Stem Cell Therapy 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 therapy.
[Smith MH. **Stem Cell Therapy Literatures.** *Stem Cell* 2013;4(1):65-118] (ISSN 1545-4570). http://www.sciencepub.net/stem. 5

Key words: stem cell; life; gene; DNA; protein; therapy

Introduction

There are over four thousand registered diseases specifically linked to genetic abnormalities. Although stem cells are unlikely to provide powerful treatment for these diseases, they are unique in their potential application to these diseases.

Indeed, in many research projects, scientists have demonstrated that stem cells can be used to replenish or rejuvenate damaged cells within the immune system of the human body and that damaged stem cells can repair themselves and their neighbors. For example, in what is regarded as the first documented case of successful gene-therapy "surgery", scientists at the Necker Hospital for Sick Children in Paris of French succeeded in treating two infants diagnosed with Severe Combined Immunodeficiency Disease, a life-threatening degenerative disease caused by defects on the male (X) chromosome. With the identification of stem cell plasticity several years ago, multiple reports raised hopes that tissue repair by stem cell transplantation could be within reach in the near future (Kashofer, 2005). In cardiovascular medicine, the possibility to cure heart failure with newly generated cardiomyocytes has created the interest of many researchers (Condorelli, 2005). Gene clone techniques can be widely used in the stem cell researches and applications (Ma, 2004).

Literatures

Abe, M., H. Yokoyama, et al. (2009). "Plasma cell leukemia maintaining complete remission by syngeneic stem cell transplantation combined with low-dose thalidomide maintenance therapy." Intern Med **48**(20): 1833-5.

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma, which is very aggressive and resistant to chemotherapy. We report a case of PCL successfully treated with syngeneic peripheral blood stem cell transplantation followed by low-dose thalidomide. As of March 2009, the patient has maintained CR for 39 months posttransplant. The clinical course of the present case suggests that autologous stem cell transplantation using a graft with reduced contamination of malignant cells followed by low-dose thalidomide maintenance therapy may improve the PCL treatment outcome.

Abkowitz, J. L., S. N. Catlin, et al. (1997). "Strategies for hematopoietic stem cell gene therapy: insights from computer simulation studies." Blood **89**(9): 3192-8.

We simulated gene therapy using parameters derived from the analysis of autologous transplantation studies in glucose-6-phosphate dehydrogenase heterozygous cats to determine how hematopoietic stem cell (HSC) biology might influence outcomes. Simulation illustrates that a successful experiment can result by chance and may not be the repeated outcome of a specific protocol design or technical approach. As importantly, in many simulated gene therapy experiments where 1, 2, or 6 of 30 transplanted HSC were labeled, there was significant variation in the contribution from marked clones over time. Variability was minimized in simulations in which large numbers of HSC were transplanted. Strategies that may permit consistent clinically successful results are presented. Taken together, these simulation studies demonstrate that the in vivo behavior of HSC must be considered when optimizing approaches to gene therapy in large animals, and perhaps by extension, in humans.

Aksentijevich, I. and I. W. Flinn (2002). "Monoclonal antibody therapy with autologous peripheral blood

stem cell transplantation for non-Hodgkin's lymphoma." Cancer Control **9**(2): 99-105.

BACKGROUND: With the introduction of novel monoclonal antibody products into the clinic, significant new strategies are being developed to improve upon existing treatment for non-Hodgkin's lymphoma. METHODS: Monoclonal antibodies are being used alone, in combination with chemotherapy, or as adjuncts to autologous bone marrow transplantation for the purpose of purging bone marrow of neoplastic cells. RESULTS: Monoclonal antibodies when used in vivo in conjunction with autologous bone marrow transplantation have been relatively well tolerated. Results from several trials seem to demonstrate a therapeutic benefit for the use of such combinations. CONCLUSIONS: Before these agents can be included in standard bone marrow transplantation regimen, long-term survival outcomes need to be obtained from randomized trials. We review the results from recent trials using monoclonal antibodies in conjunction with autologous stem cell transplantation for the treatment of non-Hodgkin's lymphoma.

Amado, L. C., K. H. Schuleri, et al. (2006). "Multimodality noninvasive imaging demonstrates in vivo cardiac regeneration after mesenchymal stem cell therapy." J Am Coll Cardiol **48**(10): 2116-24.

OBJECTIVES: The purpose of this study was to test the hypothesis, with noninvasive multimodality imaging, that allogeneic mesenchymal stem cells (MSCs) produce and/or stimulate active cardiac regeneration in vivo after myocardial infarction (MI). BACKGROUND: Although intramyocardial injection of allogeneic MSCs improves global cardiac function after MI, the mechanism(s) underlying this phenomenon are incompletely understood. METHODS: We employed magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT) imaging in MSC-treated pigs (n = 10) and control subjects (n = 12) serially for a 2-month period after anterior MI. A sub-endocardial rim of tissue, demonstrated with MDCT, was assessed for regional contraction with MRI tagging. Rim thickness was also measured on gross pathological specimens, to confirm the findings of the MDCT imaging, and the size of cardiomyocytes was measured in the sub-endocardial rim and the non-infarct zone. RESULTS: Multi-detector computed tomography demonstrated increasing thickness of sub-endocardial viable myocardium in the infarct zone in MSC-treated animals (1.0 +/- 0.2 mm to 2.0 +/- 0.3 mm, 1 and 8 weeks after MI, respectively, p = 0.028, n = 4) and a corresponding reduction in infarct scar (5.1 +/- 0.5 mm to 3.6 +/- 0.2 mm, p = 0.044). No changes occurred in control subjects (n = 4). Tagging MRI demonstrated time-dependent recovery of active contractility paralleling new tissue appearance. This rim was composed of morphologically normal cardiomyocytes, which were smaller in MSC-treated versus control subjects (11.6 +/- 0.2 mum vs. 12.6 +/- 0.2 mum, p < 0.05). CONCLUSIONS: With serially obtained MRI and MDCT, we demonstrate in vivo reappearance of myocardial tissue in the MI zone accompanied by time-dependent restoration of contractile function. These data are consistent with a regenerative process, highlight the value of noninvasive multimodality imaging to assess the structural and functional basis for myocardial regenerative strategies, and have potential clinical applications.

Anderson, E. J. (2008). "Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation." Curr Pharm Des **14**(20): 1997-2010.

Viral infections are important causes of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. Some viruses, such as the respiratory and gastrointestinal viruses, are acquired from the healthcare or community in the midst of or after HSCT. Other viruses, such as the herpes-virus family, establish latency after resolution of primary infection but then may reactivate during the immunosuppression that occurs with HSCT. Due to the improved sensitivity and turn-around time with PCR-based molecular diagnostic methods, traditional viral diagnostic methods such as viral culture and rapid shell vial are rapidly being replaced or supplemented. Prophylactic and preemptive strategies are increasingly used to limit reactivation of viruses that have established latency. Improvements in diagnostics result in earlier viral detection and antiviral initiation which may improve outcomes. Newly identified viruses such as human metapneumovirus are being increasingly recognized as pathogens in HSCT recipients. Treatment strategies for viral pathogens continue to change as our understanding of these viral diseases improves.

Asahara, T., C. Kalka, et al. (2000). "Stem cell therapy and gene transfer for regeneration." Gene Ther **7**(6): 451-7.

The committed stem and progenitor cells have been recently isolated from various adult tissues, including hematopoietic stem cell, neural stem cell, mesenchymal stem cell and endothelial progenitor cell. These adult stem cells have several advantages as compared with embryonic stem cells as their practical therapeutic application for tissue regeneration. In this review, we discuss the promising gene therapy application of adult stem and progenitor cells in terms of modifying stem cell potency, altering organ

property, accelerating regeneration and forming expressional organization.

Ashwal, S., A. Obenaus, et al. (2009). "Neuroimaging as a basis for rational stem cell therapy." Pediatr Neurol **40**(3): 227-36.

Neonatal global or focal hypoxic-ischemic brain injury remains a frequent and devastating condition, with serious long-term sequelae. An important issue in any neonatal clinical trial of neuroprotective agents relates to developing accurate measures of injury severity and also suitable measures of the response to treatment. Advanced magnetic resonance imaging techniques can acquire serial and noninvasive data about brain structure, metabolic activity, and the response to injury or treatment. These imaging methods need validation in appropriate animal models for translational research studies in human newborns. This review describes several approaches that use imaging as well as proton magnetic resonance spectroscopy to assess the severity of ischemic injury (e.g., for possible candidate selection) and for monitoring the progression and evolution of injury over time and as an indicator of recovery or response to treatment. Preliminary data are presented on how imaging can be used after neural stem cell implantation to characterize the migration rate, the magnitude of stem cell proliferation, and their final location. Imaging has the potential to allow monitoring of many dimensions of neuroprotective treatments and can be expected to contribute to efficacy and safety when clinical trials using neural stem cells or other neuroprotective agents become available.

Bang, S. M., E. K. Cho, et al. (2003). "High dose therapy followed by autologous peripheral blood stem cell transplantation as a first line treatment for multiple myeloma: a Korean Multicenter Study." J Korean Med Sci **18**(5): 673-8.

We conducted a phase II multicenter trial to estimate the response and survival of patients with newly diagnosed multiple myeloma to high dose melphalan therapy followed by autologous peripheral blood stem cell transplantation. Eligible patients who had undergone induction with vincristine, adriamycin and dexamethasone (VAD) should have adequate cardiac, pulmonary and renal function (creatinine <2 mg/dL). Melphalan at 200 mg/m2 was used as a conditioning regimen. Eighty patients were enrolled from 13 centers. The median age of the patients was 53 yr (range; 20 to 68 yr). The initial stage was IA/IIA/IIB/IIIA/IIIB in 3/8/1/54/14 patients, respectively. Beta2-microglobulin, CRP and LDH were increased in 74, 42 and 34% of the patients examined. Cytogenetic data were available in 30 patients, and 6 patients showed numeric or structural abnormalities. Two therapy-related mortalities occurred from infection. Among the 78 evaluable patients, CR/PR/MR/NC/PD were achieved in 48/26/2/1/1 patients, respectively. After a median follow-up of 30 months, the median overall and event-free survivals were 66 months (95% CI: 20-112) and 24 months (95% CI: 18-29), respectively. This study verifies the efficacy and feasibility of high dose melphalan therapy with autologous stem cell transplantation in newly diagnosed multiple myeloma.

Bang, S. M., Y. K. Kim, et al. (2005). "High-dose therapy and autologous stem cell transplantation in Korean patients with aggressive T/NK-cell lymphoma." Leuk Lymphoma **46**(11): 1599-1604.

The proportion of aggressive T/NK-cell lymphoma in Korea is larger than in the West, and it shows a lower response to conventional chemotherapy and poorer survival than diffuse large B-cell lymphoma. This study was undertaken to evaluate the response rate and survival and to document the prognostic factors in patients with T/NK-cell lymphoma who have undergone high-dose therapy (HDT). Eligibility for the study was a mature T/NK-cell lymphoma with initially poor risk (as high or high intermediate risk on age-adjusted International Prognostic Index) or relapsed cases. Twenty-eight patients from 6 centers were reviewed retrospectively. The M : F ratio was 20:8, and median age was 36 years (range 16--60 years). Twelve patients had unspecified peripheral T-cell lymphomas, 7 anaplastic large-cell lymphomas, 6 nasal T/NK-cell lymphomas, and 3 angioimmunoblastic T-cell lymphomas. Disease status at transplant were initially poor risk in 15, chemosensitive relapse in 8 and chemo-resistant relapse in 5 patients, respectively. A complete response (CR) after HDT comprised 20 patients, including 16 with continued CR. Absolute neutrophil count (> 500/microl) recovered at a median 11 days after autologous stem cell transplantation in 26 patients. Two therapy-related mortalities occurred. Estimated 3-year event-free survival and overall survival (OS) (+/- SE) were 24+/- 9 and 42+/- 10 months, respectively. Only CR status after HDT influenced OS (P=0.000). Therefore, an initial approach with effective induction and HDT may result in a better outcome in T/NK-cell lymphoma.

Baron, F., B. Sautois, et al. (2002). "Optimization of recombinant human erythropoietin therapy after allogeneic hematopoietic stem cell transplantation." Exp Hematol **30**(6): 546-54.

