Stem Cell Source Literatures

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Abstract: The definition of stem cell is "an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell". Stem Cell is the original of life. All cells come from stem cells. Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situation or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a typical and important topic of life science. This material collects some literatures on stem cell source.
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Key words: stem cell; life; gene; DNA; protein; source

Introduction

Aristotle (384-322 BC) deduced that the embryo was derived from mother's menstrual blood, which was based on the concept that living animals arose from slime or decaying matter. This concept was accepted in western world for over 2000 years, and it controlled western philosophy for over 2000 years either. In 1855, Virchow supposed that all cells in an organism are derived from preexisting cells. Now we know that all the human cells arise from a preexisting stem cell – the fertilized egg, that come from the mating of a man and a woman naturally but now can be produced in the laboratory tube. The counter hypothesis of spontaneous generation was accepted until 1864, when the French scientist Louis Pasteur demonstrated that there would be no microorganisms' growing after sterilizing and sealing.

The animal body has an unlimited source of stem cells, almost. However, the problem is not in locating these stem cells, but in isolating them from their tissue source.

Five key stem cells have been isolated from human: (1) Blastocysts; (2) Early embryos; (3) Fetal tissue; (4) Mature tissue; (5) Mature cells that can be grown into stem cells.

Up to today, only stem cells taken from adults or children (known generically as "adult stem cells") have been used extensively and effectively in the treatment of degenerative diseases.

Literatures

Abrahamsen, I. W., S. Somme, et al. (2005). "Immune reconstitution after allogeneic stem cell transplantation: the impact of stem cell source and graft-versus-host disease." Haematologica **90**(1): 86-93.

BACKGROUND AND OBJECTIVES: Bone marrow (BM) and blood stem cell (BSC) allografts differ considerably with respect to their content of progenitor cells and progenitor cell subsets as well as mature lymphocytes. The aim of this prospective, randomized study was to determine whether these differences have an impact on early post-transplant immune recovery. DESIGN AND METHODS: In a prospective randomised study, we found enhanced immune recovery in recipients of BSC allografts compared to in recipients of BM allografts despite transplantation of a lower number of lymphoid progenitors, particularly B-cell progenitors. The large number of mature lymphocytes in BSC allografts is a plausible explanation for this observation. At the progenitor cell level, we found a comparable and very high proportion of progenitor cells involved in lymphopoiesis in both study groups. RESULTS: Patients with extensive chronic GVHD, irrespective of the allograft received, had low immunoglobulin (Ig) levels in serum, low B-cell counts in blood and low numbers of B-cell progenitors in the bone marrow. They also showed high T-cell counts, particularly CD3+CD8+ T-cell counts, which was paralleled by a high number of T-cell progenitors in the bone marrow. In patients with extensive chronic GVHD we found low natural killer (NK)-cell counts which has not been reported previously. INTERPRETATION AND CONCLUSIONS: Early immune recovery is enhanced following BSC allografting compared with BM allografting. This is plausibly explained by the large inoculum of mature lymphocytes in BSC allografts. Following allografting, a higher proportion of the BM progenitor cell compartment is involved in lymphopoiesis than it is in healthy adults. However, B-lymphopoiesis is inhibited in patients with extensive chronic GVHD resulting in impaired B-cell

recovery. These patients also seem to show impaired NK-cell recovery.

Abuljadayel, I. S. (2006). "Harnessing pluripotency from differentiated cells: a regenerative source for tissue-specific stem cell therapies." Curr Stem Cell Res Ther **1**(3): 325-31.

Processes involving conversion of mature adult cells into undifferentiated cells have tremendous therapeutic potential in treating a variety of malignant and non-malignant disorders, including degenerative diseases. This can be achieved in autologous or allogeneic settings, by replacing either defective cells or regenerating those that are in deficit through reprogramming more committed cells into stem cells. The concept behind reprogramming differentiated cells to a stem cell state is to enable the switching of development towards the required cell lineage that is capable of correcting the underlying cellular dysfunction. The techniques by which differentiated cells can reverse their development, become pluripotent stem cells and transdifferentiate to give rise to new tissue or an entire organism are currently under intense investigation. Examples of reprogramming differentiation in mature adult cells include nuclear reprogramming of more committed cells using the cytoplasm of empty oocytes obtained from a variety of animal species, or cell surface contact of differentiated cells through receptor ligand interaction. Such ligands include monoclonal antibodies, cytokines or synthetic chemical compounds. Despite controversies surrounding such techniques, the concept behind identification and design/screening of biological or pharmacological compounds to enable re-switching of cell fate in-vivo or ex-vivo is paramount for current drug therapies to be able to target more specifically cellular dysfunction at the tissue/organ level. Herein, this review discusses current research in cellular reprogramming and its potential application in regenerative medicine.

Arnalich-Montiel, F., S. Pastor, et al. (2008). "Adipose-derived stem cells are a source for cell therapy of the corneal stroma." Stem Cells **26**(2): 570-9.

Most corneal diseases affect corneal stroma and include immune or infectious diseases, ecstatic disorders, traumatic scars, and corneal dystrophies. Cell-based therapy is a promising therapeutic approach to overcome the current disadvantages of corneal transplantation. We intended to search for a cell source to repopulate and regenerate corneal stroma. We investigated the ability of human processed lipoaspirate derived (PLA) cells to regenerate corneal stroma in experimental animals. In the first set of experiments, we tested the biosafety and immunogenicity of human PLA stem cells transplanted into the corneal stroma of rabbits. No immune response was elicited even though we used immune-competent animals. PLA cells survived up to 10 weeks post-transplant, maintained their shape, and remained intermingled in the stroma without disrupting its histological pattern. Interestingly, transparency was preserved even 10 weeks after the transplant, when PLA cells formed a discontinuous layer in the stroma. In the second set of experiments, regeneration of the corneal stroma by PLA cells was assessed, creating a niche by partial ablation of the stroma. After 12 weeks, human cells were disposed following a multilayered pattern and differentiated into functional keratocytes, as assessed by the expression of aldehyde-3-dehydrogenase and cornea-specific proteoglycan keratocan. Based on our results, we believe that adipose-derived adult stem cells can be a cell source for stromal regeneration and repopulation in diseased corneas. The low health impact of the surgical procedure performed to obtain the PLA cells provides this cell source with an additional beneficial feature for its possible future autologous use in human patients.

Barge, R. M., R. E. Brouwer, et al. (2001). "Comparison of allogeneic T cell-depleted peripheral blood stem cell and bone marrow transplantation: effect of stem cell source on short- and long-term outcome." Bone Marrow Transplant **27**(10): 1053-8.

We report the results of a retrospective single-center study comparing engraftment, acute and chronic GVHD, relapse and survival in patients with malignant hematological disorders transplanted with allogeneic peripheral blood stem cells (alloPBSCT, n = 40) or bone marrow cells (alloBMT, n = 42). All transplants were T cell depleted by in vitro incubation with the Campath-1 monoclonal antibody. Primary graft failure occurred in none of the patients receiving an alloPBSCT compared with 3/42 of the recipients of an alloBMT. In addition, two patients in the alloBMT group showed no platelet engraftment. Recipients of PBSC had a more rapid recovery of neutrophils (median 14 days) compared to BM transplant recipients (median 32 days). Platelet recovery was also accelerated in PBSC recipients compared to BM recipients (11 vs 38 days). There was an increase in the incidence of grade II acute GVHD and chronic GVHD in patients after alloPBSCT (18% and 23%, respectively) compared to patients receiving alloBMT (5% and 8%, respectively). The 2-year cumulative incidence of relapse was similar in both groups (47%). At 6 months after transplantation, transplant-related mortality (TRM) was lower in PBSCT recipients than in BMT recipients. However, at a follow-up of 3 years TRM was similar in both groups. The disease-free

survival rate at 3 years after transplantation did not differ between the groups (42% for PBSCT and 41% for BMT recipients). Our results indicate that T cell-depleted alloPBSCT compared to alloBMT is associated with a more rapid hematopoietic reconstitution and a decreased TRM at 6 months follow-up after transplantation. However, at a follow-up of 3 years, no sustained survival benefits were observed.

Barker, J. N., R. E. Hough, et al. (2005). "Serious infections after unrelated donor transplantation in 136 children: impact of stem cell source." Biol Blood Marrow Transplant **11**(5): 362-70.

How the infection risks compare after umbilical cord blood (UCB) and bone marrow (BM) transplantation is not known. Therefore, we compared serious infections in the 2 years after pediatric myeloablative unrelated donor transplantation with unmanipulated BM (n = 52), T cell-depleted (TCD) BM (n = 24), or UCB (n = 60) for the treatment of hematologic malignancy. Overall, the cumulative incidence of 1 or more serious infections was comparable between groups (BM, 81%; TCD, 83%; UCB, 90%; P = .12). Furthermore, by taking all serious infections into account and using multivariate techniques with unmanipulated BM as the reference, there were also no significant differences between groups (TCD relative risk [RR], 1.6; P = .10; UCB RR, 1.0; P = .84). Within the time periods days 0 to 42, days 43 to 100, and days 101 to 180, the only difference was a greater risk of viral infections from days 0 to 42 in TCD recipients (RR, 3.5; P = .02). Notably, after day 180, TCD recipients had a significantly increased infection risk (RR, 3.1; P = .03), whereas the risk in UCB recipients (RR, 0.5; P = .23) was comparable to that in BM recipients. Other factors associated with an increased infection risk in the 2 years after transplantation were age > or = 8 years, graft failure, and severe acute graft-versus-host disease. These data suggest that the risk of serious infection after pediatric UCB transplantation is comparable to that with unmanipulated BM.

Bartsch, K., H. Al-Ali, et al. (2009). "Mesenchymal stem cells remain host-derived independent of the source of the stem-cell graft and conditioning regimen used." Transplantation **87**(2): 217-21.

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 immunmodulatory 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.

Beauchamp, J. R., J. E. Morgan, et al. (1999). "Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source." J Cell Biol **144**(6): 1113-22.

Myoblasts, the precursors of skeletal muscle fibers, can be induced to withdraw from the cell cycle and differentiate in vitro. Recent studies have also identified undifferentiated subpopulations that can self-renew and generate myogenic cells (Baroffio, A., M. Hamann, L. Bernheim, M.-L. Bochaton-Pillat, G. Gabbiani, and C.R. Bader. 1996. Differentiation. 60:47-57; Yoshida, N., S. Yoshida, K. Koishi, K. Masuda, and Y. Nabeshima. 1998. J. Cell Sci. 111:769-779). Cultured myoblasts can also differentiate and contribute to repair and new muscle formation in vivo, a capacity exploited in attempts to develop myoblast transplantation (MT) for genetic modification of adult muscle. Our studies of the dynamics of MT demonstrate that cultures of myoblasts contain distinct subpopulations defined by their behavior in vitro and divergent responses to grafting. By comparing a genomic and a semiconserved marker, we have followed the fate of myoblasts transplanted into muscles of dystrophic mice, finding that the majority of the grafted cells

quickly die and only a minority are responsible for new muscle formation. This minority is behaviorally distinct, slowly dividing in tissue culture, but rapidly proliferative after grafting, suggesting a subpopulation with stem cell-like characteristics.

Broxmeyer, H. E. (1995). "Cord blood as an alternative source for stem and progenitor cell transplantation." Curr Opin Pediatr **7**(1): 47-55.

Blood collected from the umbilical cord and placenta at the birth of a child is a rich source of immature blood cell elements and has been used clinically as an alternative source of transplantable stem and progenitor cells. Studies on the proliferative and replating capacities of cord blood stem and progenitor cells have documented their extensive capacity for division and self renewal. Studies on the immune cells in cord blood have shown them to be less immunologically reactive in a number of situations. These characteristics are consistent with the experience in children receiving HLA-matched sibling cord blood cells, in which these cells have been transplantable in a large number of clinical disorders with low or absent graft-versus-host disease. Stem and progenitor cells from cord blood are efficiently transduced with new genetic material by retroviral and adeno-associated viral vectors and may be of efficacy in the future for autologous gene therapy approaches to treat disease. Efforts in banking of cryopreserved cord blood cells have been undertaken, and a number of such stored samples have been used for fully and partially HLA-matched unrelated transplantation. Efforts to better understand the cells in cord blood and their clinical utility are continuing.

Brustle, O., K. N. Jones, et al. (1999). "Embryonic stem cell-derived glial precursors: a source of myelinating transplants." Science **285**(5428): 754-6.

Self-renewing, totipotent embryonic stem (ES) cells may provide a virtually unlimited donor source for transplantation. A protocol that permits the in vitro generation of precursors for oligodendrocytes and astrocytes from ES cells was devised. Transplantation in a rat model of a human myelin disease shows that these ES cell-derived precursors interact with host neurons and efficiently myelinate axons in brain and spinal cord. Thus, ES cells can serve as a valuable source of cell type-specific somatic precursors for neural transplantation.

Champlin, R. E., N. Schmitz, et al. (2000). "Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. IBMTR Histocompatibility and Stem Cell Sources Working Committee and the European Group for Blood and Marrow Transplantation (EBMT)." Blood **95**(12): 3702-9.

