer cells with HUMSCs, and a result of HUMSCs on tumourigenesis in vivo was achieved by injection of HUMSCs into nonobese diabetic/severe combined immunodeficient mice following tumour establishment with MDA-MB231. During the co-culture, apoptosis of MDA-MB231 was noted, which was driven either by binding with HUMSC through direct cell–cell contact or by formation of a novel cell-in-cell phenomenon after internalization of HUMSC. Also, treatment with HUMSC

injection was efficacious in both *in situ* and metastatic breast cancers in the animal models. Since HUMSCs were proved to efficaciously suppress breast cancer tumourigenesis both *in vitro* and *in vivo*, it is our expectation that treatment with HUMSCs can be a viable therapy for breast cancer in the near future. In addition, we share a new point of view on the role of HUMSCs in foetal development during pregnancy.

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## **The *in vitro* and *in vivo* effects of human umbilical cord mesenchymal stem cells on the growth of breast cancer cells**

*Ma et al.. (2012). The *in vitro* and *in vivo* effects of human umbilical cord mesenchymal stem cells on the growth of breast cancer cells. Breast Cancer Research and Treatment, 133(2), 473-485. <http://dx.doi.org/10.1007/s10549-011-1774-x>.*

### **ABSTRACT**

The purpose of the study was to detect the effect and possible mechanism of human umbilical cord mesenchymal stem cells (hUCMSCs) on the *in vitro* and *in vivo* growth of stem cells isolated from primary human breast cancer cells and cell lines MDA-MB-231 and MCF-7. Primary human breast cancer cells and MDA-MB-231 and MCF-7 cells were

sorted in vitro using flow cytometry, and the ESA+, CD44+, CD24-/low cells were isolated as breast cancer stem cells (CSCs). The inhibitory effect of hUCMScs on CSCs was examined using the Cell Counting Kit-8 cell proliferation and soft agar colony formation assay. In vivo tumor inhibition was studied using a severe combined immunodeficient xenograft mouse model transplanted with MDA-MB-231 breast CSCs. The expression of phosphoinositide 3-kinase (PI3K) and AKT was examined in the xenograft tumors using immunohistochemistry. The number of colonies formed by breast CSCs co-cultured with hUCMScs at the bottom of soft agar was significantly lower than those formed by the control group ( $P < 0.01$ ). Compared with the control group, the CSCs co-cultured with hUCMScs showed a higher number of cells in the G2-M phase ( $P < 0.05$ ) and an increased number of apoptotic cells ( $P < 0.01$ ). The mice in the medium- and high-concentration hUCMSc treatment groups exhibited clearly reduced tumor volume and tumor weight, compared with the control group ( $P < 0.01$ ). Compared with the saline group, the xenograft tumor tissues from the mice treated with different concentrations of hUCMScs showed significantly reduced levels of PI3K and AKT proteins ( $P < 0.001$ ). In conclusion, hUCMSc significantly inhibited the growth of breast CSCs in vitro and in vivo. The underlying mechanism is likely related to cell cycle arrest, induction of tumor cell apoptosis, and suppressed activities of PI3K and AKT protein kinases.

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# **Human umbilical cord wharton's jelly mesenchymal stem cells do not transform to tumor-associated fibroblasts in the presence of breast and ovarian cancer cells unlike bone marrow mesenchymal stem cells**

*Subramanian et al.. (2012). Human umbilical cord wharton's jelly mesenchymal stem cells do not transform to tumor-associated fibroblasts in the presence of breast and ovarian cancer cells unlike bone marrow mesenchymal stem cells.*

*Journal of Cellular Biochemistry, 113(6), 1886-1895.*

<http://dx.doi.org/10.1002/jcb.24057>

## **ABSTRACT**

Human bone marrow mesenchymal stem cells (hBMMSCs) were shown to transform into tumor-associated fibroblasts (TAFs) when in the vicinity of breast cancer tumors and played an important role in tumor enhancement and metastasis. In early human development MSCs migrating from the yolk sac and aorta-gonad-mesonephros (AGM) via the umbilical cord to the placenta and back to the fetal bone marrow were shown to get trapped in the gelatinous Wharton's jelly of the umbilical cord. The common origin of the Wharton's jelly MSCs and the finally homed hBMMSCs prompted us to evaluate whether hWJSCs are also involved in TAF transformation. hWJSCs and hBMMSCs were grown

in the presence of breast and ovarian cancer cell conditioned medium (MDA-TCM, TOV-TCM) for 30 days. No changes were observed in the hWJSCs but the hBMMSCs transformed from short to thin long fibroblasts, their proliferation rates increased and CD marker expression decreased. The transformed hBMMSCs showed positive staining for the tumor-associated markers FSP, VEGF, EGF, and Tn-C. Real-time PCR and multiplex luminex bead analysis showed upregulation of TAF-related genes (FSP, FAP, Tn-C, Tsp-1, EGF, bFGF, IL-6,  $\alpha$ -SMA, VEGF, and TGF- $\beta$ ) for hBMMSCs with low expression for hWJSCs. The luciferase assay showed that hWJSCs previously exposed to MDA-TCM or TOV-TCM had no stimulatory growth effect on luciferase-tagged MDA or TOV cells unlike hBMMSCs. The results confirmed that hWJSCs do not transform to the TAF phenotype and may therefore not be associated with enhanced growth of solid tumors making them a safe MSC for cell based therapies.

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## Title

### *Reference*

## **ABSTRACT**

### Content

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# **STEM CELLS: LUNG CANCER**

## **Development of human umbilical cord matrix stem cell-based gene therapy for experimental lung tumors**

*Rachakatla et al.. (2007). Development of human umbilical cord matrix stem cell-based gene therapy for experimental lung tumors. Cancer Gene Therapy, 14, 828–835.*

<https://www.nature.com/articles/7701077>

### **ABSTRACT**

Umbilical cord matrix stem (UCMS) cells are unique stem cells derived from Wharton's jelly, which have been shown to express genes characteristic of primitive stem cells. To test the safety of these cells, human UCMS cells were injected both intravenously and subcutaneously in large numbers into severe combined immunodeficiency (SCID) mice and multiple tissues were examined for evidence of tumor formation. UCMS cells did not form gross or histological teratomas up to 50 days posttransplantation. Next, to

evaluate whether UCMS cells could selectively engraft in xenotransplanted tumors, MDA 231 cells were intravenously transplanted into SCID mice, followed by intravenous transplantation of UCMS cells 1 and 2 weeks later. UCMS cells were found near or within lung tumors but not in other tissues. Finally, UCMS cells were engineered to express human interferon beta – designated ‘UCMS-IFN- $\beta$ ’. UCMS-IFN- $\beta$  cells were intravenously transplanted at multiple intervals into SCID mice bearing MDA 231 tumors and their effect on tumors was examined. UCMS-IFN- $\beta$  cells significantly reduced MDA 231 tumor burden in SCID mouse lungs indicated by wet weight. These results clearly indicate safety and usability of UCMS cells in cancer gene therapy. Thus, UCMS cells can potentially be used for targeted delivery of cancer therapeutics.

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# **Placenta-Derived Multipotent Cells Exhibit Immunosuppressive Properties That Are Enhanced in the Presence of Interferon- $\gamma$**

*Chang et al.. (2004). Placenta-Derived Multipotent Cells Exhibit Immunosuppressive Properties That Are Enhanced in the Presence of Interferon- $\gamma$ . Stem Cells, 24, 2466–247.*  
<http://onlinelibrary.wiley.com/doi/10.1634/stemcells.2006-0071/full>

## **ABSTRACT**

Several types of nonhematopoietic stem cells, including bone marrow mesenchymal stem cells (BMMSCs) and embryonic stem cells, have been shown to have immunosuppressive properties. We show that human placenta-derived multipotent cells (PDMCs), which are isolated from a source without ethical concern and harbor multilineage differentiation potential, have strong immunosuppressive properties. PDMCs suppress both mitogen-induced and allogeneic lymphocyte proliferation in both CD4 and CD8 populations. The immunosuppression seen with PDMCs was significantly stronger than that with BMMSCs. Both PDMCs and BMMSCs express indoleamine 2,3-dioxygenase, but only PDMCs are positive for intracellular human leukocyte antigen-G (HLA). Mechanistically, suppression of lymphocyte reactivity by PDMCs is not due to cell death but to decreased cell proliferation and increased numbers of regulatory T cells.

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Addition of neutralizing antibodies to interleukin-10 and transforming growth factor (TGF)- $\beta$  partially restored lymphocyte proliferation. Unlike BMMSCs, PDMCs treated with interferon- $\gamma$  for 3 days only very minimally upregulated HLA-DR. On the contrary, PD-L1, a cell surface marker that plays an inhibitory role in T-cell activation, was upregulated and TGF- $\beta$  expression was seen. The immunosuppressive properties of PDMCs, along with their multilineage differentiation potential, ease of accessibility, and abundant cell numbers, may render these cells as good potential sources for future therapeutic applications.

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# STEM CELLS: CHRONIC ILLNESS

## Use of differentiated pluripotent stem cells in replacement therapy for treating disease

Fox et al.. (2014). *Use of differentiated pluripotent stem cells in replacement therapy for treating disease*. *Science*, 345(6199), 1247391.

<http://science.sciencemag.org/content/345/6199/1247391>

### ABSTRACT

### BACKGROUND

Decades of laboratory and clinical investigation have led to successful therapies using hematopoietic stem cells (HSCs), but few other cell therapies have transitioned from experimental to standard clinical care. Providing patients with autologous rather than allogeneic HSCs reduces morbidity and mortality, and in some circumstances broader use could expand the range of conditions amenable to HSC transplantation. The availability of a homogeneous supply of mature blood cells would also be advantageous. An unlimited supply of pluripotent stem cells (PSCs) directed to various cell fates holds great promise as source material for cell transplantation and minimally invasive therapies to treat

a variety of disorders. In this Review, we discuss past experience and challenges ahead and examine the extent to which hematopoietic stem cell transplantation and cell therapy for diabetes, liver disease, muscular dystrophies, neurodegenerative disorders, and heart disease would be affected by the availability of precisely differentiated PSCs.

## **ADVANCES**

Although it is not yet possible to differentiate PSCs to cells with characteristics identical to those in the many organs that need replacement, it is likely a matter of time before these “engineering” problems can be overcome. Experience with cell therapies, both in the laboratory and the clinic, however, indicate that many challenges remain for treatment of diseases other than those involving the hematopoietic system. There are issues of immunity, separate from controlling graft rejection, and identifying the optimal cell type for treatment in the case of muscular dystrophies and heart disease. Optimization is also needed for the transplant site, as in diabetes, or when dealing with disruption of the extracellular matrix in treating degenerative diseases, such as chronic liver and heart disease. Finally, when the pathologic process is diffuse and migration of transplanted cells is limited, as is the case with Alzheimer’s disease, amyotrophic lateral sclerosis, and the muscular dystrophies, identifying the best means and location for cell delivery will require further study.

## **OUTLOOK**

Considering the pace of progress in generating transplantable cells with a mature phenotype, and the

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availability of PSC-derived lineages in sufficient mass to treat some patients already, the challenges to scaling up production and eliminating cells with tumor-forming potential are probably within reach. However, generation of enough cells to treat an individual patient requires time for expansion, differentiation, selection, and testing to exclude contamination by tumorigenic precursors. Current methods are far too long and costly to address the treatment of acute organ injury or decompensated function. Immune rejection of engrafted cells, however, is likely to be overcome through transplantation of autologous cells from patient-derived PSCs. Availability of PSC-derived cell populations will have a dramatic effect on blood cell transfusion and the use of hematopoietic stem cell transplantation, and it will likely facilitate treatment of diabetes, some forms of liver disease and neurologic disorders, retinal diseases, and possibly heart disease. Close collaboration between scientists and clinicians—including surgeons and interventional radiologists—and between academia and industry will be critical to overcoming challenges and to bringing new therapies to patients in need.

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# STEM CELLS: DIABETES

## Pluripotent Stem Cells as a Potential Tool for Disease Modelling and Cell Therapy in Diabetes

*Abdelalim et al.. (2014). Pluripotent Stem Cells as a Potential Tool for Disease Modelling and Cell Therapy in Diabetes. Stem Cell Reviews and Reports, 10(3), 327-337.*  
<https://doi.org/10.1007/s12015-014-9503-6>

### ABSTRACT

Diabetes mellitus is the most prevailing disease with progressive incidence worldwide. To date, the pathogenesis of diabetes is far to be understood, and there is no permanent treatment available for diabetes. One of the promising approaches to understand and cure diabetes is to use pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced PCs (iPSCs). ESCs and iPSCs have a great potential to differentiate into all cell types, and they have a high ability to differentiate into insulin-secreting  $\beta$  cells. Obtaining PSCs genetically identical to the patient presenting with diabetes has been a longstanding dream for the in vitro modeling of disease and ultimately cell therapy. For several years, somatic cell nuclear transfer (SCNT) was the method of choice to generate patient-specific ESC lines.

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However, this technology faces ethical and practical concerns. Interestingly, the recently established iPSC technology overcomes the major problems of other stem cell types including the lack of ethical concern and no risk of immune rejection. Several iPSC lines have been recently generated from patients with different types of diabetes, and most of these cell lines are able to differentiate into insulin-secreting  $\beta$  cells. In this review, we summarize recent advances in the differentiation of pancreatic  $\beta$  cells from PSCs, and describe the challenges for their clinical use in diabetes cell therapy. Furthermore, we discuss the potential use of patient-specific PSCs as an in vitro model, providing new insights into the pathophysiology of diabetes.