OBJECTIVE: Allogeneic hematopoietic stem cell transplantation (HSCT) is associated with prolonged anemia caused by defective erythropoietin

(Epo) production. We enrolled 34 recipients of an allogeneic HSCT in three consecutive trials to determine the optimal utilization of recombinant human erythropoietin (rhEpo) therapy in this setting. MATERIALS AND METHODS: In the first trial (n = 7), rhEpo 1400 U/kg/week was given from day 1 until a hemoglobin (Hb) level of 10 g/dL was achieved, for a maximum of 60 days. In the second trial, rhEpo 500 U/kg/week was given to achieve Hb levels of 13 to 14 g/dL in 13 anemic patients with fatigue 56 to 1440 days after transplant. In the third trial, rhEpo was scheduled to start on day 35 in 14 patients at a dose of 500 U/kg/week with the aim of achieving Hb levels of 13 to 14 g/dL. RESULTS: In trial 1, erythroid recovery to 1% reticulocytes and red blood cell transfusion independence were faster, but the number of transfusions was not reduced compared to 10 controls. Responses were brisk in trial 2, with transfusion independence achieved after a median of 1 week in 12 of 13 patients, and 2-g Hb increments or Hb values of 11, 12, and 13 g/dL after 6, 7, 10, and 10 weeks, respectively. Transfusions were significantly reduced in the first month of rhEpo therapy. In trial 3, transfusion independence was obtained after a median of 1 week in 13 of 14 patients, and 2-g Hb increments or Hb values of 11, 12, and 13 g/dL after 3, 4, 6, and 8 weeks, respectively. Transfusions rates were considerably reduced compared to the previous month in the same patients or compared to controls undergoing peripheral blood or marrow transplant without rhEpo. CONCLUSIONS: Anemia after allogeneic HSCT is exquisitely sensitive to rhEpo. The benefit is minimal when it is given early post-transplant, as used in all trials to date. However, the rate of major response is greater than 90% when rhEpo is started after day 35. These data provide the basis on which to conduct a prospective, randomized, placebo-controlled trial of rhEpo therapy after allogeneic HSCT.

Baum, C. (2007). "Insertional mutagenesis in gene therapy and stem cell biology." Curr Opin Hematol **14**(4): 337-42.

PURPOSE OF REVIEW: Recent preclinical and clinical studies revealed that the semirandom insertion of transgenes into chromosomal DNA of hematopoietic cells may induce clonal competition, which potentially may even trigger leukemia or sarcoma. Insertional mutagenesis caused by gene vectors has thus led to major uncertainty among those developing advanced hematopoietic cell therapies. This review summarizes novel studies of underlying mechanisms; these studies have demonstrated the possibility of improved gene vector biosafety and generated new insights into stem cell biology. RECENT FINDINGS: The characteristic insertion pattern of various retroviral gene vector systems may be explained by properties of the viral integrase and associated cellular cofactors. Cell culture assays and animal models, including disease-specific and cancer-prone mouse models, are emerging that reveal the contributions of vector features and systemic factors to induction of clonal imbalance. Databases summarizing vector insertion sites in dominant hematopoietic clones are evolving as new tools to identify genes that regulate clonal homeostasis. SUMMARY: Mechanistic studies of insertional mutagenesis by random gene vector insertion will lead to improved tools for advanced hematopoietic cell therapy. Simultaneously, fascinating insights into gene networks that regulate cell fitness will be generated, with important consequences for the fields of hematology, oncology and regenerative medicine.

Becker, P. S. (2002). "Hematopoietic stem cell gene therapy for inherited bone marrow disorders: past accomplishments and continued challenges." J Cell Biochem Suppl **38**: 55-64.

From the time that the genes encoding the defective proteins were cloned for a number of inherited diseases, it became a goal to correct those conditions by restoring the normal gene and thereby, its product. For the inherited disorders affecting the blood and its progenitor cells, the hematopoietic stem cells were the ideal target cells for gene transfer, because the normal gene would then be transferred to all of the progeny cells, theoretically for the lifetime of the recipient. However, the tasks of isolating the hematopoietic stem cells, introducing the new genes in such a manner as to preserve engraftment of the manipulated cells, and achieving long-term gene expression, have not been straightforward in the clinical trial setting, although there has been moderate success for cells in vitro, and in murine studies. With the report of clinical efficacy of gene transfer in children with X-linked severe combined immunodeficiency disease, the dream of clinical gene transfer to hematopoietic cells has become a reality. But there are still significant impediments remaining for a number of diseases. The innovations of introduction of synthetic receptors that confer growth advantage, the use of lentiviral vectors with increased stem cell transduction efficiency, and the addition of modified promoter/enhancer sequences to augment and preserve gene expression may bring wider success to gene therapy clinical trials for bone marrow disorders in the near future.

Bhatia, V. and D. L. Porter (2001). "Novel approaches to allogeneic stem cell therapy." Expert Opin Biol Ther **1**(1): 3-15.

Traditionally, allogeneic haematopoietic stem cell transplantation (SCT) has involved administration of myeloablative doses of chemotherapy and/or radiation that may cure many patients with haematologic diseases. The high morbidity and mortality associated with the intensive conditioning regimen limits allogeneic SCT to younger and healthier patients. However, it is now known that successful allogeneic SCT is dependent, at least in part, on the antitumour properties of the donor graft independent of the conditioning regimen. This potent 'graft versus tumour' (GVT) effect can now be exploited for clinical benefit. The best evidence of a direct GVT reaction comes from the use of donor leukocyte infusions (DLI). For many patients with relapsed leukaemia after allogeneic SCT, DLI re-establishes complete and durable remissions. This has suggested a novel approach to allogeneic cell therapy (ACT) using non-myeloablative, but immunosuppressive conditioning regimens to permit engraftment of allogeneic stem cells and lymphocytes. Engrafted donor cells would then provide GVT activity in the setting of reduced conditioning regimen toxicity. The ability to minimise toxicity and maximise the immunologic GVT effect will make allogeneic transplantation applicable to patients typically ineligible for conventional allogeneic SCT. Response rates with this strategy have been impressive, although toxicity related to graft versus host disease (GVHD) and other complications remains a concern. Current trials have involved heterogeneous groups of patients using various conditioning regimens. Many issues remain unsettled, including identification of the most appropriate tumour targets and definition of the most effective, least toxic conditioning regimen. In addition, the durability of response is unknown. Nevertheless, the use of non-myeloablative conditioning and ACT may provide a new paradigm for allogeneic cell transplantation and the immunotherapy of cancer.

Boda, Z., M. Udvardy, et al. (2009). "Stem cell therapy: a promising and prospective approach in the treatment of patients with severe Buerger's disease." Clin Appl Thromb Hemost **15**(5): 552-60.

No effective blood-flow enhancement therapies are available for patients with severe peripheral arterial disease (SPAD), thus amputation remains the only option for relief of rest pain or gangrene. Autologous bone marrow-derived stem cell therapy (ABMSCT) is an emerging modality to induce angiogenesis from endothelial progenitors. A total of 5 patients with SPAD were treated by ABMSCT using isolated CD34+ cells with characterized phenotype administered by intramuscular injections. The follow-up before and 1, 3, 6, 9, and 12 months after ABMSCT was based on clinical (rest pain, walking distance without pain, nonhealing ulcers, ankle-brachial index [ABI]) and laboratory (angiography, duplex and laser ultrasonography, TcPO(2)) parameters. Significant improvement of pain and walking distance was observed in all patients. Nonhealing ulcers disappeared in 3 patients and became smaller and thinner in 1 patient. The average of ABI improved significantly on the treated limb but did not change on the contralateral limb. New collaterals were detected by angiography in 3 patients, but duplex ultrasonography detected improvement in one patient only. Laser ultrasonography showed a mild significant change, TcPO(2) values improved mainly on the foot. Severe adverse events were not observed. We conclude that ABMSCT with isolated CD34+ cells is safe, effective, and results in sustained clinical benefit for patients with SPAD.

Buchner, T., W. E. Berdel, et al. (2006). "Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia." J Clin Oncol **24**(16): 2480-9.

PURPOSE: Intensification by high-dose cytarabine in postremission or induction therapy and prolonged maintenance are established strategies to improve the outcome in patients with acute myeloid leukemia (AML). Whether additional intensification can add to this effect has not yet been determined. PATIENTS AND METHODS: A total of 1,770 patients (age 16 to 85 years) with de novo or secondary AML or high-risk myelodysplastic syndrome (MDS) were randomly assigned upfront for induction therapy containing one course with standard dose and one course with high-dose cytarabine, or two courses with high-dose cytarabine, and in the same step received postremission prolonged maintenance or busulfan/cyclophosphamide chemotherapy with autologous stem-cell transplantation. RESULTS: The complete remission rate in patients younger than 60 and > or = 60 years of age was 70% and 53%, respectively. The overall survival at 3 years in the two age groups was 42% and 19%, the relapse-free survival was 40% and 19%, and the ongoing remission duration was 48% and 22%, respectively. There were no significant differences in these results between the two randomized induction arms or between the two postremission therapy arms. There was no significant difference in any prognostic subgroup according to secondary AML/MDS, cytogenetics, WBC, lactate dehydrogenase, and early blast clearance. CONCLUSION: The regimen of one course with standard-dose cytarabine and one course with high-dose cytarabine for induction, and

prolonged maintenance for postremission chemotherapy in patients with AML is not improved by additional escalation in cytotoxic treatment.

Campbell, A. D., S. L. Cohn, et al. (2004). "Treatment of relapsed Wilms' tumor with high-dose therapy and autologous hematopoietic stem-cell rescue: the experience at Children's Memorial Hospital." J Clin Oncol **22**(14): 2885-90.

PURPOSE: To investigate whether high-dose therapy with hematopoietic stem-cell rescue (HSCR) will improve survival for patients with relapsed Wilms' tumor. PATIENTS AND METHODS: Thirteen children with relapsed Wilms' tumor were treated with one or two cycles of high-dose chemotherapy (HDT) followed by autologous HSCR. Twelve of 13 patients received reinduction chemotherapy before HDT and HSCR. The median age at diagnosis was 4.8 years, and the median time to relapse was 12 months. The histology was favorable in 12 of 13 patients. The ablative regimens included: (1) thiotepa (TT)/cyclophosphamide (CTX)/carboplatin (CP; n = 2); (2) TT/CTX (n = 5); (3) TT/etoposide (ETP; n = 1); and (4) CP/ETP/CTX (n = 1). Four patients received two cycles of HDT and HSCR. Cycle 1 consisted of CP/ETP/CTX, and melphalan/CTX were used in cycle 2. RESULTS: Seven of 13 patients are alive without evidence of disease, with a median follow-up of 30 months. The 4-year estimated event-free survival (EFS) rate is 60% (95% CI, 0.40 to 6.88), and the overall survival (OS) at 4 years is 73% (95% CI, 0.40 to 6.86). There was no transplant-related mortality. All patients engrafted to an absolute neutrophil count 500/microL at a median of 13 days (range, 8 to 62 days) and had an unsustained platelet count > 20.0 micro at a median of 16 days (range, 10 to 202 days). CONCLUSION: Our results suggest that HDT with HSCR is an effective treatment for patients with Wilms' tumor who experience relapse.

Cassileth, B. R., A. J. Vickers, et al. (2003). "Music therapy for mood disturbance during hospitalization for autologous stem cell transplantation: a randomized controlled trial." Cancer **98**(12): 2723-9.

BACKGROUND: High-dose therapy with autologous stem cell transplantation (HDT/ASCT) is a commonly used treatment for hematologic malignancies. The procedure causes significant psychological distress and no interventions have been demonstrated to improve mood in these patients. Music therapy has been shown to improve anxiety in a variety of acute medical settings. In the current study, the authors determined the effects of music therapy compared with standard care on mood during inpatient stays for HDT/ASCT. METHODS: Patients with hematologic malignancy admitted for HDT/ASCT at two sites (Memorial Sloan-Kettering Cancer Center and Ireland Cancer Center in Cleveland, Ohio) were randomized to receive music therapy given by trained music therapists or standard care. Outcome was assessed at baseline and every 3 days after randomization using the Profile of Mood States. RESULTS: Of 69 patients registered in the study, follow-up data were available for 62 (90%). During their inpatient stay, patients in the music therapy group scored 28% lower on the combined Anxiety/Depression scale (P = 0.065) and 37% lower (P = 0.01) on the total mood disturbance score compared with controls. CONCLUSIONS: Music therapy is a noninvasive and inexpensive intervention that appears to reduce mood disturbance in patients undergoing HDT/ASCT.