Peripheral blood cells are increasingly used in place of bone marrow as a source of hematopoietic stem cells for allogeneic transplantation. The relative efficacy of these 2 approaches is unknown. This retrospective multivariate analysis compared results of 288 HLA-identical sibling blood stem cell transplantations with results of 536 HLA-identical sibling bone marrow transplantations. No transplants were T-cell depleted. Median follow-up was 12 months, and analyses focused on 1-year outcomes. Recipients of blood stem cell transplants had more rapid recovery of neutrophils to at least 0.5 x 10(9)/L (median time to recovery, 14 days, compared with 19 days for marrow transplants; P <.001) and of platelets to at least 20 x 10(9)/L (median time, 18 days, compared with 25 days for marrow transplants; P <.001). There was no significant difference in the incidence of grades II to IV acute graft versus host disease (GVHD). The incidence of chronic GVHD was significantly higher after blood stem cell transplantation (1-year probability [95% confidence interval], 65% [56%-72%] compared with 53% [47%-59%]; P =.02) Relapse incidence in the 2 transplant groups did not differ significantly. Treatment-related mortality rates were lower and leukemia-free survival rates were higher with blood stem cell transplants in patients with advanced leukemia (acute leukemia in second remission or chronic myelogenous leukemia in accelerated phase) but not in early leukemia (acute leukemia in first remission or chronic myelogenous leukemia in chronic phase). The median time from transplantation to hospital discharge was 23 days after blood stem cell transplantation and 28 days after bone marrow transplantation (P =.003). Further study with longer follow-up is necessary to definitively establish the role of blood stem cells for allogeneic transplantation, especially in patients with good-risk disease. (Blood. 2000;95:3702-3709)

Chiu, R. C. (2003). "Bone-marrow stem cells as a source for cell therapy." Heart Fail Rev **8**(3): 247-51.

Bone marrow stroma contains a subgroup of cells which can be guided in vitro to differentiate, and express cardiomyocyte phenotype. In vivo, these cells can become cardiomyocytes when implanted into the myocardium, in response to signals from the microenvironment. They appear to participate in the physiologic healing process of tissue injury, such as myocardial infarction, by being recruited from the bone marrow, traffic via the circulation and home in to the injured site. Thus such cells may be employed to therapeutically augment the myocardial repair for patients who suffer cardiac damages, which may lead to heart failure. Optimization of the cell implant

strategy, and further exploration of the preliminary findings that such adult stem cells may be uniquely immuno-tolerant and thus may be used as "universal donors", will further enhance the clinical significance of adult stem cell-based regenerative therapy for heart failure.

Choi, D., M. Perrin, et al. (1998). "Dendritic cell-based vaccines in the setting of peripheral blood stem cell transplantation: CD34+ cell-depleted mobilized peripheral blood can serve as a source of potent dendritic cells." Clin Cancer Res **4**(11): 2709-16.

We are investigating the use of tumor-pulsed dendritic cell (DC)-based vaccines in the treatment of patients with advanced cancer. In the current study, we evaluated the feasibility of obtaining both CD34+ hematopoietic stem/ progenitor cells (HSCs) and functional DCs from the same leukapheresis collection in adequate numbers for both peripheral blood stem cell transplantation (PBSCT) and immunization purposes, respectively. Leukapheresis collections of mobilized peripheral blood mononuclear cells (PBMCs) were obtained from normal donors receiving granulocyte colony-stimulating factor (G-CSF) (for allogeneic PBSCT) and from intermediate grade non-Hodgkin's lymphoma or multiple myeloma patients receiving cyclophosphamide plus G-CSF (for autologous PBSCT). High enrichment of CD34+ HSCs was obtained using an immunomagnetic bead cell separation device. After separation, the negative fraction of mobilized PBMCs from normal donors and cancer patients contained undetectable levels of CD34+ HSCs by flow cytometry. This fraction of cells was then subjected to plastic adherence, and the adherent cells were cultured for 7 days in GM-CSF (100 ng/ml) and interleukin 4 (50 ng/ml) followed by an additional 7 days in GM-CSF, interleukin 4, and tumor necrosis factor alpha (10 ng/ml) to generate DCs. Harvested DCs represented yields of 4.1+/-1.4 and 5.8+/-5.4% of the initial cells plated from the CD34+ cell-depleted mobilized PBMCs of normal donors and cancer patients, respectively, and displayed a high level expression of CD80, CD86, HLA-DR, and CD11c but not CD14. This phenotypic profile was similar to that of DCs derived from non-CD34+ cell-depleted mobilized PBMCs. DCs generated from CD34+ cell-depleted mobilized PBMCs elicited potent antitetanus as well as primary allogeneic T-cell proliferative responses in vitro, which were equivalent to DCs derived from non-CD34+ cell-depleted mobilized PBMCs. Collectively, these results demonstrate the feasibility of obtaining both DCs and CD34+ HSCs from the same leukapheresis collection from G-CSF-primed normal donors and cancer patients in sufficient numbers for the purpose of combined PBSCT and immunization strategies.

Clapcote, S. J. and J. C. Roder (2004). "Survey of embryonic stem cell line source strains in the water maze reveals superior reversal learning of 129S6/SvEvTac mice." Behav Brain Res **152**(1): 35-48.

The availability of pluripotent embryonic stem (ES) cells for gene targeting has resulted in laboratory mice becoming important animal models of human neurological disease. Inbred strains of mice differ in many behavioural phenotypes, such that the same gene mutation can appear to have different phenotypic effects when introduced onto different genetic backgrounds. Prior knowledge of the behavioural phenotypes of the inbred strains used for gene targeting would, therefore, allow the selection of the most appropriate genetic background for the hypothesis to be tested. With this in mind, we tested eight strains of mice (129S1/SvImJ, 129S2/SvPasIcoCrlBR, 129S6/SvEvTac, B6129SF1/J, C57BL/6J, C57BL/6N, LP/J and SM/J), including the sources of five ES cell lines commonly used for gene targeting, in the spatial (submerged platform) version of the Morris water maze, the most widely used paradigm to evaluate the cognitive abilities of genetically modified mice. The three 129 substrain sources of ES cell lines demonstrated spatial learning in the water maze that was superior to that of C57BL/6J, the inbred strain most commonly used for the maintenance and phenotypic testing of mutations. In addition, 129S6/SvEvTac was unique amongst the eight strains tested in having a particular capacity for reversal learning, when the submerged platform was relocated to the opposite quadrant. We conclude that some substrains of 129 could provide suitable genetic backgrounds for testing gene mutations that might be expected to impair cognitive function, thus negating the need to backcross to C57BL/6J, thereby avoiding the so-called "flanking gene problem".

Crisostomo, P. R., T. A. Markel, et al. (2007). "In the adult mesenchymal stem cell population, source gender is a biologically relevant aspect of protective power." Surgery **142**(2): 215-21.

BACKGROUND: Acute treatment with bone marrow mesenchymal stem cells (MSC) reduces myocardial infarct size by multiple mechanisms, including the paracrine release of protective growth factors. Female MSCs produce more growth factor when stressed; therefore, we hypothesized that myocardial protection provoked by female MSCs would be greater than that elicited by male MSCs. METHODS: Hearts were subjected to 25 min of warm global ischemia, 40 min of reperfusion, and randomly

assigned into one of three groups: (1) vehicle treated; (2) male MSC treated; and (3) female MSC treated. Myocardial function was continuously recorded and in separate experiments, male and female MSC growth factor production was assessed by ELISA. RESULTS: All indices of functional recovery were significantly higher in the stem cell infused rat heart compared with control hearts. Interestingly, female MSC treated rat hearts demonstrated significantly greater recovery of left ventricular developed pressure, +dP/dT, and -dP/dT than male MSC treated hearts at end reperfusion. In addition, male MSCs produced significantly greater tumor necrosis factor alpha, and significantly less vascular endothelial growth factor than female MSCs. CONCLUSIONS: This study is the first to demonstrate that, in the adult mesenchymal population, source gender is a biologically relevant aspect of ultimate stem cell function in the heart.

de Medeiros, C. R., M. A. Bitencourt, et al. (2006). "Allogeneic hematopoietic stem cell transplantation from an alternative stem cell source in Fanconi anemia patients: analysis of 47 patients from a single institution." Braz J Med Biol Res **39**(10): 1297-304.

We transplanted 47 patients with Fanconi anemia using an alternative source of hematopoietic cells. The patients were assigned to the following groups: group 1, unrelated bone marrow (N = 15); group 2, unrelated cord blood (N = 17), and group 3, related non-sibling bone marrow (N = 15). Twenty-four patients (51%) had complete engraftment, which was not influenced by gender (P = 0.87), age (P = 0.45), dose of cyclophosphamide (P = 0.80), nucleated cell dose infused (P = 0.60), or use of anti-T serotherapy (P = 0.20). Favorable factors for superior engraftment were full HLA compatibility (independent of the source of cells; P = 0.007) and use of a fludarabine-based conditioning regimen (P = 0.046). Unfavorable factors were > or = 25 transfusions pre-transplant (P = 0.011) and degree of HLA disparity (P = 0.007). Intensity of mucositis (P = 0.50) and use of androgen prior to transplant had no influence on survival (P = 0.80). Acute graft-versus-host disease (GVHD) grade II-IV and chronic GVHD were diagnosed in 47 and 23% of available patients, respectively, and infections prevailed as the main cause of death, associated or not with GVHD. Eighteen patients are alive, the Kaplan-Meyer overall survival is 38% at approximately 8 years, and the best results were obtained with related non-sibling bone marrow patients. Three recommendations emerged from the present study: fludarabine as part of conditioning, transplant in patients with < 25 transfusions and avoidance of HLA disparity. In addition, an extended family search (even when consanguinity is not present) seeking for a related non-sibling donor is highly recommended.

de Witte, T., R. Brand, et al. (2006). "The role of stem cell source in autologous hematopoietic stem cell transplantation for patients with myelodysplastic syndromes." Haematologica **91**(6): 750-6.

BACKGROUND AND OBJECTIVES: Intensive chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) is a curative treatment option for patients with myelodysplastic syndromes (MDS). Peripheral blood (PB) HSCT was introduced in 1992 and PB has become the source of choice of autologous stem cells worldwide. Autologous PB stem cells result in faster hematopoietic recovery, but may be associated with a higher risk of relapse. DESIGN AND METHODS: We analyzed the data of 336 patients transplanted after 1992 with either bone marrow (BM) (n=104) or PB (n=232). RESULTS: Various factors had an impact on event-free survival in univariate analysis: age hazard ratio [HR]=1.1 per 10 years; p=0.12), source of stem cells (HR=1.2, p=0.22), interval between diagnosis and transplantation (HR=1.0 per month; p=0.87), and therapy-related vs primary disease (HR=0.5; p=0.002). In the multivariate Cox model, the event-free survival was not different after PB or BM HSCT with a HR of 0.93 (95% confidence interval of 0.67 - 1.30; p=0.67). The relapse risk after transplantation with stem cells from either source was similar with a HR of 1.1. A significant interaction (p=0.02) between age and the source of stem cells indicated a more favorable potential of autologous PB HSCT in young age groups. INTERPRETATION AND CONCLUSIONS: Autologous PB and BM HSCT result in equivalent outcomes. Therefore, given the more rapid hematopoietic recovery PB is the preferred source of stem cells.

Eapen, M., M. M. Horowitz, et al. (2004). "Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry." J Clin Oncol **22**(24): 4872-80.

PURPOSE: Peripheral-blood stem cells (PBSC) may be used as an alternative to bone marrow (BM) for allogeneic transplantation. Despite lack of data on PBSC transplantation in children, there has been a change in clinical practice, with increasing numbers of children receiving PBSC allografts. PATIENTS AND METHODS: We compared the results of 143 PBSC and 630 BM transplants from human leukocyte antigen-identical sibling donors in children aged 8 to 20 years with acute leukemia.

PBSC transplant recipients were older, and were more likely to have advanced leukemia, receive growth factors post-transplantation, and have undergone transplantation more recently. Risks of acute and chronic graft-versus-host disease (GVHD), treatment-related mortality, relapse, treatment failure (relapse or death), and overall mortality were compared using Cox proportional hazards regression to adjust for potentially confounding factors. RESULTS: Hematopoietic recovery was faster after PBSC transplantation. Risks of grade 2 to 4 acute GVHD were similar, but chronic GVHD risk was higher after PBSC transplantation (relative risk [RR], 1.85; 95% CI, 1.28 to 2.66; P = .001). In contrast to reports in adults, treatment-related mortality (RR, 1.89; 95% CI, 1.28 to 2.80; P = .001), treatment failure (RR, 1.31; 95% CI, 1.03 to 1.68; P = .03), and mortality (RR, 1.38; 95% CI, 1.07 to 1.79; P = .01) were higher after PBSC transplantation. Risks of relapse were similar. CONCLUSION: These data suggest poorer outcomes after PBSC compared with BM transplantation in children after adjusting for relevant risk factors. Given the trend toward increased use of PBSC allografts in children, prospective clinical trials are required to determine their appropriate role in this group of patients.

Fan, J., R. R. Varshney, et al. (2009). "Synovium-derived mesenchymal stem cells: a new cell source for musculoskeletal regeneration." Tissue Eng Part B Rev **15**(1): 75-86.

