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AMNIOTIC FLUID STEM CELLS

MESENCHIMAL STEM CELLS IN HUMAN APPLICATION

A SCIENTIFIC PAPERS REVIEW



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Introduction

This issue represents a collection of the most important articles related on amniotic fluid stem cells, mesenchymal stem cells and clinical trials. The review includes articles published in 2009, 2008, 2007 and 2006. The summary carries title, scientific paper, publication date, authors and promoting organization. The abstract of each article is reported.

In particular, among clinical trials articles we would like to point out the following:

- “Application of stem cells in bone repair.” (n. 65)
- “Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study.” (n.73)
- “Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy.” (n.74)
- “Dental pulp stem cells: a promising tool for bone regeneration.” (n. 78)
- “Biologic characteristics of mesenchymal stromal cells and their clinical applications in pediatric patients.” (n.80)
- “Therapeutic applications of mesenchymal stromal cells.” (n.86)
- “Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study” (n.97)

Among articles regarding amniotic fluid stem cells:

- “Human Amniotic Fluid Mesenchymal Stem Cells in combination with hyperbaric oxygen augment peripheral nerve regeneration” (n.14)
- “Production of hepatocyte-like cells from human amnion” (n.35)
- “Neuronal characteristics of amniotic fluid derived cells after adenoviral transformation” (n.39)
- “Non-invasive longitudinal tracking of human amniotic fluid stem cells in the mouse heart.” (n.40)

- “Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages.” (n.49)
- “High transduction efficiency of human amniotic fluid stem cells mediated by adenovirus vectors.” (n.55)
- “Differentiation of human amniotic fluid stem cells into cardiomyocytes through embryonic body formation” (n.57)
- “Multipotent mesenchymal stromal cells from amniotic fluid: solid perspectives for clinical application” (n.81)
- “Chondrogenic differentiation of amniotic fluid-derived stem cells.” (n.90)
- “Mesenchymal cells from human amniotic fluid survive and migrate after transplantation into adult rat brain.” (n.94)

Mesenchymal stem cells articles :

- “Mesenchymal stem cells in connective tissue engineering and regenerative medicine: applications in cartilage repair and osteoarthritis therapy” (n.1)
- “Transplantation of mesenchymal stem cells within a poly(lactide-co-ε-caprolactone) scaffold improves cardiac function in a rat myocardial infarction model” (n.3)
- “Hyperthermia-treated mesenchymal stem cells exert antitumor effects on human carcinoma cell line” (n.15)
- “Human adipose-derived mesenchymal stem cells reduce inflammatory and T-cell responses and induce regulatory T cells in vitro in rheumatoid arthritis” (n. 28)
- “Contribution of stem cells to kidney repair” (n.34)
- “Potential role of culture mediums for successful isolation and neuronal differentiation of amniotic fluid stem cells.” (n.61)
- “Cryopreserved amniotic fluid-derived cells: a lifelong autologous fetal stem cell source for heart valve tissue engineering” (n.63)
- “Preclinical regulatory validation of a 3-stage amniotic mesenchymal stem cell manufacturing protocol.” (n. 68)
- “Characterization of human amniotic fluid stem cells and their pluripotential capability” (n.83)

At the end some comparative studies:

- “Comparison of human placenta- and bone marrow-derived multipotent mesenchymal stem cells” (n.37)

- “Characterization and hepatogenic differentiation of mesenchymal stem cells from human amniotic fluid and human bone marrow: a comparative study.” (n.51)
- “Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: comparison to bone marrow mesenchymal stem cells.” (n.88)

TRADUZIONE IN ITALIANO: Introduzione

In questo fascicolo sono stati raccolti gli articoli più significativi relativi alle cellule staminali da liquido amniotico, alle cellule staminali mesenchimali e ai loro trials clinici.

La rassegna copre a ritroso i primi mesi del 2009, l'anno appena trascorso, il 2007 e il 2006; l'indice generale riporta i titoli delle ricerche, la rivista scientifica sulla quale è stato pubblicato, la data di pubblicazione, gli autori e l'ente promotore.

Per ogni articolo viene poi riportato l'abstract. Tra quelli raccolti, si evidenziano nei trials clinici i seguenti articoli:

- “Applicazione delle cellule staminali per la riparazione ossea” (n. 65)
- “Cellule staminali mesenchimali per il trattamento di pazienti con resistenza steroidea e malattia da rigetto nei confronti dell'ospite: studi di fase 2” (n.73)
- “La terapia cellulare mediante staminali mesenchimali ritarda la progressione del deficit neurologico in pazienti con atrofia del sistema multiplo” (n.74)
- “Cellule staminali dalla polpa dentaria: un promettente “attrezzo” per la rigenerazione ossea” (n. 78)
- “Caratteristiche biologiche delle cellule stromali mesenchimali ed applicazioni cliniche in pazienti pediatrici” (n.80)
- “Applicazioni terapeutiche delle cellule stromali mesenchimali” (n.86)
- “Come la terapia con le cellule staminali mesenchimali è di aiuto per i pazienti con sclerosi multipla?” (n.97)

Inoltre tra le pubblicazioni riguardo le cellule staminali da liquido amniotico e della membrana amniotica, si segnalano:

- “Le cellule staminali mesenchimali del liquido amniotico in combinazione con ossigeno iperbarico aumentano la rigenerazione nervosa periferica” (n.14)
- “Produzione di cellule simil-epatocitiche dall'arnio umano” (n.35)
- “Caratteristiche neuronali delle cellule derivanti dal liquido amniotico dopo trasformazione adenovirale” (n.39)
- “Monitoraggio longitudinale non invasivo delle cellule staminali provenienti dal liquido amniotico nel cuore di topo.” (n.40)
- “Le cellule staminali da liquido amniotico possono integrarsi e differenziarsi nelle linee epiteliali polmonari.” (n.49)
- “Alta efficienza di trasduzione delle cellule staminali del liquido amniotico mediata da vettori di adenovirus.” (n.55)
- “Differenziazione in cardiomiociti delle cellule staminali del liquido amniotico attraverso la formazione di corpi embrionici” (n.57)
- “Cellule stromali mesenchimali multipotenti dal liquido amniotico: una solida prospettiva per l'applicazione clinica” (n.81)

- *“Differenziazione condrogenica delle cellule staminali derivanti dal liquido amniotico.” (n.90)*
- *“Le cellule mesenchimali del liquido amniotico sopravvivono e migrano dopo trapianto nel cervello di ratto adulto.” (n.94)*

Tra i numerosi articoli delle cellule staminali mesenchimali sono da evidenziare:

- *“Cellule staminali mesenchimali in tessuto connettivo ingegnerizzato e nella medicina rigenerativa: applicazioni nella riparazione della cartilagine e nella terapia dell’osteoartrite.” (n.1)*
- *“Il trapianto di cellule staminali mesenchimali con una struttura di PLCL aumenta la funzionalità cardiaca nel cuore infartuato di ratto” (n.3)*
- *“Cellule staminali mesenchimali trattate al calore esercitano un effetto antitumorale nella linea cellulare di carcinoma umano” (n.15)*
- *“Le cellule staminali mesenchimali umane derivanti dal tessuto adiposo riducono l’infiammazione, la risposta dei linfociti T e inducono la regolazione delle cellule T in vitro” (n. 28)*
- *“Contributo delle cellule staminali nella riparazione renale” (n.34)*
- *“Ruolo potenziale dei mediums di cultura nell’isolamento e nella differenziazione neuronale delle cellule staminali di liquido amniotico” (n.61)*
- *“Crioconservazione di cellule amniotiche: una fonte di cellule staminali fetali per tessuti ingegnerizzati delle valvole cardiache” (n.63)*
- *“Validazione preclinica di stadio 3 del protocollo di manipolazione delle cellule staminali mesenchimali amniotiche” (n. 68)*
- *“Caratterizzazione delle cellule staminali da liquido amniotico e loro capacità di pluripotenza” (n.83)*

Infine, alcuni studi comparativi:

- *“Comparazione delle cellule staminali mesenchimali della placenta con le cellule staminali mesenchimali del midollo osseo” (n.37)*
- *“Caratterizzazione e differenziazione epatogenica delle cellule staminali mesenchimali del liquido amniotico e del midollo osseo umano: uno studio comparativo.” (n.51)*
- *“Caratterizzazione molecolare e proteomica delle cellule staminali mesenchimali umane derivanti dal liquido amniotico: comparazione con le cellule staminali mesenchimali del midollo osseo.” (n.88)*

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2. **Effect of mesenchymal stem cells and platelet-rich plasma on the healing of standardized bone defects in the alveolar ridge: a comparative histomorphometric study in minipigs**

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Mesenchymal stem cells in connective tissue engineering and regenerative medicine: applications in cartilage repair and osteoarthritis therapy.

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Defects of load-bearing connective tissues such as articular cartilage, often result from trauma, degenerative or age-related disease. Osteoarthritis (OA) presents a major clinical challenge to clinicians due to the limited inherent repair capacity of articular cartilage. Articular cartilage defects are increasingly common among the elderly population causing pain, reduced joint function and significant disability among affected patients. The poor capacity for self-repair of chondral defects has resulted in the development of a large variety of treatment approaches including Autologous Chondrocyte Transplantation (ACT), microfracture and mosaicplasty methods. In ACT, a cartilage biopsy is taken from the patient and articular chondrocytes are isolated. The cells are then expanded after several passages in vitro and used to fill the cartilage defect. Since its introduction, ACT has become a widely applied surgical method with good to

excellent clinical outcomes. More recently, classical ACT has been combined with tissue engineering and implantable scaffolds for improved results. However, there are still major problems associated with the ACT technique which relate mainly to chondrocyte de-differentiation during the expansion phase in monolayer culture and the poor integration of the implants into the surrounding cartilage tissue. Novel approaches using mesenchymal stem cells (MSCs) as an alternative cell source to patient derived chondrocytes are currently on trial. MSCs have shown significant potential for chondrogenesis in animal models. This review article discusses the potential of MSCs in tissue engineering and regenerative medicine and highlights their potential for cartilage repair and cell-based therapies for osteoarthritis and a range of related osteoarticular disorders.

2. [J Oral Maxillofac Surg](#). 2009 Feb;

Effect of mesenchymal stem cells and platelet-rich plasma on the healing of standardized bone defects in the alveolar ridge: a comparative histomorphometric study in minipigs.

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PURPOSE: The purpose of this study was to test the effect of the combination of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) incorporated into a fluorohydroxyapatite (FHA) scaffold on bone regeneration in cylindrical defects in the edentulous mandibular ridge of minipigs. **MATERIALS AND METHODS:** Two mandibular premolar teeth were extracted bilaterally in 8 adult minipigs. After 2 months, 4 standardized defects of 3.5 mm diameter and 8 mm depth were created in each root site. The defects were randomly grafted with autogenous mandibular bone, FHA alone, PRP-FHA, or MSCs-PRP-FHA. A resorbable collagen membrane was placed over the defect area and the flaps were sutured. The animals were sacrificed 3 months later and biopsy samples were taken from the defect sites for histologic and histomorphometric assessment. **RESULTS:** There was no evidence of inflammation or adverse tissue reaction with either treatment. MSCs-PRP-FHA-treated sites showed new vital bone

between residual grafting particles. PRP-FHA- and FHA-treated sites showed residual particles in a background of marrow soft tissue with a moderate quantity of newly formed bone. Autogenous bone (46.97%) and MSCs-PRP-FHA (45.28%) produced a significantly higher amount of vital bone than PRP-FHA (37.95%), or FHA alone (36.03%). Further, the MSCs-PRP-FHA-treated defects showed a significantly higher percentage of contact between graft particles and newly formed bone compared with PRP-FHA and FHA group (59.23% vs 48.37% and 46.43%, respectively). **CONCLUSIONS: Our results suggest that, in this animal model, the addition of MSCs to PRP-FHA enhances bone formation after 3 months.**

3. [Eur J Heart Fail](#). 2009 Feb

Transplantation of mesenchymal stem cells within a poly(lactide-co- ϵ -caprolactone) scaffold improves cardiac function in a rat myocardial infarction model.

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AIMS: Cardiac tissue engineering has been proposed as an appropriate method to repair myocardial infarction (MI). Evidence suggests that a cell with scaffold combination was more effective than a cell-only implant. Nevertheless, to date, there has been no research into elastic biodegradable poly(lactide-co- ϵ -caprolactone) (PLCL) scaffolds. **The aim of this study was to investigate the effect of mesenchymal stem cells (MSCs) with elastic biodegradable PLCL scaffold transplants in a rat MI model.** **METHODS AND RESULTS:** Ten days after inducing MI through the cryoinjury method, a saline control, MSC, PLCL scaffold, or MSC-seeded PLCL scaffold was transplanted onto the hearts. Four weeks after transplantation, cardiac function and histology were evaluated. Transplanted MSCs survived and differentiated into cardiomyocytes in the injured region. Left ventricular ejection fraction in the MSC + PLCL group increased by 23% compared with that in the saline group; it was also higher in the MSC

group. The infarct area in the MSC + PLCL group was decreased by 29% compared with that in the saline group; it was also reduced in the MSC group. CONCLUSION: Mesenchymal stem cells plus PLCL should be an excellent combination for cardiac tissue engineering.

4. [Transplantation](#). 2009 Jan 27;

Mesenchymal stem cells remain host-derived independent of the source of the stem-cell graft and conditioning regimen used.

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BACKGROUND: Human bone marrow contains hematopoietic stem cells and stroma cells known as mesenchymal stem cells (MSC). MSC are cells with the morphological features of fibroblasts, which, in addition to their nursing function for hematopoietic stem cells, retain the ability to differentiate into cartilage, bone, fat, muscle, and tendon and have an important immunomodulatory function. To understand in more detail hematopoietic engraftment and immune modulation after hematopoietic cell transplantation, we investigated the ability of donor MSC to engraft after hematopoietic cell transplantation in dependency to the conditioning regimen (myeloablative vs. reduced intensity) and source of the graft (bone marrow vs. peripheral blood). METHODS: Bone marrow MSC of 12 patients were analyzed, a median of 23.4 (range 0.9-137.8) months after human leukocyte antigen matched but gender mismatched bone marrow transplantation after myeloablative conditioning (n=4) or peripheral blood cell transplantation after myeloablative (n=4) or reduced intensity conditioning (n=4). MSC were characterized by morphology, positivity for CD 105+, CD73+, CD 44+, and CD 90+, and by their capacity to differentiate into adipocytic and osteogenic cells. Recipient and donor origins were determined by fluorescent in situ hybridization for sex chromosomes. RESULTS: While overall blood and bone marrow chimerism was 100% donor type, MSC remained in all patients of recipient origin (>96%). There was no difference between patients receiving bone marrow and peripheral blood grafts, nor was any difference observed between patients receiving full intensity in comparison with reduced intensity conditioning. CONCLUSIONS: We conclude that MSC remain of host type irrespective of the conditioning regimen and graft source.

5. [J Biomed Mater Res A](#), 2009 Jan 23.

Evaluation of the osteogenic potential and vascularization of 3D poly(3)hydroxybutyrate scaffolds subcutaneously implanted in nude rats.

[Rentsch C](#), [Rentsch B](#), [Breier A](#), [Hofmann A](#), [Manthey S](#), [Scharnweber D](#), [Biewener A](#), [Zwipp H](#).

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The aim of this study was to evaluate the osteogenic potential and the vascularization of embroidered, tissue engineered, and cell-seeded 3D poly(3)hydroxybutyrate (PHB) scaffolds in nude rats. Collagen I (coll I)- and collagen I/chondroitin sulfate (coll I/CS)-coated PHB scaffolds were seeded with human mesenchymal stem cells (hMSCs). Proliferation and differentiation were characterized by different biochemical assays in vitro. For animal experiments, the cells were cultivated on coll I- or coll I/CS-coated scaffolds and either expanded or osteogenically differentiated. Scaffolds were piled up to create a 3D scaffold pad and implanted subcutaneously into nude rats. In vitro hMSC showed proliferation and differentiation on PHB scaffolds. Alkaline phosphatase (ALP) and calcium increased in the differentiation medium and in the presence of coll I/CS. In vivo blood vessels were found in the scaffold-stack. Histological/immunohistological analyses of explanted scaffolds showed osteogenic markers such as osteopontin, osteonectin, and coll I around the PHB fibers. Coll I/CS-coated scaffolds with expanded hMSC showed higher values of ALP and calcium than the other combinations. Embroidered PHB scaffolds, coated with extracellular matrix components, provided an adequate environment and, therefore, a template for hMSC which could be differentiated in osteogenic direction. (c) 2009 Wiley Periodicals, Inc. *J Biomed Mater Res* 2009.

6. [J Tissue Eng Regen Med](#). 2009 Jan 23.

Mesenchymal progenitor cells derived from traumatized human muscle.

[Jackson WM](#), [Aragon AB](#), [Djouad F](#), [Song Y](#), [Koehler SM](#), [Nesti LJ](#), [Tuan RS](#).

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Mesenchymal stem cells (MSCs) derived from adult tissues are an important candidate cell type for cell-based tissue engineering and regenerative medicine. Currently, clinical applications for MSCs require additional surgical procedures to harvest the autologous MSCs (i.e. from bone marrow) or commercial allogeneic alternatives. We have recently identified a population of mesenchymal progenitor cells (MPCs) in traumatized muscle tissue that has been surgically debrided from traumatic orthopaedic extremity wounds. The purpose of this study was to evaluate whether MPCs derived from traumatized muscle may provide a clinical alternative to bone-marrow MSCs, by comparing their morphology, proliferation capacity, cell surface epitope profile and differentiation capacity. After digesting the muscle tissue with collagenase, the MPCs were enriched by a direct plating technique. The morphology and proliferation rate of the muscle-derived MPCs was similar to bone-marrow derived MSCs. Both populations expressed cell surface markers characteristic for MSCs (CD 73, CD 90 and CD105), and did not express markers typically absent on MSCs (CD14, CD34 and CD45). After 21 days in specific differentiation media, the histological staining and gene expression of the MPCs and MSCs was characteristic for differentiation into osteoblasts, chondrocytes and adipocytes, but not into myoblasts. Our findings demonstrate that traumatized muscle-derived MPCs exhibit a similar phenotype and resemble MSCs derived from the bone marrow. MPCs harvested from traumatized muscle tissue may be considered for applications in tissue engineering and regenerative medicine following orthopaedic trauma requiring circumferential debridement.

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7. [J Cell Physiol](#). 2009 Jan 23.

Perfusion affects the tissue developmental patterns of human mesenchymal stem cells in 3D scaffolds.