Castillo, M. D., K. A. Trzaska, et al. (2008). "Immunostimulatory effects of mesenchymal stem cell-derived neurons: implications for stem cell therapy in allogeneic transplantations." Clin Transl Sci **1**(1): 27-34.

Mesenchymal stem cells (MSCs) differentiate along various lineages to specialized mesodermal cells and also transdifferentiate into cells such as ectodermal neurons. MSCs are among the leading adult stem cells for application in regenerative medicine. Advantages include their immune-suppressive properties and reduced ethical concerns. MSCs also show immune-enhancing functions. Major histocompatibility complex II (MHC-II) is expected to be downregulated in MSCs during neurogenesis. Ideally, "off the shelf" MSCs would be suited for rapid delivery into patients. The question is whether these MSC-derived neurons can reexpress MHC-II in a milieu of inflammation. Western analyses demonstrated gradual decrease in MHC-II during neurogenesis, which correlated with the expression of nuclear CIITA, the master regulator of MHC-II expression. MHC-II expression was reversed by exogenous IFNY. One-way mixed lymphocyte reaction with partly differentiated neurons showed a stimulatory effect, which was partly explained by the release of the proinflammatory neurotransmitter substance P (SP), cytokines, and decreases in miR-130a and miR-206. The anti-inflammatory neurotransmitters VIP and CGRP were decreased at the peak time of immune stimulation. In summary, MSC-derived neurons show decreased MHC-II expression, which could be reexpressed by IFNY. The release of neurotransmitters could be involved in initiating inflammation, underscoring the relevance of immune responses as consideration for stem cell therapies.

Cerny, J., M. Trneny, et al. (2009). "Rituximab based therapy followed by autologous stem cell transplantation leads to superior outcome and high rates of PCR negativity in patients with indolent B-cell lymphoproliferative disorders." Hematology **14**(4): 187-97.

Autologous stem cell transplantation (ASCT) and rituximab based therapy represent effective treatments of indolent B-cell lymphoproliferative disorders (B-LPDs) that often induce molecular remission (MR). We assessed the impact of MR after treatment on prognosis of 57 patients with indolent B-LPDs. We also evaluated the impact of therapy on patients' outcome. Failure to achieve MR was identified as an independent risk factor regardless of treatment modality. PCR positive patients had shorter progression free survival (PFS) in contrast with patients in MR after rituximab (median 0.75 and 2.5 years respectively; p=0.006) or patients in MR after rituximab followed by ASCT (median 3.3 years; p=0.0032). PCR positive patients had a 5-year overall survival (OS) of only 40% compared to a 5-year OS of 76% for PCR negative patients after rituximab (p=0.0186) and 86% PCR negative patients after rituximab with ASCT (p=0.003). All nine patients transplanted with PCR positive graft relapsed (p=0.0023) with shorter PFS (p=0.0008). Rituximab based therapy induced MR in 25 (64%) compared to 18 (100%) patients after rituximab followed by ASCT (p=0.0025). We observed no difference in PFS between the transplant group (3.3 years) and rituximab based treatment (1.9 years), but the 5-year OS of patients with transplant was 85 and 59% respectively (p=0.0271). Patients with indolent B-LPDs who achieve MR have better prognosis. Rituximab based therapy induces MR in high number of patients, which can be further improved by ASCT and patients have an excellent outcome. PCR positive harvest represents a high risk of relapse after ASCT.

Chang, S. A., H. K. Kim, et al. (2008). "Restoration of left ventricular synchronous contraction after acute myocardial infarction by stem cell therapy: new insights into the therapeutic implication of stem cell therapy for acute myocardial infarction." Heart **94**(8): 995-1001.

OBJECTIVE: To evaluate the effects of stem cell therapy on restoration of the left ventricular (LV) synchronous contraction in patients with acute myocardial infarction (AMI). METHODS: 40 patients with AMI who underwent successful coronary revascularisation were randomly allocated to the cell infusion or the control group. Evaluations were performed with echocardiographic tissue synchronisation imaging to determine LV dyssynchrony and with cardiac magnetic resonance imaging to estimate LV ejection fraction (LVEF) at baseline and at 6 months. To quantify the severity of systolic LV dyssynchrony, the standard deviations of time to peak systolic velocity of the 12 LV segments (Ts-SD) were calculated. RESULTS: At 6 months, greater improvements of Ts-SD (DeltaTs-SD: -45.0 (40.2) vs 5.0 (39.9) ms, p<0.001) and LVEF (DeltaLVEF: 6.8% (9.1%) vs -0.2% (6.9%), p = 0.015) relative to the corresponding baseline values were observed in the cell infusion group than in the control group. By multivariate analysis, DeltaTs-SD and baseline LVEF emerged as the independent determinants of LVEF improvement and cell infusion, and baseline Ts-SD as the determinant of DeltaTs-SD improvement. Maximal exercise capacity measured by symptom-limited treadmill testing correlated well with Ts-SD but not with LVEF at 6 months of follow-up. CONCLUSION: Stem cell therapy had a favourable effect on the restoration of LV synchronous contraction in patients with AMI.

Cho, B. S., H. J. Kim, et al. (2007). "Successful interim therapy with imatinib prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute myeloid leukemia." Eur J Haematol **79**(2): 170-3.

OBJECTIVES: Imatinib (Glivec, STI571) has been successfully used in patients with chronic myelogenous leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome (Ph). We used imatinib interim therapy for four consecutive patients with newly diagnosed Ph+ acute myeloid leukemia (AML). We monitored the patient status for minimal residual disease by real-time quantitative polymerase chain reaction. METHODS AND RESULTS: Imatinib was administered on an interim schedule after each chemotherapy course. After the first imatinib cycle, all patients remained in sustained complete hematologic remission (CHR) with a decrease in the breakpoint cluster region of the Abelson oncogene locus transcript. All patients received a second imatinib cycle following consolidation and showed sustained CHR, including two cases with complete molecular remission. All cases underwent hematopoietic stem cell transplantation (HSCT) in favorable condition, and are still alive with a leukemia-free status at 6, 6, 9, and 25 months after HSCT. CONCLUSIONS: As a first-line interim therapy, imatinib appears to be a useful treatment strategy to provide a bridge to HSCT in patients with Ph+ AML. Further studies with a larger patient population and longer follow-up are needed for accurate assessment of the impact of imatinib on the long-term outcome of transplantation for patients with Ph+ AML.

Cho, S. G., Y. B. Koh, et al. (2005). "Successful treatment with splenectomy and interferon alpha against recurred hemophagocytic syndrome in remission state of anaplastic large cell lymphoma following high-dose therapy and autologous peripheral blood stem cell transplantation." Eur J Haematol **74**(3): 259-62.

A 25-yr-old man had been diagnosed as having CD30(+) anaplastic large cell lymphoma associated with hemophagocytic syndrome (HS). He received aggressive frontline chemotherapies and consolidation with autologous peripheral blood stem cell transplantation (PBSCT) following high-dose chemotherapy combined with splenic irradiation (720 cGy in fraction of 180 cGy). However, HS recurred on day 50 of PBSCT without radiologic evidence of lymphoma relapse. On day 56 of PBSCT, splenectomy was performed and pathology showed massive sinusoidal infiltration of histiocytes. On day 68 of PBSCT, administration of interferon alpha was started and maintained for 24 months. HS was completely resolved and he has been alive well and in complete remission (CR), 60 months after initial diagnosis.

Choi, S. M., D. G. Lee, et al. (2005). "Risk-adapted preemptive therapy for cytomegalovirus disease after allogeneic stem cell transplantation: a single-center experience in Korea." Int J Hematol **81**(1): 69-74.

Cytomegalovirus (CMV) remains a major cause of infection in recipients of hematopoietic stem cell transplants (HSCT) and results in significant mortality and morbidity. We present the results of CMV pp65 antigenemia-guided, risk-adapted preemptive therapy aimed at preventing CMV disease in allogeneic HSCT. Preemptive ganciclovir treatment was started when more than 5 CMV antigen-positive cells were detected in the low-risk group (with grade 0-I acute GVHD and matched related HSCT) and when any antigen-positive cells were seen in the high-risk group (with grade II-IV acute GVHD or matched unrelated HSCT). At least 1 episode of antigenemia was observed in 53 (59.6%) of 89 patients before day 100, and preemptive therapy was performed in 33 patients. CMV disease occurred in 6 patients (5 in the high-risk group and 1 in the low-risk group), and late CMV disease developed in 4 patients. Only 1 patient died of CMV pneumonitis before day 100. Neutropenia was observed in 51.5% of ganciclovir-treated patients, and coinfection/superinfection was observed in 42.4%. A strategy of ganciclovir treatment focusing on patients at higher risk could reduce the toxicity from the antiviral drug and be cost-effective. Extended surveillance for CMV disease using more sensitive diagnostic methods is necessary in high-risk patients.

Coombes, R. C., A. Howell, et al. (2005). "High dose chemotherapy and autologous stem cell transplantation as adjuvant therapy for primary breast cancer patients with four or more lymph nodes involved: long-term results of an international randomised trial." Ann Oncol **16**(5): 726-34.

BACKGROUND: The purpose of this study was to assess whether a short course of anthracycline containing chemotherapy followed by high dose therapy with autologous stem-cell support improves disease-free and overall survival as compared with conventional, anthracycline containing chemotherapy, in patients with primary breast cancer and four or more histologically involved lymph nodes. PATIENTS AND METHODS: Two hundred and eighty one patients entered into a randomised clinical trial were allocated to receive standard, conventional treatment (5-fluorouracil, epirubicin and cyclophosphamide-FEC for six cycles) or FEC for three cycles followed by high dose therapy consisting of cyclophosphamide, thiotepa and carboplatin and stem cell rescue (HDT). To be eligible, patients had to be free of overt metastatic disease and be < or =60 years of age. Analyses were according to intention to treat. RESULTS: At a median follow up of 68 months, 118 patients have experienced a relapse or death from breast cancer (62 in the FEC followed by HDT arm and 56 in the conventional FEC arm) and a total of 100 patients have died (54 in the FEC followed by HDT arm and 46 in the conventional FEC arm). No significant difference was observed in relapse-free survival [hazard ratio 1.06, 95% CI 0.74-1.52, p = 0.76] or overall survival [hazard ratio 1.18, 95% CI 0.80-1.75, p = 0.40]. Five patients died from treatment related causes, three as a consequence of HDT and two in the conventional FEC arm. CONCLUSIONS: At the present time, no benefit has been observed from replacing three cycles of conventional chemotherapy with the HDT regimen described here. Patients should continue to receive conventional chemotherapy as adjuvant therapy for breast cancer.

Cooper, B. W., R. J. Creger, et al. (1993). "Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy." Am J Med **94**(5): 497-504.

PURPOSE: Renal dysfunction is a common cause of morbidity after cancer therapy and bone marrow transplantation. In this study, we evaluated the effects of aminoglycosides and other nephrotoxic antibiotics on the occurrence of renal dysfunction in patients who received high-dose cisplatin-containing chemotherapy regimens. PATIENTS AND METHODS: The subjects of this analysis were 102

consecutive patients, studied from September 1985 to February 1991, who received high-dose cisplatin, administered as 40 mg/m2 for 5 consecutive days in 3% saline with saline hydration and mannitol diuresis, followed by autologous stem cell transplantation. Renal dysfunction was defined as an increase in serum creatinine greater than or equal to 44.2 mumol/L above baseline. RESULTS: Characteristics of the 43 patients who were given aminoglycosides were similar to those in patients who did not receive aminoglycosides with respect to initial renal function, age, cancer type, and previous exposure to cisplatin. Patients who experienced serious treatment-related toxicities such as hemorrhage or septicemia were more likely to have received aminoglycoside antibiotics (p = 0.005). A multivariate analysis showed that increased duration of neutropenia, advanced patient age, and amphotericin B use were predictors of renal failure. Aminoglycoside therapy did not significantly increase the risk of renal dysfunction. CONCLUSIONS: Our data suggest that with appropriate supportive care measures, aminoglycosides can safely be administered to febrile, neutropenic patients who recently have received high-dose cisplatin therapy.