Ever since synovium-derived mesenchymal stem cells (SMSCs) were first identified and successfully isolated in 2001, as a brand new member in MSC families, they have been increasingly regarded as a promising therapeutic cell species for musculoskeletal regeneration, particularly for reconstructions of cartilage, bones, tendons, and muscles. Besides the general multipotency in common among the MSC community, SMSCs excel other sourced MSCs in higher ability of proliferation and superiority in chondrogenesis. This review summarizes the latest advances in SMSC-related studies covering their specific isolation methodologies, biological insights, and practical applications in musculoskeletal therapeutics of which an emphasis is cast on engineered chondrogenesis.

Faucher, C., M. Mohty, et al. (2003). "Bone marrow as stem cell source for allogeneic HLA-identical sibling transplantation following reduced-intensity preparative regimen." Exp Hematol **31**(10): 873-80.

OBJECTIVE: Reduced-intensity conditioning regimens (RIC) and peripheral blood stem cells (PBSC) are increasingly used for allogeneic stem cell transplantation (allo-BMT). RIC has been shown to allow engraftment with minimal early transplant-related mortality (TRM). However, in the context of RIC, the use of bone marrow (BM) as stem cell source is still little evaluated. PATIENTS AND METHODS: In this report, we analyzed the outcome of 32 high-risk patients with hematological malignancies who received an HLA-identical sibling allo-BMT after RIC including fludarabine, busulfan, and anti-thymocyte globulin (ATG). RESULTS: Sustained neutrophil and platelet recovery occurred at a median of 13 days (range, 10-19) and 17 days (range, 0-45) respectively. Early and durable full donor chimerism could be established as soon as the first month after allo-BMT. Also, a sustained and early CD8(+) T-cell recovery was observed, but the CD4(+) T-cell compartment remained profoundly low. The cumulative incidences of grade II-IV acute GVHD and chronic GVHD were 26% (95% CI, 11-41%) and 31% (95% CI, 15-47%) respectively. The overall cumulative incidence of TRM was 28% (95% CI, 12-44%) occurring mainly in patients aged over 50. In this setting, GVHD showed a protective effect on disease progression or relapse with better progression-free survival for patients with GVHD as compared to patients without GVHD (p=0.03). CONCLUSIONS: Collectively, these results confirm that the use of BM grafts for RIC is feasible with durable donor engraftment and no detrimental GVHD.

Fountain, D., M. Ralston, et al. (1997). "Liquid nitrogen freezers: a potential source of microbial contamination of hematopoietic stem cell components." Transfusion **37**(6): 585-91.

BACKGROUND: The recent report of hepatitis B transmission between hematopoietic progenitor and putative stem cell (HPC) components stored in liquid nitrogen led to the questioning of whether evidence existed for similar contamination by bacterial or fungal elements. STUDY DESIGN AND METHODS: Microbial contamination rates were reviewed for 704 HPC components from 255 patients over an 18-month period. Five liquid nitrogen freezers were surveyed for microbial contamination. The literature was reviewed to ascertain the published experience of other laboratories with HPC component contamination first documented on thawing. RESULTS: Seven (1.2%) of 583 thawed components were found to be contaminated with a variety of environmental or waterborne organisms, despite a meticulous protocol to prevent contamination during thawing. All of these components had been sterile on cryopreservation. Literature review revealed a similar incidence of post-thaw contamination from other centers. Microbial survey of liquid nitrogen freezers revealed low-level contamination in four of five. The organisms represented were similar to those cultured

from thawed HPC components. One freezer was heavily contaminated by Aspergillus species. CONCLUSION: Liquid nitrogen freezers are not sterile, and both the liquid and vapor phases are potential sources of microbial contamination of HPC components. While low-level contamination by environmental organisms may be common, the occurrence of heavy contamination by potential pathogens such as Aspergillus species suggests that monitoring of liquid nitrogen sterility may be indicated. Strategies to assess and prevent microbial transmission from liquid nitrogen to HPC components need further development.

Frangoul, H., E. R. Nemecek, et al. (2007). "A prospective study of G-CSF primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children: a Pediatric Blood and Marrow Transplant Consortium (PBMTC) study." Blood **110**(13): 4584-7.

A prospective multicenter trial was conducted to evaluate the safety and feasibility of granulocyte colony-stimulating factor (G-CSF)-primed bone marrow (G-BM) in children receiving allogeneic bone marrow transplantation (BMT). A total of 42 children with a median age of 9.8 years (range, 0.8-17 years) were enrolled. Donors with median age of 9.2 years (range, 1.1-22 years) received 5 microg/kg per day of subcutaneous G-CSF for 5 consecutive days. BM was harvested on the fifth day. No donor experienced complications related to G-CSF administration or marrow har-vest. Median nucleated (NC) and CD34 cells infused was 6.7 x 10(8)/kg (range, 2.4-18.5 x 10(8)/kg) and 7.4 x 10(6)/kg (range, 2-27.6 x 10(6)/kg), respectively. Neutrophil and platelet engraftment was at a median of 19 days (range, 13-28 days) and 20 days (range, 9-44 days), respectively. A total of 13 (32%) patients developed grade 2 graft-versus-host disease (GVHD), and 5 (13%) of 40 evaluable patients developed chronic GVHD (3 limited and 2 extensive). Higher cell dose was not associated with increased risk of acute or chronic GVHD. Overall survival and event-free survival at 2 years were 81% and 69%, respectively. Collection of G-BM from pediatric donors is safe, and can result in high NC and CD34 cell doses that facilitate engraftment after myeloablative BMT without a discernable increase in the risk of GVHD.

Geisler, C. H., M. M. Hansen, et al. (1998). "BEAM+autologous stem cell transplantation in malignant lymphoma: 100 consecutive transplants in a single centre. Efficacy, toxicity and engraftment in relation to stem-cell source and previous treatment." Eur J Haematol **61**(3): 173-82.

One hundred consecutive patients with malignant lymphoma treated with high-dose chemotherapy and autologous stem cell transplantation, followed at least 1 yr post-transplant, are reported, 68 with non-Hodgkin's lymphoma and 32 with Hodgkin's disease. At transplant, 23 patients were in first remission, 69 in later chemosensitive disease and 8 were chemotherapy resistant. Based on previous treatment and stem-cell source, the patients were subdivided into 3 cohorts: BMT1: bone-marrow harvest and transplant after > or =3 treatment regimens (38 patients); BMT2: bone marrow harvest and transplant after less than 3 treatment regimens (24 patients); PBSCT: peripheral-blood stem cell transplant (38 patients, 5 of these with CD34+ cell selected PBSC). The 4-yr survival and progression-free survival of all patients was 45 and 40%, respectively. Forty-one patients have died, 27 of lymphoma, evenly distributed in the cohorts. Fourteen treatment-related deaths occurred, 13 of these in the BMT1 cohort, significantly more than in the other cohorts (p=0.001). In univariate survival analysis cohort, age, disease status at transplant and number of previous treatment regimens were significant. In multivariate survival analysis cohort, age and sex were independently significant, women having a shorter survival. The patients transplanted with unselected PBSC had significantly shorter duration of pancytopenia and hospital stay than the otherwise comparable BMT2 patients, but their progression-free survival was identical. We confirm that high-dose therapy with autologous stem cell transplant from blood or bone marrow in not-too-heavily pretreated patients is a safe procedure but will cure only half the patients.

Gorin, N. C., M. Labopin, et al. (2000). "Feasibility and recent improvement of autologous stem cell transplantation for acute myelocytic leukaemia in patients over 60 years of age: importance of the source of stem cells." Br J Haematol **110**(4): 887-93.

A total of 193 patients with acute myelocytic leukaemia (AML) [147 in first complete remission (CR1)], ranging from 60 years to 75 years of age (median 63 years), were autografted between January 1984 and December 1998. The source of stem cells was peripheral blood (PB) in 128 patients, bone marrow in 51 patients and a combination of both in 14 patients. Total body irradiation (TBI) was used in 34 cases. Ninety-seven per cent of patients had successful engraftment of neutrophils on day 15 (range days 7-71) and of platelets on day 30 (range days 9-894). In patients autografted in CR1, the transplant-related mortality (TRM) was 15 +/- 4%, the relapse incidence (RI) was 58 +/- 5%, the leukaemia-free survival (LFS) was 36 +/- 5% and the overall survival was 47 +/- 5%

at 3 years. The source and dose of stem cells were studied in particular; in patients transplanted in CR1, the RI was 44 +/- 11% in those receiving marrow compared with 63 +/- 6% in those receiving PB (P = 0.04). Patients autografted in CR1 who received higher granulocyte-macrophage colony-forming units (CFU-GM) doses (above the median) had a lower RI (47 +/- 11% vs. 79 +/- 9%, P = 0.009). There was a significant improvement in patients transplanted after March 1996; for those in CR1, the RI was 41 +/- 8% vs. 65 +/- 6% (P = 0.01), the LFS was 53 +/- 8% vs. 28 +/- 5% (P = 0.01) and the overall survival was 72 +/- 7% vs. 36 +/- 6% (P = 0.02). By multivariate analyses, significant factors for the outcome were the date of transplant with recent improvement and the source of stem cells, with a lower RI for marrow. Autologous stem cell transplantation (ASCT) is a potential therapeutic approach in patients with AML over 60 years of age; results have improved recently.

Gorin, N. C., M. Labopin, et al. (2003). "Marrow versus peripheral blood for geno-identical allogeneic stem cell transplantation in acute myelocytic leukemia: influence of dose and stem cell source shows better outcome with rich marrow." Blood **102**(8): 3043-51.

Several studies have compared bone marrow (BM) and peripheral blood (PB) as stem cell sources in patients receiving allografts, but the cell doses infused have not been considered, especially for BM. Using the ALWP/EBMT registry, we retrospectively studied 881 adult patients with acute myelocytic leukemia (AML), who received a non-T-depleted allogeneic BM (n = 515) or mobilized PB (n = 366) standard transplant, in first remission (CR1), from an HLA-identical sibling, over a 5-year period from January 1994. The BM cell dose ranged from 0.17 to 29 x 10(8)/kg with a median of 2.7 x 10(8)/kg. The PB cell dose ranged from 0.02 to 77 x 10(8)/kg with a median of 9.3 x 10(8)/kg. The median dose for patients receiving BM (2.7 x 10(8)/kg) gave the greatest discrimination. In multivariate analyses, high-dose BM compared to PB was associated with lower transplant-related mortality (RR = 0.61; 95% CI, 0.39-0.98; P =.04), better leukemia-free survival (RR = 0.65; 95% CI, 0.46-0.91; P =.013), and better overall survival (RR = 0.64; 95% CI, 0.44-0.92; P =.016). The present study in patients with AML receiving allografts in first remission indicates a better outcome with BM as compared to PB, when the dose of BM infused is rich.

Gratwohl, A., H. Baldomero, et al. (2005). "Change in stem cell source for hematopoietic stem cell transplantation (HSCT) in Europe: a report of the EBMT activity survey 2003." Bone Marrow Transplant **36**(7): 575-90.

This EBMT activity survey presents the status of hematopoietic stem cell transplantation (HSCT) in Europe 2003 and focuses on changes in stem cell source over the last decade. There were 21 028 first HSCT, 7091 allogeneic (34%), 13 937 autologous (66%) and 4179 additional re- or multiple transplants reported from 597 centers in 42 European countries in the year 2003. Main indications were leukemias (6613 (31%; 78% allogeneic)); lymphomas (11 571 (55%; 93% autologous)); solid tumors (1792 (9%; 92% autologous)) and nonmalignant disorders (898 (5%; 93% allogeneic)). In 1991, the vast majority of autologous and all allogeneic HSCT were still bone marrow (BM) transplants. Stem cell source changed rapidly to peripheral blood (PB) for autologous HSCT between 1992 and 1996. In 2003, 97% of autologous HSCT were PB derived. The change to PB for allogeneic HSCT followed 3 years later and occurred at a lower rate. In 2003, 65% of all allogeneic HSCT were PB derived. The change in stem cell source was not homogeneous. It was associated with donor type, main diagnosis, disease stage and it differed between European countries. In 2003, bone marrow remains a significant source of stem cells in some European countries for autologous HSCT and for nonmalignant disorders in allogeneic HSCT.

Gratwohl, A. and J. Hermans (1995). "Indications and donor source of hematopoietic stem cell transplants in Europe 1993: report from the European Group for Blood and Marrow Transplantation (EBMT)." Clin Transplant **9**(5): 355-63.

This report details the evolution of bone marrow transplantation in Europe over a 20-year period. In 1973, 8 teams undertook a total of 16 allogeneic bone marrow transplants; in 1983, 97 teams performed 1353 transplants. In 1993, the numbers had risen to 260 teams and 7737 transplants. Donor source in 3092 cases was an allogeneic donor (2464 HLA-identical sibling transplants, 147 non-identical family donor transplants, 25 twin donor transplants and 456 unrelated donor transplants). For 4645 patients the transplant was autologous (2450 autologous bone marrow transplants, 1830 autologous peripheral blood stem cell transplants and 365 combined autologous peripheral blood and bone marrow transplants). Indications for transplants in 1993 were leukemias in 3419 patients (44%; 2332 allogeneic, 1087 autologous), lymphoproliferative disorders in 2666 patients (34%; 197 allogeneic, 2469 autologous), solid tumors in 1077 patients (14%; 9 allogeneic, 1068 autologous), aplastic anemia in 251 patients (3%; 250 allogeneic, 1 autologous), inborn errors in 244 patients (3%; 242 allogeneic, 2 autologous) and miscellaneous

disorders in 80 patients (1%; 62 allogeneic, 18 autologous). These data illustrate the increase of hematopoietic stem cell transplants as a therapeutic modality over the last 20 years in Europe.