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### **Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo.**

*Kroon et al.. (2008). Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol, 26(4), 443-52.*  
<http://dx.doi.org/10.1038/nbt1393>.

## ABSTRACT

Development of a cell therapy for diabetes would be greatly aided by a renewable supply of human beta-cells. Here we show that pancreatic endoderm derived from human embryonic stem (hES) cells efficiently generates glucose-responsive endocrine cells after implantation into mice. Upon glucose stimulation of the implanted mice, human insulin and C-peptide are detected in sera at levels similar to those of mice transplanted with approximately 3,000 human islets. Moreover, the insulin-expressing cells generated after engraftment exhibit many properties of functional beta-cells, including expression of critical beta-cell transcription factors, appropriate processing of proinsulin and the presence of mature endocrine secretory granules. Finally, in a test of therapeutic potential, we demonstrate that implantation of hES cell-derived pancreatic endoderm protects against streptozotocin-induced hyperglycemia. Together, these data provide definitive evidence that hES cells are competent to generate glucose-responsive, insulin-secreting cells.

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## **Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells.**

*D'armour et al.. (2006). Production of pancreatic hormone-expressing endocrine cells from human embryonic stem*

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*cells. Nat Biotechnol, 24(11), 1392-401.*

<http://dx.doi.org/10.1038/nbt1259>

### **ABSTRACT**

Of paramount importance for the development of cell therapies to treat diabetes is the production of sufficient numbers of pancreatic endocrine cells that function similarly to primary islets. We have developed a differentiation process that converts human embryonic stem (hES) cells to endocrine cells capable of synthesizing the pancreatic hormones insulin, glucagon, somatostatin, pancreatic polypeptide and ghrelin. This process mimics *in vivo* pancreatic organogenesis by directing cells through stages resembling definitive endoderm, gut-tube endoderm, pancreatic endoderm and endocrine precursor--en route to cells that express endocrine hormones. The hES cell-derived insulin-expressing cells have an insulin content approaching that of adult islets. Similar to fetal beta-cells, they release C-peptide in response to multiple secretory stimuli, but only minimally to glucose. Production of these hES cell-derived endocrine cells may represent a critical step in the development of a renewable source of cells for diabetes cell therapy.

## **Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets.**

Lumelsky et al.. (2001). Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. *Science*, 292(5520), 1389-94.

<http://dx.doi.org/10.1126/science.1058866>

### **ABSTRACT**

Although the source of embryonic stem (ES) cells presents ethical concerns, their use may lead to many clinical benefits if differentiated cell types can be derived from them and used to assemble functional organs. In pancreas, insulin is produced and secreted by specialized structures, islets of Langerhans. Diabetes, which affects 16 million people in the United States, results from abnormal function of pancreatic islets. We have generated cells expressing insulin and other pancreatic endocrine hormones from mouse ES cells. The cells self-assemble to form three-dimensional clusters similar in topology to normal pancreatic islets where pancreatic cell types are in close association with neurons. Glucose triggers insulin release from these cell clusters by mechanisms similar to those employed in vivo. When injected into diabetic mice, the insulin-producing cells undergo rapid

vascularization and maintain a clustered, islet-like organization.

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## **Directed differentiation of human embryonic stem cells towards a pancreatic cell fate.**

*Shim et al.. (2007). Directed differentiation of human embryonic stem cells towards a pancreatic cell fate. Diabetologia, 50(6), 1228-38.*

<http://dx.doi.org/10.1007/s00125-007-0634-z>

### **ABSTRACT**

#### **AIMS/HYPOTHESIS:**

The relative lack of successful pancreatic differentiation of human embryonic stem cells (hESCs) may suggest that directed differentiation of hESCs into definitive endoderm and subsequent commitment towards a pancreatic fate are not readily achieved. The aim of this study was to investigate whether sequential exposure of hESCs to epigenetic signals that mimic in vivo pancreatic development can efficiently generate pancreatic endodermal cells, and whether these cells can be further matured and reverse hyperglycaemia upon transplantation.

#### **MATERIALS AND METHODS:**

The hESCs were sequentially treated with serum, activin and retinoic acid (RA) during embryoid body formation. The

patterns of gene expression and protein production associated with embryonic germ layers and pancreatic endoderm were analysed by RT-PCR and immunostaining. The developmental competence and function of hESC-derived PDX1-positive cells were evaluated after *in vivo* transplantation.

## **RESULTS:**

Sequential treatment with serum, activin and RA highly upregulated the expression of the genes encoding forkhead box protein A2 (FOXA2), SRY-box containing gene 17 (SOX17), pancreatic and duodenal homeobox 1 (PDX1) and homeobox HB9 (HLXB9). The population of pancreatic endodermal cells that produced PDX1 was significantly increased at the expense of ectodermal differentiation, and a subset of the PDX1-positive cells also produced FOXA2, caudal-type homeobox transcription factor 2 (CDX2), and nestin (NES). After transplantation, the PDX1-positive cells further differentiated into mature cell types producing insulin and glucagon, resulting in amelioration of hyperglycaemia and weight loss in streptozotocin-treated diabetic mice.

## **CONCLUSIONS/INTERPRETATION:**

Our strategy allows the progressive differentiation of hESCs into pancreatic endoderm capable of generating mature pancreatic cell types that function *in vivo*. These findings may establish the basis of further investigations for the purification of transplantable islet progenitors derived from hESCs.

# Treating Diet-Induced Diabetes and Obesity with Human Embryonic Stem Cell-Derived Pancreatic Progenitor Cells and Antidiabetic Drugs

*Bruin et al.. (2015). Treating Diet-Induced Diabetes and Obesity with Human Embryonic Stem Cell-Derived Pancreatic Progenitor Cells and Antidiabetic Drugs. Stem Cell Reports, 4(4), 605-620.*

<https://doi.org/10.1016/j.stemcr.2015.02.011>

## ABSTRACT

Human embryonic stem cell (hESC)-derived pancreatic progenitor cells effectively reverse hyperglycemia in rodent models of type 1 diabetes, but their capacity to treat type 2 diabetes has not been reported. An immunodeficient model of type 2 diabetes was generated by high-fat diet (HFD) feeding in SCID-beige mice. Exposure to HFDs did not impact the maturation of macroencapsulated pancreatic progenitor cells into glucose-responsive insulin-secreting cells following transplantation, and the cell therapy improved glucose tolerance in HFD-fed transplant recipients after 24 weeks. However, since diet-induced hyperglycemia and obesity were not fully ameliorated by transplantation alone, a second cohort of HFD-fed mice was treated with pancreatic progenitor cells combined with one of three antidiabetic drugs. All combination therapies rapidly improved body weight and co-treatment with either sitagliptin or metformin improved hyperglycemia after only 12 weeks. Therefore, a stem cell-based therapy may be effective for treating type 2

diabetes, particularly in combination with antidiabetic drugs.

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## **Reversal of diabetes with insulin-producing cells derived *in vitro* from human pluripotent stem cells**

*Rezania et al.. (2014). Reversal of diabetes with insulin-producing cells derived *in vitro* from human pluripotent stem cells. Nature Biotechnology, 32(11), 1121-33.*

<http://dx.doi.org/10.1038/nbt.3033>

### **ABSTRACT**

Transplantation of pancreatic progenitors or insulin-secreting cells derived from human embryonic stem cells (hESCs) has been proposed as a therapy for diabetes. We describe a seven-stage protocol that efficiently converts hESCs into insulin-producing cells. Stage (S) 7 cells expressed key markers of mature pancreatic beta cells, including MAFA, and displayed glucose-stimulated insulin secretion similar to that of human islets during static incubations *in vitro*.

Additional characterization using single-cell imaging and dynamic glucose stimulation assays revealed similarities but also notable differences between S7 insulin-secreting cells and primary human beta cells. Nevertheless, S7 cells rapidly reversed diabetes in mice within 40 days, roughly four times faster than pancreatic progenitors. Therefore, although S7

cells are not fully equivalent to mature beta cells, their capacity for glucose-responsive insulin secretion and rapid reversal of diabetes *in vivo* makes them a promising alternative to pancreatic progenitor cells or cadaveric islets for the treatment of diabetes.

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## **Insulin-Producing Endocrine Cells Differentiated In Vitro From Human Embryonic Stem Cells Function in Macroencapsulation Devices In Vivo**

*Agulnick et al.. (2015). Insulin-Producing Endocrine Cells Differentiated In Vitro From Human Embryonic Stem Cells Function in Macroencapsulation Devices In Vivo. Stem Cells Translation Medicine, 4(10), 1214-1222.*

<http://dx.doi.org/10.5966/sctm.2015-0079>

### **ABSTRACT**

The PEC-01 cell population, differentiated from human embryonic stem cells (hESCs), contains pancreatic progenitors (PPs) that, when loaded into macroencapsulation devices (to produce the VC-01 candidate product) and transplanted into mice, can mature into glucose-responsive insulin-secreting cells and other pancreatic endocrine cells involved in glucose metabolism. We modified the protocol for making PEC-01 cells such that 73%–80% of the cell population consisted of PDX1-positive (PDX1+) and NKX6.1+ PPs. The PPs were further

differentiated to islet-like cells (ICs) that reproducibly contained 73%–89% endocrine cells, of which approximately 40%–50% expressed insulin. A large fraction of these insulin-positive cells were single hormone-positive and expressed the transcription factors PDX1 and NKX6.1. To preclude a significant contribution of progenitors to the *in vivo* function of ICs, we used a simple enrichment process to remove remaining PPs, yielding aggregates that contained 93%–98% endocrine cells and 1%–3% progenitors. Enriched ICs, when encapsulated and implanted into mice, functioned similarly to the VC-01 candidate product, demonstrating conclusively that *in vitro*-produced hESC-derived insulin-producing cells can mature and function *in vivo* in devices. A scaled version of our suspension culture was used, and the endocrine aggregates could be cryopreserved and retain functionality. Although ICs expressed multiple important  $\beta$  cell genes, the cells contained relatively low levels of several maturity-associated markers. Correlating with this, the time to function of ICs was similar to PEC-01 cells, indicating that ICs required cell-autonomous maturation after delivery *in vivo*, which would occur concurrently with graft integration into the host.

## **Significance**

Type 1 diabetes (T1D) affects approximately 1.25 million people in the U.S. alone and is deadly if not managed with insulin injections. This paper describes the production of insulin-producing cells *in vitro* and a new protocol for producing the cells, representing another potential cell source for a diabetes cell therapy. These cells can be loaded into a protective device that is implanted under the skin. The

device is designed to protect the cells from immune rejection by the implant recipient. The implant can engraft and respond to glucose by secreting insulin, thus potentially replacing the  $\beta$  cells lost in patients with T1D.

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## **Mesenchymal stem cell-based therapy for type 1 diabetes.**

Wu, H & Mahato, R.I. (2014). Mesenchymal stem cell-based therapy for type 1 diabetes. *Discovery Medicine*, 17(93), 139-42. <https://www.ncbi.nlm.nih.gov/pubmed/24641956>

### **ABSTRACT**

Diabetes has increasingly become a worldwide health problem, causing huge burden on healthcare system and economy. Type 1 diabetes (T1D), traditionally termed "juvenile diabetes" because of an early onset age, is affecting 5-10% of total diabetic population. Insulin injection, the predominant treatment for T1D, is effective to ameliorate the hyperglycemia but incompetent to relieve the autoimmunity and to regenerate lost islets. Islet transplantation, an experimental treatment for T1D, also suffers from limited supply of human islets and poor immunosuppression. The recent progress in regenerative medicine, especially stem cell therapy, has suggested several novel and potential cures for T1D. Mesenchymal stem cell (MSC) based cell therapy is among one of them. MSCs are a type of adult stem cells residing in bone marrow,

adipose tissue, umbilical cord blood, and many other tissues. MSCs, with self-renewal potential and transdifferentiation capability, can be expanded in vitro and directed to various cell lineages with relatively less efforts. MSCs have well-characterized hypoimmunogenicity and immunomodulatory effect. All these features make MSCs attractive for treating T1D. Here, we review the properties of MSCs and some of the recent progress using MSCs as a new therapeutic in the treatment of T1D. We also discuss the strength and limitations of using MSC therapy in human trials.

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## **Mesenchymal stem cell-based treatment for microvascular and secondary complications of Diabetes mellitus**

Davey et al.. (2014). Mesenchymal stem cell-based treatment for microvascular and secondary complications of Diabetes mellitus. *Front Endocrinol (Lausanne)*, 6(5), 86.  
<http://dx.doi.org/10.3389/fendo.2014.00086>

### **ABSTRACT**

The worldwide increase in the prevalence of Diabetes mellitus (DM) has highlighted the need for increased research efforts into treatment options for both the disease itself and its associated complications. In recent years, mesenchymal stromal cells (MSCs) have been highlighted

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as a new emerging regenerative therapy due to their multipotency but also due to their paracrine secretion of angiogenic factors, cytokines, and immunomodulatory substances. This review focuses on the potential use of MSCs as a regenerative medicine in microvascular and secondary complications of DM and will discuss the challenges and future prospects of MSCs as a regenerative therapy in this field. MSCs are believed to have an important role in tissue repair. Evidence in recent years has demonstrated that MSCs have potent immunomodulatory functions resulting in active suppression of various components of the host immune response. MSCs may also have glucose lowering properties providing another attractive and unique feature of this therapeutic approach. Through a combination of the above characteristics, MSCs have been shown to exert beneficial effects in pre-clinical models of diabetic complications prompting initial clinical studies in diabetic wound healing and nephropathy. Challenges that remain in the clinical translation of MSC therapy include issues of MSC heterogeneity, optimal mode of cell delivery, homing of these cells to tissues of interest with high efficiency, clinically meaningful engraftment, and challenges with cell manufacture. An issue of added importance is whether an autologous or allogeneic approach will be used. In summary, MSC administration has significant potential in the treatment of diabetic microvascular and secondary complications but challenges remain in terms of engraftment, persistence, tissue targeting, and cell manufacture.

