



Annotated Bibliography

XIX. Miscellaneous Topics



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(also see also see mesenchymal stem cells, granulocyte transfusion, regulatory issues, autoimmune diseases, acute radiation injury, HIV positive patients)

vii. Other Items

- A. **Isolation of amniotic stem cell lines with potential for therapy.** De Coppi P, Bartsch G Jr, Siddiqui MM, Xu T, Santos CC, Perin L, Mostoslavsky G, Serre C, Snyder EY, Yoo JJ, Furth ME, Soker S, Atala A. *Nat Biotechnol.* 2007;25:100-106. [Abstract](#)

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

- B. **Human amniotic fluid-derived stem cells have characteristics of multipotent stem cells.** Kim J, Lee Y, Kim H, Hwang KJ, Kwon HC, Kim SK, Cho DJ, Kang SG, You J. *Cell Prolif.* 2007;40:75-90. [Abstract](#)

In the last decade, success in the isolation and culture of human **embryonic stem cells (ESCs)** has created new opportunities with respect to exploring the biological control of these cells and evaluating their potential for use in cell-based therapies for human disease. However, the use of ESCs has been constrained by complex social and ethical considerations. In addition, maintaining ESCs in vitro presents significant technical challenges, and they frequently undergo genomic alterations and/or chromosomal aberrations during maintenance in vitro. Most importantly, elimination of undifferentiated cells that could develop malignancy after transplantation into the human body is not yet possible.

Human bone marrow-derived mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into diverse lineages, including osteocytes, chondrocytes, adipocytes and cardiomyocytes. Although initially identified in adult bone marrow, cells resembling BM-MSCs have also been found in many other tissues including umbilical cord, umbilical cord blood, amniotic membrane and synovial fluid. Human amniotic fluid contains a variety of stem cells, and has been shown to contain cells expressing Oct-4 antigen, a specific marker of pluripotent stem cells. Thus human amniotic fluid is intriguing as a possible source of pluripotent stem cells for cell-based therapeutics. However, their use will require a much more thorough understanding of their biology.

In this publication, the authors have addressed these issues by further characterizing the in vitro growth kinetics, replicative lifespan and biological properties of human amniotic fluid-derived MSCs throughout their existence. The techniques used included reverse transcriptase-PCR, immunocytochemistry, telomerase activity assays and differentiation potential assays.

Their results demonstrate that cells obtained from human amniotic fluid possess immunophenotypes and gene expression profiles that are largely characteristic of undifferentiated cells, and therefore may have therapeutic potential that is even greater than bone marrow derived MSCs. The cells can differentiate into adipocytes, osteocytes, chondrocytes and neuronal cells, can express many pluripotent stem cell-specific genes, exhibit telomerase activity and proliferate well during ex vivo expansion. The authors conclude that they have considerable potential for use in cell-based therapeutics.

- C. **Quality of life in adults following bone marrow transplantation during childhood.** Helder DI, Bakker B, de Heer P, van der Veen F, Vossen JM, Wit JM, Kaptein AA. *Bone Marrow Transplant.* 2004;33:329-36. [Abstract](#)

Hematopoietic cell transplantation is an intensive procedure associated with lengthy hospitalization and risk of severe pretreatment and treatment-related morbidity. The long-term effects of this procedure on the quality of life (QOL) of patients and their family members are of considerable significance. This report of a detailed study provides reassuring data after assessing QOL in 22 young adults who had received a BMT an average of 14 years previously. When compared to healthy reference individuals, the scores of BMT patients on generic measures of QOL were not significantly different from those of healthy individuals. The authors concluded that having received BMT during childhood does not negatively affect the QOL of patients as adults.