Grigoryan, G. A., J. A. Gray, et al. (2000). "Conditionally immortal neuroepithelial stem cell grafts restore spatial learning in rats with lesions at the source of cholinergic forebrain projections cholinergic forebrain projections Conditionally immortal neuroepithelial stem cell grafts restore spatial leaming in rats with lesions at the source of cholinergic forebrain projections." Restor Neurol Neurosci **17**(4): 1.

Purpose: Loss of cholinergic projections from the basal forebrain (BF) to the cortex and from the medial septal area (MSA) to tbe hippocampus is a reliable correlate of cognitive deficits in aging and Alzheimer's disease (AD). We assessed the capacity of grafts of the conditionally immortal MHP36 clonal stem cell line to improve spatial learning in rats showing profound deficits after lesions to these projections. Methods: Rats were lesioned by infusions of S-AMPA unilaterally into BF or bilaterally into both BF and MSA. MHP36 cells were implanted ipsilaterally in cortex or basal forebrain two weeks after unilateral BF lesions, and in cortex and hippocampus bilaterally six months after bilateral BF-MSA lesions. Intact and lesion-only controls received vehicle. Six weeks later rats were assessed in spatial learning and memory tasks in the water maze, and then perfused for identification of grafted cells by beta-galactosidase immunohistocheniistry. Results: Lesioned rats with MHP36 grafts, whether implanted two weeks or six months after lesioning, learned to find a submerged platform in the water maze as rapidly as intact controls, and showed a strong preference for the platform quadrant on probe trials, whereas lesioned controls were impaired in all measures. Grafted cells of both neuronal and glial morphologies, migrated away from cortical implantation sites in BF Lesioned rats to the striatum, thalamus and basal forebrain lesion area. Cells implanted in basal forebrain showed a similar distribution. In rats with bilateral BF-MSA lesions, grafts implanted in the hippocampus migrated widely through all layers but cortical grafts largely escaped up the needle tract into the meninges. Conclusions: Although MHP36 grafts were functionally effective in both lesion models, the site and age of lesions and site of implantation influenced the pattern of engraftment. This flexibility encourages the development of conditionally immortal human stem cell lines with similar capacities for functional repair of variable neuronal degeneration in AD or aging.

Hall, V. (2008). "Porcine embryonic stem cells: a possible source for cell replacement therapy." Stem Cell Rev **4**(4): 275-82.

The development of porcine embryonic stem cell lines (pESC) has received renewed interest given the advances being made in the production of immunocompatible transgenic pigs. However, difficulties are evident in the production of pESCs in-vitro. This may largely be attributable to differences in porcine pre-implantation development compared to the mouse and human. Expression of oct4, nanog and sox2 differs in the zona-enclosed porcine blastocyst compared to its mouse and human counterparts, which may suggest that other factors may be responsible for maintaining porcine pluripotency in the early blastocyst. In addition, the epiblast forms considerably later, at days 7 to 8 when the porcine blastocyst begins to hatch and is maintained for 4 days before completely differentiating. This review covers an outline of the known molecular profile during porcine pre-implantation development and provides a history in the development of putative pESCs to date. Greater knowledge on the molecular mechanisms that underlie porcine pluripotency and pre-implantation development may aid in improving the development of pESCs.

Han, K., J. E. Lee, et al. (2008). "Human amnion-derived mesenchymal stem cells are a potential source for uterine stem cell therapy." Cell Prolif **41**(5): 709-25.

OBJECTIVES: Human amnion is an easy-to-obtain novel source of human mesenchymal stem cells, which poses little or no ethical dilemmas. We have previously shown that human amnion-derived mesenchymal (HAM) cells exhibit certain mesenchymal stem cell-like characteristics with respect to expression of stem cell markers and differentiation potentials. MATERIALS AND METHODS: In this study, we further characterized HAM cells' potential for in vivo therapeutic application. RESULTS: Flow cytometric analyses of HAM cells show that they express several stem cell-related cell surface markers, including CD90, CD105, CD59, CD49d, CD44 and HLA-ABC, but not CD45, CD34, CD31, CD106 or HLA-DR. HAM cells at the 10th passage showed normal karyotype. More interestingly, the AbdB-like HOXA genes HOXA9, HOXA10 and HOXA11 that are expressed in the mesenchyme of the developing female reproductive tract and pregnant uteri are also expressed in HAM cells, suggesting similarities between these two mesenchymal cell types. Progesterone receptor is also highly expressed in HAM cells and expression of genes or proteins in HAM cells could be manipulated with the aid of lentivirus technology or cell-permeable

peptides. To test potentials of HAM cells for in vivo application, we introduced enhanced green fluorescence protein (EGFP)-expressing HAM cells to mice by intrauterine infusion (into uteri) or by intravenous injection (into the circulation). Presence of EGFP-expressing cells within the uterine mesenchyme after intrauterine infusion or in lungs after intravenous injection was noted within 1-4 weeks. CONCLUSIONS: Collectively, these results suggest that HAM cells are a potential source of mesenchymal stem cells with therapeutic potential.

Hattori, H., M. Sato, et al. (2004). "Osteogenic potential of human adipose tissue-derived stromal cells as an alternative stem cell source." Cells Tissues Organs **178**(1): 2-12.

Adult bone marrow contains mesenchymal stem cells (bone marrow-derived mesenchymal stem cells; BMSCs) which contribute to the generation of mesenchymal tissue such as bone, cartilage, muscle and adipose. However, using bone marrow as a source of stem cells has the limitation of a low cell number. An alternate source of adult stem cells that could be obtained in large quantities, under local anesthesia, with minimal discomfort would be advantageous. Human adipose tissue obtained by liposuction was processed to obtain a fibroblast-like population of cells or adipose tissue-derived stromal cells (ATSCs). In this study, we compared the osteogenic differentiation of ATSCs with that of BMSCs. Both cell types were cultured in atelocollagen honeycomb-shaped scaffolds with a membrane seal (ACHMS scaffold) for three-dimensional culturing in a specific osteogenic induction medium. Optimal osteogenic differentiation in both cell types, as determined by alkaline phosphatase cytochemistry, secretion of osteocalcin, mineral (calcium phosphate) deposition and scanning electron microscopy, was obtained with the same three-dimensional culture. Furthermore, osteoblastic lining in vivo was examined using ATSC-seeded or BMSC-seeded scaffolds in nude mice. The present results show that ATSCs have a similar ability to differentiate into osteoblasts to that of BMSCs.

Heydarkhan-Hagvall, S., K. Schenke-Layland, et al. (2008). "Human adipose stem cells: a potential cell source for cardiovascular tissue engineering." Cells Tissues Organs **187**(4): 263-74.

BACKGROUND/AIMS: A crucial step in providing clinically relevant applications of cardiovascular tissue engineering involves the identification of a suitable cell source. The objective of this study was to identify the exogenous and endogenous parameters that are critical for the differentiation of human adipose stem cells (hASCs) into cardiovascular cells. METHODS: hASCs were isolated from human lipoaspirate samples, analyzed, and subjected to two differentiation protocols. RESULTS: As shown by fluorescence-activated cell sorter (FACS) analysis, a population of hASCs expressed stem cell markers including CXCR4, CD34, c-kit, and ABCG2. Further, FACS and immunofluorescence analysis of hASCs, cultured for 2 weeks in DMEM-20%-FBS, showed the expression of smooth muscle cell (SMC)-specific markers including SM alpha-actin, basic calponin, h-caldesmon and SM myosin. hASCs, cultured for 2 weeks in endothelial cell growth medium-2 (EGM-2), formed a network of branched tube-like structures positive for CD31, CD144, and von Willebrand factor. The frequency of endothelial cell (EC) marker-expressing cells was passage number-dependent. Moreover, hASCs attached and formed a confluent layer on top of electrospun collagen-elastin scaffolds. Scanning electron microscopy and DAPI staining confirmed the integration of hASCs with the fibers and formation of a cell-matrix network. CONCLUSION: Our results indicate that hASCs are a potential cell source for cardiovascular tissue engineering; however, the differentiation capacity of hASCs into SMCs and ECs is passage number- and culture condition-dependent.

Hong, Y. C., H. M. Liu, et al. (2007). "Hair follicle: a reliable source of recipient origin after allogeneic hematopoietic stem cell transplantation." Bone Marrow Transplant **40**(9): 871-4.

Blood, buccal swab and hair follicles are among the most commonly used sources for forensic science, parentage testing and personal identification. A total of 29 patients who have had a sustained engraftment from 15 months to 21.5 years after allogeneic hematopoietic stem cell transplantation (HSCT) without rejection, relapse or chronic GVHD involving oral mucosa were enrolled for a chimerism study. PCR-amplified short tandem repeat analyses were conducted per patient every 3 months for at least three consecutive times. The results for blood were all donor type except one who had a mixed chimerism, 14.5 years after receiving a transplant for lymphoma. As for buccal swab, mixed chimerism ranging from 10 to 96% donor origin was noted for 28 recipients except the one who had mixed chimerism of blood and retained total recipient type. In contrast, hair follicles were 100% recipient type for the entire group. It is concluded that the hair follicle is devoid of adult stem cell plasticity and may serve as a reliable source of recipient's origin when pre-transplant DNA fingerprinting or reference DNA is not available for people who have successfully received allogeneic HSCT while in need of a personal identification.

Iohara, K., L. Zheng, et al. (2008). "A novel stem cell source for vasculogenesis in ischemia: subfraction of side population cells from dental pulp." Stem Cells **26**(9): 2408-18.

Cell therapy with stem cells and endothelial progenitor cells (EPCs) to stimulate vasculogenesis as a potential treatment for ischemic disease is an exciting area of research in regenerative medicine. EPCs are present in bone marrow, peripheral blood, and adipose tissue. Autologous EPCs, however, are obtained by invasive biopsy, a potentially painful procedure. An alternative approach is proposed in this investigation. Permanent and deciduous pulp tissue is easily available from teeth after extraction without ethical issues and has potential for clinical use. We isolated a highly vasculogenic subfraction of side population (SP) cells based on CD31 and CD146, from dental pulp. The CD31(-);CD146(-) SP cells, demonstrating CD34+ and vascular endothelial growth factor-2 (VEGFR2)/Flk1+, were similar to EPCs. These cells were distinct from the hematopoietic lineage as CD11b, CD14, and CD45 mRNA were not expressed. They showed high proliferation and migration activities and multilineage differentiation potential including vasculogenic potential. In models of mouse hind limb ischemia, local transplantation of this subfraction of SP cells resulted in successful engraftment and an increase in the blood flow including high density of capillary formation. The transplanted cells were in proximity of the newly formed vasculature and expressed several proangiogenic factors, such as VEGF-A, G-CSF, GM-CSF, and MMP3. Conditioned medium from this subfraction showed the mitogenic and antiapoptotic activity on human umbilical vein endothelial cells. In conclusion, subfraction of SP cells from dental pulp is a new stem cell source for cell-based therapy to stimulate angiogenesis/vasculogenesis during tissue regeneration.

Kanda, Y., R. Tanosaki, et al. (2002). "Impact of stem cell source and conditioning regimen on erythrocyte recovery kinetics after allogeneic haematopoietic stem cell transplantation from an ABO-incompatible donor." Br J Haematol **118**(1): 128-31.

We evaluated erythrocyte recovery in 121 allogeneic haematopoietic stem cell transplantation (HSCT) recipients. There were 35 major and minor ABO-incompatible transplants, respectively, including 10 bi-directionally ABO-incompatible transplants. The use of peripheral blood stem cells facilitated erythrocyte recovery, regardless of the presence or absence of major ABO-incompatibility, and was associated with a frequent detection of anti-host isohaemagglutin early after minor ABO-incompatible transplantation, which was not associated with clinically relevant haemolysis. The use of a reduced-intensity regimen combining a purine analogue and busulphan did not delay erythrocyte recovery after major ABO-incompatible transplantation, suggesting this regimen had a strong activity against host plasma cell.

Kato, S., H. Yabe, et al. (2000). "Allogeneic hematopoietic transplantation of CD34+ selected cells from an HLA haplo-identical related donor. A long-term follow-up of 135 patients and a comparison of stem cell source between the bone marrow and the peripheral blood." Bone Marrow Transplant **26**(12): 1281-90.

We studied the outcome of allogeneic transplants in 135 patients who received selected BM and/or PBSC CD34+ cells from HLA haplo-identical related donors. Donor engraftment was achieved in 108 of 128 evaluable transplants. Engraftment failure occurred more often in non-malignant than in malignant diseases (10 of 25 vs 17 of 103, P = 0.010). The CD34+ cell dose was associated with the speed of neutrophil and platelet recovery, but the cell source was not. Acute GVHD (> or = grade II) developed in 21.0 +/- 3.7%. Chronic GVHD occurred more frequently in malignancies than in non-malignancies (44.1 +/- 7.6% vs 0.0%, P = 0.0075), and more in PBSC recipients than in BM recipients (53.6 +/- 9.4% vs 17.4 +/- 9.3%, P = 0.0054). Relapse rate was higher in high risk patients than in standard risk patients (78.7 +/- 7.1% vs 22.1 +/- 10.0%, P = 0.0001). Probabilities of disease-free survival (DFS) were 14.2 +/- 3.5% in malignancies and 25.7 +/- 9.2% in non-malignancies. Probabilities of DFS in standard and high risk patients were 39.4 +/- 9.2% and 5.7 +/- 2.8% (P = 0.0001). A high incidence of graft failure, infection and relapse was observed and resulted in high mortality.