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Human mesenchymal stem cells (hMSCs) developed in three-dimensional (3D) scaffolds are significantly affected by culture conditions. We hypothesized that the hydrodynamic forces generated in perfusion bioreactors significantly affected hMSC functionality in 3D scaffolds by shaping the extracellular matrix (ECM) proteins. In this study, hMSCs were grown in 3D poly(ethylene terephthalate) (PET) scaffolds in static and a parallel perfusion system under similar initial conditions for up to 35 days. Results demonstrated that even at very low media velocities ($O [10(-4) \text{ cm/sec}]$), perfusion cultures affected the ability of hMSCs to form an organized ECM network as illustrated by the immunostaining of collagen I and laminin fibrous structure. The change in the ECM microenvironment consequently influenced the nuclear shape. The hMSCs grown at the lower surface of static culture displayed a 15.2 times higher nuclear elongation than those at the upper surface, whereas cells grown in the perfusion bioreactor displayed uniform spherical nuclei on both surfaces. The difference in ECM organization and nuclear morphology associated with gene expression and differentiation characteristics of hMSCs. The cells exhibited lower CFU-F colony forming ability and decreased expressions of stem-cell genes of Rex-1 and Oct-4, implying a less primitive stem-cell phenotype was maintained in the perfusion culture relative to the static culture conditions. The significantly higher expression level of osteonectin gene in the perfusion culture at day 28 indicated an upregulation of osteogenic ability of hMSCs. The study highlights the critical role of dynamic culture conditions on 3D hMSC construct development and properties. *J. Cell. Physiol.* (c) 2009 Wiley-Liss, Inc.

8. [J Cell Physiol](#). 2009 Jan 23.

Secretome from mesenchymal stem cells induces angiogenesis via Cyr61.

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It is well known that bone marrow-derived mesenchymal stem cells (MSCs) are involved in wound healing and regeneration responses. In this study, we globally profiled the proteome of MSCs to investigate critical factor(s) that may promote wound healing. Cysteine-rich protein 61 (Cyr61) was found to be abundantly present in MSCs. The presence of Cyr61 was confirmed by immunofluorescence staining and immunoblot analysis. Moreover, we showed that Cyr61 is present in the culture medium (secretome) of MSCs. The secretome of MSCs stimulates angiogenic response in vitro, and neovascularization in vivo. Depletion of Cyr61 completely abrogates the angiogenic-inducing capability of the MSC secretome. Importantly, addition of recombinant Cyr61 polypeptides restores the angiogenic activity of Cyr61-depleted secretome. Collectively, these data demonstrate that Cyr61 polypeptide in MSC secretome contributes to the angiogenesis-promoting activity, a key event needed for regeneration and repair of injured tissues. *J. Cell. Physiol.* (c) 2009 Wiley-Liss, Inc.

Effect of Ceramide on Mesenchymal Stem Cell Differentiation Toward Adipocytes.

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Proinflammatory cytokines such as tumor necrosis factor (TNF) alpha are well known to inhibit adipocyte differentiation. TNF-alpha triggers ceramide synthesis through binding of TNF-alpha to its p55 receptor. Therefore, ceramide is implicated in many of the multiple signaling pathways initiated by TNF-alpha. In breast tissue engineering, it is important to know how to modulate adipocyte differentiation of the stem cells with exogenous additives like ceramide in vitro. We hypothesized that stem cell adipogenesis could be retained in TNF-alpha-treated preadipocytes in which ceramide synthesis was blocked and that exogenous ceramide could inhibit adipocyte differentiation. We first studied the effect of ceramide synthase inhibitor, Fumonisin B2, on the adipogenesis of murine mesenchymal stem cells (D1 cells), treated with TNF-alpha. We then studied the effect of specific exogenous C6-ceramide on D1 cell viability and differentiation. It was found that 1 ng/ml of TNF-alpha significantly inhibited D1 cell adipogenesis. Cells treated with 5 μM of Fumonisin B2 were able to undergo adipogenesis, even when treated with TNF-alpha. High concentrations of exogenous C6-ceramide (>50 μM) had an inhibitory effect, not only on the pre-confluent proliferation of the D1 cells but also on the post-confluent cell viability. High concentrations of C6-ceramide (>50 μM) also inhibited mitotic clonal expansion when D1 cell differentiation was induced by the addition of an adipogenic hormonal cocktail. C6-ceramide at low concentrations (10-25 μM) inhibited lipid production in D1 cells, demonstrated by decreased levels of both total triglyceride content and specific fatty acid composition percentages. Genetic expression of peroxisome proliferator-activated receptor (PPAR) gamma and α2 in D1 cells was reduced by C6-ceramide treatment. CCAAT/enhancer-binding protein (C/EBP) beta levels in D1 cells were reduced by C6-ceramide treatment during early differentiation; PPARgamma and α2 protein levels were reduced at terminal differentiation. C6-ceramide at lower concentrations also decreased lipid accumulation of differentiating D1 cells. Our results suggest that ceramide synthase inhibitor retains the adipogenic potential of TNF-alpha-treated mesenchymal stem cells, while exogenous ceramide at lower concentrations inhibit the adipogenesis of mesenchymal stem cells. Ceramide, therefore, could be a modulator candidate in breast tissue engineering strategies.

10. [Eur J Cell Biol.](#) 2009 Jan 22.

Expression of a functional epidermal growth factor receptor on human adipose-derived mesenchymal stem cells and its signaling mechanism.

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Adult stem cells act as a pluripotent source of regenerative cells during tissue injury. Despite expanded research in stem cell biology, understanding how growth and migration of adipose-derived adult mesenchymal stem cells (ASC) are governed by interactions with growth factors is very limited. One important property of ASC is the presence of the epidermal growth factor (EGF) receptor and the cellular response to soluble EGF. Expression of the EGF receptor was proven by PCR and Western blotting. Signal transduction was analyzed by Western blotting and PhosFlow assay. EGF caused robust phosphorylation of SHC and ERK1/2, which could be inhibited by EGF receptor antagonist AG1478 and MEK inhibitor PD98059. ASC proliferation was determined by MTT assay. Stem cell migration was analyzed in a modified Boyden chamber. Incubation with EGF led to cell proliferation and induced cell migration, but did not change the undifferentiated state of the cells. In the kidney, injured renal tubular cells express high amounts of EGF. Therefore, our results may highlight a mechanism underlying renal regeneration. Thus, future in vivo studies that focus on the effects of EGF on recruitment of ASC to sites of injury are necessary.

11. [J Cell Biochem](#). 2009 Jan 21.

Ghrelin inhibits early osteogenic differentiation of C3H10T1/2 cells by suppressing Runx2 expression and enhancing PPARgamma and C/EBPalpha expression.

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Ghrelin is a 28-residue peptide identified in the stomach as an endogenous ligand of the growth hormone secretagogue receptor that is expressed in a variety of peripheral tissues, as well as in the brain. In previous studies, ghrelin has been shown to stimulate both adipogenic differentiation from preadipocytes and osteogenic differentiation from preosteoblasts or primary osteoblasts. This study was undertaken to investigate the direct effect of ghrelin on the lineage allocation of mesenchymal stem cells (MSCs). We identified ghrelin receptor mRNA in C3H10T1/2 cells, and we found the levels of this mRNA to be attenuated during osteogenic differentiation. Treatment of cells with ghrelin resulted in both proliferation and inhibition of caspase-3 activity. In addition, ghrelin decreased serum deprivation-induced bax protein expression and release of cytochrome c from the mitochondria, whereas it increased bcl-2 protein expression. Moreover, ghrelin inhibited early osteogenic differentiation, as shown by alkaline phosphatase activity and staining, and inhibited osteoblast-specific genes expression by altering Runx2, PPARgamma, and C/EBPalpha protein expression. *J. Cell. Biochem.* (c) 2009 Wiley-Liss, Inc.

12. [Biochem Biophys Res Commun](#). 2009 Jan 20.

Development of mesenchymal stem cells partially originate from the neural crest.

[Morikawa S](#), [Mabuchi Y](#), [Niibe K](#), [Suzuki S](#), [Nagoshi N](#), [Sunabori T](#), [Shimmura S](#), [Nagai Y](#), [Nakagawa T](#), [Okano H](#), [Matsuzaki Y](#).

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Mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells isolated from many adult tissues. Previous studies reported that MSCs can differentiate to both mesodermal and neural lineages by a phenomenon referred to as "dedifferentiation" or "transdifferentiation". However, since MSCs have only been defined in vitro, much of their development in vivo is still unknown. Here, we prospectively identified MSCs in the bone marrow from adult transgenic mice encoding neural crest-specific P0-Cre/Floxed-EGFP and Wnt1-Cre/Floxed-EGFP. EGFP-positive MSCs formed spheres that expressed neural crest stem cell genes and differentiated into neurons, glial cells, and myofibroblasts. Interestingly, we observed MSCs both in the GFP(+) and GFP(-) fraction and found that there were no significant differences in the in vitro characteristics between these two populations. Our results suggest that MSCs in adult bone marrow have at least two developmental origins, one of which is the neural crest.

13. [J Craniomaxillofac Surg](#). 2009 Jan 18.

Application of a new chair-side method for the harvest of mesenchymal stem cells in a patient with nonunion of a fracture of the atrophic mandible - A case report.

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PURPOSE: This case report describes a new clinical method for chair-side processing of a cell mixture which contains mesenchymal stem cells (MSCs) which was applied for the first time in the treatment of a nonunion of an atrophic fractured mandible. METHODS: Bone marrow was aspirated and a corticocancellous bone graft was harvested from the iliac crest of a 56-year-old woman with medical comorbidities and a fracture of the atrophic mandible. The fracture was stabilized with a reconstruction bone plate, and mononuclear cells including MSCs were concentrated by centrifugation and applied in combination with a particulate bone transplant. A sample of the grafted cells was characterized by flow cytometric analysis and by their ability to differentiate into various cell types. RESULTS: The fracture healed uneventfully. No complications occurred during the 4-month follow-up. CONCLUSION: Adding MSCs is a feasible alternative to enhance bone healing. This chair-side method requires little training and no cell laboratory support.

14. [Neurochem Res.](#) 2009 Jan 17.

Human Amniotic Fluid Mesenchymal Stem Cells in Combination with Hyperbaric Oxygen Augment Peripheral Nerve Regeneration.

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Purpose Attenuation of pro-inflammatory cytokines and associated inflammatory cell deposits rescues human amniotic fluid mesenchymal stem cells (AFS) from apoptosis. Hyperbaric oxygen (HBO) suppressed stimulus-induced pro-inflammatory cytokine production in blood-derived monocyte-macrophages. Herein, we evaluate the beneficial effect of hyperbaric oxygen on transplanted AFS in a sciatic nerve injury model. Methods Peripheral nerve injury was produced in Sprague-Dawley rats by crushing the left sciatic nerve using a vessel clamp. The AFS were embedded in fibrin glue and delivered to the injured site. Hyperbaric oxygen (100% oxygen, 2 ATA, 60 min/day) was administered 12 h after operation for seven consecutive days. Transplanted cell apoptosis, oxidative stress, inflammatory cell deposits and associated chemokines, pro-inflammatory cytokines, motor function, and nerve regeneration were evaluated 7 and 28 days after injury. Results Crush injury induced an inflammatory response, disrupted nerve integrity, and impaired nerve function in the sciatic nerve. However, crush injury-provoked inflammatory cytokines, deposits of inflammatory cytokines, and associated macrophage migration chemokines were attenuated in groups receiving hyperbaric oxygen but not in the AFS-only group. No significant increase in oxidative stress was observed after administration of HBO. In transplanted AFS, marked apoptosis was detected and this event was reduced by HBO treatment. Increased nerve myelination and improved motor function were observed in AFS-transplant, HBO-administrated, and AFS/HBO-combined treatment groups. Significantly, the AFS/HBO combined treatment showed the most beneficial effect. Conclusion AFS in combination with HBO augment peripheral nerve regeneration, which may involve the suppression of apoptotic death in implanted AFS and the attenuation of an inflammatory response detrimental to peripheral nerve regeneration.

15. [Cancer](#). 2009 Jan 15;

Hyperthermia-treated mesenchymal stem cells exert antitumor effects on human carcinoma cell line.

[Cho JA](#), [Park H](#), [Kim HK](#), [Lim EH](#), [Seo SW](#), [Choi JS](#), [Lee KW](#).

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BACKGROUND:: Mesenchymal stem cells (MSCs) possess the potential for differentiation into multilineages. MSCs have been reported to play a role as precursors for tumor stroma in providing a favorable environment for tumor progression. Hyperthermia destroys cancer cells by raising the temperature of tumor-loaded tissue to 40 degrees C to 43 degrees C and causes indirect sensitizing effects when combined with chemo- and/or radiotherapy. However, how hyperthermia affects the tumor-supportive stroma is unknown. Here, the authors investigated the effects of hyperthermia-treated MSCs, from different sources, on the human ovarian cancer cell line SK-OV-3. METHODS:: MSCs from adipose tissue and amniotic fluid were untreated or heat-treated (HS-MSCs). The culture supernatant of each treatment group was collected and transferred to the SK-OV-3 cells. RESULTS:: The morphological analysis and cell proliferation assay showed a reduced viability of the tumor cells in the conditioned medium with the HS-MSCs. Further investigations revealed that the conditioned medium of the HS-MSCs induced a higher nuclear condensation and a greater number of sub-G1 cells among the tumor cells. Analysis of the mRNA expression demonstrated that the conditioned medium of the HS-MSCs induced up-regulation or down-regulation of several tumor-associated molecules. Finally, the cytokine array of each conditioned medium showed that angiogenin, insulin-like growth factor binding protein 4, neurotrophin 3, and chemokine (C-C motif) ligand 18 are involved as main factors. CONCLUSIONS:: This study showed that the conditioned medium of the HS-MSCs exerted a suppressive effect on tumor progression and malignancy, suggesting that hyperthermia enables tumor stromal cells to provide a sensitizing environment for tumor cells to undergo cell death. Cancer 2009. (c) 2009 American Cancer Society.

16. [Leukemia](#). 2009 Jan 15. [Epub ahead of print]

Human mesenchymal stem cells inhibit cancer cell proliferation by secreting DKK-1.

[Zhu Y](#), [Sun Z](#), [Han Q](#), [Liao L](#), [Wang J](#), [Bian C](#), [Li J](#), [Yan X](#), [Liu Y](#), [Shao C](#), [Zhao RC](#).

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Mesenchymal stem cells (MSCs) have an inhibitory effect on tumor proliferation, but the precise mechanisms are not fully understood. Here, we identified DKK-1 (dickkopf-1), secreted by MSCs and acting as a negative regulator of WNT signaling pathway, to be one of the molecules responsible for the inhibitory effect. When DKK-1 was neutralized by anti-DKK-1 antibodies, or when the expression of DKK-1 was downregulated by RNA interference (RNAi), the inhibitory effects of MSCs on K562 cell proliferation were attenuated. We also provide evidence that the expression of DKK-1 by MSCs is regulated by NANOG, a transcriptional factor ubiquitously expressed in some stem cells. Using the Cellmax artificial capillary modules that eliminate the immunosuppressive properties of MSCs, we further showed that MSCs were able to inhibit proliferation of K562 cells in a humoral microenvironment. Meanwhile, we recapture this effect of MSCs on primary leukemic hematopoietic progenitors from patients. MSCs probably have a general inhibitory effect on their neighboring cells, including malignant cells, en route to achieving tissue homeostasis. Leukemia advance online publication, 15 January 2009; doi:10.1038/leu.2008.384.

17. [Int Immunopharmacol](#). 2009 Jan 13.

Early modulation of inflammation by mesenchymal stem cell after acute kidney injury.

[Semedo P](#), [Palasio CG](#), [Oliveira CD](#), [Feitoza CO](#), [Gonçalves GM](#), [Cenedeze MA](#), [Wang PM](#), [Teixeira VP](#), [Reis MA](#), [Pacheco-Silva A](#), [Câmara NO](#).

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Therapy with stem cells has showed to be promising for acute kidney injury (AKI), although how it works is still controversial. Modulation of the inflammatory response is one possible mechanism. Most of published data relies on early time and whether the protection is still maintained after that is not known. Here, we analyzed whether immune modulation continues after 24 h of reperfusion. MSC were obtained from male Wistar rats. After 3-5 passages, cells were screened for CD73, CD90, CD44, CD45, CD29 and CD 31. In addition, MSC were submitted to differentiation in adipocyte and in osteocyte. AKI was induced by bilaterally clamping of renal pedicles for 60 min. Six hours after injury, MSC (2×10^5) cells were administered intravenously. MSC-treated animals presented the lowest serum creatinine compared to non-treated animals (24 h: 1.3 ± 0.21 vs. 3.23 ± 0.89 mg/dl, $p < 0.05$). The improvement in renal function was followed by a lower expression of IL-1b, IL-6 and TNF-alpha and higher expression of IL-4 and IL-10. However, 48 h after reperfusion, this cytokine profile has changed. The decrease in Th1 cytokines was less evident and IL-6 was markedly up regulated. PCNA analysis showed that regeneration occurs faster in kidney tissues of MSC-treated animals than in controls at 24 h. And also ratio of Bcl-2/Bad was higher at treated animals after 24 and 48 h. Our data demonstrated that the immunomodulatory effects of MSC occur at very early time point, changing the inflammation profile toward a Th2 profile

18. [BMC Cell Biol.](#) 2009 Jan 13;

Comparative characterization of mesenchymal stem cells from eGFP transgenic and non-transgenic mice.

[Ripoll CB](#), [Bunnell BA](#).

ABSTRACT: BACKGROUND: Adipose derived- and bone marrow-derived murine mesenchymal stem cells (mMSCs) may be used to study stem cell properties in an in vivo setting for the purposes of evaluating therapeutic strategies that may have clinical applications in the future. If these cells are to be used for transplantation, the question arises of how to track the administered cells. One solution to this problem is to transplant cells with an easily identifiable genetic marker such as enhanced green fluorescent protein (eGFP). This protein is fluorescent and therefore does not require a chemical substrate for identification and can be visualized in living cells. This study seeks to characterize and compare adipose derived- and bone marrow-derived stem cells from C57Bl/6 mice and eGFP transgenic C57Bl/6 mice. RESULTS: The expression of eGFP does not appear to affect the ability to differentiate along adipogenic or osteogenic lineages; however it appears that the tissue of origin can influence differentiation capabilities. The presence of eGFP had no effect on cell surface marker expression, and mMSCs derived from both bone marrow and adipose tissue had similar surface marker profiles. There were no significant differences between transgenic and non-transgenic mMSCs. CONCLUSIONS: Murine adipose derived and bone marrow derived mesenchymal stem cells from non-transgenic and eGFP transgenic C57Bl/6 mice have very similar characterization profiles. The availability of mesenchymal stem cells stably expressing a genetic reporter has important applications for the advancement of stem cell research.

19. [Invest Ophthalmol Vis Sci](#). 2009 Jan 10.

The use of human mesenchymal stem cell-derived feeder cells for the cultivation of transplantable epithelial sheets.

[Omoto M](#), [Miyashita H](#), [Shimmura S](#), [Higa K](#), [Kawakita T](#), [Yoshida S](#), [McGrogan M](#), [Shimazaki J](#), [Tsubota K](#).