- D. **Cord blood transplantation provides better reconstitution of hematopoietic reservoir compared with bone marrow transplantation.** Frassoni F, Podesta M, Maccario R, Giorgiani G, Rossi G, Zecca M, Bacigalupo A, Piaggio G, Locatelli F. *Blood.* 2003;102:1138-41. [Abstract](#)

The authors hypothesized that when delayed engraftment occurs with cord blood transplants, this might not be related to an insufficient number of stem cells in the graft, but to an intrinsic difficulty of these cells to undergo differentiation. To test the

hypothesis, 2 groups of children were compared; 12 received a CB transplant and 12 an adult bone marrow (BM) transplant. They studied neutrophil and platelet recovery and, at a median time of approximately 1 year after transplantation, the frequency of colony-forming cells (CFCs) and long-term culture initiating cells (LTC-ICs) in the BM of the 2 groups. Their results indicated that the frequency of committed and early progenitors was significantly higher in the marrows of children given cord blood cells, compared with BM transplant recipients. They concluded that, compared to bone marrow, cord blood can better restore the host hematopoietic progenitor cell reservoir.

- E. **Unrelated umbilical cord blood stem cell transplant after failure of haploidentical or matched unrelated donor hematopoietic stem cell transplant.** Khorshid O, de Meis E, Martin T, Jones RB, Shpall EJ, Nieto Y, Khouri I, Shahjahan M, Gajewski J, Giralto S, Champlin R, de Lima M. *Leukemia*. 2003;17:2538-40.

This article describes two adults who had graft rejection following haploidentical or matched-unrelated hematopoietic cell transplants, who achieved donor neutrophil and platelet recovery with unrelated cord blood transplants. Both patients achieved complete remissions of their hematological malignancies. However, both died, 6 months and 2 years post umbilical cord blood transplant from multiple complications related to delayed immune recovery. Both patients had received a second preparative regimen (fludarabine, ATG, ± melphalan), intended to produce further recipient immunosuppression to improve the likelihood of engraftment of the cord blood units.

- F. **Modulation of hematopoietic stem cell homing and engraftment by CD26.** Christopherson KW 2nd, Hangoc G, Mantel CR, Broxmeyer HE. *Science*. 2004;305(5686):1000-3. [Abstract](#)

The authors point out that hematopoietic stem cell homing and engraftment are crucial to transplantation efficiency, and clinical engraftment is severely compromised when donor-cell numbers are limiting. Cord blood transplants have been mainly utilized in children as a result of apprehension about limited cell numbers. Attempts at ex-vivo expansion of stem cells for clinical transplantation have not been encouraging. An alternative means to enhance engraftment is to increase HSC homing efficiency to bone marrow niches. They presented evidence from murine experiments that endogenous CD26 expression on donor cells negatively regulates homing and engraftment, and that it was possible to increase greatly the efficiency of transplantation by inhibition or deletion of CD26. These results suggest a means by which improvement of hematopoietic cell transplant efficiency may be possible in the clinic. Such findings would seem to be particularly important in cord blood transplantation.

- G. **Stem cell transplantation for chronic lymphocytic leukemia: should not more patients get a transplant?** Jabbour E, Keating MJ, Champlin RE, Khouri IF. *Bone Marrow Transplant*. 2004;34:289-97. [Abstract](#)

The authors indicate that complete remission rates in chronic lymphocytic leukemia have improved using combinations of conventional chemotherapy and monoclonal antibody. However, cure remains elusive, particularly in fludarabine-refractory patients, whose prognosis remains poor. Autologous stem cell transplantation (SCT) has been explored for such patients, lengthening the time to treatment failure in selected patients, but there is little hope that it will improve the cure rate. Allogeneic SCT remains the only curative approach, producing an extended disease-free survival in 25-60%, mainly via the graft-versus-leukemia effect. However, the treatment-related mortality with such an approach has been significant, with a 30-40% risk of death within 100 days of the transplant. Nonmyeloablative conditioning regimens may produce high response rates and lower morbidity, especially for patients with chemosensitive disease. Randomized trials designed according to the new biologic prognostic parameters described in chronic lymphocytic leukemia are required to better define the role of nonmyeloablative conditioning regimens.