Kim, S. and H. von Recum (2008). "Endothelial stem cells and precursors for tissue engineering: cell source, differentiation, selection, and application." Tissue Eng Part B Rev **14**(1): 133-47.

Endothelial cells are of great interest because of their potential in cell therapy for vascular diseases and ischemic tissue, tissue engineering for vascular grafts and vascularized tissue beds, and modeling for pharmaceutical transport across endothelial barriers. However, limited availability and proliferation capability of mature endothelial cells hampers development of these applications. Recent advances in stem cell technology have enabled researchers to derive endothelial or endothelial-like cells from stem cells or other precursor populations. The current state of these cell sources and their in vitro differentiation,

selection, and applications are discussed in this review.

Ko, J. Y., C. H. Park, et al. (2007). "Human embryonic stem cell-derived neural precursors as a continuous, stable, and on-demand source for human dopamine neurons." J Neurochem **103**(4): 1417-29.

Human embryonic stem (hES) cells can be guided to differentiate into ventral midbrain-type neural precursor (NP) cells that proliferate in vitro by specific mitogens. We investigated the potential of these NP cells derived from hES cells (hES-NP) for the large-scale generation of human dopamine (DA) neurons for functional analyses and therapeutic applications. To address this, hES-NP cells were expanded in vitro for 1.5 months with six passages, and their proliferation and differentiation properties determined over the NP passages. Interestingly, the total hES-NP cell number was increased by > 2 x 10(4)-folds over the in vitro period without alteration of phenotypic gene expression. They also sustained their differentiation capacity toward neuronal cells, exhibiting in vitro pre-synaptic DA neuronal functionality. Furthermore, the hES-NP cells can be cryopreserved without losing their proliferative and developmental potential. Upon transplantation into a Parkinson's disease rat model, the multi-passaged hES-NP cells survived, integrated into the host striatum, and differentiated toward the neuronal cells expressing DA phenotypes. A significant reduction in the amphetamine-induced rotation score of Parkinson's disease rats was observed by the cell transplantation. Taken together, these findings indicate that hES-NP cell expansion is exploitable for a large-scale generation of experimental and transplantable DA neurons of human-origin.

Korbling, M., T. M. Fliedner, et al. (1991). "Autologous blood stem cell (ABSCT) versus purged bone marrow transplantation (pABMT) in standard risk AML: influence of source and cell composition of the autograft on hemopoietic reconstitution and disease-free survival." Bone Marrow Transplant **7**(5): 343-9.

Complete and sustained hemopoietic function following myeloablative therapy can be successfully achieved by autologous transfusion of blood derived hemopoietic stem cells. It was the purpose of this study to compare autologous blood stem cell transplantation (ABSCT) in 20 patients with autologous transplantation of a mafosfamide purged marrow (pABMT) in 23 patients; all were transplanted in first complete remission (CR) of acute myelogenous leukemia (AML) using the same pretransplant regimen (14.4 Gy total body irradiation and 200 mg/kg cyclophosphamide). The autografts, mostly differing in source of hemopoietic stem cells, cell composition and CFU-GM number, were evaluated for their ability to reconstitute hemopoiesis and induce long-term disease-free survival (DFS). Prior to harvest, hemopoietic stem cells were mobilized by inducing transient myelosuppression (ara-C 100 mg/m2 every 12 h s.c. days 1-5 and daunorubicin 45 mg/m2, days 3 and 4) followed by an overshooting of peripheral stem cell concentration.(ABSTRACT TRUNCATED AT 250 WORDS)

Kottaridis, P. D., K. Peggs, et al. (2002). "Survival and freedom from progression in autotransplant lymphoma patients is independent of stem cell source: further follow-up from the original randomised study to assess engraftment." Leuk Lymphoma **43**(3): 531-6.

Peripheral blood progenitor cells (PBPCs) have become the stem cell source of choice in autologous transplantation. In a prospective randomised trial, we previously demonstrated that autologous transplantation using filgrastim-mobilised PBPCs resulted in faster haematopoietic recovery with shorter hospitalisation and reduced platelet transfusions compared to bone marrow transplant (BMT). This study is a follow-up analysis evaluating the long-term clinical outcome. Seventy-two patients with advanced Hodgkin's disease or high-grade lymphoma were randomised to receive either filgrastim-mobilised PBPCs (n = 37) or bone marrow (n = 35) after BEAM chemotherapy. Fourteen patients withdrew from the study before commencing high-dose chemotherapy. Fourteen of the 58 patients who received treatment with chemotherapy and transplant have died, 6 (19%) in the ABMT arm and 8 (30%) in the PBPC transplant (PBPCT) arm. Twenty-five patients (81%) in the ABMT arm and 17 (63%) in the PBPCT arm, who received treatment, were in complete remission at the date of last follow-up. Progression-free survival and overall survival (OS) were similar for both arms (OS 81% at 46 months for ABMT versus 63% for PBPC; p = 0.38). Further prospective studies with larger number of patients need to be done to assess which source of stem cells may translate into a long-term clinical benefit for the patient.

Kroger, N., T. Zabelina, et al. (2009). "HLA-mismatched unrelated donors as an alternative graft source for allogeneic stem cell transplantation after antithymocyte globulin-containing conditioning regimen." Biol Blood Marrow Transplant **15**(4): 454-62.

Between August 1996 and December 2004, 369 patients with a median age of 41 years (range: 1-68 years) received stem cell transplantation (SCT)

from unrelated donors after an antithymocyte-globulin (ATG)-containing conditioning regimen. In 268 patients, complete molecular typing (4-digit) of HLA-A, -B, -C, -DRB1, and -DQB1 was available: 110 patients were completely matched for 10 alleles, 91 patients had 1 allele-mismatch (9/10), and 67 patients were mismatched for 2-4 alleles (6-8/10). The incidence of grade II-IV acute graft-versus-host disease (aGVHD) was 33% in the 10/10, 41% in the 9/10, and 40% in the 6-8/10 group, respectively (P = .1). The cumulative incidence of treatment-related mortality (TRM) and relapse among the groups were similar (27%, 31%, and 32%, P = .2; and 28%, 27%, and 26%, P = .9. After a median follow-up of 35 months (range: 3-120 months), the estimated 5-year disease-free survival (DFS) was 42% and did not differ among the 10/10, the 9/10, and the 6-8/10-mismatched groups (45% versus 42% versus 39%) (P = .5). In multivariate analysis, only age (hazard ratio [HR] 1.013) (P = .004) and bad-risk disease (HR 1.975) (P < .001) were independent risk factors for DFS. In conclusion, pretransplant ATG allows allogeneic SCT from unrelated donors with HLA disparities.

Kumar, P., T. E. Defor, et al. (2008). "Allogeneic hematopoietic stem cell transplantation in adult acute lymphocytic leukemia: impact of donor source on survival." Biol Blood Marrow Transplant **14**(12): 1394-400.

We studied the relative impact of donor source on outcomes following myeloablative hematopoietic stem cell transplantation (HSCT) for adult patients with acute lymphocytic leukemia (ALL). In this single center study, 138 patients aged 18-61 (median 31) years underwent myeloablative conditioning followed by allogeneic HSCT. Stem cell source was an HLA matched related donor (MRD) in 90, HLA matched unrelated donor (URD:M) in 15, HLA mismatched unrelated donor (URD:MM) in 14, and HLA 0-2 (A, B, DRB1) mismatched umbilical cord blood (UCB) in 19 patients. At the time of HSCT, 70 patients were in first clinical remission (CR1), 57 in CR2, and 11 in > or =CR3. Twenty-one patients had T-lineage disease; 43 patients (31%) had high-risk cytogenetics of either t(9;22) (n = 33), t(4;11) or t(1,19) abnormalities, with the remainder (69%) having normal cytogenetics. White blood cell count (WBC) > or =30 x 10(9)/L at diagnosis was documented in 33%. Demographics and disease characteristics were similar in all 4 groups except all UCB recipients were treated since 1996 and received growth factors. Overall survival (OS) at 3 years for the UCB group was 66% (95% confidence interval [CI] 44%-89%) compared to 27% (95% CI 17%-36%) in the MRD group, and only 13% (95% CI 0%-31%) and 14% (95% CI 0%-33%) in the URD:M and URD:MM groups, respectively. Similarly leukemia free survival (LFS) at 3 years was better in the UCB group at 61% (95% CI 38%-84%) than 27% (95% CI 18%-36%) in the MRD and only 13% (95% CI 0%-31%) in the URD:M group and 14% (95%CI 0%-33%) in URD:MM group. Relapse rates at 3 years were 5% (95% CI 0%-15%) in the UCB group compared to 26% (95% CI 16%-35%) in the MRD, 20% (95% CI 1%-39%) in the URD:M groups, and 0% in the URD:MM groups. Transplant-related mortality (TRM) at 3 years was the lowest in the UCB group at 34% and higher in the other donor groups: MRD 47%, URD:M 67%, and URD:MM 86%. In multiple regression analysis, 5 independent risk factors were significantly associated with poorer OS and LFS: use of URD:MM (relative risk [RR] 2.5, 95% CI, 1.2-5.1, P = .01), > or =CR3 at HSCT (RR 3.5, 95% CI, 1.2-9.6, P = .02), WBC > or =30 x 10(9)/l (RR 1.9, 95% CI, 1.2-3.0, P = .01) at diagnosis, recipient and donor (R/D) cytomegalovirus (CMV) seropositive (RR 3.8, 95% CI, 2.0-7.4, P < .01), and > or =2 induction regimens to achieve initial CR (RR 3.5, 95% CI, 1.2-9.6, P = .02). Graft-versus-host disease (GVHD) was associated with improved LFS (RR 0.4, 95% CI, 0.2-0.6, P < .01). When compared with URD:M, OS with UCB was better (RR 0.3, 95% CI, 0.1-0.7, P = .01), supporting the use of UCB as an alternative stem cell source for adults with ALL.

Laino, G., A. Graziano, et al. (2006). "An approachable human adult stem cell source for hard-tissue engineering." J Cell Physiol **206**(3): 693-701.

Stem cells were obtained from deciduous dental pulp of healthy subjects, aged 6-10 years. This stem cell population was cultured, expanded, and specifically selected, detecting using a FACsorter, c-kit, CD34, and STRO-1 antigen expression. Then, c-kit+/CD34+/STRO-1+ cells were replaced in the culture medium added of 20% FBS, leading to osteoblast differentiation. In fact, these cells, after a week, showed a large positivity for CD44, osteocalcin, and RUNX-2 markers. To achieve an adipocytic differentiation, cells, after sorting, were challenged with dexamethason 10(-8) mM in the same culture medium. To obtain myotube fusion, sorted cells were co-cultured in ATCC medium with mouse myogenic C2C12 cells and, after a week, human stem cell nuclei were found to be able to fuse, forming myotubes. Differentiated osteoblasts, as assessed by a large positivity to several specific antibodies, after 30 days of culture and already in vitro, started to secrete an extracellular mineralized matrix, which, 2 weeks later, built a considerable number of 3D woven bone samples, which showed a strong positivity to alkaline phosphatase (ALP), alizarin red, calcein, other than to

specific antibodies. These bone samples, after in vivo transplantation into immunosuppressed rats, were remodeled in a lamellar bone containing entrapped osteocytes. Therefore, this study provides strong evidence that human deciduous dental pulp is an approachable "niche" of stromal stem cells, and that it is an ideal source of osteoblasts, as well as of mineralized tissue, ready for bone regeneration, transplantation, and tissue-based clinical therapies.

Lapierre, V., N. Oubouzar, et al. (2001). "Influence of the hematopoietic stem cell source on early immunohematologic reconstitution after allogeneic transplantation." Blood **97**(9): 2580-6.

Several acute hemolysis episodes, sometimes lethal, have been recently described after transplantation of allogeneic peripheral blood hematopoietic stem cells (PBHSCs). Hemolysis resulted from the production of donor-derived antibodies (Abs) directed at ABO antigens (Ags) present on recipient red blood cells (RBCs). A multicenter randomized phase III clinical study comparing allogeneic PBHSC transplantation (PBHSCT) versus bone marrow hematopoietic stem cell transplantation (BMHSCT) has been conducted in France. In the course of this study, serum anti-A and/or anti-B Ab titers were compared before the conditioning regimen and on day +30 after transplantation in 49 consecutive evaluable PBHSCT (n = 21) or BMHSCT (n = 28) recipients. PBHSCT resulted in a higher frequency of increased anti-A and/or anti-B Ab titers 30 days after transplantation as compared to BMHSCT: 8 (38%) of 21 versus 3 (11%) of 28 (P =.04). In PBHSCT recipients, increased titers were observed mostly after receiving a minor ABO mismatch transplant: 5 of 7 versus 3 of 14 in the absence of any minor ABO mismatch (P =.05), whereas this was not the case after BMHSCT: 1 of 8 versus 2 of 20. Anti-A and/or anti-B serum Abs detectable at day +30 after PBHSCT were always directed against A and/or B Ags absent both on donor and recipient RBCs. Finally, 3 of 21 PBHSCT versus 0 of 28 BMHSCT recipients developed anti-allogeneic RBC Abs other than ABO (P =.07). Overall, the data strongly suggest that immunohematologic reconstitution differs significantly after granulocyte colony-stimulating factor-mobilized PBHSCT when compared to BMHSCT. Such a difference could contribute to the acute hemolysis described after PBHSCT as well as to distinct alloreactivity after PBHSCT.