# **Efficacy and Safety of Autologous Bone Marrow-Derived Stem Cell Transplantation in Patients with Type 2 Diabetes Mellitus: A Randomized Placebo-Controlled Study**

## **ABSTRACT**

There is a growing interest in cell-based therapies in T2DM as β-cell failure is progressive and inexorable with the advancing duration of disease. This prospective, randomized, single-blinded placebo-controlled study evaluates the efficacy and safety of autologous bone marrow-derived stem cell transplantation (ABMSCT) in T2DM. Twenty-one patients with triple oral antidiabetic drug failure and requiring insulin ≥0.4 IU per kg per day with HbA1c <7.5% were randomly assigned to an intervention (n = 11) and control group (n = 10) and followed for 12 months. Patients in the intervention group received ABMSCT through a targeted approach, and after 12 weeks, a second dose of stem cells was administered through the antecubital vein

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after mobilization with G-CSF, while the control group underwent a sham procedure. The primary end point was a reduction in insulin requirement by  $\geq 50\%$  from baseline while maintaining HbA1c  $< 7\%$ . Nine out of the 11 (82%) patients in the intervention group achieved the primary end point, whereas none of the patients in the control group did over the study period ( $p = 0.002$ ). The insulin requirement decreased by 66.7% in the intervention group from 42.0 (31.0-64.0) IU per day to 14.0 (0.0-30.0) IU per day ( $p = 0.011$ ), while in controls it decreased by 32.1% from 40.5 (31.8-44.3) IU per day to 27.5 (23.5-33.3) IU per day ( $p = 0.008$ ) at 12 months. The reduction in insulin requirement was significantly more in the intervention group compared to controls at both 6 ( $p = 0.001$ ) and 12 months ( $p = 0.004$ ). There was a modest but nonsignificant increase in HbA1c (%) in cases from 6.9% (6.4-7.2%) to 7.1% (6.6-7.5%) as well as in controls from 6.9% (6.2-7.0%) to 7.0% (6.9-7.5%). Ten out of 11 (91%) patients could maintain HbA1c  $< 7\%$  in the intervention group, whereas 6 out of 10 did (60%) in the control group ( $p = 0.167$ ). The glucagon-stimulated C-

peptide significantly increased in treated cases compared to controls ( $p = 0.036$ ). The decrease in insulin requirement positively correlated with stimulated C-peptide ( $r = 0.8$ ,  $p = 0.001$ ). In conclusion, ABMSCT results in a significant decrease in the insulin dose requirement along with an improvement in the stimulated C-peptide levels in T2DM. However, a greater number of patients with a longer duration of follow-up are required to substantiate these observations.

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## **Combined Treatment of Intrapancreatic Autologous Bone Marrow Stem Cells and Hyperbaric Oxygen in Type 2 Diabetes Mellitus Randomized Clinical Trials**

*Estrada et al.. (2015). Combined Treatment of Intrapancreatic Autologous Bone Marrow Stem Cells and Hyperbaric Oxygen in Type 2 Diabetes Mellitus Randomized Clinical Trials. Molecular Therapy, 23(1), pS150.*  
[https://doi.org/10.1016/S1525-0016\(16\)33986-7](https://doi.org/10.1016/S1525-0016(16)33986-7)

## ABSTRACT

T2DM is a pandemic disease with a serious health complications, however stem cells therapy appear to be a new therapeutic option.

This prospective, open labeled, randomized controlled clinical trial a phase I/II study, comparing the benefit of hyperbaric oxygen therapy and intra-pancreatic stem cell infusion vs. control group with standard medical treatment (insulin + metformin) for type 2 diabetes mellitus.

The objective of this study was to determine whether intra-pancreatic infusion of bone marrow derived autologous stem cells in combination with hyperbaric oxygen therapy could improve metabolism in patients with type 2 diabetes mellitus. The primary endpoint was HbA1c reduction.

The Patients with T2DM enrolled were 23. They were randomized and assigned, to intervention group 13 patients and 10 to control group. They were followed for 1 year. Metabolic variables included (fasting plasma glucose, C-peptide, HbA1c, and calculation of C peptide/glucose ratio) and clinical variables (BMI, insulin requirement) were measured at baseline and at 180, 270 and 365 days.

At baseline there was no significance difference between groups in HbA1C, glucose, c-peptide, c peptide/glucose and insulin, BMI was greater in the intervention group than in the control group ( $\text{diff}=3.93$ ,  $p=0.006$ ). At 365 days in the intervention group HbA1C changes were significant ( $\text{diff}=-0.76$ ,  $p=0.05$ ), glucose ( $\text{diff}=-64.1$ ,  $\text{diff } 0.001$ ), c-peptide

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(diff=1.25, p< 0.001), c peptide/glucose (diff=0.01, p< 0.0001). Changes in A1c compared (both groups) to time 0 were not significant to the control group at any time during follow up, but were significantly decreased in the intervention group at 365 days (diff=-1.08, p<0.001).

The conclusion of this study was that combination of autologous stem cell therapy and hyperbaric oxygen treatment could favor tissue remodeling and regeneration-expansion of insulin producing cells in the treated patients vs. patients with standard medical treatment Insulin and metformin in a randomized clinical trial.

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# **STEM CELLS: PARKINSON'S DISEASE**

## **Potential for cell therapy in Parkinson's disease using genetically programmed human embryonic stem cell-derived neural progenitor cells**

*Ambasudhan et al.. (2014). Potential for cell therapy in Parkinson's disease using genetically programmed human embryonic stem cell-derived neural progenitor cells. The Journal of Comparative Neurology, 522(12), 2845–2856.*  
<http://onlinelibrary.wiley.com/doi/10.1002/cne.23617/full>

### **ABSTRACT**

Neural transplantation is a promising strategy for restoring dopaminergic dysfunction and modifying disease progression in Parkinson's disease (PD). Human embryonic stem cells (hESCs) are a potential resource in this regard because of their ability to provide a virtually limitless supply of homogenous dopaminergic progenitors and neurons of appropriate lineage. The recent advances in developing robust cell culture protocols for directed differentiation of hESCs to near pure populations of ventral mesencephalic (A9-type) dopaminergic neurons has heightened the prospects for PD cell therapy. Here, we focus our review on current state-of-the-art techniques for harnessing hESC-based strategies toward development of a stem cell

therapeutic for PD. Importantly, we also briefly describe a novel genetic-programming approach that may address many of the key challenges that remain in the field and that may hasten clinical translation.

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## **Clinical translation of stem cell transplantation in Parkinson's disease**

*Lindvall, O. (2016). Clinical translation of stem cell transplantation in Parkinson's disease. Journal of Internal Medicine, 279(1), 30–40.*

<http://onlinelibrary.wiley.com/doi/10.1111/joim.12415/full>

### **ABSTRACT**

In Parkinson's disease (PD), the main pathology underlying the motor symptoms is a loss of nigrostriatal dopaminergic neurons. Clinical trials of intrastriatal transplantation of human foetal mesencephalic tissue have shown that the grafted dopaminergic neurons re-innervate the striatum, restore striatal dopamine release and, in some cases, induce major, long-lasting improvement of motor function. However, nonmotor symptoms originating from degeneration outside the striatum or in nondopaminergic systems are not alleviated by intrastriatal implantation of dopaminergic neurons. Stem cells and reprogrammed cells could potentially be used to produce dopaminergic neurons for transplantation in patients with PD. Recent studies

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demonstrate that standardized preparations of dopaminergic neurons of the correct substantia nigra phenotype can be generated from human embryonic stem cells in large numbers, and they will soon be available for patient application. In addition, dopaminergic neurons derived from human induced pluripotent stem cells are being considered for clinical translation. Important challenges include the demonstration of potency (growth capacity and functional efficacy) and safety of the generated dopaminergic neurons in preclinical animal models. The dopaminergic neurons should subsequently be tested, using optimal patient selection and cell preparation and transplantation procedures, in controlled clinical studies.

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### **Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports.**

*Kefalopoulou et al.. (2014). Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports. JAMA Neurol, 71(1), 83-7.*

<https://www.ncbi.nlm.nih.gov/pubmed/24217017>

#### **ABSTRACT**

#### **IMPORTANCE:**

Recent advances in stem cell technologies have rekindled an interest in the use of cell replacement strategies for

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patients with Parkinson disease. This study reports the very long-term clinical outcomes of fetal cell transplantation in 2 patients with Parkinson disease. Such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation.

### **OBSERVATIONS:**

Two patients received intrastriatal grafts of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts, as restorative treatment for their Parkinson disease. To evaluate the very long-term efficacy of the grafts, clinical assessments were performed 18 and 15 years posttransplantation. Motor improvements gained gradually over the first postoperative years were sustained up to 18 years posttransplantation, while both patients have discontinued, and remained free of any, pharmacological dopaminergic therapy.

### **CONCLUSIONS AND RELEVANCE:**

The results from these 2 cases indicate that dopaminergic cell transplantation can offer very long-term symptomatic relief in patients with Parkinson disease and provide proof-of-concept support for future clinical trials using fetal or stem cell therapies.

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## Clinical translation of stem cells in neurodegenerative disorders.

*Lindvall et al.. (2012). Clinical translation of stem cells in neurodegenerative disorders. Cell Stem Cell, 10(2), 151-5.  
<https://www.ncbi.nlm.nih.gov/pubmed/22305565>*

### ABSTRACT

Stem cells and their derivatives show tremendous potential for treating many disorders, including neurodegenerative diseases. We discuss here the challenges and potential for the translation of stem-cell-based approaches into treatments for Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.

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## Improved cell therapy protocols for Parkinson's disease based on differentiation efficiency and safety of hESC-, hiPSC-, and non-human primate iPSC-derived dopaminergic neurons.

*Sundberg et al.. (2013). Improved cell therapy protocols for Parkinson's disease based on differentiation efficiency and safety of hESC-, hiPSC-, and non-human primate iPSC-*

*derived dopaminergic neurons. Stem Cells, 31(8), 1548-62.*

<https://www.ncbi.nlm.nih.gov/pubmed/23666606>

## ABSTRACT

The main motor symptoms of Parkinson's disease are due to the loss of dopaminergic (DA) neurons in the ventral midbrain (VM). For the future treatment of Parkinson's disease with cell transplantation it is important to develop efficient differentiation methods for production of human iPSCs and hESCs-derived midbrain-type DA neurons. Here we describe an efficient differentiation and sorting strategy for DA neurons from both human ES/iPS cells and non-human primate iPSCs. The use of non-human primate iPSCs for neuronal differentiation and autologous transplantation is important for preclinical evaluation of safety and efficacy of stem cell-derived DA neurons. The aim of this study was to improve the safety of human- and non-human primate iPSC (PiPSC)-derived DA neurons.

According to our results, NCAM(+) /CD29(low) sorting enriched VM DA neurons from pluripotent stem cell-derived neural cell populations. NCAM(+) /CD29(low) DA neurons were positive for FOXA2/TH and EN1/TH and this cell population had increased expression levels of FOXA2, LMX1A, TH, GIRK2, PITX3, EN1, NURR1 mRNA compared to unsorted neural cell populations. PiPSC-derived NCAM(+) /CD29(low) DA neurons were able to restore motor function of 6-hydroxydopamine (6-OHDA) lesioned rats 16 weeks after transplantation. The transplanted sorted cells also integrated in the rodent brain tissue, with robust TH+/hNCAM+ neuritic innervation of the host striatum. One year after autologous transplantation, the primate iPSC-

derived neural cells survived in the striatum of one primate without any immunosuppression. These neural cell grafts contained FOXA2/TH-positive neurons in the graft site. This is an important proof of concept for the feasibility and safety of iPSC-derived cell transplantation therapies in the future.

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## **Efficient generation of functional dopaminergic neurons from human induced pluripotent stem cells under defined conditions.**

*Swistowski et al.. (2010). Efficient generation of functional dopaminergic neurons from human induced pluripotent stem cells under defined conditions. Stem Cells, 28(10), 1893-904. <https://www.ncbi.nlm.nih.gov/pubmed/20715183>*

### **ABSTRACT**

Human induced pluripotent stem cells (iPSCs) reprogrammed from somatic cells represent a promising unlimited cell source for generating patient-specific cells for biomedical research and personalized medicine. As a first step, critical to clinical applications, we attempted to develop defined culture conditions to expand and differentiate human iPSCs into functional progeny such as dopaminergic neurons for treating or modeling Parkinson's disease (PD). We used a completely defined (xeno-free) system that we

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previously developed for efficient generation of authentic dopaminergic neurons from human embryonic stem cells (hESCs), and applied it to iPSCs. First, we adapted two human iPSC lines derived from different somatic cell types for the defined expansion medium and showed that the iPSCs grew similarly as hESCs in the same medium regarding pluripotency and genomic stability. Second, by using these two independent adapted iPSC lines, we showed that the process of differentiation into committed neural stem cells (NSCs) and subsequently into dopaminergic neurons was also similar to hESCs. Importantly, iPSC-derived dopaminergic neurons were functional as they survived and improved behavioral deficits in 6-hydroxydopamine-lesioned rats after transplantation. In addition, iPSC-derived NSCs and neurons could be efficiently transduced by a baculoviral vector delivering episomal DNA for future gene function study and disease modeling using iPSCs. We also performed genome-wide microarray comparisons between iPSCs and hESCs, and we derived NSC and dopaminergic neurons. Our data revealed overall similarity and visible differences at a molecular level. Efficient generation of functional dopaminergic neurons under defined conditions will facilitate research and applications using PD patient-specific iPSCs.