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PURPOSE: To report the efficacy of using human bone marrow derived mesenchymal stem cells as a source of feeder cells for the cultivation of transplantable corneal epithelial cell sheets.
METHODS: Human mesenchymal stem cells (MASC) were cultured in alpha MEM with 10% serum and treated with mitomycin C. Expression of cytokines in MASC were confirmed by reverse transcriptional polymerase chain reaction. Human limbal epithelial cells were co-cultured with MASC or 3T3 feeder cells to compare colony-forming efficiency (CFE). Limbal epithelial cells were cultured on MASC or 3T3 feeder cells at air-liquid interface to allow stratification, and stratified epithelial sheets were analyzed by immunohistochemistry against cytokeratin 3 (K3), K15, p63 alpha and ABCG2. Rabbit limbal epithelial cell sheets were cultivated with MASC feeder cells and transplanted to the ocular surface of the limbal deficient rabbits. Epithelial grafts were observed by slit lamp microscopy for 4 weeks and then evaluated by histology and immunohistochemistry against K3 and K4. RESULTS: MASC feeder cells expressed keratinocyte growth factor, hepatocyte growth factor and N-cadherin. The CFE of human limbal epithelial cells was similar in both MASC and 3T3 feeder groups. Stratified cell sheets were successfully cultivated with MASC feeder cells expressing K3, K15, p63 alpha and ABCG2. Transplanted epithelial sheets regenerated the corneal phenotype in limbal deficient rabbits. CONCLUSION: MASC-derived feeder cells are suitable for the engineering of epithelial sheets while avoiding the use of potentially hazardous xenogenic feeder cells.

20. [J Orthop Res](#). 2009 Jan 9.

In vitro dexamethasone pretreatment enhances bone formation of human mesenchymal stem cells in vivo.

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Bone grafting is the current standard of care for treatment of fracture nonunions, while alternative strategies such as bone marrow-derived mesenchymal stem cells are also used. MSCs can be induced towards the osteogenic lineage by in vitro treatment with dexamethasone (dex). This study aimed to determine the optimal duration of dex treatment for osteogenic differentiation of MSCs in vitro and evaluate the effect of this dex pretreatment on bone formation in vivo. To determine the optimal dex treatment, MSCs were cultivated in osteogenic medium for 5 weeks with a varying dex withdrawal schedule, such that MSCs were exposed to dex for either 0, 1, 2, 3, 4, or 5 weeks. During this period, alkaline phosphatase, calcium, and DNA assays, as well as von Kossa staining and morphological observations were performed. One and 2 week dex-treated groups returned to control levels rapidly, whereas 3 and 4 week groups retained higher levels of differentiation markers, with the 4 week group being the highest. Based on these in vitro results, MSCs (with and without dex) and control fibroblasts were seeded into ceramic cubes, cultured for 4 weeks, and implanted into SCID mice, and harvested 6 weeks postimplantation for histologic evaluation. There was no bone formation in fibroblast-seeded controls, little bone formation in control (CS 1), and extensive bone formation (CS 3-4) in dex-treated MSCs. These results indicate that pretreatment of MSCs with dex results in greater bone formation than in untreated controls. (c) 2009 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res.

21. [Exp Cell Res.](#) 2009 Jan 8.

Migration potential and gene expression profile of human mesenchymal stem cells induced by CCL25.

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Recruitment of mesenchymal stem cells (MSC) to tissue damages is a promising approach for in situ tissue regeneration. The physiological mechanisms and regulatory processes of MSC trafficking to injured tissue remain poorly understood. However, the pivotal role of chemokines in MSC recruitment has already been shown. The aim of this study was to determine the migratory potential and the gene expression profile of MSC stimulated with the CC chemokine CCL25 (TECK). Bone marrow derived human MSC were exposed to different doses of CCL25 in a standardized chemotaxis assay. Microarray gene expression profiling and pathway analysis were performed for CCL25 stimulated. Maximum migration of MSC towards CCL25 was observed at 10(3) nM. Microarray analysis revealed an induction of molecules directly involved in chemotaxis and homing of bone marrow cells (CXCL1-3, CXCL8, PDE4B), cytoskeletal and membrane reorganisation (CXCL8, PLD1, IGFBP1), cellular polarity (PLD1), and cell movement (CXCL1-3, CXCL6, CXCL8, PTGS2, PDE4B, TGM2). Respective chemokine secretion was confirmed by protein membrane-array analysis. The activation of CXCR2 ligands (CXCL1-3, CXCL5-6, CXCL8) and a LIF-receptor/gp130 ligand (LIF) indicated an involvement of the respective signaling pathways during initiation of chemotaxis and migration. These results suggest CCL25 as a new potential candidate for further in situ regeneration approaches.

22. [J Cell Biochem](#). 2009 Jan 7.

Stem cell sources to treat diabetes.

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We review progress towards the goal of utilizing stem cells as a source of engineered pancreatic beta-cells for therapy of diabetes. Protocols for the in vitro differentiation of embryonic stem (ES) cells based on normal developmental cues have generated beta-like cells that produce high levels of insulin, albeit at low efficiency and without full responsiveness to extracellular levels of glucose. Induced pluripotent stem (iPS) cells also can yield insulin-producing cells following similar approaches. An important recent report shows that when transplanted into mice, human ES-derived cells with a phenotype corresponding to pancreatic endoderm matured to yield cells capable of maintaining near-normal regulation of blood sugar [Kroon et al., 2008]. Major hurdles that must be overcome to enable the broad clinical translation of these advances include teratoma formation by ES and iPS cells, and the need for immunosuppressive drugs. Classes of stem cells that can be expanded extensively in culture but do not form teratomas, such as amniotic fluid-derived stem cells and hepatic stem cells, offer possible alternatives for the production of beta-like cells, but further evidence is required to document this potential. Generation of autologous iPS cells should prevent transplant rejection, but may prove prohibitively expensive. Banking strategies to identify small numbers of stem cell lines homozygous for major histocompatibility loci have been proposed to enable beneficial genetic matching that would decrease the need for immunosuppression. *J. Cell. Biochem.* (c) 2009 Wiley-Liss, Inc.

23. [Blood](#). 2009 Jan 7.

Mesenchymal stem/progenitor cells promote the reconstitution of exogenous hematopoietic stem cells in *Fancg*^{-/-} mice in vivo.

[Li Y](#), [Chen S](#), [Yuan J](#), [Yang Y](#), [Li J](#), [Ma J](#), [Wu X](#), [Freund M](#), [Pollok K](#), [Hanenberg H](#), [Goebel WS](#), [Yang FC](#).

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Fanconi anemia (FA) is a heterogeneous genetic disorder characterized by bone marrow failure and complex congenital anomalies. While mutations in FA genes result in a characteristic phenotype in the hematopoietic stem/progenitor cells (HSPC), little is known regarding the consequences of a nonfunctional FA pathway in other stem/progenitor cell compartments. Given the intense functional interactions between HSPCs and the mesenchymal microenvironment, we investigated the FA pathway on the cellular functions of murine mesenchymal stem/progenitor cells (MSPC) and their interactions with HSPC in vitro and in vivo. Here, we show that loss of the murine homologue of FANCG (*Fancg*) results in a defect in MSPC proliferation and in their ability to support the adhesion and engraftment of murine syngeneic HSPCs in vitro or in vivo. Transplantation of wildtype (WT) but not *Fancg*^{-/-} MSPCs into the tibiae of *Fancg*^{-/-} recipient mice enhances the HSPC engraftment kinetics, the BM cellularity and the number of progenitors per tibia of WT HSPCs injected into lethally irradiated *Fancg*^{-/-} recipients. Collectively, these data demonstrate that FA proteins are required in the BM microenvironment to maintain normal hematopoiesis and provide genetic and quantitative evidence that adoptive transfer of WT MSPCs enhances hematopoietic stem cell engraftment.

24. [Tissue Eng Part A](#). 2009 Jan 6. [Epub ahead of print]

Synthesis of a Tissue-Engineered Periosteum with Acellular Dermal Matrix and Cultured Mesenchymal Stem Cells.

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Periosteal grafts can aid in bone repair by providing bone progenitor cells and acting as a barrier to scar tissue. Unfortunately, these grafts have many of the same disadvantages as bone grafts (donor site morbidity and limited donor sites). In this article, we describe a method of synthesizing a periosteum-like material using acellular human dermis and osteoblasts or mesenchymal stem cells (MSC). We show that osteoblasts readily attach to and proliferate on the acellular human dermis in vitro. In addition, osteoblasts retained the potential for differentiation in response to bone morphogenetic protein stimulation. Cells grown on the acellular human dermis were efficiently transfected with adenoviruses with no evidence of cellular toxicity. To assess for in vivo cell delivery and bone-forming potential, the acellular human dermis was seeded with green fluorescent protein (GFP)-positive MSCs, transfected with bone morphogenetic protein 2, wrapped around the adductor muscle in syngeneic mice, and used to treat critical-sized mandibular defects in nude rats. After 3 weeks, GFP-positive cells were still present, and bone had replaced the interface between the muscle and the constructs. After 6 weeks, critical-sized bone defects had been successfully healed. In conclusion, we show that an acellular human dermis can be used to synthesize a tissue-engineered periosteum capable of delivering cells and osteoinductive proteins.

25. [Tissue Eng Part A](#). 2009 Jan 6. [Epub ahead of print]

Telomerase Immortalized Human Amnion- and Adipose-Derived Mesenchymal Stem Cells: Maintenance of Differentiation and Immunomodulatory Characteristics.

[Wolbank S](#), [Stadler G](#), [Peterbauer A](#), [Gillich A](#), [Karbiener M](#), [Streubel B](#), [Wieser M](#), [Katinger H](#), [van Griensven M](#), [Redl H](#), [Gabriel C](#), [Grillari J](#), [Grillari-Voglauer R](#).

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Cell banking of mesenchymal stem cells (SCs) from various human tissues has significantly increased the feasibility of SC-based therapies. Sources such as adipose tissue and amnion offer outstanding possibilities for allogeneic transplantation due to their high differentiation potential and their ability to modulate immune reaction. Limitations, however, concern the reduced replicative potential as a result of progressive telomere erosion, which hampers scaleable production and long-term analysis of these cells. Here we report the establishment and characterization of two human amnion-derived and two human adipose-derived SC lines immortalized by ectopic expression of the catalytic subunit of human telomerase (hTERT). hTERT overexpression resulted in continuously growing SC lines that were largely unaltered concerning surface marker profile, morphology, karyotype, and immunosuppressive capacity with similar or enhanced differentiation potential for up to 87 population doublings. While all generated lines showed equal immunomodulation compared to the parental cells, one of the amnion-derived immortalized lines resulted in significantly increased immunogenicity. Although telomerase proves as important tool for immortalizing cells, our data emphasize the need for careful and standardized characterization of each individual cell population for cell banks.

26. [Ann Biomed Eng.](#) 2009 Jan 6. [Epub ahead of print]

Pressure and Distortion Regulate Human Mesenchymal Stem Cell Gene Expression.

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While the concept that physical forces such as tension and compression are involved in mature tissue modeling is widely accepted, the role of these specific types of mechanical loading in the differentiation and maturation of uncommitted cell types like human mesenchymal stem cells (hMSCs) is currently unknown. We observed that hMSCs have the fundamental ability to distinguish between dynamic tensile and compressive loading by regulating distinct gene expression patterns and that these differences in gene expression can be related to conformational changes in cell shape and volume. Dynamic tension was found to regulate both fibroblastic and osteogenic associated genes while dynamic compression up-regulated genes associated with chondrogenesis. Identifying genes involved in the mechanotransduction of different modes of physical loading in hMSC may greatly enhance the ability to rationally design tissue regeneration systems to restore proper tissue function.

27. [Stem Cells Dev.](#) 2009 Jan 6. [Epub ahead of print]

Umbilical cord mesenchymal stem cells: role of regulatory genes in their differentiation to osteoblasts.

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Umbilical cord (UC) mesenchymal stem cells (MSC) are being currently investigated as an alternative to bone marrow (BM) MSCs for bone repair and regeneration. Here, we describe the gene regulation of their differentiation to osteogenic, adipogenic and chondrogenic precursors and demonstrate their tendency to differentiate toward the osteoblast lineage. Fibroblast-like cells from the Warthons Jelly were cultured after induction with dedicated media to obtain osteogenic, adipogenic and chondrogenic differentiated cells. After induction, a typical fibroblast-like shape with condensed fibres of F-actin was early noted in osteogenic-induced UC-MSCs, whereas those differentiating to adipocytes were flat with minor cytoskeleton relevance. Real Time PCR measured the transcription of master genes of the three lineages, thus revealing a remarkable upregulation of Runx2 in osteogenic-induced cells with respect to both PPAR α and SOX9 for adipogenic and chondrogenic differentiating UC-MSCs. However, TAZ, a coactivator of the nuclear transcription of Runx2 previously detected in BM-MSCs, was expressed in osteogenic- and, at lower magnitude, in adipogenic-induced cells, in keeping with its role in the reciprocal control of the differentiation between osteogenic- and adipogenic-induced cells. Its differential role in these cells was confirmed by its accumulation as protein product in the nuclei to activate Runx2 in osteogenic differentiating UC-MSCs. These data emphasize the predominant expression by UC-MSCs of genes engaged in the osteogenic differentiation and their tendency to differentiate into osteoblasts, being similar in this respect to BM-MSCs. They may, thus, constitute a promising option for bone remodelling in regenerative medicine.

28. [Ann Rheum Dis](#). 2009 Jan 5. [Epub ahead of print]

Human adipose-derived mesenchymal stem cells reduce inflammatory and T-cell responses and induce regulatory T cells in vitro in rheumatoid arthritis.

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OBJECTIVES: Adult mesenchymal stem cells were recently found to suppress effector T-cell and inflammatory responses and have emerged as attractive therapeutic candidates for immune disorders. In rheumatoid arthritis (RA), a loss in the immunological self-tolerance causes the activation of autoreactive T cells against joint components and subsequent chronic inflammation. The aim of this study is to characterize the immunosuppressive activity of human adipose-derived mesenchymal stem cells (hASCs) on collagen-reactive T cells from RA patients. METHODS: We investigated the effects of hASCs on collagen-reactive RA human T-cell proliferation and cytokine production, as well as on the production of inflammatory mediators by monocytes and fibroblast-like synoviocytes from RA patients. RESULTS: hASCs suppressed antigen-specific response of T cells from RA patients. hASCs inhibited the proliferative response and the production of inflammatory cytokines by collagen-activated CD4 and CD8 T cells. In contrast, the number of IL-10-producing T cells and monocytes significantly augmented upon hASC-treatment. The suppressive activity of hASCs was both cell-to-cell contact-dependent and -independent. hASCs also stimulated the generation of FoxP3-expressing CD4+CD25+ regulatory T cells with capacity to suppress collagen-specific T-cell responses. Finally, hASCs downregulated the inflammatory response and the production of matrix-degrading enzymes by synovial cells isolated from RA patients. CONCLUSIONS: Our work identifies to hASCs as key regulators of immune tolerance with capacity to suppress T-cell and inflammatory responses to induce the generation/activation of antigen-specific regulatory T cells.

29. [J Pathol](#). 2009 Jan;

Why are MSCs therapeutic? New data: new insight.

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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 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.

30. [Carcinogenesis](#). 2009 Jan; Epub 2008 Oct 9.

Development of sarcomas in mice implanted with mesenchymal stem cells seeded onto bioscaffolds.

[Tasso R](#), [Augello A](#), [Carida' M](#), [Postiglione F](#), [Tibiletti MG](#), [Bernasconi B](#), [Astigiano S](#), [Fais F](#), [Truini M](#), [Cancedda R](#), [Pennesi G](#).

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Bone marrow-derived mesenchymal stem cells (MSCs) are precursors of bone, cartilage and fat tissue. MSC can also regulate the immune response. For these properties, they are tested in clinical trials for tissue repair in combination with bioscaffolds or injected as cell suspension for immunosuppressant therapy. Experimental data, however, indicate that MSC can undergo or induce a tumorigenic process in determined circumstances. We used a modified model of ectopic bone formation in mice by subcutaneously implanting porous ceramic seeded with murine MSC. In this new model, host-derived sarcomas developed when we implanted MSC/bioscaffold constructs into syngeneic and immunodeficient recipients, but not in allogeneic hosts or when MSCs were injected as cell suspensions. The bioscaffold provided a tridimensional support for MSC to aggregate, thus producing the stimulus for triggering the process eventually leading to the transformation of surrounding cells and creating a surrogate tumor stroma. The chemical and physical characteristics of the bioscaffold did not affect tumor formation; sarcomas developed either when a stiff porous ceramic was used or when the scaffold was a smooth collagen sponge. The immunoregulatory function of MSC contributed to tumor development. Implanted MSC expanded clones of CD4+CD25+ T regulatory lymphocytes that suppressed host's antitumor immune response.

31. BJOG. 2009 Jan;

Fetal mesenchymal stem cells: isolation, properties and potential use in perinatology and regenerative medicine.

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The fetus is a source of nonembryonic stem cells (SC), with potential applications in perinatal medicine. Cells derived from the placenta, membranes, amniotic fluid or fetal tissues are higher in number, expansion potential and differentiation abilities compared with SC from adult tissues. Although some obstacles keep SC biology at distance from clinical application, the feasibility of using (homologous) SC for tissue engineering for the fetus with a congenital birth defect has been demonstrated. Also, other pathologies may benefit from SC technology.

32. Curr Stem Cell Res Ther. 2009 Jan;

Multi- and inter-disciplinary science in personalized delivery of stem cells for tissue repair.

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Stem cell therapy has a place for future application in the treatment of degenerative diseases. Regardless of the origin of the stem cell, when placed within a milieu of inflammatory mediator, they will show varied functions. This review focuses on human mesenchymal stem cells (MSCs) and discusses neuronal replacement using multi- and inter-disciplinary approaches. We caution the enthusiasm of scientists since there is always the potential for tumor formation, even for adult stem cells. The review places RE-1 silencing transcription factor (REST) gene as central to the understanding of stem cell behavior in the microenvironment of tissue injury. REST is relevant in the development of dopaminergic and peptidergic neurons from MSCs. Premature downregulation of REST by the pro-inflammatory mediator, IL-1alpha, can prematurely lead to the expression of neurotransmitters, which in turn, could develop rapid crosstalk with immune cells. In-depth inter- and multi-disciplinary research will lead to rapid and safe translation of MSCs to patients. An understanding of the changes induced in MSCs by cytokines and other mediators will establish future application of MSCs and other stem cells for safe and effective treatments. This study also alludes to the potential of personalized medicine through engineering and mathematics.

33. [Proteomics](#), 2009 Jan;

Comparative proteomic analysis of human mesenchymal and embryonic stem cells: towards the definition of a mesenchymal stem cell proteomic signature.

[Roche S](#), [Delorme B](#), [Oostendorp RA](#), [Barbet R](#), [Caton D](#), [Noel D](#), [Boumediene K](#), [Papadaki HA](#), [Cousin B](#), [Crozet C](#), [Milhavet O](#), [Casteilla L](#), [Hatzfeld J](#), [Jorgensen C](#), [Charbord P](#), [Lehmann S](#).