Levy, Y. S., M. Stroomza, et al. (2004). "Embryonic and adult stem cells as a source for cell therapy in Parkinson's disease." J Mol Neurosci **24**(3): 353-86.

The rationale behind the use of cells as therapeutic modalities for neurodegenerative diseases in general, and in Parkinson's disease (PD) in particular, is that they will improve patient's functioning by replacing the damaged cell population. It is reasoned that these cells will survive, grow neurites, establish functional synapses, integrate best and durably with the host tissue mainly in the striatum, renew the impaired wiring, and lead to meaningful clinical improvement. To increase the generation of dopamine, researchers have already transplanted non-neuronal cells, without any genetic manipulation or after introduction of genes such as tyrosine hydroxylase, in animal models of PD. Because these cells were not of neuronal origin, they developed without control, did not integrate well into the brain parenchyma, and their survival rates were low. Clinical experiments using cell transplantation as a therapy for PD have been conducted since the 1980s. Most of these experiments used fetal dopaminergic cells originating in the ventral mesencephalic tissue obtained from fetuses. Although it was shown that the transplanted cells survived and some patients benefited from this treatment, others suffered from severe dyskinesia, probably caused by the graft's excessive and uncontrolled production and release of dopamine. It is now recognized that cell-replacement strategy will be effective in PD only if the transplanted cells have the same abilities, such as dopamine synthesis and control release, reuptake, and metabolizing dopamine, as the original dopaminergic neurons. Recent studies on embryonic and adult stem cells have demonstrated that cells are able to both self-renew and produce differentiated tissues, including dopaminergic neurons. These new methods offer real hope for tissue replacement in a wide range of diseases, especially PD. In this review we summarize the evidence of dopaminergic neuron generation from embryonic and adult stem cells, and discuss their application for cell therapy in PD.

Lipton, J. M. (2003). "Peripheral blood as a stem cell source for hematopoietic cell transplantation in children: is the effort in vein?" Pediatr Transplant **7 Suppl 3**: 65-70.

Since 1968 HSCT utilizing bone marrow as a stem cell source has become an accepted treatment modality for a variety of immunologic, hematologic and malignant disorders. However, with widespread use it became apparent that BM donation is inconvenient, uncomfortable and not without risk. These observations led to a search for a more easily and safely acquired hematopoietic stem cell source. Recent experience suggests that peripheral blood may serve as an alternative to marrow. Indeed if the current trend continues PBSC will soon replace BM in adults

as the preferred stem cell source for both HLA-matched and unrelated HSCT. Furthermore adults who have experienced both seem to prefer PBSC to BM donation. Recently a number of small trials support the feasibility of PBSC harvest from HLA-matched minor sibling donors. With regard to the recipient, data indicate more rapid engraftment, an acceptable incidence of acute and chronic GVHD, decreased infection and an increased survival for patients with malignancies (suggesting an increased GVT/L effect) when PBSC are utilized. These observations based almost entirely on the adult experience are far from definitive when children are considered. The relatively lower risk and severity of acute and chronic GVHD, the more frequent use of HSCT for non-malignant disorders and the diminished role of GVT/L in the treatment of typical malignancies are factors particular to pediatric HSCT. In addition the sense that mobilization and harvest of PBSC may pose unique and significant risk for the young donor suggest to some that PBSC may not posses sufficient advantage to warrant their use in the pediatric transplant setting. Thus both the available adult-derived data and experience suggest clinical equipoise with regard to the choice of stem cell product, under certain circumstances, when children are considered. This circumstance strongly supports the need for a comprehensive study evaluating the safety and efficacy of PBSC vs. BM HSCT in children.

Mahmoud, H., O. Fahmy, et al. (1999). "Peripheral blood vs bone marrow as a source for allogeneic hematopoietic stem cell transplantation." Bone Marrow Transplant **24**(4): 355-8.

In this randomized prospective study, we included 30 patients with different hematological diseases (acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome or severe aplastic anemia) to compare peripheral blood stem cells (PBSC) (15 patients; mean age 23) and bone marrow (BM) (15 patients; mean age 21.8) as a source for allogeneic transplantation regarding the tempo of hematopoietic recovery and the incidence of acute graft-versus-host disease (GVHD). In the BM group, the median nucleated cell count harvested was 1.3 x 10(10), while in the PBSC group, the aphereses contained a median of 4.4 x 10(6) CD34+/kg recipient weight. PBSC transplantation (PBSCT) was associated with faster hematopoietic reconstitution measured as absolute neutrophil count (ANC) >0.5 x 10(9)/l (log-rank P value <0.0018) and platelet count >25 x 10(9)/l (log-rank P value <0.0098). Seven patients (46.7%) in the BM group vs only one patient (6.7%) in the PBSC group developed acute GVHD (P = 0.013). Therefore, we conclude that PBSCT is associated with faster hematopoietic recovery and the incidence of acute GVHD does not exceed that seen with BMT.

McCloskey, K. E., M. E. Gilroy, et al. (2005). "Use of embryonic stem cell-derived endothelial cells as a cell source to generate vessel structures in vitro." Tissue Eng **11**(3-4): 497-505.

Embryonic stem (ES) cells could potentially serve as an excellent cell source for various applications in regenerative medicine and tissue engineering. Our laboratory is particularly interested in generating a reproducible endothelial cell source for the development of prevascularized materials for tissue/organ reconstruction. After developing methods to isolate highly purified (>96%) proliferating populations of endothelial cells from mouse embryonic stem cells, we tested their ability to form three-dimensional (3-D) vascular structures in vitro. The ES cell-derived endothelial cells were embedded in 3-D collagen gel constructs with rat tail collagen type I (2 mg/mL) at a concentration of 10(6) cells/mL of gel. The gels were observed daily with a phase-contrast microscope to analyze the time course for endothelial cell assembly. The first vessels were observed between days 3 and 5 after gel construct formation. The number and complexity of structures steadily increased, reaching a maximum before beginning to regress. By 2 weeks, all vessel-like structures had regressed back to single cells. Histology and fluorescent images of the vessel-like structures verified that tube structures were multicellular and could develop patent lumens. We have shown that endothelial cells derived, purified and expanded in vitro from ES cells sustain an important endothelial cell function, the ability to undergo vasculogenesis in collagen gels, indicating that endothelial products derived in vitro from stem cells could be useful in regenerative medicine applications.

McMillen, M. A. and R. L. Simmons (1986). "Long-term bone marrow culture as a stem cell source for transplantation." J Surg Res **40**(3): 193-7.

Stem cells in bone marrow capable of inducing spleen colonies in lethally irradiated mice can be maintained in liquid culture for up to 100 days if an appropriate marrow-derived feeder layer is provided. Marrow from some mouse strains cannot be maintained in such cultures. Neither duration of culture nor in vitro cultivation of marrow on allogeneic feeder layer in any way modulates the occurrence of graft-versus-host disease. Cocultivation of marrow with allogeneic feeder layers does not induce tolerance to feeder-layer-type skin grafts in lethally irradiated syngenic recipients. Though an excellent source of stem cells, long-term marrow cultures require further modification before successful

allogeneic marrow transplantation without graft-versus-host reaction can be carried out.

Murrell, W., A. Wetzig, et al. (2008). "Olfactory mucosa is a potential source for autologous stem cell therapy for Parkinson's disease." Stem Cells **26**(8): 2183-92.

Parkinson's disease is a complex disorder characterized by degeneration of dopaminergic neurons in the substantia nigra in the brain. Stem cell transplantation is aimed at replacing dopaminergic neurons because the most successful drug therapies affect these neurons and their synaptic targets. We show here that neural progenitors can be grown from the olfactory organ of humans, including those with Parkinson's disease. These neural progenitors proliferated and generated dopaminergic cells in vitro. They also generated dopaminergic cells when transplanted into the brain and reduced the behavioral asymmetry induced by ablation of the dopaminergic neurons in the rat model of Parkinson's disease. Our results indicate that Parkinson's patients could provide their own source of neuronal progenitors for cell transplantation therapies and for direct investigation of the biology and treatments of Parkinson's disease. Disclosure of potential conflicts of interest is found at the end of this article.

Nagasawa, M., Y. Zhu, et al. (2005). "Analysis of serum soluble CD40 ligand (sCD40L) in the patients undergoing allogeneic stem cell transplantation: platelet is a major source of serum sCD40L." Eur J Haematol **74**(1): 54-60.

CD40 ligand (CD40L) is expressed not only on activated T cells but also on activated platelets. A soluble CD40 ligand (sCD40L) is released from the activated T cells and platelets by ill-defined proteolytic process in vitro. It has been reported that sCD40L is elevated in the serum of patients with systemic lupus erythematosus, unstable angina, essential thrombocythemia, and autoimmune thrombocytopenic purupura. However, source of sCD40L in vivo remains to be elucidated. We investigated the serial sCD40L in the serum in patients undergoing allogeneic stem cell transplantation and compared with the platelets number and soluble IL2R, which is a marker of activated T cells. The value of sCD40L was well correlated with platelet number or thrombopoiesis. In cases of severe graft vs. host disease with markedly increased sIL2R, sCD40L was not increased in vivo. These results indicate that sCD40L in vivo is released mainly from the platelets or in the process of platelet production but not from the activated T cells.

Narayan, A. D., A. Ersek, et al. (2005). "The effect of hypoxia and stem cell source on haemoglobin switching." Br J Haematol **128**(4): 562-70.

This study investigated whether relative changes that accompany the naturally occurring shifts in haematopoietic sites during human development play a role in haemoglobin (Hb) switching or whether Hb switching is innately programmed into cells. CD34(+)/Lineage(-) haematopoietic stem/progenitor cells (HSCs) were isolated from human fetal liver (F-LVR), cord blood (CB), and adult bone marrow (ABM), and the Hb was characterized by flow cytometry on cultures that generated enucleated red cells. All feeder layers (stroma from F-LVR, ABM, and human fetal aorta) enhanced cell proliferation and erythropoiesis but did not affect Hb type. HSCs from CB and F-LVR generated the same Hb profile under normoxia and hypoxia. HSCs from ABM had single-positive HbA and double-positive HbA and HbF cells at normoxia and almost entirely double-positive cells at hypoxia. Further characterization of these ABM cultures was determined by following mRNA expression for the transcription factors erythroid Kruppel-like factor (EKLF) and fetal Kruppel-like factor (FKLF) as a function of time in cultures under hypoxia and normoxia. The erythroid-specific isoform of 5-amino-levulinate synthase (ALAS2) was also expressed under hypoxic conditions. We conclude that Hb switching is affected by the environment but not all HSCs are preprogrammed to respond.

Nardi, N. B. (2005). "All the adult stem cells, where do they all come from? An external source for organ-specific stem cell pools." Med Hypotheses **64**(4): 811-7.

Stem cells can self-renew and maintain the ability to differentiate into mature lineages. Whereas the "stemness" of embryonic stem cells is not discussed, the primitiveness of a stem cell type within adult organisms is not well determined. Data presently available are either inconclusive or controversial regarding two main topics: maintenance or senescente of the adult stem cell pool; and pluripotentiality of the cells. While programmed senescence or apoptosis following uncorrected mutations represent no problem for mature cells, the maintenance of the stem cell pool itself must be assured. Two different mechanisms can be envisaged for that. In the first mechanism, which is generally accepted, stem cells originate during ontogeny along with the organ which they are responsible for, and remain there during all the lifespan of the organism. Several observations derived from recent reports allow the suggestion of a second mechanism. These observations include: organ-specific stem cells are senescent; adult stem cells circulate in the organism; stem cell niches are

essential for the existence and function of stem cells; adult stem cells can present lineage markers; embryo-like, pluripotent stem cells are present in adult organisms, as shown by the development of teratomas, tumors composed of derivatives of the three germ layers; and the fact that the gonads may be a reservoir of embryo-like, pluripotent stem cells in adult organisms. The second mechanism for the maintenance of adult stem cells compartments implies a source external to the organ they belong, consisting of pluripotent, embryo-like cells of unrestricted life span, presenting efficient mechanisms for avoiding or correcting mutations and capable to circulate in the organism. According to this model, primitive stem cells exist in a specific organ in adult organisms. They undergo asymmetrical divisions, which originate one "true" stem cell and another one which enters the pool of adult stem cells, circulating through the entire organism. Upon signals liberated by organ-specific niches, this cell becomes activated to express lineage-specific genes, homes to that particular organ and repopulates its stem cell compartment, differentiating thus in what is seen as the organ-specific stem cell. The gonads are the natural candidates for homing the primitive stem cells in adult organisms. The model proposed in this work for the maintenance of organ-specific stem cell pools from an external source, represented by primitive, embryo-like germinal stem cells present in testes and ovaries, may contribute to the more complete understanding of this complex issue.

Novotny, J. R., C. Rosenthal, et al. (2004). "Disease- or therapy-related bone marrow damage cannot be overcome by changes in stem cell source or dose in allogeneic transplantation." Eur J Haematol **73**(1): 1-9.