Costa, L. J., I. N. Micallef, et al. (2008). "Time of relapse after initial therapy significantly adds to the prognostic value of the IPI-R in patients with relapsed DLBCL undergoing autologous stem cell transplantation." Bone Marrow Transplant **41**(8): 715-20.

We explored the concomitant effect of the International Prognostic Index at the time of relapse (IPI-R) and the time from initial diagnosis to relapse (TTR) on outcome of 80 uniformly treated patients receiving BEAM conditioning followed by SCT for relapsed, chemosensitive diffuse large B-cell lymphoma. Median age at the time of transplantation was 62 years (range 26-77). Median follow-up of survivors was 31.4 months. Median overall survival (OS) from the time of transplant for patients with TTR >18 months vs < or =18 months was not reached and 50 months, respectively (P=0.01). Median OS for patients with IPI-R > or =3 was 23.3 months and not reached for patients with IPI-R <3 (P=0.01). These factors were independent in multivariate analysis with relative risk for death of 0.91 (0.80-0.99; P=0.04) for each 6-month increment in TTR and 0.63 (0.42-0.96; P=0.03) for IPI-R <3. TTR < or =18 months and IPI-R > or =3 were combined in a prognostic system where patients with none (n=32), one (n=39) or two (n=9) of these factors had median OS not reached, of 50 and 5 months, respectively (P<0.01). Patients with early, high IPI-R relapse after first-line therapy have a dismal outcome with SCT and should receive experimental therapies.

Couri, C. E. and J. C. Voltarelli (2008). "Potential role of stem cell therapy in type 1 diabetes mellitus." Arq Bras Endocrinol Metabol **52**(2): 407-15.

Type 1 diabetes mellitus is the result of the autoimmune response against pancreatic beta-cell(s). At the time of clinical diagnosis near 70% of beta-cell mass is been destroyed as a consequence of the auto-destruction that begins months or even years before the clinical diagnosis. Although marked reduction of chronic complications was seen after development and progression of insulin therapy over the years for type 1 diabetic population, associated risks of chronic end-organ damage and hypoglycemia still remain. Besides tight glucose control, beta-cell mass preservation and/or increase are known to be other important targets in management of type 1 diabetes as long as it reduces chronic microvascular complications in the eyes, kidneys and nerves. Moreover, the larger the beta-cell mass, the lower the incidence of hypoglycemic events. In this article, we discuss some insights about beta-cell regeneration, the importance of regulation of the autoimmune process and what is being employed in human type 1 diabetes in regard to stem cell repertoire to promote regeneration and/or preservation of beta-cell mass.

Daadi, M. M. and G. K. Steinberg (2009). "Manufacturing neurons from human embryonic stem cells: biological and regulatory aspects to develop a safe cellular product for stroke cell therapy." Regen Med **4**(2): 251-63.

Demographic trends, particularly those related to longer life expectancy, suggest that the demand for tissue and organ transplants will further increase since many disorders result from degeneration, injury or organ failure. The most urgent problem in transplantation medicine is the shortage or lack of suitable donor organs and tissue, leading to ethical and societal problems such as organ trafficking. The discovery of stem cells in the inner cell mass of developing embryos and in adult tissue has revolutionized the medical field by introducing new therapeutic dimensions to consider for previously untreatable diseases and injuries. The unlimited self-renewal ability and pluripotent capacity to become any cell type of the organism make human embryonic stem cells (hESCs) a compelling source of cells to study tissue histogenesis and to apply in a wide array of tissue engineering, cell transplantation therapy and drug discovery applications. In this article, we will focus on hESCs and address the derivation of therapeutic neural stem cell lines from hESCs, as well

as the biological and regulatory aspects to developing a safe cellular product for stroke cell therapy.

Dahlke, M. H., F. C. Popp, et al. (2004). "Stem cell therapy of the liver--fusion or fiction?" Liver Transpl **10**(4): 471-9.

Various stem cell populations have been described in distinct models of liver regeneration. This review provides an overview of these different stem cell populations aimed at unifying diverse views of liver stem cell biology. Embryonic stem cells, hemopoietic stem cells, mesenchymal stem cells, liver-derived hepatic stem cells, bone marrow-derived hepatic stem cells, and mature hepatocytes (as cells with stemlike properties) are considered separately. In so doing, we seek to clarify the nomenclature of putative liver stem cell types. Experiments that address the question of cellular fusion versus transdifferentiation as explanations for observed liver regeneration are highlighted. This review concludes with a series of open questions that should be addressed in the context of clinical liver disease before attempts at human therapeutic interventions.

Dazzi, F. and N. J. Horwood (2007). "Potential of mesenchymal stem cell therapy." Curr Opin Oncol **19**(6): 650-5.

PURPOSE OF REVIEW: Mesenchymal stem cells have the capacity to differentiate into several mesenchymal tissues, including the components of the hematopoietic stem cell niche. Mesenchymal stem cells also exhibit a powerful immunosuppressive activity. Here we review the most recent data to identify the properties of therapeutic significance. RECENT FINDINGS: Mesenchymal stem cells are attractive not only in regenerative medicine but also for the treatment of autoimmune diseases and graft-versus-host disease. Initial experience in animal models and the clinical setting have produced very encouraging results whereby mesenchymal stem cells have been shown to accelerate recovery after myocardial infarction, improve growth velocity in children with osteogenesis imperfecta, and ameliorate severe graft-versus-host disease as well as, in mouse models, rheumatoid arthritis and multiple sclerosis. Their use in the clinical setting, however, must be considered with caution because there is evidence that mesenchymal stem cells may also contribute to the maintenance of cancer stem cells. SUMMARY: The interest generated by mesenchymal stem cells has rapidly favored several initiatives to test their therapeutic potentials. There is still much to investigate to characterize their phenotype, understand their mechanisms of action, and optimize their in-vitro expansion for clinical use.

Dingli, D., S. V. Rajkumar, et al. (2005). "Combination therapy with thalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not undergoing upfront autologous stem cell transplantation: a phase II trial." Haematologica **90**(12): 1650-4.

BACKGROUND AND OBJECTIVES: Thalidomide plus dexamethasone (Thal/Dex) has emerged as an effective alternative to vincristine, doxorubicin and dexamethasone as a pre-transplant induction therapy for newly diagnosed multiple myeloma. However, many patients treated initially with Thal/Dex do not proceed to autologous stem cell transplantation (ASCT) and the time to progression and other outcome measures with Thal/Dex as primary therapy for multiple myeloma are not known. We present the first data on the outcome of patients with newly diagnosed multiple myeloma treated with Thal/Dex who did not undergo upfront ASCT. DESIGN AND METHODS: We identified 21 patients with newly diagnosed multiple myeloma treated with Thal/Dex on a phase II clinical trial who did not undergo ASCT due to age, comorbidity or the patient's refusal. Patients received thalidomide at a dose of 200 mg/day orally and dexamethasone 40 mg daily on days 1-4, 9-12, 17-20 (odd months) and days 1-4 (even months). Cycles were repeated every 28 days. RESULTS: The median age was 66 years (range 36-78). The median duration of follow-up was 21 months (range 1-52). One (5%) patient achieved a complete response, and 9 (43%) had a partial response, so the overall response rate was 48%. Of the remaining patients, 7 (33.3%) had stable disease, one patient did not respond, and three died while on therapy prior to response assessment. The median overall survival and time to progression were 21 months and 18 months, respectively. INTERPRETATION AND CONCLUSIONS: The median time to disease progression in patients with multiple myeloma who receive initial therapy with Thal/Dex and who do not undergo ASCT is 18 months.

Dreger, P., N. von Neuhoff, et al. (1997). "Sequential high-dose therapy and autologous stem cell transplantation for treatment of mantle cell lymphoma." Ann Oncol **8**(4): 401-3.

BACKGROUND: Mantle cell lymphoma (MC) is not curable with conventional chemotherapy. To improve the prognosis of patients with this disease, we prospectively studied an intensive sequential therapy consisting of the Dexa-BEAM regimen (dexamethasone, BCNU, etoposide, ara-C, melphalan) followed by myeloablative therapy with autologous stem cell reinfusion. PATIENTS AND METHODS: Nine consecutive patients with stage III/IV MC were included. Two had untreated disease, four were in first

remission, whereas three had more advanced disease. All patients underwent one to two cycles of Dexa-BEAM chemotherapy to reduce the tumor load and to mobilize peripheral blood progenitor cells (PBPC). Subsequently, patients were treated with high-dose radiochemotherapy followed by PBPC reinfusion and were prospectively analyzed for residual disease by clinical methods as well as by PCR amplification clonal CDRIII rearrangements. RESULTS: With an overall response rate of 100%, the initial Dexa-BEAM cycles effectively reduced the tumor load. All patients proceeded to high-dose therapy and subsequent stem cell rescue. Engraftment was prompt, and procedure-related deaths did not occur. With a median follow-up of 12 (3-33) months post transplant, all patients are alive in continuing clinical and molecular remission. CONCLUSIONS: Sequential intensive therapy consisting of Dexa-BEAM and high-dose radiochemotherapy appears to be a highly effective treatment for patients with MC. However, the data are still preliminary, and larger patient numbers and a longer follow-up are required.

Dryden, G. W. (2009). "Overview of stem cell therapy for Crohn's disease." Expert Opin Biol Ther **9**(7): 841-7.

BACKGROUND: Crohn's disease (CD) therapy is rapidly evolving. Recent and ongoing clinical trials using immunologically active stem cells (SC) for the treatment of CD demonstrate the potential for this novel therapy to induce complete and long-lasting remission of symptoms in settings where 'standard' therapies have been unsuccessful. OBJECTIVE/METHODS: This review of SC, including mesenchymal stem cell (MSC) therapy for CD discusses how the immunological effects of MSC may correct some of the pathophysiological defects underpinning CD, and examines the latest clinical trial data providing evidence of their efficacy in the treatment of Crohn's disease. RESULTS/CONCLUSIONS: Given the beneficial effects on mucosal healing seen in animal models of inflammation and results from early clinical trials, MSC may serve as a candidate therapy for patients who have failed to respond to biological therapy.

Du, Y., E. C. Carlson, et al. (2009). "Stem cell therapy restores transparency to defective murine corneas." Stem Cells **27**(7): 1635-42.

Corneal scarring from trauma and inflammation disrupts vision for millions worldwide, but corneal transplantation, the primary therapy for corneal blindness, is unavailable to many affected individuals. In this study, stem cells isolated from adult human corneal stroma were examined for the ability to correct stromal opacity in a murine model by direct injection of cells into the corneal stroma. In wild-type mice, injected human stem cells remained viable for months without fusing with host cells or eliciting an immune T-cell response. Human corneal-specific extracellular matrix, including the proteoglycans lumican and keratocan, accumulated in the treated corneas. Lumican-null mice have corneal opacity similar to that of scar tissue as a result of disruption of stromal collagen organization. After injection with human stromal stem cells, stromal thickness and collagen fibril defects in these mice were restored to that of normal mice. Corneal transparency in the treated mice was indistinguishable from that of wild-type mice. These results support the immune privilege of adult stem cells and the ability of stem cell therapy to regenerate tissue in a manner analogous to organogenesis and clearly different from that of normal wound healing. The results suggest that cell-based therapy can be an effective approach to treatment of human corneal blindness.

Efrat, S. (2004). "Generation of insulin-producing cells from stem cells for cell replacement therapy of type 1 diabetes." Isr Med Assoc J **6**(5): 265-7.