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Mesenchymal stem cells (MSC) are adult multipotential progenitors which have a high potential in regenerative medicine. They can be isolated from different tissues throughout the body and their homogeneity in terms of phenotype and differentiation capacities is a real concern. To address this issue, we conducted a 2-DE gel analysis of mesenchymal stem cells isolated from bone marrow (BM), adipose tissue, synovial membrane and umbilical vein wall. We confirmed that BM and adipose tissue derived cells were very similar, which argue for their interchangeable use for cell therapy. We also compared human mesenchymal to embryonic stem cells and showed that umbilical vein wall stem cells, a neo-natal cell type, were closer to BM cells than to embryonic stem cells. Based on these proteomic data, we could propose a panel of proteins which were the basis for the definition of a mesenchymal stem cell proteomic signature.

34. [Curr Stem Cell Res Ther.](#) 2009 Jan;

Contribution of stem cells to kidney repair.

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A current explanation for development of chronic renal injury is the imbalance between injurious mechanism and regenerative repair. The possibility that stem cells contribute to the repair of glomerular and tubular damage is of great interest for basic and translational research. Endogenous bone marrow-derived stem cells have been implicated in the repair of renal tissue, although the lineage of stem cells recruited has not been determined. If endogenous bone marrow-derived stem cells repopulate injured nephrons directly or act indirectly over a paracrine/endocrine mechanism remains also controversial. Therapeutic administration of exogenous bone marrow derived stem cells in animal models of acute renal injury suggests that a stem cell-based therapy may improve the recovery of both glomerular and tubular compartments. Whereas the therapeutic benefit of sorted hematopoietic stem cells remains uncertain, several studies showed a beneficial effect of mesenchymal stem cell administration in models of acute tubular injury and of endothelial progenitors in acute glomerular injury. Recent studies demonstrate the presence of resident stem cells within the adult kidney. These cells are capable, when injected in animals with acute tubular injury, to localize to renal compartments and contribute to regeneration. This review summarizes the current literature on the physiological role of endogenous stem cells in renal regeneration and on the therapeutic potential of exogenous stem cell administration. Moreover, critical points that still need clarification, such as the homing mechanisms of stem cells to injured tissue, the secreted factors underlying the paracrine/endocrine mechanisms and the long-term behaviour of in vivo administered stem cells, are discussed.

35. Methods Mol Biol. 2009;

Production of hepatocyte-like cells from human amnion.

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Cells isolated from the placenta have been the subject of intense investigation because many of the cells express characteristics of multipotent or even pluripotent stem cells. Cells from the placental tissues such as amnion and chorion have been reported to display multilineage differentiation and surface marker and gene expression patterns consistent with embryonic stem (ES) and mesenchymal stem cells, respectively. We have reported that epithelial cells isolated from term placenta contain cells that express surface markers such as the stage-specific embryonic antigens (SSEA) and a gene expression profile that is similar to ES cells. When subjected to specific differentiation protocols, amniotic epithelial cells display markers of differentiation to cardiomyocytes, neurons, pancreatic cells and hepatocytes. If specific and efficient methods could be developed to induce differentiation of these cells to hepatocytes, the amnion may become a useful source of cells for hepatocyte transplants. Cells isolated from amnion also have some unique properties as compared to some other stem cell sources in that they are isolated from a tissue that is normally discarded following birth, they are quite plentiful and easily isolated and they do not produce tumors when transplanted. Cells isolated from the amnion may be a uniquely useful and noncontroversial stem cell source.

36. [Artif Organs](#). 2008 Dec;

Tissue-engineered skin containing mesenchymal stem cells improves burn wounds.

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There is increasing evidence showing that adult stem cells are useful for tissue regeneration. Bone marrow mesenchymal stem cells (MSCs) are self-renewing and are potent in differentiating into multiple cells and tissues. To investigate the practicability of repairing burn wounds with tissue-engineered (TE) skin combined with bone MSCs, we established a burn wound model in the porcine skin. With a controlling temperature and time of the burning device to obtain different degrees of burn wounds, a deep dermal partial thickness burn was introduced to the porcine skin using a heated-brass contact injury at 100 degrees C for 20 s. Collagen-GAG scaffolds were utilized as the matrix; MSCs separated from pigs were seeded on them to form the skin equivalent. When grafted to the burn wounds, the TE skin containing MSCs showed better healing and keratinization, less wound contraction, and more vascularization. Grafts proliferated well and contributed to the neo-tissues. These data suggest that TE skin containing MSCs in a burn defect can accelerate wound healing and receive satisfactory effects.

37. [Stem Cells Dev.](#) 2008 Dec;

Comparison of human placenta- and bone marrow-derived multipotent mesenchymal stem cells.

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Bone marrow is the traditional source of human multipotent mesenchymal stem cells (MSCs), but placenta appears to be an alternative and more readily available source. This study comprehensively compared human placenta-derived MSC (hpMSC) and human bone marrow-derived MSC (hbmMSC) in terms of cell characteristics, optimal growth conditions and in vivo safety specifically to determine if hpMSC could represent a source of human MSC for clinical trial. MSC were isolated from human placenta (hpMSC) and human bone marrow (hbmMSC) and expanded ex vivo using good manufacturing practice-compliant reagents. hpMSC and hbmMSC showed similar proliferation characteristics in different basal culture media types, fetal calf serum (FCS) concentrations, FCS heat-inactivation experiments, flask types and media replacement responsiveness. However, hpMSC and hbmMSC differed with respect to their proliferation capabilities at different seeding densities, with hbmMSC proliferating more slowly than hpMSC in every experiment. hpMSC had greater long-term growth ability than hbmMSC. MSC from both sources exhibited similar light microscopy morphology, size, cell surface phenotype, and mesodermal differentiation ability with the exception that hpMSC consistently appeared less able to differentiate to the adipogenic lineage. A comparison of both hbmMSC and hpMSC from early and medium passage cultures using single-nucleotide polymorphism (SNP) GeneChip analysis confirmed GTG-banding data that no copy number changes had been acquired during sequential passaging. In three of three informative cases (in which the gender of the delivered baby was male), hpMSC were of maternal origin. Neither hpMSC nor hbmMSC caused any acute toxicity in normal mice when injected intravenously at the same, or higher, doses than those currently used in clinical trials of hbmMSC. This study suggests that human placenta is an acceptable alternative source for human MSC and their use is currently being evaluated in clinical trials

38. [Cell Mol Immunol](#). 2008 Dec;

Transplantation of human bone marrow mesenchymal stem cell ameliorates the autoimmune pathogenesis in MRL/lpr mice.

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Recent evidence indicates that mesenchymal stem cells (MSC) possess immunosuppressive properties both in vitro and in vivo. We previously demonstrated the functional abnormality of bone marrow derived MSC in patients with systemic lupus erythematosus (SLE). In this study, we aimed to investigate whether transplantation of human bone marrow derived MSC affects the autoimmune pathogenesis in MRL/lpr mice. We found that human MSC from healthy donors reduced the proliferation of T lymphocytes from MRL/lpr mice in a dose-dependent fashion. Two weeks after in vivo transfer of MSC, we detected significantly reduced serum levels of anti ds-DNA antibodies and 24 hour proteinuria in MRL/lpr mice as compared with control groups without MSC transplantation. Moreover, flow cytometric analysis revealed markedly reduced number of CD4(+) T cells while increased Th1 subpopulation in MSC group and MSC + CTX group when compared with controls. Histopathological examination showed significantly reduced renal pathology in MSC-treated mice. Immunohistochemical studies further revealed reduced expression of TGF-beta, FN, VEGF and the deposition of complement C3 in renal tissue after MSC and MSC + CTX treatment. Taken together, we have demonstrated that transplantation of human MSC can significantly inhibit the autoimmune progression in MRL/lpr mice.

39. [Cell Biol Int](#). 2008 Dec;Epub 2008 Sep 25.

Neuronal characteristics of amniotic fluid derived cells after adenoviral transformation.

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Efficient transformation of primary human amniocytes by E1 gene functions of human adenovirus serotype 5 (Ad5) yield in stable cell lines, which exhibit morphological features of epithelial like cells. A thorough investigation using immunocytochemistry confirmed the expression of epithelial cell markers. The analysis also revealed the expression of neuronal and glial marker proteins, such as nestin, vimentin, A2B5 and GFAP. Using RT-PCR, transcripts of the neurotrophic factors nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial cell line derived neurotrophic factor (GDNF), and neurotrophin 3 (NT-3) could be detected. Neurotrophic factors could also be detected in the cell culture supernatants of transformed amniocytes. In line with previous experimental data on a human Ad5 E1-transformed embryonal kidney cell line (HEK-293), the results suggest a co-expression of epithelial and neuronal marker proteins in E1-transformed human amniotic fluid derived cells and thus a preferential transformation into neuronal-like cells.

40. [Stem Cells Dev.](#) 2008 Dec;

Non-invasive longitudinal tracking of human amniotic fluid stem cells in the mouse heart.

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Human stem cells from various sources have potential therapeutic applications. The clinical implementation of these therapies introduces the need for methods of noninvasive tracking of cells. The purpose of this study was to evaluate a high resolution magnetic resonance imaging (MRI) technique for in vivo detection and tracking of superparamagnetic micron sized iron oxide particle (MPIO)-labeled human amniotic fluid stem (hAFS) cells injected in the mouse heart. Because of the small subject size, MR signal and resolution of the in vivo MRI were increased using strong gradients, a 7.0 Tesla magnet, and an ECG and respiratory gated gradient echo sequence. MRI images of mouse heart were acquired during a 4 week course of this longitudinal study. At the end of the study, histological analysis was used to correlate cell localization with the MRI results. Introduction of MPIOs into hAFS had no significant effect upon cell proliferation and differentiation. Results of flow cytometry analysis indicated that hAFS cells remained labeled for up to 4 weeks. MRI of MPIO-labeled hAFS cells injected in agarose gels resulted in significant hypointense regions. Labeled hAFS cells injected into mouse hearts produced hypointense regions in the MR images that could be detected 24 hours and 7, 14, 21 and 28 days post injection. The co-localization of labeled cells within the hypointense regions was confirmed by histological analysis. These results indicate that high resolution MRI can be used successfully for noninvasive longitudinal tracking of hAFS cells injected in the mouse heart. The potential utility of this finding is that injected stem cells can be tracked in vivo and might serve to monitor cell survival, proliferation and integration into myocardial tissue.

41. [Sheng Wu Yi Xue Gong Cheng Xue Za Zhi](#), 2008 Dec

[Preliminary studies on repairing osteochondral defects in the rabbit knee joint by using porous PA66/n-HA combination mesenchymal stem cells]

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We have investigated the effects of repairing knee osteochondral defects in rabbit by using porous polyamide 66/nano-Hydroxyapatite (PA66/n-HA) combination bone marrow mesenchymal stem cells (MSCs). Eighteen 6-month-old New Zealand rabbits were used to produce the models of 4 mm x 4 mm osteochondral defect in the middle trochlea groove of femur. These models were randomly divided into 3 groups: PA66/n-HA + MSCs Group (Group A), PA66/n-HA group (Group B) and Operation control-group (Group C) in which operation for osteochondral defects was performed but neither material nor cells were implanted. The materials in Group A were seeded with MSCs (5×10^5) in vitro before being implanted in to defects. The materials in groups A and B were 0.5 - 0.8 mm lower than normal cartilage. The animals were killed 1 and 4 months after operation. We assessed the effects by means of macroscopic observation, HE staining, toluidine blue staining, immunohistochemistry assay for type I and type II collagen. Group A displayed a little effect at the 1 month, but at the 4th month, Group A showed better results, compared to Groups B and C. At this time point, the repair tissue of Group A was regular; it presented more metachromatic substance visualized by toluidine blue staining, and it expressed type II collagen(+ +) and type I collagen(+). These results demonstrate that the repair tissue in Group A is nearly hyaline cartilage. So we presume that porous PA66/n-HA provides biomechanical support, and at the same time, MSCs enhance the repair effects.

42. [Liver Int.](#) 2008 Dec 29. [Epub ahead of print]

Mesenchymal stem cells from human umbilical cords ameliorate mouse hepatic injury in vivo.

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Abstract Aims: To investigate human umbilical cord-derived mesenchymal stem cells (hUCMSCs) for use in the reversal of mouse hepatic injury. **Methods:** Human umbilical cord-derived mesenchymal stem cells, characterized by flow cytometry, were transplanted into carbon tetrachloride (CCl₄)-injured mice, and then followed for determination of localization and differentiation. Reverse transcriptase-polymerase chain reaction for the human 17alpha gene and fluorescence in situ hybridization analysis for the human X chromosome were used to locate exogenous hUCMSCs in mouse livers. Peripheral blood and liver specimens were collected at 7, 14 and 21 days after transplantation. For evaluating the recovery of injured liver tissues, serum aminotransferase was measured, and the pathological state of the hepatocytes was assessed. **Results:** The hUCMSCs were positive for the human MSC-specific markers CD13, CD29, CD44, CD105 and nerve growth factor receptor, but negative for the haematopoietic lineage markers CD31, CD34, CD38, CD45 and HLA-DR. Under conditions favouring differentiation in vivo, the expression of tryptophan 2,3-dioxygenase, human alpha-fetoprotein, cytokeratin 18, fibroblast secretory protein 1 and alpha-smooth-muscle-actin was detectable after hUCMSCs administration to mice subjected to liver injury. Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate (dUTP)-biotin nick end labelling and proliferating cell nuclear antigen staining showed that transplanted hUCMSCs could inhibit hepatocyte apoptosis and facilitate proliferation. Serum aminotransferases were decreased after transplantation of hUCMSCs into the injured mice, and hepatocyte denaturation was reduced. **Conclusions:** Human umbilical cord-derived mesenchymal stem cells can enhance recovery of CCl₄-injured mouse liver, providing evidence that such therapy could be useful for liver disorders or injury.

43. [Clin Chim Acta](#). 2008 Dec 25.

The free fatty acid metabolome in cerebral ischemia following human mesenchymal stem cell transplantation in rats.

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BACKGROUND: Mesenchymal stem cells (MSCs) have the potential to promote brain repair and improve recovery following stroke. We investigated changes in free fatty acids (FFAs) following intravenous human MSC (hMSC) transplantation into rats that had undergone transient middle cerebral artery occlusion (MCAo). METHODS: Rats were subjected to 2-hours MCAo, followed by intravenous transplantation of hMSC or phosphate-buffered saline (PBS) at one day after MCAo. All rats were sacrificed 5 days after MCAo. Metabolic profiling of free fatty acids (FFAs) level was assessed in plasma and brain from control rats (n=8), PBS-treated MCAo rats (n=6), and hMSC-treated MCAo rats (MCAo+hMSC, n=6). RESULTS: The levels of some FFAs in plasma and brain samples of the MCAo and MCAo+hMSC groups were significantly different from those of the control group. The percentage composition of myristic acid in plasma and those of myristic acid, linoleic acid, and eicosenoic acid in brain tissues of the MCAo+hMSC group were significantly reduced compared to those in the untransplanted MCAo group. CONCLUSION: Our metabolic approach has provided insights into understanding the complexity of biochemical and physiological events that occur in ischemic brain injury and the transplantation effects of MSCs in stroke.

44. [Acta Biomater.](#) 2008 Dec 24. [Epub ahead of print]

Ability of polyurethane foams to support cell proliferation and the differentiation of MSCs into osteoblasts.

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In bone tissue reconstruction, the use of engineered constructs created by mesenchymal stem cells (MSCs) that differentiate and proliferate into three-dimensional porous scaffolds is an appealing alternative to autologous and heterologous bone grafts. Scaffolds considered in this work are represented by polyurethane (PU) foams. Two PU foams (EC-1 and EC-2) were synthesized and characterized for morphology, mechanical properties and in vitro interaction with the osteoblast-like cell line MG63 and MSCs from human bone marrow. EC-1 and EC-2 showed similar densities (0.20gcm(-3)) with different morphologies: EC-1 showed a more homogeneous pore size (average $\Phi=691\mu\text{m}$) and distribution, with a 35% open porosity, whereas EC-2 evidenced a wide range of pore dimension, with an average pore size of 955 μm and a 74% open porosity. The compressive properties of the two foams were similar in the dry condition and both showed a strong decrease in the wet condition. In vitro tests showed good MG63 cell proliferation, as confirmed by the results of the MTT assay and scanning electron microscopy (SEM) observations, with a higher cell viability on EC-2 foam 7 days post-seeding. In the experiments with MSCs, SEM observations showed the presence of an inorganic phase deposition starting day 7 onto EC-1, day 14 onto EC-2. The inorganic particles (CaP) deposition was much more evident onto the pore surface of both foams at day 30, indicating good differentiation of MSCs into osteoblasts. Both PU foams therefore appeared to stimulate cell adhesion and proliferation in vitro, sustaining the MSCs' growth and differentiation into osteoblasts.

45. [Haematologica](#). 2008 Dec 23. [Epub ahead of print]

Mesenchymal stem cells: the fibroblasts' new clothes?

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Mesenchymal stem cells are adherent stromal cells, initially isolated from the bone marrow, characterized by their ability to differentiate into mesenchymal tissues such as bone, cartilage and fat. They have also been shown to suppress immune responses in vitro. Because of these properties, mesenchymal stem cells have recently received a very high profile. Despite the dramatic benefits reported in early phase clinical trials, their functions remain poorly understood. Particularly, several questions remain concerning the origin of mesenchymal stem cells and their relationship to other stromal cells such as fibroblasts. Whereas clear gene expression signatures are imprinted in stromal cells of different anatomical origins, the anti-proliferative effects of mesenchymal stem cells and fibroblasts and their potential to differentiate appear to be common features between these two cell types. In this review, we summarize recent studies in the context of historical and often neglected stromal cell literature, and present the evidence that mesenchymal stem cells and fibroblasts share much more in common than previously recognized.

46. [Am J Ther.](#) 2008 Dec 15. [Epub ahead of print]

Stem Cell Therapy for the Kidney?

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The kidney has a remarkable capacity to regenerate after injury, as it is not a terminally differentiated organ. This regenerative potential is somehow incomplete, however, and as the insult continues, progressive and irreversible scarring results in chronic renal disease. Dialysis and organ transplantation are nonspecific and incomplete methods of renal replacement therapy. Stem cells may provide a more efficacious method for both prevention and amelioration of renal disease of many etiologies. Although many reports have claimed the existence of renal-specific stem or progenitor cells isolated and characterized by various methods, the results have been diverse and debatable. The bone marrow stem cells seem to play a minor role in renal regeneration after acute ischemia in mice through transdifferentiation and cell fusion, but their immediate paracrine effects result in considerable improvements in renal function. Therefore, as in stem cell therapy for the heart, bone marrow-derived stem cells show promise in regeneration of the kidney. Although more research is needed in the basic science of renal regeneration, clinical research in animals has demonstrated the versatility of stem cell therapy. The first phase of clinical trials of bone marrow mesenchymal cells in protection against acute kidney injury may begin shortly. This will enable further exploration of stem cell therapy in renal patients with multiple comorbidities.