OBJECTIVE: To test whether the functional impairment of the host bone marrow (BM) microenvironment pre-existing at the time of transplantation could be overcome by the increased content of immature cells in allogeneic peripheral blood stem cell transplantation (PBSCT) when compared with bone marrow transplantation (BMT). METHODS: Cobble stone area forming cells (CAFC) were assayed in normal BM and BM after allogeneic BMT and PBSCT after stable engraftment. Groups were compared by two-tailed t-test. RESULTS: While BM from 11 normal controls contained an average of 778.8 CAFC-d35 per 10(6) low density bone marrow cells (LDBMC, range 453-1231 per 10(6) LDBMC), BM from patients after BMT contained an average of 123.7 CAFC-d35 per 10(6) LDBMC (range 38-257) per 10(6) LDBMC. BM from patients transplanted with PBSC after myeloablative conditioning contained 128.3 (range 46-305) CAFC-d35 per 10(6) LDBMC (P = 0.89 compared with BMT). Similar results were obtained when patients after PBSCT with non-myeloablative conditioning were included (P = 0.62 compared with BMT). CAFC numbers in patients transplanted in early stages of myeloid leukaemia (acute myeloid leukaemia first remission, chronic myeloid leukaemia first chronic phase) were significantly higher than CAFC numbers in patients transplanted in more advanced stages (P = 0.008) or myelodysplastic syndrome (P = 0.023). The lowest CAFC numbers were found in two cases of retransplantation. CONCLUSION: Our findings indicate that the functional state of the BM microenvironment rather than stem cell dose or source is limiting for the homing and engraftment of immature haemopoietic cells in clinical transplantation.

Ogawa, D., Y. Okada, et al. (2009). "Evaluation of human fetal neural stem/progenitor cells as a source for cell replacement therapy for neurological disorders: properties and tumorigenicity after long-term in vitro maintenance." J Neurosci Res **87**(2): 307-17.

It is expected that human neural stem/progenitor cells (hNS/PCs) will some day be used in cell replacement therapies. However, their availability is limited because of ethical issues, so they have to be expanded to obtain sufficient amounts for clinical application. Moreover, in-vitro-maintained hNS/PCs may have a potential for tumorigenicity that could be manifested after transplantation in vivo. In the present study, we demonstrate the in vitro and in vivo properties of long-term-expanded hNS/PCs, including a 6-month bioluminescence imaging (BLI) study of their in vivo tumorigenicity. hNS/PCs cultured for approximately 250 days in vitro (hNS/PCs-250) exhibited a higher growth rate and greater neurogenic potential than those cultured for approximately 500 days in vitro (hNS/PCs-500), which showed greater gliogenic potential. In vivo, both hNS/PCs-250 and -500 differentiated into neurons and astrocytes 4 weeks after being transplanted into the striatum of immunodeficient mice, and hNS/PCs-250 exhibited better survival than hNS/PCs-500 at this time point. We also found that the grafted hNS/PCs-250 survived stably and differentiated properly into neurons and astrocytes even 6 months after the surgery. Moreover, during the 6-month observation period by BLI, we did not detect any evidence of rapid tumorigenic growth of the grafted hNS/PCs, and neither PCNA/Ki67-positive proliferating cells nor significant malignant invasive features were detected histologically. These findings support the idea that hNS/PCs may represent a nontumorigenic, safe, and appropriate cell source for regenerative therapies for neurological disorders.

Paek, H. J., J. R. Morgan, et al. (2005). "Sequestration and synthesis: the source of insulin in cell clusters differentiated from murine embryonic stem cells." Stem Cells **23**(7): 862-7.

The source of insulin released from insulin-releasing cell clusters (IRCCs) differentiated from embryonic stem cells remains unclear. Rajagopal et al. have suggested that IRCCs do not synthesize but secrete insulin that had been absorbed from media during the multistep protocol. We report here further data relevant to this controversy. No radioisotopic labeling of insulin was observed when IRCCs were incubated in a medium containing 35S-cysteine. Less than 1% of the extra-cellular stoichiometric C-peptide equivalent to insulin was secreted during glucose stimulation. However, intracellular immunostaining and immunogold labeling were both positive for C-peptide. Finally, a mass balance calculation showed that simple equilibration of IRCCs by Fickian diffusion from media accounted for at most 4% of secreted insulin. These findings and further analysis of the results of others suggest that the mechanism of insulin secretion by IRCCs is a combination of sequestration and de novo synthesis.

Papaccio, G., A. Graziano, et al. (2006). "Long-term cryopreservation of dental pulp stem cells (SBP-DPSCs) and their differentiated osteoblasts: a cell source for tissue repair." J Cell Physiol **208**(2): 319-25.

It is not known whether cells derived from stem cells retain their differentiation and morpho-functional properties after long-term cryopreservation. This information is of importance to evaluate their potential for long-term storage with a view to subsequent use in therapy. Here, we describe the morpho-functional properties of dental pulp stem cells (SBP-DPSCs), and of their differentiated osteoblasts, recovered after long-term cryopreservation. After storage for 2 years, we found that stem cells are still capable of differentiation, and that their differentiated cytotypes proliferate and produce woven bone tissue. In addition, cells still express all their respective surface antigens, confirming cellular integrity. In particular, SBP-DPSCs differentiated into pre-osteoblasts, showing diffuse positivity for ALP, BAP, RUNX-2, and calcein. Recovered osteoblasts expressed bone-specific markers and were easily recognizable ultrastructurally, with no alterations observed at this level. In addition, after in vivo transplantation, woven bone converted into a 3D lamellar bone type. Therefore, dental pulp stem cells and their osteoblast-derived cells can be long-term cryopreserved and may prove to be attractive for clinical applications.

Perillo, A., M. Corallo, et al. (2008). "The number, subset and source of cells injected remain critical factors affecting engraftment after in-utero stem cell transplantation via the intracelomic route." Eur J Obstet Gynecol Reprod Biol **138**(2): 248-9.

Pickering, S. J., P. R. Braude, et al. (2003). "Preimplantation genetic diagnosis as a novel source of embryos for stem cell research." Reprod Biomed Online **7**(3): 353-64.

The generation of human embryonic stem (hES) cells has captured the public and professional imagination, largely due their potential as a means of overcoming many debilitating and degenerative diseases by cell replacement therapy. Despite this potential, few well-characterized hES cell lines have been derived. Indeed, in the UK, despite several centres having been active in this area for more than 2 years, there are as yet no published reports of human embryonic stem cells having been generated. Part of the reason for this lack of progress may relate to the quality of embryos available for research. Embryos surplus to therapeutic requirements following routine assisted reproduction treatment are often of poor quality and a large proportion may be aneuploid. This study reports a new approach to hES cell derivation. Embryos surplus to therapeutic requirements following preimplantation genetic diagnosis were used. Although unsuitable for embryo transfer due to the high risk of genetic disease, these embryos are from fertile couples and thus may be of better quality than fresh embryos surplus to assisted reproduction treatment cycles. Embryos donated after cryopreservation were also used, and putative hES lines were derived from both sources of embryos. The cell lines described here are thought to be the first reported hES cell lines to have been derived in the UK.

Pomp, O., I. Brokhman, et al. (2008). "PA6-induced human embryonic stem cell-derived neurospheres: a new source of human peripheral sensory neurons and neural crest cells." Brain Res **1230**: 50-60.

Human embryonic stem cells (hESC) have been directed to differentiate into CNS cells with clinical importance. However, for study of development and regeneration of the human PNS, and peripheral neuropathies, it would be useful to have a source of human PNS derivatives. We have demonstrated that peripheral sensory neuron-like cells (PSN) can also be derived from hESC via neural crest-like (NC) intermediates, and from neural progenitors induced from hESC using noggin. Here we report the generation of higher purity PSN from passagable neurospheres (NSP) induced by murine PA6 stromal

cells. hESC were cultured with PA6, and colonies that developed a specific morphology were cut from the plates. Culture of these colonies under non-adhesive conditions yielded NSPs. Several NC marker genes were expressed in the NSP, and these were also detected in 3-5week gestation human embryos containing migrating NC. These NSPs passaged for 2-8weeks and re-plated on PA6 gave rise to many Brn3a+/peripherin+ cells, characteristic of early sensory-like neurons. Re-culturing PA6-induced NSP cells with PA6 resulted in about 25% of the human cells in the co-cultures differentiating to PSN after 1week, compared to only about 10% PSN obtained after 3 weeks when noggin-induced NSP were used. Two month adherent cultures of PA6-induced NSP cells contained neurons expressing several PSN neuropeptides, and voltage-dependent currents and action potentials were obtained from a molecularly identified PSN. hESC-derived PA6-induced NSP cells are therefore an excellent potential source of human PSN for study of differentiation and modeling of PNS disease.

Prummer, O. and T. M. Fliedner (1986). "The fetal liver as an alternative stem cell source for hemolymphopoietic reconstitution." Int J Cell Cloning **4**(4): 237-49.

In mammalian ontogeny, the liver constitutes the primary hematopoietic organ for some time. Fetal liver cells (FLC) are rich in hematopoietic stem cells with a high proliferative potential but contain few post-thymic T cells. In animal studies, FLC restored hematopoiesis without severe graft-versus-host disease. However, genetic disparity between donor and host frequently limited durable engraftment and prevented or protracted complete immune reconstitution in most fully allogeneic recipients. Some children with severe combined immunodeficiency have been cured by FLC infusion, whereas favorable effects in aplastic anemia, acute leukemia, and inborn errors of metabolism have been limited and badly understood. Fetal liver transplantation in animals may serve as a model for the analysis and management of complications associated with the transfer of purified hematopoietic stem cell grafts and aid in the development of future therapeutic strategies requiring rapidly proliferating stem cell populations.

Prusa, A. R., E. Marton, et al. (2003). "Oct-4-expressing cells in human amniotic fluid: a new source for stem cell research?" Hum Reprod **18**(7): 1489-93.

BACKGROUND: It is the hope of investigators and patients alike that in future the isolation of pluripotent human stem cells will allow the establishment of therapeutic concepts for a wide variety of diseases. A major aim in this respect is the identification of new sources for pluripotent stem cells. Oct-4 is a marker for pluripotent human stem cells so far known to be expressed in embryonal carcinoma cells, embryonic stem cells and embryonic germ cells. METHODS: Cells from human amniotic fluid samples were analysed for mRNA expression of Oct-4, stem cell factor, vimentin and alkaline phosphatase via RT-PCR. Oct-4 protein expression was investigated by Western blot analysis and immunocytochemistry. Oct-4-positive cells were also analysed for the expression of cyclin A protein via double immunostaining. RESULTS: Performing RT-PCR, Western blot and immunocytochemical analyses revealed that in human amniotic fluid in the background of Oct-4-negative cells a distinct population of cells can be found, which express Oct-4 in the nucleus. Oct-4-positive amniotic fluid cell samples also express stem cell factor, vimentin and alkaline phosphatase mRNA. The Oct-4-positive amniotic fluid cells are actively dividing, proven by the detection of cyclin A expression. CONCLUSIONS: The results presented here suggest that human amniotic fluid may represent a new source for the isolation of human Oct-4-positive stem cells without raising the ethical concerns associated with human embryonic research.

Romagnani, P., F. Annunziato, et al. (2005). "CD14+CD34low cells with stem cell phenotypic and functional features are the major source of circulating endothelial progenitors." Circ Res **97**(4): 314-22.

Endothelial progenitor cells (EPCs) seem to be a promising tool for cell therapy of acute myocardial infarction, but their nature is still unclear. We show here that EPCs obtainable from peripheral blood (PB) derive from the adhesion-related selection in culture of a subset of CD14+ cells, which, when assessed by the highly-sensitive antibody-conjugated magnetofluorescent liposomes (ACMFL) technique, were found to express CD34. These CD14+CD34low cells represented a variable proportion at individual level of CD14+ cells, ranging from 0.6% to 8.5% of all peripheral-blood leukocytes, and constituted the dominant population among circulating KDR+ cells. By using the ACMFL technique, virtually all CD14+ cells present in the bone marrow were found to be CD14+CD34low double-positive cells. EPCs, as well as purified circulating CD14+CD34low cells, exhibited high expression of embryonic stem cell (SC) markers Nanog and Oct-4, which were downregulated in a STAT3-independent manner when they differentiated into endothelial cells (ECs). Moreover, circulating CD14+CD34low cells, but not CD14+CD34- cells, proliferated in response to SC

growth factors, and exhibited clonogenicity and multipotency, as shown by their ability to differentiate not only into ECs, but also into osteoblasts, adipocytes, or neural cells. The results of this study may reconcile apparently contradictory data of the literature, showing the generation of PB-derived EPCs from either CD34+ or CD14+ cells. We suggest that the use of this previously unrecognized population of circulating CD14+CD34low cells, which exhibit both phenotypic and functional features of SCs, may be useful in improving cell-based therapies of vascular and tissue damage.

Russell, J. A., L. Larratt, et al. (1999). "Allogeneic blood stem cell and bone marrow transplantation for acute myelogenous leukemia and myelodysplasia: influence of stem cell source on outcome." Bone Marrow Transplant **24**(11): 1177-83.