- H. **Unrelated Donor Marrow Transplantation for B-Cell Chronic Lymphocytic Leukemia After Using Myeloablative Conditioning: Results From the Center for International Blood and Marrow Transplant Research.** Steven Z. Pavletic, Issa F. Khouri, Michael Haagenson, Roberta J. King, Philip J. Bierman, Michael R. Bishop, Michael Carston, Sergio Giralto, Arturo Molina, Edward A. Copelan, Olle Ringdén, Vivek Roy, Karen Ballen, Douglas R. Adkins, Philip McCarthy, Daniel Weisdorf, Emili Montserrat, Claudio Anasetti. *Journal of Clinical Oncology*. 2005;23:5788-5794. [Abstract](#)

This is a report of 38 CLL patients who received a matched URD transplant using bone marrow procured by the National Marrow Donor Program. The median age was 45 years (range, 26 to 57 years), the median time from diagnosis was 51 months, and the median number of prior chemotherapy regimens was three. Fifty-five percent of patients were chemotherapy refractory and 89% had received fludarabine. Conditioning included total-body irradiation in 92% of patients. Graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate with cyclosporine or tacrolimus for 82% of patients.

Twenty-one patients (58%) achieved complete response and six (17%) achieved partial response. Incidences of grades 2 to 4 acute GVHD were 45% at 100 days and incidences of chronic GVHD were 85% at 5 years. Eleven patients are alive and disease free at a median of 6 years (range, 3.0 to 9.0 years). Five-year overall survival, failure-free survival, disease progression rates, and treatment-related mortality (TRM) were 33%, 30%, 32%, and 38% respectively.

The authors concluded that lasting remissions can be achieved after URD transplantation in patients with advanced CLL. The high TRM suggests that myeloablative conditioning and HLA-mismatched donors should be avoided in future protocols, and it is mandatory to investigate transplant strategies with a lower morbidity and mortality, including the use of nonmyeloablative regimens.

- I. **Donor CD4+CD25+ T cells promote engraftment and tolerance following MHC-mismatched hematopoietic cell transplantation.** Hanash AM, Levy RB. *Blood*. 2005;105:1828-36. [Abstract](#)

Identifying cell populations capable of supporting allogeneic hematopoietic stem/progenitor cell engraftment without inducing GVHD would broaden the pool of acceptable donors. Although unfractionated CD4(+) T cells have not been shown to be an efficient facilitating population, **CD4(+)CD25(+) regulatory cells (T-reg's)** were examined for their capacity to support allogeneic hematopoietic engraftment. In a murine fully major histocompatibility complex (MHC)-mismatched BMT model, cotransplantation of donor B6 T-reg's into sublethally conditioned BALB/c recipients supported significantly greater lineage-committed and multipotential donor progenitors in recipient spleens 1 week after transplantation and significantly increased long-term multilineage donor chimerism. Donor engraftment occurred without GVHD-related weight loss or lethality and was associated with tolerance to donor and host antigens by *in vitro* and *in vivo* analyses. Donor CD4(+)CD25(+) T cells may therefore represent a potential alternative to unfractionated T cells for promotion of allogeneic engraftment in clinical hematopoietic cell transplantation.

- J. **Failure of a sibling umbilical cord blood transplantation to correct hemophilia A.** Andolina M, Maximova N, Rabusin M, Bruno G, Cerneca F. *Haematologica*. 2004;89(7):ECR22. ([e-case report](#))

If the hematopoietic stem cells or the mesenchymal cells of bone marrow were able to mature into endothelial cells, a bone marrow transplantation could theoretically cure hemophilia A. The authors report the case of a child whose outcome seems to

rule out this hypothesis.

A 6-year old child, suffering from both hemophilia A (Factor VIII:c <5%, normal value 50-134) and acute lymphatic leukemia was submitted to a cord blood transplantation in second remission. The donor was an HLA identical sister who was heterozygous for haemophilia (aPTT-ratio 1.21, normal value 0.8-1.18; Factor VIII:c 48%). After a conditioning regimen consisting of TBI, thiotepa and cyclophosphamide, 980×10^6 nucleated cells (3.3×10^6 CD34+) were infused.

The follow-up was almost uneventful and the engraftment, confirmed by DNA polymorphism and blood group, was complete. Nevertheless after 2 years no changes were observed in the levels of factor VIII:c.

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