47. [Ann Hematol](#). 2008 Dec 6.

Baculovirus-transduced mouse amniotic fluid-derived stem cells maintain differentiation potential.

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Amniotic fluid-derived stem cells have attracted considerable attention in the field of regenerative medicine. Approach of genetic modification probably enhances their regenerative potential. In this work, we wanted to determine whether baculovirus as a new gene vector could efficiently and safely transduce mouse amniotic fluid-derived stem cells (mAFSs). Cells were isolated from mouse amniotic fluid and cultured in vitro. These cells were analyzed by examining phenotypes and differentiation potential. They were further transduced with baculovirus. Baculovirus-transduced mAFSs were induced to differentiate into adipogenic, osteogenic, myogenic, and neurogenic lineages. Mouse amniotic fluid-derived stem cells were successfully isolated and cultured in vitro. They were positive for CD29 and Sca-1, but negative for CD34, CD45, or CD11b. Furthermore, they could differentiate into adipocytes, osteocytes, myocytes, and neurocytes in vitro. Baculovirus could efficiently transduce mAFSs. More importantly, baculovirus-transduced mAFSs retained differentiation potential. Thus, baculovirus vector effective and safe transduction is an attractive promise for genetic modification of mAFSs. Baculovirus genetically modified mAFSs will probably be more suitable as vehicles for regenerative medicine.

48. [Br J Haematol](#). 2008 Dec 5. [Epub ahead of print]

Manufacturing of human placenta-derived mesenchymal stem cells for clinical trials.

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Summary Mesenchymal stem cells (MSC) are being used increasingly in clinical trials for a range of regenerative and inflammatory diseases. Bone marrow is the traditional source but is relatively inaccessible in large volume. MSC have now been derived from tissues other than bone marrow including placenta and adipose tissue. We have used placenta obtained after delivery as a source of MSC and have been unable to detect any marked differences from marrow-derived MSC in terms of cell surface phenotype, chemokine receptor display, mesodermal differentiation capacity or immunosuppressive ability. This report described our manufacturing process for isolating and expanding placenta-derived human MSC and their safe infusion into the first patient in a clinical trial program of human placenta-derived MSC.

49. [Stem Cells](#), 2008 Nov; Epub 2008 Aug 21.

Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages.

[Carraro G](#), [Perin L](#), [Sedrakyan S](#), [Giuliani S](#), [Tiozzo C](#), [Lee J](#), [Turcatel G](#), [De Langhe SP](#), [Driscoll B](#), [Bellusci S](#), [Minoo P](#), [Atala A](#), [De Filippo RE](#), [Warburton D](#).

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A new source of stem cells has recently been isolated from amniotic fluid; these amniotic fluid stem cells have significant potential for regenerative medicine. These cells are multipotent, showing the ability to differentiate into cell types from each embryonic germ layer. We investigated the ability of human amniotic fluid stem cells (hAFSC) to integrate into murine lung and to differentiate into pulmonary lineages after injury. Using microinjection into cultured mouse embryonic lungs, hAFSC can integrate into the epithelium and express the early human differentiation marker thyroid transcription factor 1 (TTF1). In adult nude mice, following hyperoxia injury, tail vein-injected hAFSC localized in the distal lung and expressed both TTF1 and the type II pneumocyte marker surfactant protein C. Specific damage of Clara cells through naphthalene injury produced integration and differentiation of hAFSC at the bronchioalveolar and bronchial positions with expression of the specific Clara cell 10-kDa protein. These results illustrate the plasticity of hAFSC to respond in different ways to different types of lung damage by expressing specific alveolar versus bronchiolar epithelial cell lineage markers, depending on the type of injury to recipient lung. Disclosure of potential conflicts of interest is found at the end of this article.

50. [Nat Clin Pract Urol](#). 2008 Nov, Epub 2008 Oct 14.

Stem cells in urology.

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The shortage of donors for organ transplantation has stimulated research on stem cells as a potential resource for cell-based therapy in all human tissues. Stem cells have been used for regenerative medicine applications in many organ systems, including the genitourinary system. The potential applications for stem cell therapy have, however, been restricted by the ethical issues associated with embryonic stem cell research. Instead, scientists have explored other cell sources, including progenitor and stem cells derived from adult tissues and stem cells derived from the amniotic fluid and placenta. In addition, novel techniques for generating stem cells in the laboratory are being developed. These techniques include somatic cell nuclear transfer, in which the nucleus of an adult somatic cell is placed into an oocyte, and reprogramming of adult cells to induce stem-cell-like behavior. Such techniques are now being used in tissue engineering applications, and some of the most successful experiments have been in the field of urology. Techniques to regenerate bladder tissue have reached the clinic, and exciting progress is being made in other areas, such as regeneration of the kidney and urethra. Cell therapy as a treatment for incontinence and infertility might soon become a reality. Physicians should be optimistic that regenerative medicine and tissue engineering will one day provide mainstream treatment options for urologic disorders.

51. [Cell Biol Int](#), 2008 Nov; Epub 2008 Aug 20

Characterization and hepatogenic differentiation of mesenchymal stem cells from human amniotic fluid and human bone marrow: a comparative study.

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Since stem cells can differentiate into hepatocyte, stem cell-based therapy becomes a potential alternative treatment for terminal liver diseases. However, an appropriate source of human mesenchymal stem cells (hMSCs) for hepatocytes has not yet been clearly elucidated. The aim of the present study was to investigate the in vitro biological characterization and hepatic differentiation potential of human amniotic fluid-derived mesenchymal stem cells (AF-hMSCs) and human bone marrow-derived mesenchymal stem cells (BM-hMSCs). Our results show that AF-hMSCs possess higher proliferation and self-renewal capacity than BM-hMSCs. Cytogenetic studies indicate that AF-hMSCs are as genetically stable as BM-hMSCs. Following incubation with specific hepatogenic agents, AF-hMSCs showed a higher hepatic differentiation potential than BM-hMSCs. Expression of several liver-specific markers was significantly greater in AF-hMSCs than in BM-hMSCs, as shown by real time RT-PCR and immunofluorescence (IF). In conclusion, AF-hMSCs possess superior potential for hepatic differentiation, making them more suitable for diverse terminal liver diseases.

52. Stem Cells. 2008 Nov; Epub 2008 Aug 21.

Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages.

[Carraro G](#), [Perin L](#), [Sedrakyan S](#), [Giuliani S](#), [Tiozzo C](#), [Lee J](#), [Turcatel G](#), [De Langhe SP](#), [Driscoll B](#), [Bellusci S](#), [Minoo P](#), [Atala A](#), [De Filippo RE](#), [Warburton D](#).

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A new source of stem cells has recently been isolated from amniotic fluid; these amniotic fluid stem cells have significant potential for regenerative medicine. These cells are multipotent, showing the ability to differentiate into cell types from each embryonic germ layer. We investigated the ability of human amniotic fluid stem cells (hAFSC) to integrate into murine lung and to differentiate into pulmonary lineages after injury. Using microinjection into cultured mouse embryonic lungs, hAFSC can integrate into the epithelium and express the early human differentiation marker thyroid transcription factor 1 (TTF1). In adult nude mice, following hyperoxia injury, tail vein-injected hAFSC localized in the distal lung and expressed both TTF1 and the type II pneumocyte marker surfactant protein C. Specific damage of Clara cells through naphthalene injury produced integration and differentiation of hAFSC at the bronchioalveolar and bronchial positions with expression of the specific Clara cell 10-kDa protein. These results illustrate the plasticity of hAFSC to respond in different ways to different types of lung damage by expressing specific alveolar versus bronchiolar epithelial cell lineage markers, depending on the type of injury to recipient lung. Disclosure of potential conflicts of interest is found at the end of this article.

53. [Int J Gynaecol Obstet](#). 2008 Nov;. Epub 2008 Aug 29.

Isolation of human mesenchymal stem cells from third-trimester amniotic fluid.

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OBJECTIVE: To determine whether mesenchymal stem cells (MSCs) can be isolated in third-trimester amniotic fluid (AF) and their differentiation induced. METHOD: Sufficient numbers of MSCs were isolated from the AF of 15 healthy women undergoing cesarean delivery in the third trimester to be cultured and induced to differentiate into osteocytes. RESULTS: Reverse-transcriptase polymerase chain reaction showed the MSCs to express the pluripotency marker gene OCT4, and flow cytometry showed these cells to be positive for CD29, CD73, CD90, and CD105 and negative for CD31, CD45, and CD61. The MSCs were also determined to be nontumorigenic. CONCLUSION: Multipotent MSCs can be obtained from AF in the third trimester, which may be less dangerous than the second trimester to women and their fetuses.

54. [Transpl Int](#). 2008 Nov 1. [Epub ahead of print]

Potential of mesenchymal stem cells as immune therapy in solid-organ transplantation.

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Over the last decade, there has been a rising interest in the use of mesenchymal stem cells (MSCs) for clinical applications. This interest stems from the beneficial properties of MSCs, which include multi-lineage differentiation and immunosuppressive ability, suggesting there is a role for MSC therapy for tissue regeneration and in immunologic disease. Despite recent clinical trials investigating the use of MSCs in treating immune-mediated disease, their applicability in solid-organ transplantation is still unknown. In this review, we identified topics that are important when considering MSC therapy in clinical organ transplantation. Whereas, from other clinical studies, it would appear that administration of MSCs is safe, issues like dosing, timing, route of administration, and in particular the use of autologous or donor-derived MSCs may be of crucial importance for the functional outcome of MSCs treatment in organ transplantation. We discuss these topics and assess the feasibility of MSCs therapy in organ transplantation.

55. [Stem Cells Dev.](#) 2008 Oct;

High transduction efficiency of human amniotic fluid stem cells mediated by adenovirus vectors.

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In the last few years some studies have shown the possibility of deriving progenitors with various potential from the amniotic fluid. Amniocentesis is a widely accepted method for prenatal diagnosis; it is associated with low risk both for the mother and the fetus and overcomes the ethical problems commonly associated to other sources. Recently we have described that amniotic fluid stem (AFS) cells, for their ability to differentiate to various lineages, could represent a good candidate for therapeutic applications. For gene therapy purposes human AFS (hAFS) cells should be genetically modified with a therapeutic gene and delivered systematically or injected directly into the tissue of interest. The aim of this study was to investigate the feasibility of transducing hAFS cells with adenoviral vectors and to determine whether transduced stem cells retain the ability to differentiate into different lineages. Herein, we showed that hAFS cells could be efficiently infected by first generation adenovirus vectors. In addition, we demonstrated that infection and expression of two different marker genes, LacZ and EGFP, have no effect on cells phenotype and differentiation potential. In particular, on undifferentiated status, hAFS cells continued to express both the transgenes and stemness cell markers OCT4 and SSEA4. When cultured under mesenchymal conditions, infected cells could still differentiate into osteocytes and adipocytes expressing lineage specific genes. These preliminary findings suggest that adenovirus may be useful to engineer populations of pluripotent stem cells, which may be used in a wide range of gene therapy treatments.

56. [Fertil Steril](#). 2008 Sep; Epub 2007 Nov 26.

Deleted in Azoospermia-Like (DAZL) gene-expressing cells in human amniotic fluid: a new source for germ cells research?

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OBJECTIVE: To evaluate whether amniotic fluid cells contain a germ-like cell subpopulation. DESIGN: Experimental study. SETTING: University hospital. PATIENT(S): None. INTERVENTION(S): Cells from human amniotic fluid samples were analyzed for messenger RNA expression of Deleted in Azoospermia-Like gene (DAZL) and Oct-4 by reverse transcriptase polymerase chain reaction. DAZL and C-kit protein expression was assessed by flow cytometry. Immunocytochemistry also was performed to determine DAZL-, stage-specific embryonic antigen 4 (SSEA-4)-, and Oct-4-positive cells. MAIN OUTCOME MEASURE(S): DAZL gene expression in amniotic fluid cells. RESULT(S): Reverse transcriptase polymerase chain reaction, flow cytometric, and immunocytochemical analyses revealed that human amniotic fluid consists of a distinct cell population that expresses DAZL, C-kit, SSEA-4, and Oct-4. CONCLUSION(S): Our results suggest that human amniotic fluid represents a new source for the isolation of human DAZL-, C-kit-, SSEA-4-, and Oct-4-positive stem cells without raising the ethical issues associated with human embryonic research.

57. [Sheng Wu Gong Cheng Xue Bao](#). 2008 Sep;

Differentiation of human amniotic fluid stem cells into cardiomyocytes through embryonic body formation

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To isolate human amniotic fluid stem cells (hASCs) and induce hASCs into cardiomyocytes after forming the embryonic bodies. We cultivated hASCs isolated from the amniotic fluid continually for over 42 passages. The biological characteristics of hASCs were detected by immunocytochemistry, RT-PCR and flow cytometer, hASCs at 10-15th passage were suspension cultured to form embryonic bodies that were induced to cardiomyocytes. Fibroblastoid-type hASCs were obtained. Immunocytochemistry, RT-PCR and flow cytometry analysis demonstrated that hASCs were positive for some specific makers of the embryonic stem cell. hASCs could form embryonic bodies that were alkaline-phosphatase positive and expressed fgf5, zeta-globin and alpha-fetoprotein. The embryonic bodies could differentiate into cardiomyocytes showing alpha-actin positive and Tbx5, Nkx2.5, GATA4 and alpha-MHC positive. We concluded that hASCs obtained from human amniotic fluid could differentiate into cardiomyocytes through the formation of embryonic bodies

58. [Amino Acids](#), 2008 Aug; Epub 2007 Aug 21

Human amniotic fluid stem cells: a new perspective.

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The discovery of amniotic fluid stem cells initiated a new and very promising field in stem cell research. In the last four years amniotic fluid stem cells have been shown to express markers specific to pluripotent stem cells, such as Oct-4. Due to their high proliferation potential, amniotic fluid stem cell lineages can be established. Meanwhile, they have been shown to harbor the potential to differentiate into cells of all three embryonic germ layers. It will be a major aim for the future to define the potential of this new source of stem cells for therapies related to specific diseases.

59. [Proc Am Thorac Soc](#). 2008 Aug 15;

Stem/progenitor cells in lung development, injury repair, and regeneration.

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At least two populations of epithelial stem/progenitor cells give rise to the lung anlage, comprising the laryngo-tracheal complex versus the distal lung below the first bronchial bifurcation. Amplification of the distal population requires FGF9-FGF10-FGFR2b-Sprouty signaling. Residual pools of adult stem cells are hypothesized to be the source of lung regeneration and repair. These pools have been located within the basal layer of the upper airways, within or near pulmonary neuroendocrine cell rests, at the bronchoalveolar junction as well as within the alveolar epithelial surface. Rapid repair of the denuded alveolar surface after injury is clearly key to survival. Strategies to enhance endogenous alveolar epithelial repair could include protection of epithelial progenitors from injury and/or stimulation of endogenous progenitor cell function. Protection with inosine or FGF signaling are possible small molecule therapeutic options. Alternatively, exogenous stem/progenitor cells can be delivered into the lung either intravenously, intratracheally, or by direct injection. Sources of exogenous stem/progenitor cells that are currently under evaluation in the context of acute lung injury repair include embryonic stem cells, bone marrow- or fat-derived mesenchymal stem cells, circulating endothelial progenitors, and, recently, amniotic fluid stem/progenitor cells. Further work will be needed to translate stem/progenitor cell therapy for the lung.

60. [Neurochem Res.](#) 2008 Aug 9.

Combination of G-CSF Administration and Human Amniotic Fluid Mesenchymal Stem Cell Transplantation Promotes Peripheral Nerve Regeneration.

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Amniotic fluid mesenchymal stem cells (AFS) harbor the potential to improve peripheral nerve injury by inherited neurotrophic factor secretion, but present the drawback of the short-term survival after transplantation. Granulocyte-colony stimulating factor (G-CSF) has a diversity of functions, including anti-inflammatory and anti-apoptotic effects. This study was conducted to evaluate whether G-CSF could augment the neuroprotective effect of transplanted AFS against peripheral nerve injury. The potential involvement of anti-inflammation/anti-apoptosis effect was also investigated. Peripheral nerve injury was produced in Sprague-Dawley rats by crushing left sciatic nerve using a vessel clamp. The AFS were embedded in fibrin glue and delivered to the injured site. G-CSF (50 mug/kg) was administrated by intra-peritoneal injection for 7 consecutive days. Cell apoptosis, inflammatory cytokines, motor function, and nerve regeneration were evaluated 7 or 28 days after injury. Crush injury induced inflammatory response, disrupted nerve integrity, and impaired nerve function in sciatic nerve. Crush injury-provoked inflammation was attenuated in groups receiving G-CSF but not in AFS only group. In transplanted AFS, marked apoptosis was detected and this event was reduced by G-CSF treatment. Increased nerve myelination and improved motor function were observed in AFS transplanted, G-CSF administrated, and AFS/G-CSF combined treatment groups. Significantly, the combined treatment showed the most beneficial effect. In conclusion, the concomitant treatment of AFS with G-CSF augments peripheral nerve regeneration which may involve the suppression of apoptotic death in implanted AFS and the attenuation of inflammatory response.

61. [Int J Immunopathol Pharmacol](#). 2008 Jul-Sep;

Potential role of culture mediums for successful isolation and neuronal differentiation of amniotic fluid stem cells.

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In recent years, the use of stem cells has generated increasing interest in regenerative medicine and cancer therapies. The most potent stem cells derive from the inner cell mass during embryonic development and their use yields serious ethical and methodological problems. Recently, a number of reports suggests that another suitable source of multipotent stem cells may be the amniotic fluid. Amniotic fluid mesenchymal stem cells (AFMSCs) are capable of extensive self-renewal, able to differentiate in specialized cells representative of all three germ layers, do not show ethical restriction, and display minimal risks of teratomas and a very low immunogenicity. For all these reasons, amniotic fluid appears as a promising alternative source for stem cell therapy. Their recent discovery implies a lack of knowledge of their specific features as well as the existence of a protocol universally recognized as the most suitable for their isolation, growth and long-term conservation. In this study, we isolated stem cells from six amniotic fluids; these cells were cultured with three different culture mediums (Mesenchymal Stem Cell Medium (MSCGM), PC-1 and RPMI-1640), characterized by cytofluorimetric analysis, and then either frozen or induced to neuronal differentiation. Even if the immunophenotype seemed not to be influenced by culture medium (all six samples cultured in the above-mentioned mediums expressed surface antigens commonly found on stem cells), cells showed different abilities to differentiate into neuron-like cells and to re-start the culture after short/long-term storage. Cells isolated and cultured in MSCGM showed the highest proliferation rate, and formed neuron-like cells when sub-plated with neuronal differentiation medium. Cells from PC-1, on the contrary, displayed an increased ability to re-start culture after short/long term storage. Finally, cells from RPMI-1640, even if expressing stem cells markers, were not able to differentiate in neuron-like cells. Further studies are still needed in order to assess the effective role of culture medium for a successful isolation, growth, differentiation and storage of AFMSCs, but our data underline the importance of finding a universally accepted protocol for the use of these cells.