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# Are Stem Cell-Based Therapies for Parkinson's Disease Ready for the Clinic in 2016?

Barker et al.. (2016). *Are Stem Cell-Based Therapies for Parkinson's Disease Ready for the Clinic in 2016?.* *Journal of Parkinson's Disease*, 6(1), 57-63.

<https://content.iospress.com/articles/journal-of-parkinsons-disease/jpd160798>

## ABSTRACT

Recent news of an impending clinical cell transplantation trial in Parkinson's disease using parthenogenetic stem cells as a source of donor tissue have raised hopes in the patient community and sparked discussion in the research community. Based on discussions held by a global collaborative initiative on translation of stem cell therapy in Parkinson's disease, we have identified a set of key questions that we believe should be addressed ahead of every clinical stem cell-based transplantation trial in this disorder. In this article, we first provide a short history of cell therapy in Parkinson's disease and briefly describe the current state-of-art regarding human stem cell-derived dopamine neurons for use in any patient trial. With this background information as a foundation, we then discuss each of the key questions in relation to the upcoming therapeutic trial and critically assess if the time is ripe for clinical translation of parthenogenetic stem cell technology in Parkinson's disease.

## **Development of stem cell-based therapy for Parkinson's disease**

*Han et al.. (2015). Development of stem cell-based therapy for Parkinson's disease. Translational Neurodegeneration, 4(16). <https://doi.org/10.1186/s40035-015-0039-8>*

### **ABSTRACT**

Parkinson's disease (PD) is one of the most common neurodegenerative disorders of aging, characterized by the degeneration of dopamine neurons (DA neurons) in the substantia nigra, leading to the advent of both motor symptoms and non-motor symptoms. Current treatments include electrical stimulation of the affected brain areas and dopamine replacement therapy. Even though both categories are effective in treating PD patients, the disease progression cannot be stopped. The research advance into cell therapies provides exciting potential for the treatment of PD. Current cell sources include neural stem cells (NSCs) from fetal brain tissues, human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs) and directly induced dopamine neurons (iDA neurons). Here, we evaluate the research progress in different cell sources with a focus on using iPSCs as a valuable source and propose key challenges for developing cells suitable for large-scale clinical applications in the treatment of PD.

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# STEM CELLS: DEMENTIA & ALZHEIMER'S

## Alzheimer's disease, dementia, and stem cell therapy

Duncan, M & Valenzuela, M. (2017). *Alzheimer's disease, dementia, and stem cell therapy*. *Stem Cell Research & Therapy*, 8, 111. <https://doi.org/10.1186/s13287-017-0567-5>

### ABSTRACT

Alzheimer's disease (AD) represents arguably the most significant social, economic, and medical crisis of our time. Characterized by progressive neurodegenerative pathology, AD is first and foremost a condition of neuronal and synaptic loss. Repopulation and regeneration of depleted neuronal circuitry by exogenous stem cells is therefore a rational therapeutic strategy. This review will focus on recent advances in stem cell therapies utilizing animal models of AD, as well as detailing the human clinical trials of stem cell therapies for AD that are currently undergoing development.

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# **Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease.**

*Blurton-jones et al.. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci U S A, 106(32), 13594-9.*

<https://www.ncbi.nlm.nih.gov/pubmed/19633196?dopt=Abstract>

## **ABSTRACT**

Neural stem cell (NSC) transplantation represents an unexplored approach for treating neurodegenerative disorders associated with cognitive decline such as Alzheimer disease (AD). Here, we used aged triple transgenic mice (3xTg-AD) that express pathogenic forms of amyloid precursor protein, presenilin, and tau to investigate the effect of neural stem cell transplantation on AD-related neuropathology and cognitive dysfunction. Interestingly, despite widespread and established A<sub>β</sub> plaque and neurofibrillary tangle pathology, hippocampal neural stem cell transplantation rescues the spatial learning and memory deficits in aged 3xTg-AD mice. Remarkably, cognitive function is improved without altering A<sub>β</sub> or tau pathology. Instead, the mechanism underlying the improved cognition involves a robust enhancement of hippocampal synaptic density, mediated by brain-derived neurotrophic factor (BDNF). Gain-of-function studies show that recombinant BDNF mimics the beneficial effects of NSC transplantation.

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Furthermore, loss-of-function studies show that depletion of NSC-derived BDNF fails to improve cognition or restore hippocampal synaptic density. Taken together, our findings demonstrate that neural stem cells can ameliorate complex behavioral deficits associated with widespread Alzheimer disease pathology via BDNF.

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### **Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss.**

Ager et al.. (2015). *Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss*. *Hippocampus*, 25(7), 813-26.

<https://www.ncbi.nlm.nih.gov/pubmed/25530343?dopt=Abstract>

#### **ABSTRACT**

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder, affecting over 35 million people worldwide. Pathologically, AD is characterized by the progressive accumulation of  $\beta$ -amyloid (A $\beta$ ) plaques and neurofibrillary tangles within the brain. Together, these pathologies lead to marked neuronal and synaptic loss and

## Compendium of Research: STEM CELLS

corresponding impairments in cognition. Current treatments, and recent clinical trials, have failed to modify the clinical course of AD; thus, the development of novel and innovative therapies is urgently needed. Over the last decade, the potential use of stem cells to treat cognitive impairment has received growing attention. Specifically, neural stem cell transplantation as a treatment for AD offers a novel approach with tremendous therapeutic potential. We previously reported that intrahippocampal transplantation of murine neural stem cells (mNSCs) can enhance synaptogenesis and improve cognition in 3xTg-AD mice and the CaM/Tet-DT(A) model of hippocampal neuronal loss. These promising findings prompted us to examine a human neural stem cell population, HuCNS-SC, which has already been clinically tested for other neurodegenerative disorders. In this study, we provide the first evidence that transplantation of research grade HuCNS-SCs can improve cognition in two complementary models of neurodegeneration. We also demonstrate that HuCNS-SC cells can migrate and differentiate into immature neurons and glia and significantly increase synaptic and growth-associated markers in both 3xTg-AD and CaM/Tet-DTA mice. Interestingly, improvements in aged 3xTg-AD mice were not associated with altered A $\beta$  or tau pathology. Rather, our findings suggest that human NSC transplantation improves cognition by enhancing endogenous synaptogenesis. Taken together, our data provide the first preclinical evidence that human NSC transplantation could be a safe and effective therapeutic approach for treating AD.

## **Mesenchymal stem cells rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated tau.**

*Zilka et al.. (2011). Mesenchymal stem cells rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated tau. Neuroscience, 193, 330-7.*

<https://www.ncbi.nlm.nih.gov/pubmed/21763758?dopt=Abstract>

### **ABSTRACT**

We have developed a stably transfected human cell model for Alzheimer's disease with doxycycline-inducible expression of human misfolded truncated tau protein (AT tau). We have showed that AT tau reduced the metabolic activity of the AT tau cells, slowed down cell proliferation, and induced caspase-3-independent apoptosis-like programmed cell death, tauoptosis. The aim of this study was to test the possible capability of rat mesenchymal stem cells (MSCs) to interfere with AT tau protein-induced cell death. AT tau cells after treatment with 10 µM all-trans retinoic acid were either co-cultivated with MSCs or supplemented with MSC secretome for 6 and 9 days. We found that both MSCs and MSC secretome promoted survival and increased the metabolic activity of the cells. Moreover stem cells induced cell differentiation and

formation of neurites with numerous varicosities. Strikingly, treatment had no effect on tau expression suggesting that MSC induced self-protecting mechanism that prevented AT tau cells from tauoptosis. Our results showed that mesenchymal stem cells and their secretome are able to rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated tau. We suggest that cell therapy may represent an alternative therapeutic avenue for treatment of human Alzheimer's disease and related tauopathies.

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## **Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation.**

*Lee et al.. (2012). Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. Neurobiol Aging, 33(3), 588-602.*

<https://www.ncbi.nlm.nih.gov/pubmed/20471717?dopt=Abstract>

## ABSTRACT

Human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC) have a potential therapeutic role in the treatment of neurological disorders, but their current clinical usage and mechanism of action has yet to be ascertained in Alzheimer's disease (AD). Here we report that hUCB-MSC transplantation into amyloid precursor protein (APP) and presenilin1 (PS1) double-transgenic mice significantly improved spatial learning and memory decline. Furthermore, amyloid- $\beta$  peptide (A $\beta$ ) deposition,  $\beta$ -secretase 1 (BACE-1) levels, and tau hyperphosphorylation were dramatically reduced in hUCB-MSC transplanted APP/PS1 mice. Interestingly, these effects were associated with reversal of disease-associated microglial neuroinflammation, as evidenced by decreased microglia-induced proinflammatory cytokines, elevated alternatively activated microglia, and increased anti-inflammatory cytokines. These findings lead us to suggest that hUCB-MSC produced their sustained neuroprotective effect by inducing a feed-forward loop involving alternative activation of microglial neuroinflammation, thereby ameliorating disease pathophysiology and reversing the cognitive decline associated with A $\beta$  deposition in AD mice.

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# **Placenta-derived mesenchymal stem cells improve memory dysfunction in an A $\beta$ 1-42-infused mouse model of Alzheimer's disease.**

*Yun et al.. (2013). Placenta-derived mesenchymal stem cells improve memory dysfunction in an A $\beta$ 1-42-infused mouse model of Alzheimer's disease. Cell Death Dis, 12(4), e958.*

<https://www.ncbi.nlm.nih.gov/pubmed/24336078?dopt=Abstract>

## **ABSTRACT**

Mesenchymal stem cells (MSCs) promote functional recoveries in pathological experimental models of central nervous system (CNS) and are currently being tested in clinical trials for neurological disorders, but preventive mechanisms of placenta-derived MSCs (PD-MSCs) for Alzheimer's disease are poorly understood. Herein, we investigated the inhibitory effect of PD-MSCs on neuronal cell death and memory impairment in A $\beta$ 1-42-infused mice. After intracerebroventrical (ICV) infusion of A $\beta$ 1-42 for 14 days, the cognitive function was assessed by the Morris water maze test and passive avoidance test. Our results showed that the transplantation of PD-MSCs into A $\beta$ 1-42-infused mice significantly improved cognitive impairment, and behavioral changes attenuated the expression of APP, BACE1, and A $\beta$ , as well as the activity of  $\beta$ -secretase and  $\gamma$ -secretase. In addition, the activation of glia cells and the expression of inducible nitric oxide synthase (iNOS) and

cyclooxygenase-2 (COX-2) were inhibited by the transplantation of PD-MSCs. Furthermore, we also found that PD-MSCs downregulated the release of inflammatory cytokines as well as prevented neuronal cell death and promoted neuronal cell differentiation from neuronal progenitor cells in A $\beta$ 1-42-infused mice. These data indicate that PD-MSC mediates neuroprotection by regulating neuronal death, neurogenesis, glia cell activation in hippocampus, and altering cytokine expression, suggesting a close link between the therapeutic effects of MSCs and the damaged CNS in Alzheimer's disease.

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## **Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an A $\beta$ PP/PS1 transgenic mouse model**

*Hui et al.. (2013). Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an A $\beta$ PP/PS1 transgenic mouse model. Stem Cell Research & Therapy, 4(76).*

<https://doi.org/10.1186/scrt227>

### **ABSTRACT**

#### **Introduction**

Cell therapy is a potential therapeutic approach for neurodegenerative disorders, such as Alzheimer disease

(AD). Neuronal differentiation of stem cells before transplantation is a promising procedure for cell therapy. However, the therapeutic impact and mechanisms of action of neuron-like cells differentiated from human umbilical cord mesenchymal stem cells in AD have not been determined.

## Methods

In this study, we used tricyclodecan-9-yl-xanthogenate (D609) to induce human mesenchymal stem cells isolated from Wharton jelly of the umbilical cord (HUMSCs) to differentiate into neuron-like cells (HUMSC-NCs), and transplanted the HUMSC-NCs into an A $\beta$ PP/PS1 transgenic AD mouse model. The effects of HUMSC-NC transplantation on the cognitive function, synapsin I level, amyloid  $\beta$ -peptides (A $\beta$ ) deposition, and microglial function of the mice were investigated.

## Results

We found that transplantation of HUMSC-NCs into A $\beta$ PP/PS1 mice improved the cognitive function, increased synapsin I level, and significantly reduced A $\beta$  deposition in the mice. The beneficial effects were associated with “alternatively activated” microglia (M2-like microglia). In the mice transplanted with HUMSC-NCs, M2-like microglial activation was significantly increased, and the expression of antiinflammatory cytokine associated with M2-like microglia, interleukin-4 (IL-4), was also increased, whereas the expression of proinflammatory cytokines associated with classic microglia (M1-like microglia), including interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), was significantly reduced. Moreover, the expression of A $\beta$ -

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degrading factors, insulin-degrading enzyme (IDE) and neprilysin (NEP), was increased substantially in the mice treated with HUMSC-NCs.

### Conclusions

HUMSC-NC transplantation decreased A $\beta$  deposition and improved memory in A $\beta$ PP/PS1 mice by a mechanism associated with activating M2-like microglia and modulating neuroinflammation. Transplantation of neuron-like cells differentiated from mesenchymal stem cells might be a promising cell therapy for Alzheimer disease.