Type 1 diabetes mellitus is caused by an autoimmune destruction of pancreatic islet beta cells, leading to insulin deficiency. Beta-cell replacement is considered the optimal treatment for type 1 diabetes, however it is severely limited by the shortage of human organ donors. An effective cell-replacement strategy depends on the development of an abundant supply of beta cells and their protection from recurring immune destruction. Stem/progenitor cells, which can be expanded in tissue culture and induced to differentiate into multiple cell types, represent an attractive source for generation of cells with beta-cell properties: insulin biosynthesis, storage, and regulated secretion in response to physiologic signals. Embryonic stem cells have been shown to spontaneously differentiate into insulin-producing cells at a low frequency, and this capacity could be further enhanced by tissue culture conditions, soluble agents, and expression of dominant transcription factor genes. Progenitor cells from fetal and adult tissues, such as liver and bone marrow, have also been shown capable of differentiation towards the beta-cell phenotype in vivo, or following expression of dominant transcription factors in vitro. These approaches offer novel ways for generation of cells for transplantation into patients with type 1 diabetes.

Elad, S., T. Thierer, et al. (2008). "A decision analysis: the dental management of patients prior to hematology cytotoxic therapy or hematopoietic stem cell transplantation." Oral Oncol **44**(1): 37-42.

There is a controversy regarding whether dental treatment before chemotherapy protocols, including hematopoietic stem cell transplantation (HSCT), is helpful to prevent infections during the consequent immunosuppression. The aim of this study was to develop a decision analysis framework that would test the effect of dental treatment prior to chemotherapy on the survival of the patient. A decision tree was created to compare the clinical outcomes of two treatment alternatives for a base-case patient receiving cytotoxics or undergoing HSCT. The variables used to build the model were "systemic infection", "unmet dental needs", "dental needs". The outcomes evaluate to compare the two strategies was "survival". We performed MEDLINE and PubMed searches of English-language literature according to a list of related terms. The decision analysis model selected dental treatment prior to chemotherapy as the preferred strategy for the base case analysis. The results of this study suggest that dental treatment prior to chemotherapy is the preferred treatment strategy. Using our base case data, 1.8 of every 1000 hemato-oncologic patients or HSCT patients will die compared to the non-treatment prior to chemotherapy strategy.

Ellor, S., T. Shupe, et al. (2008). "Stem cell therapy for inherited metabolic disorders of the liver." Exp Hematol **36**(6): 716-25.

Modern medicine has conquered an enormous spectrum of health concerns, from the neonatal to the geriatric, the chronically ill to the acutely injured. Among the unmet challenges remaining in modern medicine are inborn disorders of metabolism within the liver. Such inherited metabolic disorders (IMDs) often leave an otherwise healthy individual with a crippling imbalance. As the principal regulator of the body's many metabolic pathways, malencoded hepatic enzymes can drastically disrupt homeostasis throughout the entire body. Severe phenotypes are usually detected within the first few days of life, and treatments range from palliative lifestyle modifications to aggressive surgical procedures. While orthotopic liver transplantation is the single last resort "cure" for these conditions, research during the past few years has brought new therapeutic technologies ever closer to the clinic. Stem cells, therapeutic viral vectors, or a combination thereof, are projected to be the next, best, and final cure for IMDs, which is well-reflected by this generation's research initiatives.

Emery, D. W. and G. Stamatoyannopoulos (1999). "Stem cell gene therapy for the beta-chain hemoglobinopathies. Problems and progress." Ann N Y Acad Sci **872**: 94-107; discussion 107-8.

Virus vectors hold great promise for the stem cell gene therapy of beta-chain hemoglobinopathies. However, conventional vectors suffer from low gene transfer rates, low expression levels, and inconsistent or short-lived expression in vivo. In this review we summarize the current status of vector systems for the transduction of hematopoietic stem cells, including the development of novel vector systems and methods for selection of transduced stem cells in vivo. We also summarize efforts to achieve therapeutic expression levels of transferred globin genes with retrovirus vectors, including the manipulation of transcription cassettes, the use of globin gene enhancers, and advances in the use of chromatin insulators for improving the frequency of gene expression following hematopoietic stem cell transduction.

Endo, T., N. Sato, et al. (2004). "Peripheral blood stem cell mobilization following CHOP plus rituximab therapy combined with G-CSF in patients with B-cell non-Hodgkin's lymphoma." Bone Marrow Transplant **33**(7): 703-7.

We mobilized peripheral blood stem cells (PBSC) following CHOP plus rituximab (CHOP-R) therapy, and compared with the findings following CHOP therapy without rituximab. All patients were given G-CSF starting from day 11 after CHOP therapy. Patients in the CHOP-R group (n=8) were given rituximab on day 12. Target CD34(+) cells number was collected in a single leukapheresis on day 14, from all the eight patients in the CHOP-R group. PBSC mobilization kinetics, CD34(+) cells yield and colony-forming ability in the graft collection, toxicity during mobilization, and engraftment after transplantation of CHOP-R group were not significantly different from those in the CHOP group (n=8). In all patients given CHOP-R therapy, CD20(+) cells and immunoglobulin heavy chain (IgH) rearrangement in the graft collection were undetectable by flow-cytometric analysis and Southern blot analysis, respectively, but with PCR analysis two of eight grafts were positive for IgH rearrangement. While further studies are needed to evaluate the efficacy of purging and the outcome of patients undergoing autologous transplantation, CHOP-R therapy can be safely and effectively used in the mobilization phase of PBSC collection, without excess clinical toxicity or deleterious effect on PBSC mobilization kinetics or engraftment time.

Engelmann, M. G. and W. M. Franz (2006). "Stem cell therapy after myocardial infarction: ready for clinical application?" Curr Opin Mol Ther **8**(5): 396-414.

The discovery of stem cells capable of generating angiogenic or contractile cells and

structures might offer new treatment options for patients suffering from heart disease. In particular, embryonic stem cells are considered to have great potential for regenerative medicine and tissue engineering. Studies suggest that delivery or mobilization of stem and progenitor cells might improve tissue perfusion and contractile performance of the damaged heart; however, the underlying mechanisms are poorly understood. Fusion or trans-differentiation into cardiomyocytes or vascular cells are considered rare events of cellular engraftment, and adult stem cells are now considered as 'regenerator cells', acting via paracrine effects of cytokines, or by activation of resident stent cells, thereby supporting the myocardial healing mechanisms after injury. Administration of autologous hematopoietic stem cells or mobilization of endogenous stem cells has been shown to be safe after myocardial infarction or cardiomyopathies, whereas skeletal myoblasts are considered to be hazardous due to the occurrence of life-threatening arrhythmias. This review focuses on the use of adult human stem cells for treating myocardial infarction and cardiomyopathy, and discusses recent preliminary efficacy data, which suggest that 'regenerator cells' might have the potential to improve myocardial perfusion and contractile performance in patients suffering from myocardial infarction, severe ischemic heart disease and chronic heart failure.

Erlich, S., S. R. Miranda, et al. (1999). "Fluorescence-based selection of gene-corrected hematopoietic stem and progenitor cells from acid sphingomyelinase-deficient mice: implications for Niemann-Pick disease gene therapy and the development of improved stem cell gene transfer procedures." Blood **93**(1): 80-6.

The general utility of a novel, fluorescence-based procedure for assessing gene transfer and expression has been demonstrated using hematopoietic stem and progenitor cells. Lineage-depleted hematopoietic cells were isolated from the bone marrow or fetal livers of acid sphingomyelinase-deficient mice, and retrovirally transduced with amphotropic or ecotropic vectors encoding a normal acid sphingomyelinase (ASM) cDNA. Anti-c-Kit antibodies were then used to label stem- and progenitor-enriched cell populations, and the Bodipy fluorescence was analyzed in each group after incubation with a Bodipy-conjugated sphingomyelin. Only cells expressing the functional ASM (ie, transduced) could degrade the sphingomyelin, thereby reducing their Bodipy fluorescence as compared with nontransduced cells. The usefulness of this procedure for the in vitro assessment of gene transfer into hematopoietic stem cells was evaluated, as well as its ability to provide an enrichment of transduced stem cells in vivo. To show the value of this method for in vitro analysis, the effects of retroviral transduction using ecotropic versus amphotropic vectors, various growth factor combinations, and adult bone marrow versus fetal liver stem cells were assessed. The results of these studies confirmed the fact that ecotropic vectors were much more efficient at transducing murine stem cells than amphotropic vectors, and that among the three most commonly used growth factors (stem cell factor [SCF] and interleukins 3 and 6 [IL-3 and IL-6]), SCF had the most significant effect on the transduction of stem cells, whereas IL-6 had the most significant effect on progenitor cells. In addition, it was determined that fetal liver stem cells were only approximately twofold more "transducible" than stem cells from adult bone marrow. Transplantation of Bodipy-selected bone marrow cells into lethally irradiated mice showed that the number of spleen colony-forming units that were positive for the retroviral vector (as determined by polymerase chain reaction) was 76%, as compared with 32% in animals that were transplanted with cells that were nonselected. The methods described within this manuscript are particularly useful for evaluating hematopoietic stem cell gene transfer in vivo because the marker gene used in the procedure (ASM) encodes a naturally occurring mammalian enzyme that has no known adverse effects, and the fluorescent compound used for selection (Bodipy sphingomyelin) is removed from the cells before transplantation.

Fefer, A., N. Robinson, et al. (1997). "Interleukin-2 therapy after bone marrow or stem cell transplantation for hematologic malignancies." Cancer J Sci Am **3 Suppl 1**: S48-53.

PURPOSE: Autologous or allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT) for advanced hematologic malignancies is associated with a high relapse rate. It has been postulated that recombinant interleukin-2 (rIL-2) administered as consolidative immunotherapy early after BMT or SCT, at a time of minimal residual disease, might reduce the relapse rate. We review here preliminary results from a series of studies designed to investigate the safety, immunomodulatory effects, and clinical benefits of rIL-2 therapy following autologous and allogeneic BMT and SCT. PATIENTS AND METHODS: Patients with hematologic malignancies underwent autologous or allogeneic BMT or SCT and received rIL-2 by continuous intravenous infusion a median of 33 to 56 days later. In all trials, the rIL-2 regimen consisted of a moderate induction dose for 4 to 5 days in the hospital, 4 to 6 days of rest, and a low maintenance dose for 10 days in the outpatient setting. A phase I trial of Roche rIL-2 after autoBMT, a feasibility trial of autologous lymphokine-activated

killer cells with rIL-2, and another phase I/II trial of Chiron rIL-2 after autoBMT were performed. A similar phase I trial of IL-2 after alloBMT was also performed in children with acute leukemia beyond first complete remission. RESULTS: An rIL-2 regimen has been identified that can be tolerated early after transplantation. Administration of this rIL-2 regimen induces marked increases in CD3+CD8+ T lymphocytes and CD3-CD56+ natural killer cells and enhances their antitumor cytolytic activity. Encouraging but somewhat inconsistent clinical outcomes were noted in phase I/II trials in patients with lymphoma and acute myeloid leukemia. CONCLUSIONS: The results of phase I/II trials are sufficiently encouraging to justify prospectively randomized phase III trials to determine whether rIL-2 after autologous SCT will reduce the rate of posttransplantation relapse and improve survival in patients with advanced hematologic malignancies.

Flohr, T., G. Hess, et al. (2002). "Rituximab in vivo purging is safe and effective in combination with CD34-positive selected autologous stem cell transplantation for salvage therapy in B-NHL." Bone Marrow Transplant **29**(9): 769-75.

The purpose of this study was to evaluate feasibility and efficacy of Rituximab included into a sequential salvage protocol for CD20(+) B-NHL in relapse or induction failure. Twenty-seven patients with CD20(+) B-NHL in relapse or induction failure received Rituximab combined with DexaBEAM (R-DexaBEAM) for stem cell mobilization. Additional ex vivo selection of CD34-positive cells was performed using the CliniMacs device. Two doses of Rituximab were included in the high-dose therapy regimen (HDT). R-DexaBEAM was well tolerated and 26 of 27 patients mobilized sufficient numbers of CD34(+) blood stem cells. Application of R-DexaBEAM resulted in significant depletion of peripheral B cells. No treatment-related deaths occurred after HDT and all patients showed stable engraftment of hematopoesis. Combined immunodeficiency was observed post HDT and eight patients developed CMV antigenemia. Remission rate post HDT was 96% (CR, 24/26; PR, 1/26). Overall and progression-free survival (PFS) at 16 months post HDT (range 6-27) is 95% and 77%, respectively. With regard to histology, PFS was 71% in aggressive lymphoma (n = 11), 74% in indolent FCL (n = 10) and 100% in MCL (n = 5). The treatment protocol has proven feasible, with high purging efficiency and encouraging remission rates.