Adult stem cells and their trans-differentiation potential-perspectives and therapeutic applications.

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Stem cells are self-renewing multipotent progenitors with the broadest developmental potential in a given tissue at a given time. Normal stem cells in the adult organism are responsible for renewal and repair of aged or damaged tissue. Adult stem cells are present in virtually all tissues and during most stages of development. In this review, we introduce the reader to the basic information about the field. We describe selected stem cell isolation techniques and stem cell markers for various stem cell populations. These include makers for endothelial progenitor cells (CD146/MCAM/MUC18/S-endo-1, CD34, CD133/prominin, Tie-2, Flk1/KD/VEGFR2), hematopoietic stem cells (CD34, CD117/c-Kit, Sca1), mesenchymal stem cells (CD146/MCAM/MUC18/S-endo-1, STRO-1, Thy-1), neural stem cells (CD133/prominin, nestin, NCAM), mammary stem cells (CD24, CD29, Sca1), and intestinal stem cells (NCAM, CD34, Thy-1, CD117/c-Kit, Flt-3). Separate section provides a concise summary of recent clinical trials involving stem cells directed towards improvement of a damaged myocardium. In the last part of the review, we reflect on the field and on future developments.

63. [J Heart Valve Dis.](#) 2008 Jul;

Cryopreserved amniotic fluid-derived cells: a lifelong autologous fetal stem cell source for heart valve tissue engineering.

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BACKGROUND AND AIM OF THE STUDY: Fetal stem cells represent a promising cell source for heart valve tissue engineering. In particular, amniotic fluid-derived cells (AFDC) have been shown to lead to autologous fetal-like heart valve tissues in vitro for pediatric application. In order to expand the versatility of these cells also for adult application, cryopreserved AFDC were investigated as a potential life-long available cell source for heart valve tissue engineering. **METHODS:** Human AFDC were isolated using CD133 magnetic beads, and then differentiated and analyzed. After expansion of CD133- as well as CD133+ cells up to passage 7, a part of the cells was cryopreserved. After four months, the cells were re-cultured and phenotyped by flow cytometry and immunohistochemistry, including expression of CD44, CD105, CD90, CD34, CD31, CD141, eNOS and vWF, and compared to their non-cryopreserved counterparts. The stem cell potential was investigated in differentiation assays. The viability of cryopreserved AFDC for heart valve tissue engineering was assessed by creating heart valve leaflets in vitro. **RESULTS:** After cryopreservation, amniotic fluid-derived CD133- and CD133+ cells retained their stem cell-like phenotype, expressing mainly CD44, CD90 and CD105. This staining pattern was comparable to that of their non-cryopreserved counterparts. Moreover, CD133- cells demonstrated differentiation potential into osteoblast-like and adipocyte-like cells. CD133+ cells showed characteristics of endothelial-like cells by eNOS, CD141 and beginning vWF expression. When used for the fabrication of heart valve leaflets, cryopreserved CD133- cells produced extracellular matrix elements comparable to their non-cryopreserved counterparts. Moreover, the resulting tissues showed a cellular layered tissue formation covered by functional endothelia. The mechanical properties were similar to those of tissues fabricated from non-cryopreserved cells. **CONCLUSION: The study results suggest that the use of cell bank technology fetal amniotic fluid-derived stem cells might represent a life-long available autologous cell source for heart valve tissue engineering, and also for adult application.**

64. Diabetes. 2008 Jul;

Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes.

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Mesenchymal stem cells (MSCs) are pluripotent stromal cells that have the potential to give rise to cells of diverse lineages. Interestingly, MSCs can be found in virtually all postnatal tissues. The main criteria currently used to characterize and identify these cells are the capacity for self-renewal and differentiation into tissues of mesodermal origin, combined with a lack in expression of certain hematopoietic molecules. Because of their developmental plasticity, the notion of MSC-based therapeutic intervention has become an emerging strategy for the replacement of injured tissues. MSCs have also been noted to possess the ability to impart profound immunomodulatory effects *in vivo*. Indeed, some of the initial observations regarding MSC protection from tissue injury once thought mediated by tissue regeneration may, in reality, result from immunomodulation. Whereas the exact mechanisms underlying the immunomodulatory functions of MSC remain largely unknown, these cells have been exploited in a variety of clinical trials aimed at reducing the burden of immune-mediated disease. This article focuses on recent advances that have broadened our understanding of the immunomodulatory properties of MSC and provides insight as to their potential for clinical use as a cell-based therapy for immune-mediated disorders and, in particular, type 1 diabetes.

65. Skeletal Radiol. 2008 Jul

Application of stem cells in bone repair.

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Bone has the ability to repair minor injuries through remodeling. However, when the host source of osteoprogenitors is compromised at the defect site, one effective treatment may be cell-based therapy, as it replenishes the area of bone loss with cells possessing osteogenic potential. This review is a concise comparison of different types of stem cells that have the potential to be used in tissue-engineered scaffolds for bone repair. The clinical use of mesenchymal stem or stromal cells isolated from the bone marrow for treating various diseases has been well documented. However, the scarcity of these cells prompts the search for alternative sources of multipotential cells such as amniotic fluid stem cells and umbilical cord perivascular cells. Embryonic stem cells are another controversial source of cells with osteogenic potential. These cells have the ability to differentiate into all cell types of the adult body. Issues such as the use of human embryos and the risk of contamination from animal-derived culture components continue to prevent the therapeutic use of ESCs. As a result, abundant research has been carried out to design defined culture conditions for culturing ESCs, and alternative strategies such as the generation of induced pluripotent stem cells are being developed to eliminate the need for using embryos for cell derivation. In addition to the cell source, the ability to control stem cell differentiation into functional bone and the choice of biomaterial are also paramount objectives that are being examined in research and clinical trials.

66. [J Tissue Eng Regen Med](#). 2008 Jun;

Updates on stem cells and their applications in regenerative medicine.

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Stem cells have the capacity for self-renewal and capability of differentiation to various cell lineages. Thus, they represent an important building block for regenerative medicine and tissue engineering. These cells can be broadly classified into embryonic stem cells (ESCs) and non-embryonic or adult stem cells. ESCs have great potential but their use is still limited by several ethical and scientific considerations. The use of bone marrow-, umbilical cord-, adipose tissue-, skin- and amniotic fluid-derived mesenchymal stem cells might be an adequate alternative for translational practice. In particular, bone marrow-derived stem cells have been used successfully in the clinic for bone, cartilage, spinal cord, cardiac and bladder regeneration. Several preclinical experimental studies are under way for the application of stem cells in other conditions where current treatment options are inadequate. Stem cells can be used to improve healthcare by either augmenting the body's own regenerative potential or developing new therapies. This review is not meant to be exhaustive but gives a brief outlook on the past, present and the future of stem cell-based therapies in clinical practice.

67. [Reprod Biomed Online](#). 2008 Jun;

Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy.

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Regenerative treatment of dilated, non-ischæmic cardiomyopathy represents a significant unmet clinical need. Intracoronary administration of autologous bone marrow stem cells has demonstrated positive results in treatment of post-infarct and chronic ischæmic patients. Limitations of this procedure include: invasiveness of bone marrow extraction and cardiac catheterization, and dependence on stem cell populations that are aged and possibly senescent. Here, the use of intravenously administered allogeneic placental matrix derived mesenchymal stem cells for treatment of dilated cardiomyopathy is discussed. Safety of this cell population has already been established in completed Phase I and II trials; however, to date, clinical implementation for dilated cardiomyopathy has not been reported. Preclinical studies have demonstrated that mesenchymal stem cells: (i) inhibit myocardial inflammation; (ii) inhibit cardiomyocyte apoptosis; (iii) stimulate angiogenesis; and (iv) display therapeutic activity in models of dilated cardiomyopathy. Clinical studies have demonstrated the ability of mesenchymal stem cells to inhibit post-infarct remodelling, as well as potentially block inflammatory processes in graft versus host and Crohn disease. Presented here is case report of a patient with dilated cardiomyopathy treated with intravenous allogeneic mesenchymal stem cells and expanded umbilical cord blood CD34 cells who underwent a profound clinical improvement.

68. [J Pediatr Surg](#). 2008 Jun;

Preclinical regulatory validation of a 3-stage amniotic mesenchymal stem cell manufacturing protocol.

[Steigman SA](#), [Armant M](#), [Bayer-Zwirello L](#), [Kao GS](#), [Silberstein L](#), [Ritz J](#), [Fauza DO](#).

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PURPOSE: Because of the 4 to 6-month interval between a diagnostic amniocentesis and birth, clinical application of amniotic mesenchymal stem cell (AMSC)-based therapies demands a 3-stage cell manufacturing process, including isolation/primary expansion, cryopreservation, and thawing/secondary expansion. We sought to determine the feasibility and cell yield of such a staged cell manufacturing process, within regulatory guidelines. **METHODS:** Human AMSCs isolated from diagnostic amniocentesis samples (n = 11) were processed under Food and Drug Administration-accredited good manufacturing practice. Expanded cells were characterized by flow cytometry and cryopreserved for 3 to 5 months. Cell release criteria included more than 90% CD29+, CD73+, and CD44+; less than 5% CD34+ and CD45+; negative mycoplasma quantitative polymerase chain reaction (QPCR) and endotoxin assay; and at least 70% viability. **RESULTS:** Isolation and ample expansion of AMSCs was achieved in 54.5% (6/11) of the samples. Early processing and at least a 2-mL sample were necessary for reliable cell manufacturing. Cell yield before cryopreservation was 223.2 +/- 65.4 x 10(6) cells (44.6-fold expansion), plus a 14.7 x 10(6)-cell backup, after 36.3 +/- 7.8 days. Cell viability postthaw was 88%. Expanded cells maintained a multipotent mesenchymal progenitor profile. **CONCLUSIONS:** Human amniotic mesenchymal stem cells can be manufactured in large numbers from diagnostic amniocentesis, by an accredited staged processing, under definite procurement guidelines. These data further support the viability of clinical trials of amniotic mesenchymal stem cell-based therapies

69. Pain Physician. 2008 May-Jun;

Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells.

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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 **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.

70. [Gynecol Endocrinol](#). 2008 May;

Oxytocin receptor- and Oct-4-expressing cells in human amniotic fluid.

[Stefanidis K](#), [Loutradis D](#), [Anastasiadou V](#), [Bletsas R](#), [Kiapekou E](#), [Drakakis P](#), [Beretsos P](#), [Elenis E](#), [Mesogitis S](#), [Antsaklis A](#).

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BACKGROUND/AIMS: The present clinical and molecular study aimed at investigating the presence of the genes encoding oxytocin receptor (OT-R) and Oct-4 in human amniotic fluid cells. **METHODS:** Amniotic fluid samples were obtained from amniocentesis. Cells from human amniotic fluid samples were analyzed for mRNA expression of OT-R and Oct-4 via reverse transcription-polymerase chain reaction (RT-PCR). Immunocytochemistry was also performed with OT-R and Oct-4 antibodies. **RESULTS:** RT-PCR from 10 independent amniocentesis samples demonstrated the expression of OT-R and Oct-4 mRNA. The cells also showed strong immunoreactivity for molecular markers of OT-R and Oct-4. **CONCLUSION:** OT-R and Oct-4 are expressed in human amniotic fluid cells. The role of oxytocin in the physiology and pathophysiology of amniotic fluid cells remains to be settled.

71. Nippon Rinsho. 2008 May;

Regenerative medicine for heart failure

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Heart failure is one of the most important cardiovascular health problems throughout the world and has high mortality, and there is a need to develop more effective therapeutic strategies to replace such specialized treatment as mechanical circulatory support and cardiac transplantation. Mesenchymal stem cells (MSC) are multipotent plastic-adherent cells obtained from bone marrow, adipose tissue, and other tissues and can be easily expanded in culture. MSC exert their role in cardiac regeneration not only by differentiating into specific cell types such as cardiomyocytes and vascular endothelial cells but also through paracrine effects via secretion of angiogenic and antiapoptotic factors. On the basis of information obtained from basic and translational research, several clinical trials have recently been started to evaluate the safety and efficacy of autologous MSC for heart failure.

72. Shock. 2008 May;

Human amniotic epithelial cells ameliorate behavioral dysfunction and reduce infarct size in the rat middle cerebral artery occlusion model.

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Human amniotic epithelial cells (hAECs), having the characteristics of both embryonic and pluripotent stem cells, have the potential to differentiate into various cells. A good deal of research has explored the clinical therapeutic potential of hAECs; rat amniotic epithelial cells have been reported to ameliorate functional deficits after stroke in rats, likely due to neuronal differentiation and cytokine secretion by these cells. We isolated hAECs and transfected them with glial cell line-derived neurotrophic factor (GDNF) or enhanced green fluorescent protein (EGFP) gene using lentiviral vectors. These cells were then transplanted into the brains of rats subjected to a transient middle cerebral artery occlusion. The hAECs survived and migrated to the ischemic area of rats, and some of the transplanted hAECs expressed the neuronal marker MAP2 and the neuronal progenitor marker Nestin, together with the astrocyte marker glial fibrillary acidic protein, and hAEC-EGFP can significantly ameliorate behavioral dysfunction and reduce infarct volume of ischemic rats. By transfecting the cells with lentiviral vectors, GDNF can be stably overexpressed in hAECs, and hAEC-GDNF can more rapidly rescue the deficits of rats after middle cerebral artery occlusion compared with hAEC-EGFP-treated rats. Moreover, the nontransduced cells also had effects comparable to the GDNF-transduced cells on caspase-3 and lesion volume. Because hAECs are in unlimited supply, and their use is not encumbered by ethical arguments, hAECs have a great advantage for stem cell therapy. This model holds tremendous potential for development into wide use in cell-mediated gene therapy in the future.

73. Lancet. 2008 May 10;

Comment in:

Lancet. 2008 May 10;

Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study.

Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardo ME, Remberger M, Dini G, Egeler RM, Bacigalupo A, Fibbe W, Ringdén O; Developmental Committee of the European Group for Blood and Marrow Transplantation.

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BACKGROUND: Severe graft-versus-host disease (GVHD) is a life-threatening complication after allogeneic transplantation with haemopoietic stem cells. Mesenchymal stem cells modulate immune responses in vitro and in vivo. We aimed to assess whether mesenchymal stem cells could ameliorate GVHD after haemopoietic-stem-cell transplantation. **METHODS:** Patients with steroid-resistant, severe, acute GVHD were treated with mesenchymal stem cells, derived with the European Group for Blood and Marrow Transplantation ex-vivo expansion procedure, in a multicentre, phase II experimental study. We recorded response, transplantation-related deaths, and other adverse events for up to 60 months' follow-up from infusion of the cells. **FINDINGS:** Between October, 2001, and January, 2007, 55 patients were treated. The median dose of bone-marrow derived mesenchymal stem cells was 1.4×10^6 (min-max range $0.4\text{--}9 \times 10^6$) cells per kg bodyweight. 27 patients received one dose, 22 received two doses, and six three to five doses of cells obtained from HLA-identical sibling donors (n=5), haploidentical donors (n=18), and third-party HLA-mismatched donors (n=69). 30 patients had a complete response and nine showed improvement. No patients had side-effects during or immediately after infusions of mesenchymal stem cells. Response rate was not related to donor HLA-match. Three patients had recurrent malignant disease and one developed de-novo acute myeloid leukaemia of recipient origin. Complete responders had lower transplantation-related mortality 1 year after infusion than did patients with partial or no response (11 [37%] of 30 vs 18 [72%] of 25; $p=0.002$) and higher overall survival 2 years after haemopoietic-stem-cell transplantation (16 [53%] of 30 vs four [16%] of 25; $p=0.018$). **INTERPRETATION:** Infusion of mesenchymal stem cells expanded in vitro, irrespective of the donor, might be an effective therapy for patients with steroid-resistant, acute GVHD.

74. Clin Pharmacol Ther. 2008 May;Epub 2007 Sep 26.

Comment in:

Clin Pharmacol Ther. 2008 May;

Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy.

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We evaluated the feasibility and safety of therapy with mesenchymal stem cells (MSCs) through consecutively intra-arterial and three repeated intravenous injections and compared the long-term prognosis between MSC-treated (n=11) and control multiple system atrophy (MSA) patients (n=18). The MSC-treated patients showed significantly greater improvement on the unified MSA rating scale (UMSARS) than the control patients at all visits throughout the 12-month study period. Orthostasis in UMSARS I items and cerebellar dysfunction-related items of UMSARS II items were significantly different in favor of MSC treatment compared to controls. Serial positron emission tomography scan in the MSC-treated group showed that increased fluorodeoxyglucose uptake from baseline was noted in cerebellum and frontal white matters. No serious adverse effects related to MSC therapy occurred. This study demonstrated that MSC therapy in patients with MSA was safe and delayed the progression of neurological deficits with achievement of functional improvement in the follow-up period.

75. J Gastroenterol Hepatol. 2008 May;

Liver stem cells: a scientific and clinical perspective.

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The promise of liver stem cells lie in their potential to provide a continual and readily available source of liver cells that can be used for gene therapy, cellular transplant, bioartificial liver-assisted devices, drug toxicology testing and use as an in vitro model to understand the developmental biology of the liver. Both the rodent and human embryonic stem cell, bone marrow hematopoietic stem cell, mesenchymal stem cell, umbilical cord blood cell, fetal liver progenitor cell, adult liver progenitor cell as well as the mature hepatocyte have been reported to be capable of self-renewal, giving rise to daughter hepatocytes both in vivo and in vitro. These cells can repopulate livers in animal models of liver injury and seemingly improve liver function. However, significant challenges still exist before these cells can be used in humans. These include lack of consensus in immunophenotype of liver progenitor cells, uncertainty of the physiological role of reported candidate stem/progenitor cell, practicality in obtaining sufficient quantity of cells for clinical use and concerns over ethics, long-term efficacy and safety. Current molecular techniques of stem cell identification are confounded by cell fusion, horizontal gene transfer, incomplete differentiation and fetal microchimerism. Reports of stem cell transplantation and phase 1 trials of bone marrow transplantation in humans for liver diseases are exciting but require more robust verification. We review the evidence for various candidate stem cells, human clinical trials reported to date and highlight the challenges facing clinicians in their quest to use liver stem cells to save lives.

76. Pediatr Res. 2008 May;

Stem cell and regenerative science applications in the development of bioengineering of renal tissue.

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A rising number of patients with acute and chronic renal failure worldwide have created urgency for clinicians and investigators to search out alternative therapies other than chronic renal dialysis and/or organ transplantation. This review focuses on the recent achievements in this area, and discusses the various approaches in the development of bioengineering of renal tissue including recent discoveries in the field of regenerative medicine research and stem cells. A variety of stem cells, ranging from embryonic, bone marrow, endogenous, and amniotic fluid, have been investigated and may prove useful as novel alternatives for organ regeneration both in vitro and in vivo. Tissue engineering, developmental biology, and therapeutic cloning techniques have significantly contributed to our understanding of some of the molecular mechanisms involved in renal regeneration and have demonstrated that renal tissue can be generated de novo with similar physiologic functions as native tissue. Ultimately all of these emerging technologies may provide viable therapeutic options for regenerative medicine applications focused on the bioengineering of renal tissue for the future.