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## **Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model.**

*Kim et al.. (2013). Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model.*

*Neurobiol Aging, 34(10), 2408-20.*

<https://www.ncbi.nlm.nih.gov/pubmed/23623603?dopt=Abstract>

### **ABSTRACT**

Amyloid beta (A $\beta$ ) plays a major role in Alzheimer's disease (AD), and neuroinflammatory processes mediated by A $\beta$  plaque-induced microglial cells and astrocytes contribute to AD pathogenesis. The present study examined human

placenta amniotic membrane-derived mesenchymal stem cells (AMSCs), which have potent immunomodulatory and paracrine effects in a Tg2576 (APPswe) transgenic mouse model of AD. AMSCs secreted high levels of transforming growth factor- $\beta$  under in vitro inflammatory environment conditions. Six weeks after the intravenous injection of AMSCs, APPswe mice showed evidence of improved spatial learning, which significantly correlated with the observation of fewer A $\beta$  plaques in brain. The number of ED1-positive phagocytic microglial cells associated with A $\beta$  plaques was higher in AMSC-injected mice than in phosphate-buffered saline-injected mice, and the level of A $\beta$ -degrading enzymes (matrix metallopeptidase-9 and insulin-degrading enzyme) was also significantly higher. Furthermore, the level of proinflammatory cytokines, interleukin-1 and tumor necrosis factor- $\alpha$ , was lower and that of anti-inflammatory cytokines, interleukin-10 and transforming growth factor- $\beta$ , was higher in AMSC-injected mice than phosphate-buffered saline-injected mice. These effects lasted until 12 weeks after AMSC injection. Taken together, these results collectively suggest that injection of AMSCs might show significant long-lasting improvement in AD pathology and memory function via immunomodulatory and paracrine mechanisms.

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## **Stem Cell Therapy for Alzheimer's Disease**

Ager, R. R. and LaFerla, F. M. (2015). *Stem Cell Therapy for Alzheimer's Disease. Reviews in Cell Biology and Molecular*

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*Medicine.* 1:1–27.

<http://onlinelibrary.wiley.com/doi/10.1002/3527600906.mcb.201500009/abstract>

### ABSTRACT

The escalating prevalence of Alzheimer's disease (AD) is on course to exact an immense medical, social, and economic impact on the United States, and most of the western world. Current therapies are palliative, providing only marginal symptomatic relief in some patients, and there is an urgent need to develop more effective interventions, particularly those that exert disease-modifying effects. Several emerging treatment strategies designed to inhibit disease progression by directly targeting the production and degradation of the amyloid-beta peptide have been tested in clinical trials. Unfortunately, many of these new strategies have failed to significantly ameliorate cognitive deficits, and some have actually exacerbated cognitive decline. The emerging field of stem cell biology offers tremendous therapeutic potential for chronic neurological conditions such as AD, particularly if combined with a multitargeted therapeutic approach. The current advances on stem cells therapies in AD animal models are summarized in this chapter, and potential roadblocks for transitioning this novel treatment into AD patients are discussed.

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# Alzheimer's Disease and Stem Cell Therapy

*Choi et al.. (2014). Alzheimer's Disease and Stem Cell Therapy. Experimental Neurobiology, 23(1), 45-52.*

<https://doi.org/10.5607/en.2014.23.1.45>

## ABSTRACT

The loss of neuronal cells in the central nervous system may occur in many neurodegenerative diseases. Alzheimer's disease is a common senile disease in people over 65 years, and it causes impairment characterized by the decline of mental function, including memory loss and cognitive impairment, and affects the quality of life of patients. However, the current therapeutic strategies against AD are only to relieve symptoms, but not to cure it. Because there are only a few therapeutic strategies against Alzheimer's disease, we need to understand the pathogenesis of this disease. Cell therapy may be a powerful tool for the treatment of Alzheimer's disease. This review will discuss the characteristics of Alzheimer's disease and various available therapeutic strategies.

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# **Stem cell therapy for Alzheimer's disease and related disorders: current status and future perspectives**

*Tong, L.M, Fong, H & Huang, Y. (2015). Stem cell therapy for Alzheimer's disease and related disorders: current status and future perspectives. Experimental & Molecular Medicine, 47(E151). <https://www.nature.com/articles/emm2014124>*

## **ABSTRACT**

Underlying cognitive declines in Alzheimer's disease (AD) are the result of neuron and neuronal process losses due to a wide range of factors. To date, all efforts to develop therapies that target specific AD-related pathways have failed in late-stage human trials. As a result, an emerging consensus in the field is that treatment of AD patients with currently available drug candidates might come too late, likely as a result of significant neuronal loss in the brain. In this regard, cell-replacement therapies, such as human embryonic stem cell- or induced pluripotent stem cell-derived neural cells, hold potential for treating AD patients. With the advent of stem cell technologies and the ability to transform these cells into different types of central nervous system neurons and glial cells, some success in stem cell therapy has been reported in animal models of AD. However, many more steps remain before stem cell therapies will be clinically feasible for AD and related disorders in humans. In this review, we will discuss current research advances in AD

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pathogenesis and stem cell technologies; additionally, the potential challenges and strategies for using cell-based therapies for AD and related disorders will be discussed.

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# STEM CELLS: LYME DISEASE

## Treatment of Lyme Disease with Human Embryonic Stem Cells: A Case Series

Shroff, G. (2015). *Treatment of Lyme Disease with Human Embryonic Stem Cells: A Case Series*. *Journal of Neuroinfectious Diseases*, 6(1).

<https://pdfs.semanticscholar.org/5ff4/ba0610a5a1d07bc9a18d02a7f94fc2e7b0da.pdf>

### ABSTRACT

#### Background:

Lyme Disease (LD) is a tick-borne disease caused by *Borrelia burgdorferi* (Bb) and transmitted in humans by *Ixodes scapularis*. LD can affect any organ of the body. The present study evaluated the efficacy and safety of human embryonic stem cell (hESC) therapy for the treatment of LD.

#### Methods:

Patients included in the present study had experienced symptoms of LD to varying degree of severities and intensities. The study consisted of treatment phases separated by gap phases in between.

#### Results:

Improvement in symptoms was observed after receiving hESC therapy. hESC therapy showed considerable improvement in the condition of the patients who were unable to walk straight or maintain balance while sitting and standing. These patients had regained their balance and had started to perform their regular activities with less effort after receiving hESC therapy. In addition, patients showed improvement in blurred vision, tremors, had higher energy levels, improved stamina, appetite, decreased numbness in the upper limb, decreased stiffness, regained balance, and had no slurring of speech after receiving hESC therapy.

**Conclusion:**

In conclusion, hESC therapy has shown significant improvement in patients with LD. No adverse events were observed in the patients.

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## **Single-photon emission tomography imaging in patients with Lyme disease treated with human embryonic stem cells.**

Shroff, G. (2018). *Single-photon emission tomography imaging in patients with Lyme disease treated with human embryonic stem cells*. Neuroradiol J.

<http://dx.doi.org/10.1177/1971400917742470>

## ABSTRACT

### Aim

The purpose of this study was to evaluate the longitudinal changes in brain perfusion in patients with Lyme disease treated with human embryonic stem cells. Material and methods The study included 59 (age range  $41.68 \pm 16.37$  years) patients with Lyme disease whose single-photon emission tomography imaging was performed before and after the human embryonic stem cell therapy. Technetium-hexa methyl propylene aminoxime single-photon emission tomography imaging was used to assess the hypoperfused lesions/regions in the brain prior to the therapy, as well as the improvement in perfusion after human embryonic stem cell treatment.

**Results** After receiving human embryonic stem cell therapy, single-photon emission tomography imaging reflects a significant ( $>60\%$ ) improvement in 43 patients along with moderate (30-60%) and mild ( $<30\%$ ) improvement in 12 and four patients, respectively. The cerebral perfusion flow improved and the degree of hypoperfusion in the other regions significantly decreased after the human embryonic stem cell therapy. Interpretation of single-photon emission tomography imaging of brain images (before and after therapy) clearly presented the changes in color at various brain regions which represent the improvements in patients.

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**Conclusion** Single-photon emission tomography imaging could be used as a potential diagnostic tool to assess the response of Lyme disease patients to human embryonic stemcell therapy.

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# **STEM CELLS: MULTIPLE SCLEROSIS**

## **The potential of mesenchymal stromal cells as a novel cellular therapy for multiple sclerosis**

*Auletta et al.. (2012). The potential of mesenchymal stromal cells as a novel cellular therapy for multiple sclerosis. Immunotherapy, 4(5), 529–547.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3381871/>

### **ABSTRACT**

Multiple sclerosis (MS) is an inflammatory neurodegenerative disease of the CNS for which only partially effective therapies exist. Intense research defining the underlying immune pathophysiology is advancing both the understanding of MS as well as revealing potential targets for disease intervention. Mesenchymal stromal cell (MSC) therapy has the potential to modulate aberrant immune responses causing demyelination and axonal injury associated with MS, as well as to repair and restore damaged CNS tissue and cells. This article reviews the pathophysiology underlying MS, as well as providing a cutting-edge perspective into the field of MSC therapy based upon the experience of authors intrinsically involved in MS

## **Human Bone Marrow-derived Mesenchymal Stem Cells Induce Th2-Polarized Immune Response and Promote Endogenous Repair in Animal Models of Multiple Sclerosis**

*Bai et al.. (2009). Human Bone Marrow-derived Mesenchymal Stem Cells Induce Th2-Polarized Immune Response and Promote Endogenous Repair in Animal Models of Multiple Sclerosis. Glia, 57(11), 1192–1203.*  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706928/>

### **ABSTRACT**

Cell based therapies are attractive approaches to promote myelin repair. Recent studies demonstrated a reduction in disease burden in mice with EAE treated with mouse mesenchymal stem cells (MSCs). Here we demonstrated human bone marrow derived MSCs (BM-hMSCs) promote functional recovery in both chronic and relapsing-remitting models of mouse EAE, traced their migration into the injured CNS and assayed their ability to modulate disease progression and the host immune response. Injected BM-hMSCs accumulated in the CNS, reduced the extent of damage and increased oligodendrocyte lineage cells in

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lesion areas. The increase in oligodendrocytes in lesions may reflect BM-hMSC induced changes in neural fate determination since neurospheres from treated animals gave rise to more oligodendrocytes and less astrocytes than non-treated neurospheres. Host immune responses were also influenced by BM-hMSCs. Inflammatory T-cells including interferon gamma (IFN- $\gamma$ ) producing Th1 cells and IL-17 producing Th17 inflammatory cells and their associated cytokines were reduced along with concomitant increases in IL-4 producing Th2 cells and anti-inflammatory cytokines. Together these data suggest the BM-hMSCs represent a viable option for therapeutic approaches.

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# **Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis**

*Karussis et al.. (2010). Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis. Arch Neurol, 67(10), 1187–1194.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036569/>

### **ABSTRACT**

#### **Objective**

## Compendium of Research: STEM CELLS

To evaluate the feasibility, safety, and immunological effects of intrathecal and intravenous administration of autologous mesenchymal stem cells (MSCs) (also called mesenchymal stromal cells) in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).

### **Design**

A phase 1/2 open-safety clinical trial.

### **Patients**

Fifteen patients with MS (mean [SD] Expanded Disability Status Scale [EDSS] score, 6.7 [1.0]) and 19 with ALS (mean [SD] Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS] score, 20.8 [8.0]) were enrolled.

### **Intervention**

After culture, a mean (SD) of  $63.2 \times 10^6$  ( $2.5 \times 10^6$ ) MSCs was injected intrathecally (n=34) and intravenously (n=14). In 9 cases, MSCs were magnetically labeled with the superparamagnetic iron oxide ferumoxides (Feridex).

### **Main Outcome Measures**

The main outcome measure was the recording of side effects. Follow-up ( $\leq 25$  months) included adverse events evaluation, neurological disability assessment by means of the EDSS, magnetic resonance imaging to exclude unexpected pathologies and track the labeled stem cells,

and immunological tests to assess the short-term immunomodulatory effects of MSC transplantation.

## Results

Twenty-one patients had injection-related adverse effects consisting of transient fever, and 15 reported headache. No major adverse effects were reported during follow-up. The mean ALSFRS score remained stable during the first 6 months of observation, whereas the mean (SD) EDSS score improved from 6.7 (1.0) to 5.9 (1.6). Magnetic resonance imaging visualized the MSCs in the occipital horns of the ventricles, indicating the possible migration of ferumoxides-labeled cells in the meninges, subarachnoid space, and spinal cord. Immunological analysis revealed an increase in the proportion of CD4+ CD25+ regulatory T cells, a decrease in the proliferative responses of lymphocytes, and the expression of CD40+, CD83+, CD86+, and HLA-DR on myeloid dendritic cells at 24 hours after MSC transplantation.

## Conclusion

Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects.

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# **The mesenchymal stem cells in multiple sclerosis (MSCIMS) trial protocol and baseline cohort characteristics: an open-label pre-test: post-test study with blinded outcome assessments**

*Connick et al.. (2011). The mesenchymal stem cells in multiple sclerosis (MSCIMS) trial protocol and baseline cohort characteristics: an open-label pre-test: post-test study with blinded outcome assessments. Trials, 12(62).*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059276/>

## **ABSTRACT**

### **Background**

No treatments are currently available that slow, stop, or reverse disease progression in established multiple sclerosis (MS). The Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS) trial tests the safety and feasibility of treatment with a candidate cell-based therapy, and will inform the wider challenge of designing early phase clinical trials to evaluate putative neuroprotective therapies in progressive MS.

Illustrated by the MSCIMS trial protocol, we describe a novel methodology based on detailed assessment of the anterior visual pathway as a model of wider disease processes - the "sentinel lesion approach".

### **Methods/design**

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MSCIMS is a phase IIA study of autologous mesenchymal stem cells (MSCs) in secondary progressive MS. A pre-test : post-test design is used with healthy controls providing normative data for inter-session variability. Complementary eligibility criteria and outcomes are used to select participants with disease affecting the anterior visual pathway.