Flores, F. X., P. D. Brophy, et al. (2008). "Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group." Pediatr Nephrol **23**(4): 625-30.

Pediatric stem cell transplant (SCT) recipients commonly develop acute renal failure (ARF). We report the demographic and survival data of pediatric SCT patients enrolled in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry. Since 1 January 2001, 51/370 (13.8%) patients entered in the ppCRRT Registry had received a SCT. Median age was 13.63 (0.53-23.52) years. The primary reasons for the initiation of continuous renal replacement therapy (CRRT) were treatment of fluid overload (FO) and electrolyte imbalance (49%), FO only (39%), electrolyte imbalance only (8%) and other reasons (4%). The CRRT modalities included continuous veno-veno hemodialysis (CVVHD), 43%, continuous veno-veno hemofiltration (CVVH), 37% and continuous veno-veno hemodiafiltration (CVVHDF), 20%. Seventy-six percent had multi-organ dysfunction syndrome (MODS), 72% received ventilatory support and the mean FO was 12.41 +/- 3.70%. Forty-five percent of patients survived. Patients receiving convective therapies had better survival rates (59% vs 27%, $P < 0.05$). Patients requiring ventilatory support had worse survival (35% vs 71%, $P < 0.05$). Mean airway pressure (Paw) at the end of CRRT was lower in survivors (8.7 +/- 2.94 vs 25.76 +/- 2.03 mmH(2)O, $P < 0.05$). Development of high mean airway pressure in non-survivors is likely related to non-fluid injury, as it was not prevented by early and aggressive fluid management by CRRT therapy.

Franzius, C., S. Bielack, et al. (2001). "High-activity samarium-153-EDTMP therapy followed by autologous peripheral blood stem cell support in unresectable osteosarcoma." Nuklearmedizin **40**(6): 215-20.

PURPOSE: Despite highly efficacious chemotherapy, patients with osteosarcomas still have a poor prognosis if adequate surgical control cannot be obtained. These patients may benefit from therapy with radiolabeled phosphonates. PATIENTS AND METHODS: Six patients (three male, three female; seven to 41 years) with unresectable primary osteosarcoma (n = 3) or unresectable recurrent sites of osteosarcomas (n = 3) were treated with high-activity of Sm-153-EDTMP (150 MBq/kg BW). In all patients autologous peripheral blood stem cells had been collected before Sm-153-EDTMP therapy. RESULTS: No immediate adverse reactions were observed in the patients. In one patient bone pain increased during the first 48 hrs after therapy. Three patients received pain relief. Autologous peripheral blood stem cell reinfusion was performed on day +12 to +27 in all patients to overcome potentially irreversible damage

to the hematopoietic stem cells. In three patient external radiotherapy of the primary tumor site was performed after Sm-153-EDTMP therapy and in two of them polychemotherapy was continued. Thirty-six months later one of these patients is still free of progression. Two further patients are still alive. However, they have developed new metastases. The three patients who had no accompanying external radiotherapy, all died of disease progression five to 20 months after therapy. CONCLUSION: These preliminary results show that high-dose Sm-153-EDTMP therapy is feasible and warrants further evaluation of efficacy. The combination with external radiation and polychemotherapy seems to be most promising. Although osteosarcoma is believed to be relatively radioresistant, the total focal dose achieved may delay local progression or even achieve permanent local tumor control in patients with surgically inaccessible primary or relapsing tumors.

Fukuda, K. (2003). "Application of mesenchymal stem cells for the regeneration of cardiomyocyte and its use for cell transplantation therapy." Hum Cell **16**(3): 83-94.

We have isolated a cardiomyogenic cell line (CMG cell) from murine bone marrow mesenchymal stem cells. The cells showed a fibroblast-like morphology, but the morphology changed after 5-azacytidine exposure. They began spontaneous beating after 2 weeks, and expressed ANP and BNP. Electron microscopy revealed a cardiomyocyte-like ultrastructure. These cells had several types of action potentials; sinus node-like and ventricular cell-like action potentials. The isoform of contractile protein genes indicated that their muscle phenotype was similar to fetal ventricular cardiomyocytes. They expressed alpha1A, alpha1B, alpha1D, beta1, and beta2 adrenergic and M1 and M2 muscarinic receptors. Stimulation with phenylephrine, isoproterenol and carbachol increased ERK phosphorylation and second messengers. Isoproterenol increased the beating rate, which was blocked with CGP20712A (beta1-selective blocker). These findings indicated that cell transplantation therapy for the patients with heart failure might possibly be achieved using the regenerated cardiomyocytes from autologous bone marrow cells in the near future.

Ghobrial, I. M., F. Buadi, et al. (2004). "High-dose intravenous methotrexate followed by autologous stem cell transplantation as a potentially effective therapy for neurolymphomatosis." Cancer **100**(11): 2403-7.

BACKGROUND: Neurolymphomatosis (NL) is a rare neurologic manifestation of systemic lymphoma characterized by lymphomatous infiltration of the peripheral nervous system. The diagnosis of NL is difficult and requires a multidisciplinary approach for obtaining an adequate biopsy specimen of the suspected nerve. The prognosis of patients with NL has been poor because adequate penetration of chemotherapy into the nervous system is difficult. METHODS: The authors presented the case of a 37-year-old man who was treated for Ann Arbor Stage IVB diffuse large B-cell lymphoma. The patient developed disease recurrence in the sciatic nerve without systemic involvement. RESULTS: The patient achieved a clinical response after receipt of high-dose intravenous methotrexate followed by high-dose chemotherapy and autologous stem cell transplant. CONCLUSIONS: The authors reported this case to highlight the effectiveness of this regimen in a rare and fatal disorder. In the current study they also reviewed the literature regarding the diagnosis, prognosis, and treatment of NL.

Gilliland, D. G. and J. G. Gribben (2002). "Evaluation of the risk of therapy-related MDS/AML after autologous stem cell transplantation." Biol Blood Marrow Transplant **8**(1): 9-16.

A major complication of autologous stem cell transplantation (ASCT) is the development of therapy-related myelodysplastic syndromes (MDS) and acute myelogenous leukemia (AML). This complication likely results from previous exposure of the autologous stem cells to chemotherapy as well as to the high doses of chemotherapy and radiation therapy that are used as part of the conditioning regimen. A number of centers are reporting that, second to disease relapse, therapy-related MDS and AML are among the major causes of morbidity and mortality after ASCT. There is abundant evidence that therapy-related MDS and AML are clonal hemopathies that are consequence of an acquired somatic mutation that confers a proliferative and/or survival advantage to hematopoietic progenitors. However, no single mutation or gene rearrangement is sufficient for the development of therapy-related AML, and the identification of a singlegene rearrangement or point mutation may not necessarily be predictive of the development of therapy-related AML in the post-ASCT setting, a caveat that must be kept in mind when risk is assessed. There are at least 5 methods for assessing risk based on the presence of clonal abnormalities in hematopoietic cells, including standard cytogenetics, interphase fluorescence in situ hybridization, analysis for loss of heterozygosity, polymerase chain reaction for point mutations, and X-inactivation-based clonality assays. Each of these approaches has strengths and weaknesses that are discussed here in detail.

Goebel, W. S., M. C. Yoder, et al. (2002). "Donor chimerism and stem cell function in a murine congenic transplantation model after low-dose radiation conditioning: effects of a retroviral-mediated gene transfer protocol and implications for gene therapy." Exp Hematol **30**(11): 1324-32.

OBJECTIVE: We investigated low-dose radiation conditioning for the transplantation of retrovirus-transduced cells in a C57Bl6/J murine model. MATERIALS AND METHODS: The effect of low-dose radiation on stem cell function was investigated using a competitive repopulation assay. Stem cell function of marrow cells that underwent a retroviral-mediated gene transfer (RMGT) protocol was examined by this assay, and donor chimerism of these cells when transplanted into 160-cGy conditioned syngeneic hosts was compared to fresh marrow. RESULTS: Irradiation with 300 or 160 cGy substantially decreased stem cell function as measured by competitive repopulation. Animals conditioned with 160 cGy and transplanted with 20 x 10(6) fresh marrow cells permitted donor cell engraftment of 53.6% +/- 11.4% 6 months after transplant compared to 100% donor cell engraftment after 1100 cGy irradiation. Lymphoid and myeloid engraftment did not significantly differ from total engraftment in submyeloablated hosts. When transplanted into lethally irradiated hosts, the competitive repopulating activity of marrow treated with a single dose of 5-fluorouracil followed by ex vivo culture according to a standard RMGT protocol was equal to 5-fluorouracil-only treated marrow. However, cells treated with 5-fluorouracil or 5-fluorouracil plus ex vivo culture for RMGT repopulated less well than fresh marrow cells in 160 cGy conditioned hosts. CONCLUSIONS: Low-dose irradiation decreases host stem cell function, allowing engraftment of both fresh and RMGT protocol-treated marrow, although the engraftment of 5-fluorouracil-treated cells was reduced at least two-fold, and 5-fluorouracil plus RMGT protocol-treated cells at least three-fold, compared to fresh marrow. Modification of current RMGT protocols may be important for optimizing engraftment under these conditions.

Goessler, U. R., K. Riedel, et al. (2006). "Perspectives of gene therapy in stem cell tissue engineering." Cells Tissues Organs **183**(4): 169-79.

Tissue engineering is an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain or improve tissue function. It is hoped that forming tissue de novo will overcome many problems in plastic surgery associated with such areas as wound healing and the immunogenicity of transplanted tissue that lead to dysfunctional repair. Gene therapy is the science of the transfer of genetic material into individuals for therapeutic purposes by altering cellular function or structure at the molecular level. Recently, tissue engineering has been used in conjunction with gene therapy as a hybrid approach. This combination of stem-cell-based tissue engineering with gene therapy has the potential to provide regenerative tissue cells within an environment of optimal regulatory protein expression and would have many benefits in various areas such as the transplantation of skin, cartilage or bone. The aim of this review is to outline tissue engineering and possible applications of gene therapy in the field of biomedical engineering as well as basic principles of gene therapy, vectors and gene delivery.

Gopal, A. K., T. L. Metcalfe, et al. (2008). "High-dose therapy and autologous stem cell transplantation for chemoresistant Hodgkin lymphoma: the Seattle experience." Cancer **113**(6): 1344-50.

BACKGROUND: High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment for patients with chemosensitive relapsed/refractory Hodgkin lymphoma (HL), but this therapy is commonly denied to patients with resistant disease. We explored the utility of HDT and ASCT for chemoresistant HL because there are few established therapies for these patients. METHODS: Sixty-four chemoresistant HL patients underwent HDT followed by ASCT at our center. Baseline characteristics included median age = 35 years (range, 14-59 years), stage III/IV = 49 (77%), nodular sclerosis histology = 51 (80%), and prior radiation = 32 (50%). Twenty-six patients (41%) received total body irradiation (TBI)-based regimens, and 38 (59%) underwent non-TBI conditioning. RESULTS: The estimated 5-year overall survival (OS) and progression-free survival (PFS) were 31% and 17%, respectively (median follow-up = 4.2 years). Multivariate analysis only identified year of transplant as independently associated with improved OS (P = .008) and PFS (P = .04), with patients receiving transplants in later years having better outcome. The probabilities of 3-year PFS for patients receiving transplants during 1986 to 1989, 1990 to July 1993, August 1993 to 1999, and 2000 to 2005 were 9%, 21%, 33%, and 31%, respectively. CONCLUSIONS: These data suggest that HDT and ASCT may result in prolonged remissions and survival for a subset of chemoresistant HL patients, with improved outcomes in patients receiving transplants more recently.

Gribben, J. G. (2005). "Salvage therapy for CLL and the role of stem cell transplantation." Hematology Am Soc Hematol Educ Program: 292-8.