77. Stem Cell Rev. 2008 Spring;

Sources of stem cells for regenerative medicine.

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The shortage of organ donors for regenerative medicine has stimulated research on stem cells as a potential resource for cell-based therapy. Stem cells have been used widely for regenerative medicine applications. The development of innovative methods to generate stem cells from different sources suggests that there may be new alternatives for cell-based therapies. Here, we provide an overview of human embryonic stem cells (hES) and the methods for obtaining these cells and other broadly multipotent or pluripotent cell types. These methods include somatic cell nuclear transfer, single cell embryo biopsy, arrested embryos, altered nuclear transfer, and reprogramming somatic cells. We also discuss the use of amniotic-fluid derived stem cells (AFS) for potential patient-specific therapies.

78. Stem Cell Rev. 2008 Spring;

Dental pulp stem cells: a promising tool for bone regeneration.

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Human tissues are different in term of regenerative properties. Stem cells are a promising tool for tissue regeneration, thanks to their particular characteristics of proliferation, differentiation and plasticity. Several "loci" or "niches" within the adult human body are colonized by a significant number of stem cells. However, access to these potential collection sites often is a limiting point. The interaction with biomaterials is a further point that needs to be considered for the therapeutic use of stem cells. Dental pulp stem cells (DPSCs) have been demonstrated to answer all of these issues: access to the collection site of these cells is easy and produces very low morbidity; extraction of stem cells from pulp tissue is highly efficiency; they have an extensive differentiation ability; and the demonstrated interactivity with biomaterials makes them ideal for tissue reconstruction. SBP-DPSCs are a multipotent stem cell subpopulation of DPSCs which are able to differentiate into osteoblasts, synthesizing 3D woven bone tissue chips in vitro and that are capable to synergically differentiate into osteoblasts and endotheliocytes. Several studied have been performed on DPSCs and they mainly found that these cells are multipotent stromal cells that can be safety cryopreserved, used with several scaffolds, that can extensively proliferate, have a long lifespan and build in vivo an adult bone with Havers channels and an appropriate vascularization. A definitive proof of their ability to produce dentin has not been yet done. Interestingly, they seem to possess immunoprivileges as they can be grafted into allogenic tissues and seem to exert anti-inflammatory abilities, like many other mesenchymal stem cells. The easy management of dental pulp stem cells make them feasible for use in clinical trials on human patients.

79. [Curr Opin Pharmacol](#). 2008 Apr; Epub 2008 Mar 4.

Heart regeneration: what cells to use and how?

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Coronary artery disease (CAD) is the leading cause of death in modern societies. Recent achievements in the treatment of CAD including statins, ACE inhibitors, beta blockers, and interventional procedure improved the outcome of patients with CAD, but this conventional approach failed to control cardiovascular mortality. Nowadays, cells (stem cells) and their potential role in managing patients with heart disease is a field of intensive research. Various types of cells have been used for transplantation targeting heart regeneration, including bone marrow cells (BMCs), cardiac stem cells (CSCs), endothelial progenitor cells (EPCs), skeletal myoblasts (SMs), adipose stroma tissue cells (ATSCs), mesenchymal cells (MCs), and embryonic stem cells (ESCs). Several routes have been used to deliver these cells to human myocardium or to the coronary circulation such as, intracoronary injection, intravenous infusion, direct injection into the ventricular wall, or transepicardial/transendocardial infusions. Although the results of the recent clinical trials in this area are rather conflicting, these therapeutic approaches seem to be promising for the treatment of ischemic heart disease.

80. J Pediatr Hematol Oncol. 2008 Apr;

Biologic characteristics of mesenchymal stromal cells and their clinical applications in pediatric patients.

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In the past few years, intensive research in the understanding of the biologic characteristics of the mesenchymal stromal cells has already led to some early clinical applications. The aim of this review is to summarize the latest information from basic science advances and the outcome of their use in clinical practice with a particular focus in pediatric patients. The minimum criteria required to identify mesenchymal stromal cells, their immunosuppressive-nonimmunogenic properties and their attribution in the treatment of graft-versus-host disease, in the acceleration of hematopoietic recovery, in tissue repair/tissue engineering and in the treatment of selected inherited disorders are discussed. Appropriate preclinical models, completion of ongoing and development of new clinical trials will establish the role of these cells in the treatment of both adult and pediatric patients.

81. [Haematologica](#). 2008 Mar; Epub 2008 Feb 11.

Multipotent mesenchymal stromal cells from amniotic fluid: solid perspectives for clinical application.

[Sessarego N](#), [Parodi A](#), [Podestà M](#), [Benvenuto F](#), [Mogni M](#), [Raviolo V](#), [Lituanica M](#), [Kunkl A](#), [Ferlazzo G](#), [Bricarelli FD](#), [Uccelli A](#), [Frassoni F](#).

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BACKGROUND: Mesenchymal stromal cells are multipotent cells considered to be of great promise for use in regenerative medicine. However, the cell dose may be a critical factor in many clinical conditions and the yield resulting from the ex vivo expansion of mesenchymal stromal cells derived from bone marrow may be insufficient. Thus, alternative sources of mesenchymal stromal cells need to be explored. In this study, mesenchymal stromal cells were successfully isolated from second trimester amniotic fluid and analyzed for chromosomal stability to validate their safety for potential utilization as a cell therapy product. DESIGN AND METHODS: Mesenchymal stromal cells were expanded up to the sixth passage starting from amniotic fluid using different culture conditions to optimize large-scale production. RESULTS: The highest number of mesenchymal stromal cells derived from amniotic fluid was reached at a low plating density; in these conditions the expansion of mesenchymal stromal cells from amniotic fluid was significantly greater than that of adult bone marrow-derived mesenchymal stromal cells. Mesenchymal stromal cells from amniotic fluid represent a relatively homogeneous population of immature cells with immunosuppressive properties and extensive proliferative potential. Despite their high proliferative capacity in culture, we did not observe any karyotypic abnormalities or transformation potential in vitro nor any tumorigenic effect in vivo. CONCLUSIONS: Fetal mesenchymal stromal cells can be extensively expanded from amniotic fluid, showing no karyotypic abnormalities or transformation potential in vitro and no tumorigenic effect in vivo. They represent a relatively homogeneous population of immature mesenchymal stromal cells with long telomeres, immunosuppressive properties and extensive proliferative potential. Our results indicate that amniotic fluid represents a rich source of mesenchymal stromal cells suitable for banking to be used when large amounts of cells are required.

82. [Cell Transplant](#). 2008;

Different cardiovascular potential of adult- and fetal-type mesenchymal stem cells in a rat model of heart cryoinjury.

[Iop L](#), [Chiavegato A](#), [Callegari A](#), [Bollini S](#), [Piccoli M](#), [Pozzobon M](#), [Rossi CA](#), [Calamelli S](#), [Chiavegato D](#), [Gerosa G](#), [De Coppi P](#), [Sartore S](#).

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Efficacy of adult (bone marrow, BM) versus fetal (amniotic fluid, AF) mesenchymal stem cells (MSCs) to replenish damaged rat heart tissues with new cardiovascular cells has not yet been established. We investigated on the differentiation potential of these two rat MSC populations in vitro and in a model of acute necrotizing injury (ANI) induced by cryoinjury. Isolated BM-MSCs and AF-MSCs were characterized by flow cytometry and cytocentrifugation and their potential for osteogenic, adipogenic, and cardiovascular differentiation assayed in vitro using specific induction media. The left anterior ventricular wall of syngeneic Fisher 344 (n = 48) and athymic nude (rNu) rats (n = 6) was subjected to a limited, nontransmural epicardial ANI in the approximately one third of wall thickness without significant hemodynamic effects. The time window for in situ stem cell transplantation was established at day 7 postinjury. Fluorochrome (CMTMR)-labeled BM-MSCs (2×10^6) or AF-MSCs (2×10^6) were injected in syngeneic animals (n = 26) around the myocardial lesion via echocardiographic guidance. Reliability of CMTMR cell tracking in this context was ascertained by transplanting genetically labeled BM-MSCs or AF-MSCs, expressing the green fluorescent protein (GFP), in rNu rats with ANI. Comparison between the two methods of cell tracking 30 days after cell transplantation gave slightly different values (1420.58 ± 129.65 cells/mm² for CMTMR labeling and 1613.18 ± 643.84 cells/mm² for genetic labeling; p = NS). One day after transplantation about one half CMTMR-labeled AF-MSCs engrafted to the injured heart (778.61 ± 156.28 cells/mm²) in comparison with BM-MSCs (1434.50 ± 173.80 cells/mm², p < 0.01). Conversely, 30 days after cell transplantation survived MSCs were similar: 1275.26 ± 74.51 /mm² (AF-MSCs) versus 1420.58 ± 129.65 /mm² for BM-MSCs (p = NS). Apparent survival gain of AF-MSCs between the two time periods was motivated by the cell proliferation rate calculated at day 30, which was lower for BM-MSCs (6.79 ± 0.48) than AF-MSCs (10.83 ± 3.50 ; p < 0.01), in the face of a similar apoptotic index (4.68 ± 0.20 for BM-MSCs and 4.16 ± 0.58 for AF-MSCs; p = NS). These cells were also studied for their expression of markers specific for endothelial cells (ECs), smooth muscle cells (SMCs), and cardiomyocytes (CMs) using von Willebrand factor (vWf), smooth muscle (SM) alpha-actin, and cardiac troponin T, respectively. Grafted BM-MSCs or AF-MSCs were found as single cell/small cell clusters or incorporated in the wall

of microvessels. A larger number of ECs (227.27 +/- 18.91 vs. 150.36 +/- 24.08 cells/mm², p < 0.01) and CMs (417.91 +/- 100.95 vs. 237.43 +/- 79.99 cells/mm², p < 0.01) originated from AF-MSCs than from BM-MSCs. Almost no SMCs were seen with AF-MSCs, in comparison to BM-MSCs (98.03 +/- 40.84 cells/mm²), in concordance with lacking of arterioles, which, instead, were well expressed with BM-MSCs (71.30 +/- 55.66 blood vessels/mm²). The number of structurally organized capillaries was slightly different with the two MSCs (122.49 +/- 17.37/mm² for AF-MSCs vs. 148.69 +/- 54.41/mm² for BM-MSCs; p = NS). Collectively, these results suggest that, in the presence of the same postinjury microenvironment, the two MSC populations from different sources are able to activate distinct differentiation programs that potentially can bring about a myocardial-capillary or myocardial-capillary-arteriole reconstitution.

83. [Methods Cell Biol.](#) 2008;

Characterization of human amniotic fluid stem cells and their pluripotential capability.

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Over the past decade, there has been ever-increasing emphasis placed on stem cells and their potential role in regenerative medicine for reconstruction of bio-artificial tissues and organs. Scientists have looked at various sources for pluripotential cells ranging from embryonic stem cells to adult stem cells. Amniocentesis is a well-established technique for the collection of cells derived from the human embryo. In this chapter, we are going to describe how to isolate, maintain in culture, and characterize the pluripotential capabilities of stem cells derived from amniocentesis in an in vitro and in vivo system. Cell samples are obtained from human pregnancies, and the progenitor cells are isolated from male fetuses with a normal karyotype in order to confirm the absence of maternal admixed cells. Progenitor cells express embryonic-specific cell markers, they show a high self-renewal capacity with 350 population doublings, and normal ploidy is confirmed by cell-cycle analyses. They maintain their undifferentiated state, pluripotential ability, clonogenicity, and telomere length over the population doublings. The progenitor cells are inducible to different cell lineages (osteogenic, adipogenic, skeletal muscle, endothelial, neuronal, and hepatic cells) under specific growth conditions. The ability to induce cell-type-specific differentiation is confirmed by phenotypic changes, immunocytochemistry, gene expression, and functional analyses. In addition, we will describe an application of these cells in an ex vivo and in vivo system for potential in organ (renal) regeneration. The progenitor cells described in this chapter have a high potential for expansion, and may be a good source for research and therapeutic applications where large numbers of cells are needed. Progenitor cells isolated during gestation may be beneficial for fetuses diagnosed with malformations and could be cryopreserved for future self-use.

84. Cell Transplant. 2008;

Comparative characterization of cultured human term amnion epithelial and mesenchymal stromal cells for application in cell therapy.

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Emerging evidence suggests human amnion tissue as a valuable source of two distinct types of pluripotent cells, amnion epithelial cells (hAECs) and mesenchymal stromal cells (hAMSCs), for applications in cell replacement therapy. For some approaches, it may be necessary to culture and differentiate these cells before they can be transplanted. No systematic attempt has been yet made to determine the quantity and quality of amnion cells after isolation and culture. We looked at amnion cell isolates from 27 term placentas. Following our optimized protocol, primary yields were 6.3×10^6 hAECs and 1.7×10^6 hAMSCs per gram amnion. All 27 cases gave vital cultures of hAMSCs, while one third of cases (9 of 27) failed to give adherent cultures of hAECs. Primary cultures contained significantly more proliferating than apoptotic cells (hAECs: 16.4% vs. 4.0%; hAMSCs: 9.5% vs. 2.4%). Neither hAECs nor hAMSCs were clonogenic. They showed slow proliferation that almost stopped beyond passage 5. Microscopic follow-up revealed that hAEC morphology gradually changed towards mesenchymal phenotype over several passages. Flow cytometric characterization of primary cultures showed expression of mesenchymal progenitor markers CD73, CD90, CD105, and CD166, as well as the embryonic stem cell markers SSEA-3 and -4 on both amnion cell types. These profiles were grossly maintained in secondary cultures. Reverse transcriptase-PCR analysis exhibited transcripts of Oct-3/4 and stem cell factor in primary and secondary cultures of all cases, but no telomerase reverse transcriptase. Immunocytochemistry confirmed translation into Oct-3/4 protein in part of hAEC cultures, but not in hAMSCs. Further, both amnion cell types stained for CD90 and SSEA-4. Osteogenic induction studies with amnion cells from four cases showed significantly stronger differentiation of hAECs than hAMSCs; this capacity to differentiate greatly varied between cases. In conclusion, hAECs and hAMSCs in culture exhibit and maintain a similar marker profile of mesenchymal progenitors. hAECs were found as a less reliable source than hAMSCs and altered morphology during subculture.

85. Minim Invasive Ther Allied Technol. 2008;

Adult mesenchymal stromal stem cells for therapeutic applications.

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Mesenchymal stromal stem cells (MSC) can be found in almost any adult organ. They can be isolated and expanded within several weeks up to hundreds of millions of cells. The cell isolation based on the surface antigen expression may significantly enrich for the desired cell population and reduce the time required for cell expansion. MSC display a unique molecular signature which clearly discriminates them from other stem cell types. MSC can be differentiated into the cells of several lineages. Additionally, the unique biological properties of MSC are mediated by strong immunomodulatory activity and by paracrine mechanisms. Potential therapeutic applications of the cells require clinically compliant protocols for cell isolation and expansion. The therapeutic utility of MSC has been evaluated and found to be useful in several pre-clinical animal models as well as in clinical trials.

86. Semin Cell Dev Biol. 2007 Dec; Epub 2007 Sep 18.

Therapeutic applications of mesenchymal stromal cells.

Brooke G, Cook M, Blair C, Han R, Heazlewood C, Jones B, Kambouris M, Kollar K, McTaggart S, Pelekanos R, Rice A, Rossetti T, Atkinson K.

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Mesenchymal stromal cells (MSC) are multipotent cells that can be derived from many different organs and tissues. They have been demonstrated to play a role in tissue repair and regeneration in both preclinical and clinical studies. They also have remarkable immunosuppressive properties. We describe their application in settings that include the cardiovascular, central nervous, gastrointestinal, renal, orthopaedic and haematopoietic systems. Manufacturing of MSC for clinical trials is also discussed. Since tissue matching between MSC donor and recipient does not appear to be required, MSC may be the first cell type able to be used as an "off-the-shelf" therapeutic product.

87. Stem Cell Rev. 2007 Dec;

Stem cells in amniotic fluid as new tools to study human genetic diseases.

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In future, the characterization and isolation of different human stem cells will allow the detailed molecular investigation of cell differentiation processes and the establishment of new therapeutic concepts for a wide variety of diseases. Since the first successful isolation and cultivation of human embryonic stem cells about 10 years ago, their usage for research and therapy has been constrained by complex ethical consideration as well as by the risk of malignant development of undifferentiated embryonic stem cells after transplantation into the patient's body. Adult stem cells are ethically acceptable and harbor a low risk of tumor development. However, their differentiation potential and their proliferative capacity are limited. About 4 years ago, the discovery of amniotic fluid stem cells, expressing Oct-4, a specific marker of pluripotent stem cells, and harboring a high proliferative capacity and multilineage differentiation potential, initiated a new and promising stem cell research field. In between, amniotic fluid stem cells have been demonstrated to harbor the potential to differentiate into cells of all three embryonic germ layers. These stem cells do not form tumors in vivo and do not raise the ethical concerns associated with human embryonic stem cells. Further investigations will reveal whether amniotic fluid stem cells really represent an intermediate cell type with advantages over both, adult stem cells and embryonic stem cells. The approach to generate clonal amniotic fluid stem cell lines as new tools to investigate molecular and cell biological consequences of human natural occurring disease causing mutations is discussed.

Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: comparison to bone marrow mesenchymal stem cells.

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Human mesenchymal stem cells (hMSCs) constitute a population of multipotent adherent cells able to give rise to multiple mesenchymal lineages such as osteoblasts, adipocytes, or chondrocytes. So far, the most common source of MSCs has been the bone marrow (BM); however BM-MSC harvesting and processing exhibits major drawbacks and limitations. Thus, identification and characterization of alternative sources of MSCs are of great importance. In the present study, we isolated and expanded fetal MSCs from second-trimester amniotic fluid (AF). We documented that these cells are of embryonic origin, can differentiate under appropriate conditions into cell types derived from all three germ layers, and express the pluripotency marker Oct-4, the human Nanog protein, and the stage-specific embryonic antigen-4 (SSEA-4). Furthermore, we systematically tested the immunophenotype of cultured MSCs by flow cytometry analysis using a wide variety of markers. Direct comparison of this phenotype to the one derived from cultured BM-MSCs demonstrated that cultured MSCs from both sources exhibit similar expression patterns. Using the two-dimensional gel electrophoresis and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) approach, we have generated for the first time the protein map of cultured AF-MSCs by identifying 261 proteins, and we compared it directly to that of cultured BM-MSCs. The functional pattern of the identified proteins from both sources was similar. However, cultured AF-MSCs displayed a number of unique proteins related to proliferation and primitive phenotype, which may confer to the distinct features of the two types. Considering the easy access to this new cell source and the yield of expanded MSCs for stem cell research, AF may provide an excellent source of MSCs both for basic research and for potential therapeutic applications.