We have compared the outcomes of 87 patients with acute myelogenous leukemia (AML) and myelodysplasia (MDS) receiving matched sibling transplants with stem cells from peripheral blood (blood cell transplant, BCT) or bone marrow (BMT). In good risk patients (AML in CR1) granulocytes recovered to 0.5 x 10(9)/l a median of 14 days after BCT compared with 19 days after BMT ($P < 0.0001$). For patients with poor risk disease (AML beyond CR1 and MDS) corresponding figures were 16 vs 26 days ($P < 0.0001$). Platelet recovery to 20 x 10(9)/l was also faster after BCT (good risk 12 vs 20 days, $P < 0.0001$; poor risk 17 vs 22 days, $P = 0.04$). Red cell transfusions were unaffected by cell source, but BCT recipients required less platelet transfusions (good risk 1 vs 5, $P = 0.002$; poor risk 5 vs 11, $P = 0.004$). Blood cell transplants resulted in more chronic GVHD (86% vs 48%, $P = 0.005$) and a significantly higher proportion of recipients with KPS of 80% or less (48% vs 5%, $P = 0.004$). Disease-free survival at 4 years was 23% for both groups of poor risk patients but outcome in good risk patients was better after BCT (93% vs 62%, $P = 0.047$) related mainly to less relapse. While disease-free survival may be better after BCT than BMT for AML in CR1, quality of life may be relatively impaired.

Sakaguchi, Y., I. Sekiya, et al. (2005). "Comparison of human stem cells derived from various mesenchymal tissues: superiority of synovium as a cell source." Arthritis Rheum **52**(8): 2521-9.

OBJECTIVE: To compare the properties of human mesenchymal stem cells (MSCs) isolated from bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. METHODS: Human mesenchymal tissues were obtained from 8 donors during knee surgery for ligament injury. After collagenase digestion or gradient-density separation, nucleated cells were plated at an appropriate density for expansion at the maximum rate without colony-to-colony contact. Yield, expandability, differentiation potential, and epitope profile were compared among MSCs from the 5 different tissue sources. RESULTS: Colony number per 10(3) nucleated cells was lower, and cell number per colony was higher, in bone marrow than in other mesenchymal tissues. When the cells were replated at low density every 14 days, bone marrow-, synovium-, and periosteum-derived cells retained their proliferation ability even at passage 10. In chondrogenesis studies in which the cells were pelleted and cultured in vitro, pellets from bone marrow-, synovium-, and periosteum-derived cells were shown to be larger and stained more extensively for cartilage matrix. Synovium-derived cells, in particular, had the greatest ability for chondrogenesis. In adipogenesis experiments, the frequency of oil red O-positive colonies was highest in synovium- and adipose tissue-derived cells. In studies of osteogenesis, the rate of alizarin red-positive colonies was highest in bone marrow-, synovium-, and periosteum-derived cells. For epitope profiling, 15 surface antigens were measured. Most appeared to have similar epitope profiles irrespective of cell source. CONCLUSION: Our findings indicate that there are significant differences in MSC properties according to tissue source, beyond donor and experimental variation. Superiority of synovium as a potential source of MSCs for clinical applications was demonstrated.

Saulnier, N., C. Di Campli, et al. (2005). "From stem cell to solid organ. Bone marrow, peripheral blood or umbilical cord blood as favorable source?" Eur Rev Med Pharmacol Sci **9**(6): 315-24.

Adult stem cells (ASC) have becoming a great domain of research by their promising interest for the regenerative medicine. For some years, the number of publications has been increasing, displaying the potential of ASC to differentiate in all tissue-lineages, challenging the previous dogma that ASC were restricted to give rise only to specific cells from their tissue of origin. Among the diversity of ASC, hematopoietic stem cells (HSC) have been the most studied and their use in the clinical setting is largely documented. Commonly, HSC have been harvested from the bone marrow, but for some years, two others sources, the peripheral blood and the umbilical cord blood have been introduced. All these HSC posses their own molecular characteristics and degree of maturity and represent a more or less good candidate to participate in the cellular-based tissue regeneration. We have reviewed the different parameters allowing to define which subset could be the more favorable such as the accessibility to the pool

of HSC; the quantity of available cells; the tolerability of host-engraftment and the capacity of the cells to home correctly to the required site of damaged. Besides, recently, the molecular profiling of HSC has allowed identifying which subset posses the more promising characteristics.

Schmidt, D., J. Achermann, et al. (2008). "Cryopreserved amniotic fluid-derived cells: a lifelong autologous fetal stem cell source for heart valve tissue engineering." J Heart Valve Dis **17**(4): 446-55; discussion 455.

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.

Shields, L. E., L. Gaur, et al. (2005). "The use of CD 34(+) mobilized peripheral blood as a donor cell source does not improve chimerism after in utero hematopoietic stem cell transplantation in non-human primates." J Med Primatol **34**(4): 201-8.

In utero hematopoietic stem cell transplantation is a therapeutic procedure that could potentially cure many developmental diseases affecting the immune and hematopoietic systems. In most clinical and experimental settings of fetal hematopoietic transplantation the level of donor cell engraftment has been low, suggesting that even in the fetus there are significant barriers to donor cell engraftment. In postnatal hematopoietic transplantation donor cells obtained from mobilized peripheral blood engraft more rapidly than cells derived from marrow. We tested the hypothesis that use of donor hematopoietic/stem cells obtained from mobilized peripheral blood would improve engraftment and the level of chimerism after in utero transplantation in non-human primates. Despite the potential competitive advantage from the use of CD 34(+) from mobilized peripheral blood, the level of chimerism was not appreciably different from a group of animals receiving marrow-derived CD 34(+) donor cells. Based on these results, it is unlikely that this single change in cell source will influence the clinical outcome of fetal hematopoietic transplantation.

Wan, C., Q. He, et al. (2006). "Nonadherent cell population of human marrow culture is a complementary source of mesenchymal stem cells (MSCs)." J Orthop Res **24**(1): 21-8.

To obtain enough quantity of osteogenic cells is a challenge for successful cell therapy in bone defect treatment, and cell numbers were usually achieved by culturing bone marrow cells in a relatively long duration. This study reports a simple and cost-effective method to enhance the number of mesenchymal stem cells (MSCs) by collecting and replating the nonadherent cell population of marrow MSCs culture. Bone marrow MSCs were isolated from 11 patients, cultured at a density of 1 x 10(5)/cm(2) to 1 x 10(6)/cm(2) in flasks. For the first three times of media change, the floating cells were centrifuged and replated in separate flasks. The total number of cells in both the primary and replating flasks were counted at day 21. Cell proliferation rate, potentials for osteogenic, chondrogenic, and adipogenic differentiation were examined in both cell types in vitro. In vivo osteogenic potentials of the cells were also tested in mice implantation model. The results showed that MSCs derived from nonadherent

cell population of marrow cell cultures have similar cell proliferation and differentiation potentials as the originally attached MSCs in vitro. When implanted with hydroxyapatite/tricalcium phosphate (HA-TCP) materials subcutaneously in serve combined immune deficiency (SCID) mice, newly formed bony tissues were found in both cell type groups with osteocalcin expression. We have obtained 36.6% (20.70%-44.97%) more MSCs in the same culture period when the nonadherent cell populations were collected. The findings confirmed that the nonadherent cell population in the bone marrow culture is a complementary source of MSCs, collecting these cells is a simple and cost-effective way to increase MSCs numbers and reduce the time required for culturing MSCs for clinical applications.

Wu, K. H., B. Cui, et al. (2006). "Stem cells: new cell source for myocardial constructs tissue engineering." Med Hypotheses **67**(6): 1326-9.

Cardiovascular diseases like myocardial infarction, complex congenital heart disease, and subsequent heart failure are a leading cause of morbidity and mortality. Recent advances in tissue engineering arise to address the lack of available tissues and organs for transplantation because cells alone are not capable of recreating complex tissues upon transplantation. Consequently, a very promising approach to repair large scar areas and congenital heart defects may be the use of tissue engineering, in which cells are seeded in three-dimensional matrices of biodegradable polymers to form myocardial constructs. In recent years, there has been a tremendous increase in the understanding of stem cell biology. Stem cells have clonogenic and self-renewing capabilities, and under certain conditions, can differentiate into multiple cell lineages. Recent studies have shown that stem cells can be isolated from a wide variety of tissues, including bone marrow, peripheral blood, muscle, and adipose tissue. We hypothesize that tissue-engineered myocardial constructs with stem cells may fulfill the requirements of native heart muscle and, in the long run, may allow replacement of the injured heart and repair of congenital cardiac defects possible.

Yamaguchi, H., E. Ishii, et al. (1996). "Umbilical vein endothelial cells are an important source of c-kit and stem cell factor which regulate the proliferation of haemopoietic progenitor cells." Br J Haematol **94**(4): 606-11.

The expression and production of c-kit and its ligand, stem cell factor (SCF), in cord blood and neonates were studied. Serum SCF levels were significantly higher in cord blood, neonates aged 1-30 d, and in 4-month-old infants than in the maternal serum ($P < 0.01$). SCF levels decreased in children from 7 months to 15 years of age ($P < 0.01$). The serum soluble c-kit levels were significantly higher in cord ($P < 0.01$) and neonatal blood ($P < 0.05$) than in the maternal blood. SCF and c-kit levels in placental tissue homogenates and the culture media of decidual cells and trophoblasts were low. To determine the sites of high SCF and c-kit production in cord blood and in early neonates. SCF and c-kit mRNA expression was analysed in various tissues by polymerase chain reaction. High SCF mRNA expression was observed in human umbilical vein endothelial cells (HUVEC). Moderate c-kit mRNA expression was detected in HUVEC, the bone marrow, and cord blood. These findings suggest that endothelial cells mainly produce the SCF in cord blood and in early neonates. To confirm the role of endothelial cells in haemopoiesis, colony-forming assays were performed in the presence of HUVEC culture media, which induced the formation of high numbers of granulocyte and erythroid colonies in cord blood. IL-3, IL-6 and SCF levels were elevated in the media. Our findings suggest that endothelial cells have an important role in the maintenance and proliferation of progenitor cells in neonatal blood via the interaction of c-kit and SCF with other factors. The ex vivo expansion of cord progenitor cells in the presence of endothelial cells needs to be investigated further.

Zeng, X. and M. S. Rao (2007). "Human embryonic stem cells: long term stability, absence of senescence and a potential cell source for neural replacement." Neuroscience **145**(4): 1348-58.

Unlike normal somatic cells, human embryonic stem cells (hESCs) can proliferate indefinitely in culture in an undifferentiated state where they do not appear to undergo senescence and yet remain nontransformed. Cells maintain their pluripotency both in vivo and in vitro, exhibit high telomerase activity, and maintain telomere length after prolonged in vitro culture. Thus, hESCs may provide an unlimited cell source for replacement in a number of aging-related neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease as well as other neurological disorders including spinal cord injuries. The ability of hESCs to bypass senescence is lost as hESCs differentiate into fully differentiated somatic cells. Evidence has been accumulated that differences in telomere length, telomerase activity, cell cycle signaling, DNA repair ability, as well as the lack of genomic, mitochondrial and epigenetic changes, may contribute to the lack of senescence in hESC. In this manuscript, we will review recent advances in characterizing hESCs and monitoring changes in these aspects in prolonged cultures. We will focus on the potential roles of several cellular

pathways including the telomerase, p53 and the Rb pathways in escaping senescence in hESCs. We will also discuss the genomic and epigenetic changes in long-term hESC culture and their potential roles in bypassing senescence.

Zweigerdt, R., M. Burg, et al. (2003). "Generation of confluent cardiomyocyte monolayers derived from embryonic stem cells in suspension: a cell source for new therapies and screening strategies." Cytotherapy **5**(5): 399-413.

BACKGROUND: Cellular cardiomyoplasty is evolving as a new strategy to treat cardiac diseases. A prerequisite is a reliable source of pure cardiomyocytes, which could also help in the exploitation of recent advances in genomics and drug screening. Our goal was to establish a robust lab-scale process for the generation of embryonic stem (ES)-cell-derived cardiomyocytes in suspension. METHODS: A 71 ES cell clone carrying a construct consisting of the alpha-cardiac myosin heavy chain (alphaMHC) promoter driving the neomycin resistance gene was used for antibiotic-driven cardiomyocyte enrichment. Rotating suspension culture was established to initiate embryoid body (EB) formation. To track growth and differentiation kinetics, cell count and flow cytometry for SSEA-I, E-cadherin (stem-cell marker)and sarcomeric myosin (cardiomyocytes marker) was performed. Oct4 expression was measured via real time (RT)-PCR. RESULTS: Cultures comprising 2.5-8 x 10(6) differentiating FS cells/mL were obtained after 9 days in rotating suspension. Upon G418 addition,vigorous contracting spheres, termed cardiac bodies (CB), developed. These cultures consisted of about 2.1 x 10(5) enriched cardiomyocytes/mL after 6- 10 days of selection. Suspensions comprising 90- 95%viable single cells were generated using an improved dissociation method. Seeding of cardiomyocytes with 7 x 10(4) cell/cm(2) resulted in a homogeneous monolayer of synchronously contracting cells. Myocyte specific immunohistochemistry indicated purity of > 99%. DISCUSSION: We have established a reliable lab-scale protocol to generate cultures of highly enriched cardiomyocytes in suspension. This will facilitate development of larger-scale processes for stem-cell based cardiomyocyte supply. An improved method is provided to derive vital suspensions of cardiomyocytes, which could be utilized for transplantation as well as for drug screening purposes.

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