### **Results**

Ten participants with MS and eight healthy controls were recruited between October 2008 and March 2009.

Mesenchymal stem cells were successfully isolated, expanded and characterised in vitro for all participants in the treatment arm.

### **Conclusions**

In addition to determining the safety and feasibility of the intervention and informing design of future studies to address efficacy, MSCIMS adopts a novel strategy for testing neuroprotective agents in MS - the sentinel lesion approach - serving as proof of principle for its future wider applicability.

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# **Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study**

*Connick et al.. (2012). Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol, 11(2), 150–156.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3279697/>

## **ABSTRACT**

### **Background**

More than half of patients with multiple sclerosis have progressive disease characterised by accumulating disability. The absence of treatments for progressive multiple sclerosis represents a major unmet clinical need. On the basis of evidence that mesenchymal stem cells have a beneficial effect in acute and chronic animal models of multiple sclerosis, we aimed to assess the safety and efficacy of these cells as a potential neuroprotective treatment for secondary progressive multiple sclerosis.

### **Methods**

Patients with secondary progressive multiple sclerosis involving the visual pathways (expanded disability status score 5·5–6·5) were recruited from the East Anglia and north

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London regions of the UK. Participants received intravenous infusion of autologous bone-marrow-derived mesenchymal stem cells in this open-label study. Our primary objective was to assess feasibility and safety; we compared adverse events from up to 20 months before treatment until up to 10 months after the infusion. As a secondary objective, we chose efficacy outcomes to assess the anterior visual pathway as a model of wider disease. Masked endpoint analyses was used for electrophysiological and selected imaging outcomes. We used piecewise linear mixed models to assess the change in gradients over time at the point of intervention. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number [NCT00395200](https://clinicaltrials.gov/ct2/show/NCT00395200).

### Findings

We isolated, expanded, characterised, and administered mesenchymal stem cells in ten patients. The mean dose was  $1\cdot6 \times 10^6$  cells per kg bodyweight (range  $1\cdot1\text{--}2\cdot0$ ). One patient developed a transient rash shortly after treatment; two patients had self-limiting bacterial infections 3–4 weeks after treatment. We did not identify any serious adverse events. We noted improvement after treatment in visual acuity (difference in monthly rates of change  $-0\cdot02$  logMAR units, 95% CI  $-0\cdot03$  to  $-0\cdot01$ ;  $p=0\cdot003$ ) and visual evoked response latency ( $-1\cdot33$  ms,  $-2\cdot44$  to  $-0\cdot21$ ;  $p=0\cdot020$ ), with

an increase in optic nerve area (difference in monthly rates of change  $0.13 \text{ mm}^2$ ,  $0.04$  to  $0.22$ ;  $p=0.006$ ). We did not identify any significant effects on colour vision, visual fields, macular volume, retinal nerve fibre layer thickness, or optic nerve magnetisation transfer ratio.

### **Interpretation**

Autologous mesenchymal stem cells were safely given to patients with secondary progressive multiple sclerosis in our study. The evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection.

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# **STEM CELLS: AMYOTROPHIC LATERAL SCLEROSIS (ALS)**

## **Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis**

*Karussis et al.. (2010). Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis. Arch Neurol, 67(10), 1187–1194.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036569/>

### **ABSTRACT**

#### **Objective**

To evaluate the feasibility, safety, and immunological effects of intrathecal and intravenous administration of autologous mesenchymal stem cells (MSCs) (also called mesenchymal stromal cells) in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).

## **Design**

A phase 1/2 open-safety clinical trial.

## **Patients**

Fifteen patients with MS (mean [SD] Expanded Disability Status Scale [EDSS] score, 6.7 [1.0]) and 19 with ALS (mean [SD] Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS] score, 20.8 [8.0]) were enrolled.

## **Intervention**

After culture, a mean (SD) of  $63.2 \times 10^6$  ( $2.5 \times 10^6$ ) MSCs was injected intrathecally (n=34) and intravenously (n=14). In 9 cases, MSCs were magnetically labeled with the superparamagnetic iron oxide ferumoxides (Feridex).

## **Main Outcome Measures**

The main outcome measure was the recording of side effects. Follow-up ( $\leq 25$  months) included adverse events evaluation, neurological disability assessment by means of the EDSS, magnetic resonance imaging to exclude unexpected pathologies and track the labeled stem cells, and immunological tests to assess the short-term immunomodulatory effects of MSC transplantation.

## **Results**

Twenty-one patients had injection-related adverse effects consisting of transient fever, and 15 reported headache. No

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major adverse effects were reported during follow-up. The mean ALSFRS score remained stable during the first 6 months of observation, whereas the mean (SD) EDSS score improved from 6.7 (1.0) to 5.9 (1.6). Magnetic resonance imaging visualized the MSCs in the occipital horns of the ventricles, indicating the possible migration of ferumoxides-labeled cells in the meninges, subarachnoid space, and spinal cord. Immunological analysis revealed an increase in the proportion of CD4+ CD25+ regulatory T cells, a decrease in the proliferative responses of lymphocytes, and the expression of CD40+, CD83+, CD86+, and HLA-DR on myeloid dendritic cells at 24 hours after MSC transplantation.

### **Conclusion**

Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects.

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# STEM CELLS: AUTISM

## Stem Cell Therapy for Autism

*Ichim et al.. (2007). Stem Cell Therapy for Autism. J Transl Med, 5(30).*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1914111/>

### ABSTRACT

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions whose incidence is reaching epidemic proportions, afflicting approximately 1 in 166 children. Autistic disorder, or autism is the most common form of ASD. Although several neurophysiological alterations have been associated with autism, immune abnormalities and neural hypoperfusion appear to be broadly consistent. These appear to be causative since correlation of altered inflammatory responses, and hypoperfusion with symptomology is reported. Mesenchymal stem cells (MSC) are in late phases of clinical development for treatment of graft versus host disease and Crohn's Disease, two conditions of immune dysregulation. Cord blood CD34+ cells are known to be potent angiogenic stimulators, having demonstrated positive effects in not only peripheral ischemia, but also in models of cerebral ischemia. Additionally, anecdotal clinical cases have reported responses in autistic children receiving cord blood CD34+ cells. We propose the combined use of MSC and cord blood CD34+cells may be useful in the treatment of

autism.

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## **Autism Spectrum Disorders: Is Mesenchymal Stem Cell Personalized Therapy the Future?**

*Siniscalco et al.. (2012). Autism Spectrum Disorders: Is Mesenchymal Stem Cell Personalized Therapy the Future?. J Biomed Biotechnol, 2012(480289.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3303614/>

### **ABSTRACT**

Autism and autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental disorders. They are enigmatic conditions that have their origins in the interaction of genes and environmental factors. ASDs are characterized by dysfunctions in social interaction and communication skills, in addition to repetitive and stereotypic verbal and nonverbal behaviours. Immune dysfunction has been confirmed with autistic children. There are no defined mechanisms of pathogenesis or curative therapy presently available. Indeed, ASDs are still untreatable. Available treatments for autism can be divided into behavioural, nutritional, and medical approaches, although no defined standard approach exists. Nowadays, stem cell therapy represents the great promise for the future of molecular medicine. Among the stem cell population, mesenchymal stem cells (MSCs) show probably best potential good results

in medical research. Due to the particular immune and neural dysregulation observed in ASDs, mesenchymal stem cell transplantation could offer a unique tool to provide better resolution for this disease.

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## **Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism**

*Lv et al.. (2013). Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med, 11(196).*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765833/>

### **ABSTRACT**

#### **Background**

Autism is a pervasive neurodevelopmental disorder. At present there are no defined mechanisms of pathogenesis and therapy is mostly limited to behavioral interventions. Stem cell transplantation may offer a unique treatment strategy for autism due to immune and neural dysregulation observed in this disease. This non-randomized, open-label, single center phase I/II trial investigated the safety and efficacy of combined transplantation of human cord blood mononuclear cells (CBMNCs) and umbilical cord-derived mesenchymal stem cells (UCMSCs) in treating children with autism.

## **Methods**

37 subjects diagnosed with autism were enrolled into this study and divided into three groups: CBMNC group (14 subjects, received CBMNC transplantation and rehabilitation therapy), Combination group (9 subjects, received both CBMNC and UCMSC transplantation and rehabilitation therapy), and Control group (14 subjects, received only rehabilitation therapy). Transplantations included four stem cell infusions through intravenous and intrathecal injections once a week. Treatment safety was evaluated with laboratory examinations and clinical assessment of adverse effects. The Childhood Autism Rating Scale (CARS), Clinical Global Impression (CGI) scale and Aberrant Behavior Checklist (ABC) were adopted to assess the therapeutic efficacy at baseline (pre-treatment) and following treatment.

## **Results**

There were no significant safety issues related to the treatment and no observed severe adverse effects. Statistically significant differences were shown on CARS, ABC scores and CGI evaluation in the two treatment groups compared to the control at 24 weeks post-treatment ( $p < 0.05$ ).

## **Conclusions**

Transplantation of CBMNCs demonstrated efficacy compared to the control group; however, the combination of CBMNCs and UCMSCs showed larger therapeutic effects than the CBMNC transplantation alone. There were no safety issues noted during infusion and the whole monitoring period.

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# STEM CELLS: SICKLE CELL DISEASE

**Autologous bone marrow stromal cells are promising candidates for cell therapy approaches to treat bone degeneration in sickle cell disease.**

*Lebouvier et al.. (2015). Autologous bone marrow stromal cells are promising candidates for cell therapy approaches to treat bone degeneration in sickle cell disease. Stem Cell Res, 15(3), 584-594.*

[https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retrieve&list\\_uids=26492634](https://www.ncbi.nlm.nih.gov/pubmed?db=PubMed&cmd=Retrieve&list_uids=26492634)

## ABSTRACT

Osteonecrosis of the femoral head is a frequent complication in adult patients with sickle cell disease (SCD). To delay hip arthroplasty, core decompression combined with concentrated total bone marrow (BM) treatment is currently performed in the early stages of the osteonecrosis. Cell therapy efficacy depends on the quantity of implanted BM stromal cells. For this reason, expanded bone marrow stromal cells (BMSCs, also known as bone marrow derived mesenchymal stem cells) can be used to improve osteonecrosis treatment in SCD patients. In this study, we quantitatively and qualitatively evaluated the function of

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BMSCs isolated from a large number of SCD patients with osteonecrosis (SCD-ON) compared with control groups (patients with osteonecrosis not related to SCD (ON) and normal donors (N)). BM total nuclear cells and colony-forming efficiency values (CFE) were significantly higher in SCD-ON patients than in age and sex-matched controls. The BMSCs from SCD-ON patients were similar to BMSCs from the control groups in terms of their phenotypic and functional properties. SCD-ON patients have a higher frequency of BMSCs that retain their bone regeneration potential. Our findings suggest that BMSCs isolated from SCD-ON patients can be used clinically in cell therapy approaches. This work provides important preclinical data that is necessary for the clinical application of expanded BMSCs in advanced therapies and medical products.

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# STEM CELLS: ERECTILE DYSFUNCTION

## Stem cell treatment of erectile dysfunction

Alwaal et al.. (2015). *Stem cell treatment of erectile dysfunction. Advanced Drug Delivery Reviews*, 82-82, 137-144. <https://doi.org/10.1016/j.addr.2014.11.012>

### ABSTRACT

Erectile Dysfunction (ED) is a common disease that typically affects older men. While oral type-5 phosphodiesterase inhibitors (PDE5Is) represent a successful first-line therapy, many patients do not respond to this treatment leading researchers to look for alternative treatment modalities. Stem cell (SC) therapy is a promising new frontier for the treatment of those patients and many studies demonstrated its therapeutic effects. In this article, using a Medline database search of all relevant articles, we present a summary of the scientific principles behind SCs and their use for treatment of ED. We discuss specifically the different types of SCs used in ED, the methods of delivery tested, and the methods attempted to enhance SC therapy effect. In addition, we review the current preclinical literature on SC therapy for ED and present a summary of its findings in addition to the single clinical trial published.

# **STEM CELLS: REHABILITATION AND RECOVERY POST STEM CELL TREATMENT**

## **Neural Stem Cell Therapy and Rehabilitation in the Central Nervous System: Emerging Partnerships**

*Ross et al.. (2016). Neural Stem Cell Therapy and Rehabilitation in the Central Nervous System: Emerging Partnerships. Physical Therapy, 96(5), 734–742.*

<https://doi.org/10.2522/ptj.20150063>

### **ABSTRACT**

The goal of regenerative medicine is to restore function through therapy at levels such as the gene, cell, tissue, or organ. For many disorders, however, regenerative medicine approaches in isolation may not be optimally effective. Rehabilitation is a promising adjunct therapy given the beneficial impact that physical activity and other training modalities can offer. Accordingly, “regenerative rehabilitation” is an emerging concentration of study, with the specific goal of improving positive functional outcomes by enhancing tissue restoration following injury. This article

focuses on one emerging example of regenerative rehabilitation—namely, the integration of clinically based protocols with stem cell technologies following central nervous system injury. For the purposes of this review, the state of stem cell technologies for the central nervous system is summarized, and a rationale for a synergistic benefit of carefully orchestrated rehabilitation protocols in conjunction with cellular therapies is provided. An overview of practical steps to increase the involvement of physical therapy in regenerative rehabilitation research also is provided.