Chronic lymphocytic leukaemia (CLL) remains an incurable disease and, notwithstanding the excellent remission rates now achieved with purine analogs and monoclonal antibodies, the vast majority of patients with CLL are destined to relapse after primary treatment. The management of relapsed CLL patients is then dependent upon a number of factors, most importantly age, performance status, previous therapy administered, the response and duration of response to such therapy, and time from last therapy. Although prior therapy and response to such therapy are important factors in determining next therapy, it is often difficult to determine their importance from published studies. Furthermore, the goal of therapy, whether palliative or aggressive, must also be weighed into the decision when deciding on the next line of treatment. With many potential treatments available, the sequence of treatments and the timing of procedures such as stem cell transplantation remain controversial and are the focus of ongoing clinical trials.

Gu, Y. C., M. S. Rao, et al. (2009). "Human cord blood stem cell applications in cell therapy." J Stem Cells **4**(2): 95-103.

Human umbilical cord blood (UCB) is a valuable alternative source of ethically acceptable, clinically competent stem cells that is most likely closest to embryonic stem cells. Development of reliable methods for the expansion of cord blood stem cells is critical to ensure their clinical application. In the present article, advances in cord blood stem cell isolation, culture expansion methods through co-culture with human mesenchymal stem cells, culture optimization techniques with defined media and cord blood stem cell banking aspects have been reviewed. Refined methods of isolation as well as defined culture conditions of expansion that favor retention of stem cell phenotype and proper cryogenic storage can significantly increase the use of cord blood stem cells in human cell therapy applications.

Haas, R., H. Schmid, et al. (1997). "Tandem high-dose therapy with ifosfamide, epirubicin, carboplatin and peripheral blood stem cell support is an effective adjuvant treatment for high-risk primary breast cancer." Eur J Cancer **33**(3): 372-8.

We evaluated the therapeutic efficacy and toxicity of a tandem high-dose therapy with peripheral blood stem cell (PBSC) support in 40 patients with high-risk, primary breast cancer (stage II-III) and involvement of ten or more positive axillary lymph nodes. Their median age was 44 years (range 23-56). Two cycles of cytotoxic chemotherapy with ifosfamide (10000 mg/m2) and epirubicin (100 mg/m2) were administered. Granulocyte colony-stimulating factor (G-CSF) was given to hasten neutrophil reconstitution and to mobilise PBSC during marrow recovery. Leukaphereses were performed following the first and/or second cycle. Tandem high-dose therapy consisted of two cycles with ifosfamide (15 or 12 g/m2) and epirubicin (150 mg/m2), while carboplatin (900 mg/m2) was added for the last 24 patients included. Using an immunocytochemical method, two of 11 patients had cytokeratin-positive tumour cells in three leukapheresis products that were collected following the first G-CSF-supported cycle with ifosfamide and epirubicin, whereas only two harvests obtained following the second cycle in 26 patients contained cytokeratin-positive tumour cells. The number of CD34+ cells/kg re-infused following both high-dose cycles was similar (4.20 +/- 0.29 x 10(6), first cycle and 5.25 +/- 0.63 x 10(6), second cycle), and no notable difference was noted in the speed of haematological reconstitution. An absolute neutrophil count (ANC) of 0.5 x 10(9)/1 was reached after a median time of 13 days, while an unsupported platelet count of 20.0 x 10(9)/1 was achieved after a median time of 8 (first cycle) and 9 (second cycle) days post-transplantation. Patients autografted with more than 7.5 x 10(6) CD34+ cells/kg had platelet counts above 20 x 10(9)/1 within less than 10 days. 6 patients relapsed between 7 and 11 months (median 8 months) post-transplantation. 37 patients are alive and in remission with a median follow-up time of 11 months (range 1-38). This translates into a probability of disease-free survival (DFS) of 77% (95% CI 32-95%) at 38 months. The probability of overall survival is 85%, since 3 patients with local relapse achieved a second complete remission following surgery and involved-field radiotherapy. In conclusion, a sequential high-dose therapy including ifosfamide, epirubicin, carboplatin and PBSC support is well tolerated and effective in patients with high-risk primary breast cancer. Involved-field irradiation should be performed post-transplantation to reduce the risk of local relapse.

Hahn, T., D. Wall, et al. (2005). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review." Biol Blood Marrow Transplant **11**(11): 823-61.

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute lymphoblastic leukemia (ALL) in children is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations based on the evidence

are presented in a table in this review (Summary of Treatment Recommendations Made by the Expert Panel for Pediatric Acute Lymphoblastic Leukemia) and were reached unanimously by a panel of ALL experts. The priority areas of needed future research in pediatric ALL are unrelated marrow or blood donor versus unrelated cord blood donor allogeneic SCT; alternative, nonfamily allogeneic donor versus autologous SCT; better methods for identifying high-relapse-risk patients; assessments of the effect of current chemotherapy regimens on early relapse; and use of pre-SCT detection of minimal residual disease to predict post-SCT outcomes.

Hahn, T., D. Wall, et al. (2006). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review." Biol Blood Marrow Transplant **12**(1): 1-30.

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute lymphoblastic leukemia in adults (> or =15 years) is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published medical literature and for grading the quality and strength of the evidence, and the strength of the treatment recommendations. Treatment recommendations based on the evidence are presented and were reached unanimously by a panel of acute lymphoblastic leukemia experts. The priority areas of needed future research for adult acute lymphoblastic leukemia are: definition of patients at high risk in first complete remission, beyond Philadelphia chromosome positive; outcomes of SCT in older (>50 years) adults; determination if reduced intensity versus myeloablative conditioning regimens yield an equivalent graft-versus-leukemia effect with reduced toxicity; monitoring of minimal residual disease to achieve disease control before SCT; and the use of cord blood and other alternative sources of stem cells for use in adult SCT recipients.

Hahn, T., J. R. Wingard, et al. (2003). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review." Biol Blood Marrow Transplant **9**(1): 4-37.

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of multiple myeloma (MM) is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published medical literature and for grading the quality of the evidence, the strength of the evidence, and the strength of the treatment recommendations. Treatment recommendations based on the evidence presented in the review were made unanimously by a panel of MM experts. Recommendations for SCT as an effective therapy for MM include the following: SCT is preferred to standard chemotherapy as de novo therapy; SCT is preferred as de novo rather than salvage therapy; autologous peripheral blood stem cell transplantation (PBSCT) is preferred to bone marrow transplantation (BMT); and melphalan is preferred to melphalan plus total body irradiation as the conditioning regimen for autologous SCT. Recommendations that SCT is not effective include the following: current purging techniques of bone marrow. Recommendations of equivalence include the following: PBSCT using CD34+ selected or unselected stem cells. No recommendation is made for indications or transplantation techniques that have not been adequately studied, including the following: SCT versus standard chemotherapy as salvage therapy, tandem autologous SCT, autologous or allogeneic SCT as a high-dose sequential regimen, allogeneic BMT versus PBSCT, a preferred allogeneic myeloablative or non-myeloablative conditioning regimen, and maintenance therapy post-autologous SCT with interferon alpha post-SCT. The priority area of needed future research is maintenance therapy posttransplantation with nothing versus interferon alpha versus other agents such as corticosteroids or thalidomide or its derivatives.

Hao, J., W. Zhu, et al. (2009). "Human parthenogenetic embryonic stem cells: one potential resource for cell therapy." Sci China C Life Sci **52**(7): 599-602.

Pluripotent stem cells derived from somatic cells through such processes as nuclear transfer or induced pluripotent stem (iPS) cells present an important model for biomedical research and provide potential resources for cell replacement therapies. However, the overall efficiency of the conversional nuclear transfer is very low and the safety issue remains a major concern for iPS cells. Embryonic stem cells (ESCs) generated from parthenogenetic embryos are one attractive alternative as a source of histocompatible cells and tissues for cell therapy. Recent studies on human parthenogenetic embryonic stem cells (hPG ESCs) have revealed that these ESCs are very similar to the hESCs derived from IVF or in vivo produced blastocysts in gene expression and other characteristics, but full differentiation and development potential of these hPG ESCs have to be further investigated before clinical research and therapeutic interventions. To generate various pluripotent stem cells, diverse reprogramming techniques and approaches will be developed and integrated. This may help elucidate the fundamental

mechanisms underlying reprogramming and stem cell biology, and ultimately benefit cell therapy and regenerative medicine.

Hussain, M. A. and N. D. Theise (2004). "Stem-cell therapy for diabetes mellitus." Lancet **364**(9429): 203-5.

CONTEXT: Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic beta cells, with pancreas or islet-cell transplants. However, shortage of donor organs spurs research into alternative means of generating beta cells from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Stem-cell therapy here implies the replacement of diseased or lost cells from progeny of pluripotent or multipotent cells. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to generate surrogate beta cells or otherwise restore beta-cell functioning. STARTING POINT: Recently, Andreas Lechner and colleagues failed to see transdifferentiation into pancreatic beta cells after transplantation of bone-marrow cells into mice (Diabetes 2004; 53: 616-23). Last year, Jayaraj Rajagopal and colleagues failed to derive beta cells from embryonic stem cells (Science 2003; 299: 363). However, others have seen such effects. WHERE NEXT? As in every emerging field in biology, early reports seem confusing and conflicting. Embryonic and adult stem cells are potential sources for beta-cell replacement and merit further scientific investigation. Discrepancies between different results need to be reconciled. Fundamental processes in determining the differentiation pathways of stem cells remain to be elucidated, so that rigorous and reliable differentiation protocols can be established. Encouraging studies in rodent models may ultimately set the stage for large-animal studies and translational investigation.

Imaizumi, M., A. Watanabe, et al. (2001). "Improved survival of children with advanced neuroblastoma treated by intensified therapy including myeloablative chemotherapy with stem cell transplantation: a retrospective analysis from the Tohoku Neuroblastoma Study Group." Tohoku J Exp Med **195**(2): 73-83.

In the hospitals of the Tohoku Neuroblastoma Study Group (TNBSG), treatment for children with advanced neuroblastoma (NB) was intensified in the mid-1990's with the introduction of myeloablative therapy (MT) with stem cell transplantation (SCT) including the use of autologous peripheral blood stem cells (PBSC) and bone marrow transplantation (BMT). In this report, we examined whether the intensified therapy improved the outcome of children with advanced NB (age> 12 months) who were diagnosed between 1991 and 1997. Patients were 36 children (23 boys and 13 girls) with an average age of 3.4 years (range; 1 to 14 years). Six of them had stage III disease, and the other 30 had stage IV. They were treated initially with induction chemotherapy, surgery, and post-operative chemoradiotherapy, after which 17 of them continued further chemotherapy and the other 19 received MT/SCT (18 with PBSCT and 1 with BMT). Progression-free survival (PFS) rate at seven years from diagnosis was 43.5% for all patients, 66.7% for stage III patients and 38.2% for stage IV patients. The difference between stage III and IV patients was not significant. Among the 30 patients with stage IV disease, PFS at seven years was significantly higher in the 19 patients who received MT/SCT (55.6%) than in the 11 patients who did not receive it (12.5%). There was no difference in clinical and biological risk factors between these two groups, except for the proportion of patients with favorable response to initial therapy (36% and 80% for patients without and with MT/SCT, respectively). Furthermore, the proportion of patients with N-myc amplification was significantly higher in patients with progressive disease (PD) after MT/SCT than in those in CR after MT/SCT. The results of this retrospective study of children with advanced NB suggest that therapy intensification involving MT/SCT might result in lengthened survival time for patients with stage IV disease, and that post-transplant PD remains a risk for patients with high levels of N-myc amplification.

Iohara, K., M. Nakashima, et al. (2004). "Dentin regeneration by dental pulp stem cell therapy with recombinant human bone morphogenetic protein 2." J Dent Res **83**(8): 590-5.