89. Cell Prolif. 2007 Dec;

Renal differentiation of amniotic fluid stem cells.

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OBJECTIVES: The role of stem cells in regenerative medicine is evolving rapidly. Here, we describe the application, for kidney regeneration, of a novel non-genetically modified stem cell, derived from human amniotic fluid. We show that these pluripotent cells can develop and differentiate into de novo kidney structures during organogenesis in vitro. MATERIALS AND METHODS: Human amniotic fluid-derived stem cells (hAFSCs) were isolated from human male amniotic fluid obtained between 12 and 18 weeks gestation. Green fluorescent protein and Lac-Z-transfected hAFSCs were microinjected into murine embryonic kidneys (12.5-18 days gestation) and were maintained in a special co-culture system in vitro for 10 days. Techniques of live microscopy, histology, chromogenic in situ hybridization and reverse transcriptase polymerase chain reaction were used to characterize the hAFSCs during their integration and differentiation in concert with the growing organ. RESULTS: Green fluorescent protein and Lac-Z-transfected hAFSCs demonstrated long-term viability in organ culture. Histological analysis of injected kidneys revealed that hAFSCs were capable of contributing to the development of primordial kidney structures including renal vesicle, C- and S-shaped bodies. Reverse transcriptase polymerase chain reaction confirmed expression of early kidney markers for: zona occludens-1, glial-derived neurotrophic factor and claudin. CONCLUSIONS: Human amniotic fluid-derived stem cells may represent a potentially limitless source of ethically neutral, unmodified pluripotential cells for kidney regeneration.

Chondrogenic differentiation of amniotic fluid-derived stem cells.

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For regenerating damaged articular cartilage, it is necessary to identify an appropriate cell source that is easily accessible, can be expanded to large numbers, and has chondrogenic potential. Amniotic fluid-derived stem (AFS) cells have recently been isolated from human and rodent amniotic fluid and shown to be highly proliferative and broadly pluripotent. The purpose of this study was to investigate the chondrogenic potential of human AFS cells in pellet and alginate hydrogel cultures. Human AFS cells were expanded in various media conditions, and cultured for three weeks with growth factor supplementation. There was increased production of sulfated glycosaminoglycan (sGAG) and type II collagen in response to transforming growth factor-beta (TGF-beta) supplementation, with TGF-beta1 producing greater increases than TGF-beta3. Modification of expansion media supplements and addition of insulin-like growth factor-1 during pellet culture further increased sGAG/DNA over TGF-beta1 supplementation alone. Compared to bone marrow-derived mesenchymal stem cells, the AFS cells produced less cartilaginous matrix after three weeks of TGF-beta1 supplementation in pellet culture. Even so, this study demonstrates that AFS cells have the potential to differentiate along the chondrogenic lineage, thus establishing the feasibility of using these cells for cartilage repair applications.

91. Chang Gung Med J. 2007 Sep-Oct;

Isolation and differentiation of human mesenchymal stem cells obtained from second trimester amniotic fluid; experiments at Chang Gung Memorial Hospital.

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BACKGROUND: The aims of this study were to evaluate the efficacy of current techniques for isolating mesenchymal stem cells (MSCs) from amniotic fluid obtained by second-trimester amniocentesis as well as to determine their differentiation potential. **METHODS:** We collected 50 samples of amniotic fluid by second-trimester amniocentesis. To obtain MSCs from amniotic fluid, the fluid was cultured using the two-stage culture protocol described in previous literature. Reverse transcription-polymerase chain reaction (RT-PCR) of a stem cell-specific transcription factor, octamer-binding protein 4 (Oct-4), was used to identify the characteristics of the MSCs cultured from amniotic fluid. Osteogenic differentiation of these MSCs was confirmed by the presence of osteocalcin (a mineral-binding protein uniquely synthesized by osteoblasts) using RT-PCR and Von Kossa staining. Adipogenic differentiation of these MSCs was displayed by RT-PCR of adipocyte lipid-binding protein (a lipid-binding protein specifically in adipocytes) and Oil Red O staining. **RESULTS:** Amniotic fluid-derived MSCs were successfully isolated and cultured from six samples. These cells could express the pluripotent stem cell-specific transcription factor Oct-4 as confirmed by RT-PCR. Under specific culture conditions, amniotic fluid-derived MSCs could be successfully induced to differentiate into adipocytes and osteocytes, based on product analysis by RT-PCR and specific staining. **CONCLUSION:** Based on our experiment, we estimate the efficacy of isolating mesenchymal stem cells from second-trimester amniotic fluid obtained by amniocentesis to be about 12%. Human MSCs from second-trimester amniotic fluid had the ability to differentiate in vitro into adipocytes and osteocytes under specific culture conditions. The multilineage differentiation potential of these amniotic fluid-derived MSCs may be applicable to cell transplantation and regenerative medicine.

92. Cell Cycle. 2007 Sep;Epub 2007 Sep 24.

Biochemical heterogeneity of mesenchymal stem cell populations: clues to their therapeutic efficacy.

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Mesenchymal stem cells (MSCs) were initially identified by their capacity to differentiate into connective tissue cell types. In the past decade MSCs were also shown to exhibit unexpected plasticity, which was thought to account for their broad therapeutic efficacy in animal models of disease and human clinical trials. More recent evidence indicates that their capacity to alter the microenvironment via secretion of soluble factors contributes more significantly than their plasticity in effecting tissue repair. However, the production by MSCs of a diverse array of trophic factors is inconsistent with their designation as stem cells, which by definition lie at the apex of a hierarchy of cellular differentiation and lineage specification. Analysis of the MSC transcriptome has led to the identification of sub populations that express a variety of regulatory proteins that function in angiogenesis, hematopoiesis, neural activities, and immunity and defense. These activities reflect the varied functions of distinct stromal subtypes in marrow that play important roles in tissue homeostasis. Evidence is provided that the biochemical heterogeneity of these subpopulations contributes more significantly to the therapeutic potential of MSCs than their stem-like characteristics.

Stem cells: a revolution in therapeutics-recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies.

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Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders. Among them, age-related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive and recurrent cancers could be successfully treated by stem cell-based therapies. This review focuses on the recent advancements in adult stem cell biology in normal and pathological conditions. We describe how these results have improved our understanding on critical and unique functions of these rare sub-populations of multipotent and undifferentiated cells with an unlimited self-renewal capacity and high plasticity. Finally, we discuss some major advances to translate the experimental models on ex vivo and in vivo expanded and/or differentiated stem cells into clinical applications for the development of novel cellular therapies aimed at repairing genetically altered or damaged tissues/organs in humans. A particular emphasis is made on the therapeutic potential of different tissue-resident adult stem cell types and their in vivo modulation for treating and curing specific pathological disorders.

94. Cell Biol Int. 2007 Aug;. Epub 2007 Feb 9.

Mesenchymal cells from human amniotic fluid survive and migrate after transplantation into adult rat brain.

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Amniotic fluid has been recently suggested as an alternative source of mesenchymal stem cells. However, the fate of amniotic fluid-derived mesenchymal stem cells (AF-MSCs) after in vivo transplantation has yet to be determined. In the present study we explored whether human AF-MSCs could survive and migrate following transplantation into the striatum of normal and ischemic rat. We found that the grafted cells could survive and migrate towards multiple brain regions in the normal animals, while they moved towards the injured region in the ischemic rat. Double-immunostaining analyses showed that the implanted human AF-MSCs express markers for immature neurons (Doublecortin) at 10 days, and for astrocytes (GFAP) at 10, 30 and 90 after transplantation. This study provides the first evidence that human amniotic fluid contains cells having the potential to survive and integrate into adult rat brain tissue and, therefore, to function as effective stem cells for therapeutic strategies.

95. J Pediatr Surg. 2007 Jun; discussion 979-80.

Tissue engineering from human mesenchymal amniocytes: a prelude to clinical trials.

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PURPOSE: The surgical treatment of congenital anomalies using tissues engineered from amniotic fluid-derived mesenchymal cells has been validated experimentally. As a prerequisite for testing the clinical feasibility of this therapeutic concept, this study was aimed to expand human mesenchymal amniocytes in the absence of animal products. **METHODS:** Human mesenchymal cells were isolated from amniotic fluid samples (n = 12) obtained at 20 to 37 weeks' gestation. Their phenotypic profiles and cell proliferation rates were compared during expansion under 2 different media, containing either fetal bovine serum or allogeneic human AB serum. Statistical analyses were by the 2-sided Wilcoxon signed rank test and linear regression ($P < .05$). **RESULTS:** Mesenchymal cells could be isolated and expanded at any gestational age. There was a greater than 9-fold logarithmic expansion of mesenchymal cells, with no significant differences in the overall proliferation rates based on serum type ($P = .94$), or gestational age ($P = .14$). At any passage, cells expanded for up to 50 days remained positive for markers consistent with a multipotent mesenchymal progenitor lineage, regardless of the medium used. **CONCLUSIONS:** Human mesenchymal amniocytes retain their progenitor phenotype and can be dependably expanded ex vivo in the absence of animal serum. Clinical trials of amniotic fluid-based tissue engineering are feasible within preferred regulatory guidelines.

96. J Tissue Eng Regen Med. 2007 Mar-Apr;

Engineering tissues, organs and cells.

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Patients suffering from diseased and injured organs may be treated with transplanted organs; however, there is a severe shortage of donor organs that is worsening yearly, given the ageing population. In the field of regenerative medicine and tissue engineering, scientists apply the principles of cell transplantation, materials science and bioengineering to construct biological substitutes that will restore and maintain normal function in diseased and injured tissues. Therapeutic cloning, where the nucleus from a donor cell is transferred into an enucleated oocyte in order to extract pluripotent embryonic stem cells, offers a potentially limitless source of cells for tissue engineering applications. The stem cell field is also advancing rapidly, opening new options for therapy, including the use of amniotic and placental fetal stem cells. This review covers recent advances that have occurred in regenerative medicine and describes applications of these technologies using chemical compounds that may offer novel therapies for patients with end-stage organ failure. 2007 John Wiley & Sons, Ltd

97. Iran J Immunol. 2007 Mar;

Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study.

Mohyeddin Bonab M, Yazdanbakhsh S, Lotfi J, Alimoghaddom K, Talebian F, Hooshmand F, Ghavamzadeh A, Nikbin B.

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BACKGROUND: Mesenchymal stem cells (MSCs) with their potential to differentiate into mesodermal and non-mesodermal lineages have several immunomodulatory characteristics. These properties make them promising tools in cell and gene therapy. **OBJECTIVE:** To evaluate the potential therapeutic applications of autologous MSC in improving clinical manifestations of MS patients. **METHODS:** Ten patients were included in this pilot study. All had progressive disease that had not responded to disease modifying agents including Mitoxantrone. Their Expanded Disability Status Scale (EDSS) score ranged from 3.5 to 6. Patients were injected intrathecally with culture expanded MSCs. They were followed with monthly neurological assessment and a MRI scan at the end of the first year. **RESULTS:** During 13 to 26 months of follow up (mean: 19 months), the EDSS of one patient improved from 5 to 2.5 score. Four patients showed no change in EDSS. Five patients' EDSS increased from 0.5 to 2.5. In the functional system assessment, six patients showed some degree of improvement in their sensory, pyramidal, and cerebellar functions. One showed no difference in clinical assessment and three deteriorated. The result of MRI assessment after 12 months was as following: seven patients with no difference, two showed an extra plaque, and one patient showed decrease in the number of plaques. **CONCLUSION:** This preliminary report emphasizes on the feasibility of autologous MSC for treatment of MS patients. However, in order to draw a definitive conclusion a larger sample size is required.

98. Cell Prolif. 2007 Feb;

Human amniotic fluid-derived stem cells have characteristics of multipotent stem cells.

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OBJECTIVES: To characterize mesenchymal stem cell-like cells isolated from human amniotic fluid for a new source of therapeutic cells. MATERIALS: Fibroblastoid-type cells obtained from amniotic fluid at the time of birth. METHODS: The ability of ex vivo expansion was investigated until senescence, and stem cell-like characteristics were analyzed by examining differentiation potential, messenger RNA expression and immunophenotypes. RESULTS AND CONCLUSIONS: A morphologically homogenous population of fibroblastoid-type (HAFFTs) cells, similar to mesenchymal stem cells from bone marrow (BM-MSCs), was obtained at the third passage. The cells became senescent after 27 passages over a period of 8 months while undergoing 66 population doublings. Under appropriate culture conditions, by the 8th passage they differentiated into adipocytes, osteocytes, chondrocytes and neuronal cells, as revealed by oil red O, von Kossa, Alcian blue and anti-NeuN antibody staining, respectively. Immunophenotype analyses at the 17th passage demonstrated the presence of TRA-1-60; SSEA-3 and-4; collagen types I, II, III, IV and XII; fibronectin; alpha-SMA; vimentin; desmin; CK18; CD44; CD54; CD106; FSP; vWF; CD31; and HLA ABC. Reverse transcriptase-polymerase chain reaction analysis of the HAFFTs from passages 6-20 showed consistent expression of Rex-1, SCF, GATA-4, vimentin, CK18, FGF-5 and HLA ABC genes. Oct-4 gene expression was observed up to the 19th passage but not at the 20th passage. HAFFTs showed telomerase activity at the 5th passage with a decreased level by the 21st passage. Interestingly, BMP-4, AFP, nestin and HNF-4alpha genes showed differential gene expression during ex vivo expansion. Taken together, these observations suggest that HAFFTs are pluripotent stem cells that are less differentiated than BM-MSCs, and that their gene expression profiles vary with passage number during ex vivo expansion.

99. Nat Biotechnol. 2007 Jan; Epub 2007 Jan 7.

Comment in:

Nat Biotechnol. 2007 Jan;

Nat Biotechnol. 2007 Nov;

Nat Biotechnol. 2008 Mar;

Isolation of amniotic stem cell lines with potential for therapy.

De Coppi P, Bartsch G Jr, Siddiqui MM, Xu T, Santos CC, Perin L, Mostoslavsky G, Serre AC, Snyder EY, Yoo JJ, Furth ME, Soker S, Atala A.

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Stem cells capable of differentiating to multiple lineages may be valuable for therapy. We report the isolation of human and rodent amniotic fluid-derived stem (AFS) cells that express embryonic and adult stem cell markers. Undifferentiated AFS cells expand extensively without feeders, double in 36 h and are not tumorigenic. Lines maintained for over 250 population doublings retained long telomeres and a normal karyotype. AFS cells are broadly multipotent. Clonal human lines verified by retroviral marking were induced to differentiate into cell types representing each embryonic germ layer, including cells of adipogenic, osteogenic, myogenic, endothelial, neuronal and hepatic lineages. Examples of differentiated cells derived from human AFS cells and displaying specialized functions include neuronal lineage cells secreting the neurotransmitter L-glutamate or expressing G-protein-gated inwardly rectifying potassium channels, hepatic lineage cells producing urea, and osteogenic lineage cells forming tissue-engineered bone.

100. Rev Med Liege. 2007;

Mesenchymal stem cells: a new versatile therapeutic option

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Mesenchymal stem cells (MSC) reside in the stromal compartment of the hematopoietic bone marrow. Although present in small numbers in vivo, MSC may be easily isolated and expanded in cell culture. MSC are able to generate bone, cartilage, fat, and under specific conditions, liver, muscle and nerve. Numerous studies have suggested a potential use of MSC to repair degenerative or traumatic lesions, in organs where tissue repair is limited. Furthermore, MSC are endowed with immunosuppressive properties, utilized to control graft versus host disease and rejection of allogenic hematopoietic stem cell transplants.

A real-time PCR approach to evaluate adipogenic potential of amniotic fluid-derived human mesenchymal stem cells.

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Regulation of adipocyte differentiation is an important process in the control of adipose tissue development. So far, adipogenesis has been investigated through the use of various experimental models. In this work, we used human mesenchymal stem cells (hMSCs) obtained from amniotic fluid (AF) as an alternative model more representative of what naturally happens in vivo. In our opinion, these hMSCs are still not influenced by differentiation stimuli and could act in a way more correspondent to the physiological process of adipogenesis, representing also an ethically acceptable alternative to totipotent human embryonic stem cells (ES). Adipocyte differentiation was monitored following the expressions of key genes. We measured the expression levels of PPARgamma2, PPARgamma-C1alpha, UCP-1, adipsin, and leptin genes using quantitative real-time PCR. We tested our experimental model with two different media. Understanding in vivo adipogenesis mechanisms will shed light on the pathophysiology of many diseases.

The role of stem cells in physiology, pathophysiology, and therapy of the liver.

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The objectives of the present review is to update readers with the rapidly changing concepts in liver stem cell biology and related clinical applications. The liver has adapted to the inflow of ingested toxins by the evolutionary development of unique regenerative properties and responds to injury or tissue loss by rapid division of the mature cells, hepatocytes, and bile duct epithelial cells. Proliferation of the parenchymal cells is regulated by numerous cytokine/growth factor-mediated pathways and is timely synchronized with extracellular matrix degradation and the restoration of the vasculature. The putative role of stem cells in physiology, pathophysiology, and therapy is not yet precisely known but currently is under intensive investigation. Resident hepatic stem/ progenitor cells have been identified in small numbers and implicated in liver tissue repair, when hepatocyte and bile duct replication capacity is exhausted or experimentally inhibited. Several independent reports have suggested that bone marrow cells can give rise to different hepatic epithelial cells types, including hepatic stem cells, hepatocytes, and bile duct epithelium. These observations have resulted in the hypothesis that extrahepatic stem cells, specifically bone marrow-derived stem cells, are an important source for liver epithelial cell replacement, particularly during chronic injury. Most of published data, however, now suggest that they do not play a relevant role in replacement of epithelial cells in any known form of hepatic injury. In vitro differentiation protocols for various adult extrahepatic stem cells might eventually provide valuable sources of cells for transplantation and therapy. Amniotic epithelial stem cells, fetal liver progenitor cells as well as embryonic stem cells currently emerge as alternative stem cell sources and open new possibilities for cellular therapies of liver disease.

103. Methods Enzymol. 2006;

Amniotic fluid and placental stem cells.

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Human amniotic fluid has been used in prenatal diagnosis for more than 70 years. It has proven to be a safe, reliable, and simple screening tool for a wide variety of developmental and genetic diseases. However, there is now evidence that amniotic fluid may have more use than only as a diagnostic tool and may be the source of a powerful therapy for a multitude of congenital and adult disorders. A subset of cells found in amniotic fluid and placenta has been isolated and found to be capable of maintaining prolonged undifferentiated proliferation as well as able to differentiate into multiple tissue types encompassing the three germ layers. It is possible that in the near future, we will see the development of therapies using progenitor cells isolated from amniotic fluid and placenta for the treatment of newborns with congenital malformations as well as of adults, using cryopreserved amniotic fluid and placental stem cells. In this chapter, we describe a number of experiments that have isolated and characterized pluripotent progenitor cells from amniotic fluid and placenta. We also discuss various cell lines derived from amniotic fluid and placenta and future directions for this area of research.



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