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## **The Synergistic Effect of Treadmill Running on Stem-Cell Transplantation to Heal Injured Skeletal Muscle**

*Ambrosio et al.. (2010). The Synergistic Effect of Treadmill Running on Stem-Cell Transplantation to Heal Injured Skeletal Muscle. Tissue Engineering Part A, 16(3), 839-849.*  
<https://doi.org/10.1089/ten.tea.2009.0113>

### **ABSTRACT**

Muscle-derived stem-cell (MDSC) transplantation presents a promising method for the treatment of muscle injuries. This study investigated the ability of exercise to enhance MDSC transplantation into the injured muscle. Mice were divided

into four groups: contusion + phosphate-buffered saline (C + PBS; n = 14 muscles), C + MDSC transplantation (n = 12 muscles), C + PBS + treadmill running (C + PBS + TM; n = 17 muscles), and C + MDSC + TM (n = 13 muscles). One day after injury, the TM groups began running for 1 or 5 weeks. Two days after injury, muscles of C + MDSC and C + MDSC + TM groups were injected with MDSCs. One or 5 weeks later, the number and differentiation of transplanted MDSCs, myofiber regeneration, collagen I formation, and vascularity were assessed histologically. In vitro, MDSCs were subjected to mechanical stimulation, and growth kinetics were quantified. In vitro, mechanical stimulation decreased the MDSC population doubling time ( $18.6 \pm 1.6$  h) and cell division time ( $10.9 \pm 0.7$  h), compared with the controls (population doubling time:  $23.0 \pm 3.4$  h; cell division time:  $13.3 \pm 1.1$  h) ( $p = 0.01$  and  $0.03$ , respectively). In vivo, 5 weeks of TM increased the myogenic contribution of transplanted MDSCs, compared with the controls ( $p = 0.02$ ). C + MDSC, C + PBS + TM, and C + MDSC + TM demonstrated decreased fibrosis at 5 weeks, compared with the C + PBS controls ( $p = 0.00$ ,  $p = 0.03$ , and  $p = 0.02$ , respectively). Results suggest that the mechanical stimulation favors MDSC proliferation, both in vitro and in vivo, and that exercise enhances MDSC transplantation after injury.

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# **Neuromuscular Electrical Stimulation as a Method to Maximize the Beneficial Effects of Muscle Stem Cells Transplanted into Dystrophic Skeletal Muscle**

*Distefano et al.. (2013). Neuromuscular Electrical Stimulation as a Method to Maximize the Beneficial Effects of Muscle Stem Cells Transplanted into Dystrophic Skeletal Muscle. PLoS ONE, 8(3), e54922.*

<https://doi.org/10.1371/journal.pone.0054922>

## **ABSTRACT**

Cellular therapy is a potential approach to improve the regenerative capacity of damaged or diseased skeletal muscle. However, its clinical use has often been limited by impaired donor cell survival, proliferation and differentiation following transplantation. Additionally, functional improvements after transplantation are all-too-often negligible. Because the host microenvironment plays an important role in the fate of transplanted cells, methods to modulate the microenvironment and guide donor cell behavior are warranted. The purpose of this study was to investigate whether the use of neuromuscular electrical stimulation (NMES) for 1 or 4 weeks following muscle-derived stem cell (MDSC) transplantation into dystrophic skeletal muscle can modulate the fate of donor cells and enhance their contribution to muscle regeneration and

functional improvements. Animals submitted to 4 weeks of NMES after transplantation demonstrated a 2-fold increase in the number of dystrophin+ myofibers as compared to control transplanted muscles. These findings were concomitant with an increased vascularity in the MDSC+NMES group when compared to non-stimulated counterparts. Additionally, animals subjected to NMES (with or without MDSC transplantation) presented an increased maximal specific tetanic force when compared to controls. Although cell transplantation and/or the use of NMES resulted in no changes in fatigue resistance, the combination of both MDSC transplantation and NMES resulted in a faster recovery from fatigue, when compared to non-injected and non-stimulated counterparts. We conclude that NMES is a viable method to improve MDSC engraftment, enhance dystrophic muscle strength, and, in combination with MDSC transplantation, improve recovery from fatigue. These findings suggest that NMES may be a clinically-relevant adjunct approach for cell transplantation into skeletal muscle.

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## **Regenerative rehabilitation: a call to action**

*Ambrosio , F & Russell , R. (2010). Regenerative rehabilitation: a call to action. Journal of Rehabilitation Research & Development, 47(3), xi+.*

<http://go.galegroup.com/ps/anonymous?id=GALE%7CA2418>

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[61756&sid=googleScholar&v=2.1&it=r&linkaccess=fulltext&issn=07487711&p=AONE&sw=w&authCount=1&isAnonymousEntry=true](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC61756/)

### ABSTRACT

We have battled against disease since the beginning of time. As science and technology have evolved, so have the weapons in our antidisease arsenal improved. Indeed, in the last 50 years, the sheer volume of knowledge about human biology has doubled every 8 years. This means that the foundation on which the design and delivery of healthcare is built is 1,000 times stronger at the end of our lives than at the beginning. In the next century, we will add therapies that can restore lost function to ailing tissues and organs to the arsenal of health-aging technologies. This "regenerative medicine" will eventually open the door to battling crippling diseases like diabetes, Parkinson, and heart failure, as well as the impacts of traumatic injury. Success in the laboratory, where all such endeavors must begin, will drive the commercial activities toward products that subsequently become available to patients. Regenerative medicine is a multidisciplinary field incorporating expertise from engineers, biologists, and chemists, to name a few. The goal of regenerative medicine is to restore tissue and organ function lost as a result of aging, injury, or disease. It uses a variety of tools to divert the default pathways of wound healing in humans, which typically result in a patchwork of scar tissue, toward pathways that recapitulate restoration of original tissue/organ architecture and function. Regenerative medicine scientists seek to harness tissue and organ regeneration that was once only possible as a fetus or

newborn. We believe that rehabilitation science and technology will be critical in the success of any regenerative therapy and therefore the two fields must pay increasingly more attention to each other. We suggest herein a variety of mechanisms for the rehabilitation community to be the enablers of regenerative therapies. Because regenerative therapies are outcome-driven rather than technology-specific, the community needs to engage in this interdisciplinary cross-fertilization with an understanding of the different tools that can be used to restore lost organ and tissue function. Our ability to restore damaged tissues and organs today relies on three large categories of interventional approaches: (1) medical devices/artificial organs, in which tissue function is replaced with entirely synthetic constructs and machines; (2) tissue engineering and biomaterials, in which temporary scaffolds are used to bridge large tissue-gap defects; and (3) cellular therapies, including the transplantation of stem cells and genetically manipulated cells for the repair of damaged or diseased tissue. The Figure illustrates the concept of vertical integration of rehabilitation and regeneration. Traditionally, regenerative medicine and rehabilitation have existed as serial processes in patient treatment and care plans, despite common end points. In contrast, we propose that the vertical integration of rehabilitation and regeneration, in which the two tracks are "fused" at the onset of therapeutic development, will allow us to achieve functional goals faster and more effectively. Conjoined education in these disciplines must be the vehicle through which each field can learn where the overlaps exist and how to exploit

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opportunities.

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## **The Emerging Relationship Between Regenerative Medicine and Physical Therapeutics**

*Ambrosio et al.. (2010). The Emerging Relationship Between Regenerative Medicine and Physical Therapeutics. Physical Therapy, 90(12), 1807–1814.*  
<https://doi.org/10.2522/ptj.20100030>

### **ABSTRACT**

Dramatic changes in the health care landscape over the next few decades undoubtedly will affect rehabilitation specialists' practice. In the multidisciplinary field of regenerative medicine, cell, tissue, or organ substitutes are used to enhance the healing potential of the body. Given that the restoration of normal functioning of injured or diseased tissues is expected to be the ultimate goal of these therapies, the future of regenerative medicine is, undeniably, tightly intertwined with that of rehabilitation. Rehabilitation specialists not only must be aware of cutting-edge medical advances as they relate to regenerative medicine but also must work closely with basic scientists to guide the development of clinically relevant protocols. The purposes of this article are to provide a current perspective on biological approaches to the management of musculoskeletal disorders and to highlight the needed integration of physical

therapeutics with regenerative medicine.

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## **Physical activity-mediated functional recovery after spinal cord injury: potential roles of neural stem cells**

*Teng et al.. (2006). Physical activity-mediated functional recovery after spinal cord injury: potential roles of neural stem cells. REGENERATIVE MEDICINE, 1(6).*

<https://doi.org/10.2217/17460751.1.6.763>

### **ABSTRACT**

As data elucidating the complexity of spinal cord injury pathophysiology emerge, it is increasingly being recognized that successful repair will probably require a multifaceted approach that combines tactics from various biomedical disciplines, including pharmacology, cell transplantation, gene therapy and material sciences. Recently, new evidence highlighting the benefit of physical activity and rehabilitation interventions during the post-injury phase has provided novel possibilities in realizing effective repair after spinal cord injury. However, before a comprehensive therapeutic strategy that optimally utilizes the benefits of each of these disciplines can be designed, the basic mechanisms by which these various interventions act must be thoroughly explored and important synergistic and antagonistic interactions identified. In examining the mechanisms by which physical

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activity-based functional recovery after spinal cord injury is effected, endogenous neural stem cells, in our opinion, engender a potentially key role. Multipotent neural stem cells possess many faculties that abet recovery, including the ability to assess the local microenvironment and deliver biofactors that promote neuroplasticity and regeneration, as well as the potential to replenish damaged or eradicated cellular elements. Encouragingly, the functional recovery owing to physical activity-based therapies appears relatively robust, even when therapy is initiated in the chronic stage of spinal cord injury. In this article, we review experimental outcomes related to our hypothesis that endogenous neural stem cells mediate the functional recovery noted in spinal cord injury following physical activity-based treatments. Overall, the data advocates the incorporation of increased physical activity as a component of the multidimensional treatment of spinal cord injury and underscores the critical need to employ research-based mechanistic approaches for developing future advances in the rehabilitation of neurological injury and disorders.

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# **STEM CELLS: CONCUSSION & HYPERBARIC OXYGEN THERAPY**

**Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy.**

*Shandley et al.. (2017). Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy. Journal of the Undersea and Hyperbaric Medical Society, 44(3), 257-269.*  
<http://europepmc.org/abstract/med/28779582>

## **ABSTRACT**

Traumatic brain injury (TBI) may cause persistent cognitive dysfunction. A pilot clinical study was performed to determine if hyperbaric oxygen (HBO<sub>2</sub>) treatment improves cognitive performance. It was hypothesized that stem cells, mobilized by HBO<sub>2</sub> treatment, are recruited to repair damaged neuronal tissue. This hypothesis was tested by measuring the relative abundance of stem cells in peripheral blood and cognitive performance during this clinical trial. The subject population consisted of 28 subjects with persistent

cognitive impairment caused by mild to moderate TBI suffered during military deployment to Iraq or Afghanistan. Fluorescence-activated cell sorting (FACS) analysis was performed for stem cell markers in peripheral blood and correlated with variables resulting from standard tests of cognitive performance and post-traumatic stress disorder: ImPACT, BrainCheckers and PCL-M test results. HBO□ treatment correlated with stem cell mobilization as well as increased cognitive performance. Together these results support the hypothesis that stem cell mobilization may be required for cognitive improvement in this population.

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## **Hyperbaric oxygen promotes neural stem cell proliferation by activating vascular endothelial growth factor/extracellular signal-regulated kinase signaling after traumatic brain injury**

*Yang et al.. (2017). Hyperbaric oxygen promotes neural stem cell proliferation by activating vascular endothelial growth factor/extracellular signal-regulated kinase signaling after traumatic brain injury. NeuroReport, 28(18), 1232–1238.*

[https://journals.lww.com/neuroreport/Abstract/2017/12030/Hyperbaric\\_oxygen\\_promotes\\_neural\\_stem\\_cell.8.aspx](https://journals.lww.com/neuroreport/Abstract/2017/12030/Hyperbaric_oxygen_promotes_neural_stem_cell.8.aspx)

## ABSTRACT

Hyperbaric oxygen (HBO) therapy and neural stem cell (NSC) transplantation can improve traumatic brain injury (TBI) clinically. This study aimed to investigate the mechanism of HBO promoting NSC proliferation and neurological recovery after TBI. Twenty-four Sprague–Dawley rats were divided randomly into three groups: a sham group, a TBI group (constructed using Feeney's free-fall method), and an HBO-treated TBI group. Neurological function was evaluated by Neurological Severity Scores on days 1, 3, and 7, and we found that TBI-induced poor neurological function was improved by HBO. On day 7 after TBI, we observed that TBI promoted NSC proliferation, migration to the lesion area, and the levels of vascular endothelial growth factor (VEGF), VEGFR2, Raf-1, MEK1/2, and phospho-extracellular signal-regulated kinase (ERK) 1/2 protein, which were further boosted by HBO, from immunohistochemistry, immunofluorescence, and Western blot experiments. In vitro, cell injury was applied to NSCs isolated from neonatal Sprague–Dawley rats by the Cell Injury Controller II system. Moreover, data from the BrdU Kit and Western blot showed that in-vitro HBO significantly accelerated NSC proliferation and the levels of proteins related to cell cycle and the VEGF/ERK pathway after cell injury, which was suppressed by the VEGFR2 inhibitor. Taken together, this study indicated that HBO may promote NSC proliferation by activating VEGF/ERK signaling and play a crucial role in neuroprotection after TBI.

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# **Umbilical cord-derived mesenchymal stem cell transplantation combined with hyperbaric oxygen treatment for repair of traumatic brain injury**

*Zhou et al.. (2016). Umbilical cord-derived mesenchymal stem cell transplantation combined with hyperbaric oxygen treatment for repair of traumatic brain injury. Neural Regen Res, 11(1), 107–113.*

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4774201/>

## **ABSTRACT**

Transplantation of umbilical cord-derived mesenchymal stem cells (UC-MSCs) for repair of traumatic brain injury has been used in the clinic. Hyperbaric oxygen (HBO) treatment has long been widely used as an adjunctive therapy for treating traumatic brain injury. UC-MSC transplantation combined with HBO treatment is expected to yield better therapeutic effects on traumatic brain injury. In this study, we established rat models of severe traumatic brain injury by pressurized fluid (2.5–3.0 atm impact force). The injured rats were then administered UC-MSC transplantation via the tail vein in combination with HBO treatment. Compared with monotherapy, aquaporin 4 expression decreased in the injured rat brain, but growth-associated protein-43 expression, calaxon-like structures, and CM-Dil-positive cell number increased. Following combination therapy, however, rat cognitive and neurological function significantly improved. UC-MSC transplantation combined with HBO therapy for

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repair of traumatic brain injury shows better therapeutic effects than monotherapy and significantly promotes recovery of neurological functions.

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# **STEM CELLS: IMMUNOSUPPRESSIVE (ORGAN TRANSPLANTS)**

## **Immunosuppressive Properties of Mesenchymal Stem Cells: Advances and Applications**

*P de Miguel et al.. (2012). Immunosuppressive Properties of Mesenchymal Stem Cells: Advances and Applications. Current Molecular Medicine, 12(5), 574-591.*  
<https://doi.org/10.2174/156652412800619950>

### **ABSTRACT**

Mesenchymal stem cells (MSCs) have been isolated from a variety of tissues, such as bone marrow, skeletal muscle, dental pulp, bone, umbilical cord and adipose tissue. MSCs are used in regenerative medicine mainly based on their capacity to differentiate into specific cell types and also as bioreactors of soluble factors that will promote tissue regeneration from the damaged tissue cellular progenitors.

In addition to these regenerative properties, MSCs hold an immunoregulatory capacity, and elicit immunosuppressive effects in a number of situations. Not only are they immunoprivileged cells, due to the low expression of class II

Major Histocompatibility Complex (MHC-II) and costimulatory molecules in their cell surface, but they also interfere with different pathways of the immune response by means of direct cell-to-cell interactions and soluble factor secretion. In vitro, MSCs inhibit cell proliferation of T cells, B-cells, natural killer cells (NK) and dendritic cells (DC), producing what is known as division arrest anergy. Moreover, MSCs can stop a variety of immune cell functions: cytokine secretion and cytotoxicity of T and NK cells; B cell maturation and antibody secretion; DC maturation and activation; as well as antigen presentation. It is thought that MSCs need to be activated to exert their immunomodulation skills. In this scenario, an inflammatory environment seems to be necessary to promote their effect and some inflammation-related molecules such as tumor necrosis factor- $\alpha$  and interferon- $\gamma$  might be implicated. It has been observed that MSCs recruit T-regulatory lymphocytes (Tregs) to both lymphoid organs and graft. There is great controversy concerning the mechanisms and molecules involved in the immunosuppressive effect of MSCs. Prostaglandin E2, transforming growth factor- $\beta$ , interleukins- 6 and 10, human leukocyte antigen-G5, matrix metalloproteinases, indoleamine-2,3-dioxygenase and nitric oxide are all candidates under investigation.

In vivo studies have shown many discrepancies regarding the immunomodulatory properties of MSCs. These studies have been designed to test the efficacy of MSC therapy in two different immune settings: the prevention or treatment of allograft rejection episodes, and the ability to suppress abnormal immune response in autoimmune and

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inflammatory diseases. Preclinical studies have been conducted in rodents, rabbits and baboon monkeys among others for bone marrow, skin, heart, and corneal transplantation, graft versus host disease, hepatic and renal failure, lung injury, multiple sclerosis, rheumatoid arthritis, diabetes and lupus diseases. Preliminary results from some of these studies have led to human clinical trials that are currently being carried out. These include treatment of autoimmune diseases such as Crohn's disease, ulcerative colitis, multiple sclerosis and type 1 diabetes mellitus; prevention of allograft rejection and enhancement of the survival of bone marrow and kidney grafts; and treatment of resistant graft versus host disease. We will try to shed light on all these studies, and analyze why the results are so contradictory.

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### **Placenta-Derived Multipotent Cells Exhibit Immunosuppressive Properties That Are Enhanced in the Presence of Interferon- $\gamma$**

*Chang et al.. (2006). Placenta-Derived Multipotent Cells Exhibit Immunosuppressive Properties That Are Enhanced in the Presence of Interferon- $\gamma$ . Stem Cells, 24(0), 2466–2477.*

<http://onlinelibrary.wiley.com/doi/10.1634/stemcells.2006-0071/full>

## ABSTRACT

Several types of nonhematopoietic stem cells, including bone marrow mesenchymal stem cells (BMMSCs) and embryonic stem cells, have been shown to have immunosuppressive properties. We show that human placenta-derived multipotent cells (PDMCs), which are isolated from a source without ethical concern and harbor multilineage differentiation potential, have strong immunosuppressive properties. PDMCs suppress both mitogen-induced and allogeneic lymphocyte proliferation in both CD4 and CD8 populations. The immunosuppression seen with PDMCs was significantly stronger than that with BMMSCs. Both PDMCs and BMMSCs express indoleamine 2,3-dioxygenase, but only PDMCs are positive for intracellular human leukocyte antigen-G (HLA). Mechanistically, suppression of lymphocyte reactivity by PDMCs is not due to cell death but to decreased cell proliferation and increased numbers of regulatory T cells. Addition of neutralizing antibodies to interleukin-10 and transforming growth factor (TGF)- $\beta$  partially restored lymphocyte proliferation. Unlike BMMSCs, PDMCs treated with interferon- $\gamma$  for 3 days only very minimally upregulated HLA-DR. On the contrary, PD-L1, a cell surface marker that plays an inhibitory role in T-cell activation, was upregulated and TGF- $\beta$  expression was seen. The immunosuppressive properties of PDMCs, along with their multilineage differentiation potential, ease of accessibility, and abundant cell numbers, may render these cells as good potential sources for future therapeutic applications.

# Immunomodulatory effects of stem cells.

Wada, N, Gronthos, S & Bartold, P.M. (2013).

*Immunomodulatory effects of stem cells. Periodontol 2000, 63(1), 198-216.*

<https://www.ncbi.nlm.nih.gov/pubmed/23931061>

## ABSTRACT

Adult-derived mesenchymal stem cells have received considerable attention over the past two decades for their potential use in tissue engineering, principally because of their potential to differentiate into multiple stromal-cell lineages. Recently, the immunomodulatory properties of mesenchymal stem cells have attracted interest as a unique property of these cells that may be harnessed for novel therapeutic approaches in immune-mediated diseases.

Mesenchymal stem cells have been shown to inhibit the proliferation of activated T-cells both *in vitro* and *in vivo* but to stimulate T-regulatory cell proliferation. Mesenchymal stem cells are also known to be weakly immunogenic and to exert immunosuppressive effects on B-cells, natural killer cells, dendritic cells and neutrophils through various mechanisms. Furthermore, intravenous administration of allogeneic mesenchymal stem cells has shown a marked suppression of host immune reactions in preclinical animal models of large-organ transplant rejection and in various autoimmune- and inflammatory-based diseases. Some clinical trials utilizing human mesenchymal stem cells have also produced promising outcomes in patients with graft-vs.-

host disease and autoimmune diseases. Mesenchymal stem cells identified from various dental tissues, including periodontal ligament stem cells, also possess multipotent and immunomodulatory properties. Hence, dental mesenchymal stem cells may represent an alternate cell source, not only for tissue regeneration but also as therapies for autoimmune- and inflammatory-mediated diseases. These findings have elicited interest in dental tissue mesenchymal stem cells as alternative cell sources for modulating alloreactivity during tissue regeneration following transplantation into human leukocyte antigen-mismatched donors. To examine this potential in periodontal regeneration, future work will need to assess the capacity of allogeneic periodontal ligament stem cells to regenerate periodontal ligament in animal models of periodontal disease. The present review describes the immunosuppressive effects of mesenchymal stem cells on various types of immune cells, the potential mechanisms through which they exert their mode of action and the preclinical animal studies and human clinical trials that have utilized mesenchymal stem cells, including those populations originating from dental structures.

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## **Mesenchymal Stromal Cells: Facilitators of Successful Transplantation?**

*English, K, French, A & Wood, K.J. (2010). Mesenchymal Stromal Cells: Facilitators of Successful Transplantation?.*

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*Cell Stem Cell*, 7(4), 431-442.

<https://doi.org/10.1016/j.stem.2010.09.009>

### **ABSTRACT**

Mesenchymal stromal/stem cells (MSCs) possess immunomodulatory and reparative properties. Through specific interactions with immune cells that participate in both innate and adaptive responses, MSCs exposed to an inflammatory microenvironment can downregulate many immune effector functions. Clinical trials focusing on MSCs to treat graft-versus-host disease (GvHD) and autoimmune diseases are underway. Current analyses suggest that MSCs will improve cell and solid organ transplantation by ameliorating rejection and possibly eliminating the requirement for prolonged regimens of conventional immunosuppressive drugs. This review examines the in vitro and in vivo evidence for the clinical use of bone marrow derived MSCs.

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# STEM CELLS: GENE AND DRUG DELIVERY

## Mesenchymal stem cells as therapeutics and vehicles for gene and drug delivery

*Porada, C.D & Almeida-porada, G. (2010). Mesenchymal stem cells as therapeutics and vehicles for gene and drug delivery. Advanced Drug Delivery Reviews, 62(12), 1156-1166. <https://doi.org/10.1016/j.addr.2010.08.010>*

### ABSTRACT

Mesenchymal stem cells (MSCs) possess a set of several fairly unique properties which make them ideally suited both for cellular therapies/regenerative medicine, and as vehicles for gene and drug delivery. These include: 1) relative ease of isolation; 2) the ability to differentiate into a wide variety of seemingly functional cell types of both mesenchymal and non-mesenchymal origin; 3) the ability to be extensively expanded in culture without a loss of differentiative capacity; 4) they are not only hypoimmunogenic, but they produce immunosuppression upon transplantation; 5) their pronounced anti-inflammatory properties; and 6) their ability to home to damaged tissues, tumors, and metastases following in vivo administration. In this review, we summarize the latest research in the use of mesenchymal stem cells in regenerative medicine, as immunomodulatory/anti-

inflammatory agents, and as vehicles for transferring both therapeutic genes in genetic disease and genes designed to destroy malignant cells.

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## **Mesenchymal Stem Cells as Therapeutics**

*Parekkadan, B & Milwid, J.M. (2010). Mesenchymal Stem Cells as Therapeutics. Annual Review of Biomedical Engineering, 12, 87-117.*

<https://www.annualreviews.org/doi/abs/10.1146/annurev-bioeng-070909-105309>

### **ABSTRACT**

Mesenchymal stem cells (MSCs) are multipotent cells that are being clinically explored as a new therapeutic for treating a variety of immune-mediated diseases. First heralded as a regenerative therapy for skeletal tissue repair, MSCs have recently been shown to modulate endogenous tissue and immune cells. Preclinical studies of the mechanism of action

suggest that the therapeutic effects afforded by MSC transplantation are short-lived and related to dynamic, paracrine interactions between MSCs and host cells. Therefore, representations of MSCs as drug-loaded particles may allow for pharmacokinetic models to predict the therapeutic activity of MSC transplants as a function of drug delivery mode. By integrating principles of MSC biology, therapy, and engineering, the field is armed to usher in the next generation of stem cell therapeutics.

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## **Wharton's Jelly Mesenchymal Stem Cells as Off-The-Shelf Cellular Therapeutics: A Closer Look into their Regenerative and Immunomodulatory Properties**

*Prasanna, S.J & Jahnvi, V.S. (2011). Wharton's Jelly Mesenchymal Stem Cells as Off-The-Shelf Cellular Therapeutics: A Closer Look into their Regenerative and Immunomodulatory Properties. The Open Tissue Engineering and Regenerative Medicine Journal, 4, 28-38.*  
<https://benthamopen.com/ABSTRACT/TOTERMJ-4-28>

### **ABSTRACT**

Mesenchymal stem/stromal cells (MSCs) are isolated from most post-natal tissues and are broadly reported to have similar immuno-phenotype, mesenchymal lineage-

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differentiation potential and bio-distribution in peri-vascular niches. Thus, several stromal substitutes of bone marrow mesenchymal stem cells (BMMSCs) are being considered for regenerative therapy. Wharton's jelly mesenchymal stem cells (WJMSCs) seem to be the most promising alternative because of easy donor accessibility, high proliferative capacity and greater sample to sample identity. Recent in vitro and in vivo evidences also support the usage of WJMSCs in tissue repair and regeneration. Key to these observations is secretion of trophic and immune regulatory factors, which aid repair, and resolution of injury. In order to extrapolate these results for clinical usage key questions that need to be addressed are: extrapolation of "allogeneic" transplantation ability of BMMSCs to WJMSCs, survival of allogeneic/xenogeneic WJMSCs in transplantation scenario and actual mechanisms of immune-modulation in an "inflammatory" setting. This review focuses on comparing the in vitro and in vivo studies on immune regulatory properties of WJMSCs and BMMSCs and speculates the usage of WJMSCs for immuno-modulation in a disease scenario. Despite commonalities, different tissue-derived MSCs are reported to have unique gene expression signatures. We would evaluate whether WJMSCs have unique inherent properties, owing to their bio-distribution and primitiveness, as compared to BMMSCs. Further, we debate whether these differences remain conserved on in vitro propagation and impact the immune properties of WJMSCs and speculate the pros and cons of using WJMSCs for allogeneic transplantation.

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