Regenerative medicine is based on stem cells, signals, and scaffolds. Dental pulp tissue has the potential to regenerate dentin in response to noxious stimuli, such as caries. The progenitor/stem cells are responsible for this regeneration. Thus, stem cell therapy has considerable promise in dentin regeneration. Culture of porcine pulp cells, as a three-dimensional pellet, promoted odontoblast differentiation compared with monolayers. The expression of dentin sialophosphoprotein (Dspp) and enamelysin/matrix metalloproteinase 20 (MMP20) mRNA confirmed the differentiation of pulp cells into odontoblasts and was stimulated by the morphogenetic signal, bone morphogenetic protein 2 (BMP2). Based on the in vitro experiments, an in vivo evaluation of pulp progenitor/stem cells in the dog was performed. The autogenous transplantation of the BMP2-treated pellet culture onto the amputated pulp stimulated reparative dentin formation. In conclusion, BMP2 can

direct pulp progenitor/stem cell differentiation into odontoblasts and result in dentin formation.

Ishii, M., Y. Numaguchi, et al. (2009). "Mesenchymal stem cell-based gene therapy with prostacyclin synthase enhanced neovascularization in hindlimb ischemia." Atherosclerosis **206**(1): 109-18.

OBJECTIVE: Bone marrow cell therapy contributes to collateral formation through the secretion of angiogenic factors by progenitor cells and muscle cells per se, thereby presenting a novel option for patients with critical limb ischemia. However, some cases are refractory to this therapy due to graft failure. Therefore, we used genetic modification of mesenchymal stem cells (MSCs) to overexpress a vasoregulatory protein, prostacyclin (PGI(2)), to examine whether it could enhance engraftment and neovascularization in hindlimb ischemia. METHODS AND RESULTS: We engineered the overexpression of PGI(2) synthase (PGIS) within MSCs, which resulted in higher expression levels of phosphorylated Akt and Bcl-2 than in control. Under hypoxic conditions, the overexpression of PGIS led to upregulated expression of cyclooxigenase-2 and peroxisome proliferator-activated receptor delta, following a 40% increased rate of proliferation in MSCs. We then produced unilateral hindlimb ischemia in C57BL6/J mice, which were injected either with MSCs transfected with GFP, with MSCs overexpressing PGIS, or with vehicle. Laser Doppler analyses demonstrated that the administration of MSCs effectively recovered blood perfusion, and that the peak blood flow was reached within 7 days of surgery in mice with MSCs overexpressing PGIS, which was earlier than that in mice with MSCs transfected with GFP. This beneficial effect was correlated to enhanced collateral formation and muscle bundle proliferation. CONCLUSION: Sustained release of PGI(2) enhanced the proangiogenic function of MSCs and subsequent muscle cell regrowth in the ischemic tissue suggesting potential therapeutic benefits of cell-based gene therapy for critical limb ischemia.

Jabbour, E., N. Peslin, et al. (2005). "Prognostic value of the age-adjusted International Prognostic Index in chemosensitive recurrent or refractory non-Hodgkin's lymphomas treated with high-dose BEAM therapy and autologous stem cell transplantation." Leuk Lymphoma **46**(6): 861-7.

High-dose therapy (HDT) is now recommended for patients under 60 years of age with chemosensitive relapsed aggressive non-Hodgkin's lymphoma. However, approximately half of these patients will be cured by HDT. Prognostic factors are needed to predict which patients with chemosensitive lymphoma to second-line therapy could benefit from HDT. We retrospectively investigated the prognostic value of the widely used age-adjusted International Prognostic Index (AA-IPI) calculated at the time of relapse (35 patients) or just before second-line salvage therapy for primary refractory disease (5 patients). The median age was 51 years (range 18-64 years). Thirty-six patients had diffuse large B-cell lymphoma. Salvage cytoreductive therapy before HDT was DHAP/ESHAP (cytarabine, cysplatin, etoposide, steroids) in 17 patients, VIM3-Ara-c/MAMI (high-dose cytarabine, ifosfamide, methyl-gag, amsacrine) in 17 patients, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or reinforced CHOP in 4 patients, high-dose cyclophosphamide and etoposide in 2 patients. The HDT regimen consisted of BEAM (carmusine, cytarabine, etoposide, melphalan) in all cases. Eleven patients were in partial remission and 29 in complete remission at the time of HDT. Ten patients had an IPI >1, 16 had relapsed early (<6 months after first-line therapy) or disease was refractory to first-line therapy (5 of the 16 patients). The median follow-up was 6.07 years (range 1.24-9.74 years). Overall survival was not statistically different in patients with refractory disease or in those who relapsed early compared with late failures (>6 months after first-line chemotherapy) (P=1), but the AA-IPI >1 was associated with a poor outcome (P=0.03). In conclusion, the AA-IPI could have a prognostic value in patients with chemosensitive recurrent lymphoma treated with BEAM HDT.

Janssens, S. (2007). "Stem cell therapy in acute myocardial infarction." Acta Clin Belg **62**(5): 342-7.

Despite state-of-the-art therapy, clinical outcome remains poor in myocardial infarction (MI) patients with reduced left ventricular (LV) function with yearly mortality rates of approximately 15% and rehospitalization rates for heart failure or recurrent infarction within the first year exceeding 20%. Progenitor cell-mediated repair of the damaged heart is a promising new development in cardiovascular medicine. Progenitor cells residing in bone marrow and presumably also in the heart are capable of improving LV function in preclinical MI models but underlying mechanisms remain incompletely understood. Recent placebo-controlled, randomized bone marrow cell transfer trials in MI patients have shown augmented recovery of global LV function of variable magnitude. The observed changes were associated with a favourable effect on myocardial perfusion, with greater infarct size reduction, or with enhanced regional contraction in the infarct border zones. There is now growing consensus that these beneficial effects of bone marrow-derived progenitor cell transfer, as applied in post-MI patients thus far,

occur independent of cardiomyocyte formation. At the same time, we have recognized that insufficient homing and survival of transplanted cells into the ischaemic milieu limits the full potential of cell-based cardiac repair. A better understanding of underlying molecular mechanisms of these critical steps in cell-based repair will, however, facilitate the development of improved clinical strategies to enhance functional recovery after myocardial infarction in the years to come.

Joggerst, S. J. and A. K. Hatzopoulos (2009). "Stem cell therapy for cardiac repair: benefits and barriers." Expert Rev Mol Med **11**: e20.

Cardiovascular disease remains the leading cause of death worldwide. Acute ischaemic injury and chronic cardiomyopathies lead to permanent loss of cardiac tissue and ultimately heart failure. Current therapies aim largely to attenuate the pathological remodelling that occurs after injury and to reduce risk factors for cardiovascular disease. Studies in animal models indicate that transplantation of mesenchymal stem cells, bone-marrow-derived haematopoietic stem cells, skeletal myoblasts, or embryonic stem cells has the potential to improve the function of ventricular muscle after ischaemic injury. Clinical trials using primarily bone-marrow-derived cells and skeletal myoblasts have also produced some encouraging results. However, the current experimental evidence suggests that the benefits of cell therapy are modest, the generation of new cardiac tissue is low, and the predominant mechanisms of action of transplanted stem cells involve favourable paracrine effects on injured myocardium. Recent studies show that the adult heart possesses various pools of putative resident stem cells, raising the hope that these cells can be isolated for therapy or manipulated in vivo to improve the healing of cardiac muscle after injury. This article reviews the properties and potential of the various stem cell populations for cardiac repair and regeneration as well as the barriers that might lie ahead.

Johansson, M. K., T. J. de Vries, et al. (2007). "Hematopoietic stem cell-targeted neonatal gene therapy reverses lethally progressive osteopetrosis in oc/oc mice." Blood **109**(12): 5178-85.

Infantile malignant osteopetrosis (IMO) is a fatal disease caused by lack of functional osteoclasts, and the only available treatment is hematopoietic stem cell (HSC) transplantation. In the majority of patients, the TCIRG1 gene, coding for a subunit of a proton pump essential for bone resorption, is mutated. Oc/oc mice have a deletion in the homologue gene (tcirg1) and die at 3 to 4 weeks, but can be rescued by neonatal transplantation of HSCs. Here, HSC-targeted gene therapy of osteopetrosis in the oc/oc mouse model was developed. Oc/oc fetal liver cells depleted of Ter119-expressing erythroid cells were transduced with a retroviral vector expressing tcirg1 and GFP, and subsequently transplanted intraperitoneally to irradiated neonatal oc/oc mice. Eight of 15 mice survived past the normal life span of oc/oc mice. In vitro osteoclastogenesis revealed formation of GFP-positive osteoclasts and bone resorption, albeit at a lower level than from wild-type cells. The skeletal phenotype was analyzed by X-ray and histopathology and showed partial correction at 8 weeks and almost normalization after 18 weeks. In summary, osteopetrosis in oc/oc mice can be reversed by neonatal transplantation of gene-modified HSCs leading to long-term survival. This represents a significant step toward the development of gene therapy for osteopetrosis.

Josting, A., I. Katay, et al. (1998). "Favorable outcome of patients with relapsed or refractory Hodgkin's disease treated with high-dose chemotherapy and stem cell rescue at the time of maximal response to conventional salvage therapy (Dex-BEAM)." Ann Oncol **9**(3): 289-95.

BACKGROUND: Disease status before high-dose chemotherapy with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell transplantation (PBSCT) is an important predictor of transplantation-related toxicity and event-free survival (EFS) for patients with relapsed or refractory Hodgkin's disease (HD). We performed a phase II study in patients with relapsed or refractory HD to evaluate the feasibility of four cycles of Dexa-BEAM followed by high-dose chemotherapy with ABMT or PBSCT. PATIENTS AND METHODS: Twenty-six patients (median age 30, range 20-40 years) were treated with 2-4 courses of dexamethasone, carmustine, etoposide, cytarabine and melphalan (Dexa-BEAM) as salvage chemotherapy in order to attain maximal response. Patients achieving complete response (CR) or partial response (PR) received high-dose chemotherapy with ABMT or PBSCT. The conditioning regimen used was CVB (cyclophosphamide, carmustine, etoposide). RESULTS: Eighteen patients responded to Dexa-BEAM, resulting in a response rate of 69%. At the time of transplant 16 patients were in CR two patients in PR. At present 14 patients transplanted are in continuous CR (median follow-up 40 months, range 14-60 months). Two patients with PR after four courses of Dexa-BEAM relapsed and died three months posttransplantation. Two patients with CR at the time of transplant relapsed after nine and 13 months respectively. Eight patients had rapid progressive disease after 2-4 cycles of Dexa-BEAM.

One patient with progressive disease died in gram-negative sepsis after four cycles of Dexa-BEAM. There was no transplantation-related death. CONCLUSION: These data suggests the use of high-dose chemotherapy followed by stem cell transplantation at the time of maximal response.

Kalka, C. and I. Baumgartner (2008). "Gene and stem cell therapy in peripheral arterial occlusive disease." Vasc Med **13**(2): 157-72.

Peripheral arterial occlusive disease (PAOD) is a manifestation of systemic atherosclerosis strongly associated with a high risk of cardiovascular morbidity and mortality. In a considerable proportion of patients with PAOD, revascularization either by endovascular means or by open surgery combined with best possible risk factor modification does not achieve limb salvage or relief of ischaemic rest pain. As a consequence, novel therapeutic strategies have been developed over the last two decades aiming to promote neovascularization and remodelling of collaterals. Gene and stem cell therapy are the main directions for clinical investigation concepts. For both, preclinical studies have shown promising results using a wide variety of genes encoding for growth factors and populations of adult stem cells, respectively. As a consequence, clinical trials have been performed applying gene and stem cell-based concepts. However, it has become apparent that a straightforward translation into humans is not possible. While several trials reported relief of symptoms and functional improvement, other trials did not confirm this early promise of efficacy. Ongoing clinical trials with an improved study design are needed to confirm the potential that gene and cell therapy may have and to prevent the gaps in our scientific knowledge that will jeopardize the establishment of angiogenic therapy as an additional medical treatment of PAOD. This review summarizes the experimental background and presents the current status of clinical applications and future perspectives of the therapeutic use of gene and cell therapy strategies for PAOD.

Kasten, P., I. Beyen, et al. (2008). "Instant stem cell therapy: characterization and concentration of human mesenchymal stem cells in vitro." Eur Cell Mater **16**: 47-55.

In regenerative medicine, there is an approach to avoid expansion of the mesenchymal stem cell (MSC) before implantation. The aim of this study was to compare methods for instant MSC therapy by use of a portable, automatic and closed system centrifuge that allows for the concentration of MSCs. The main outcome measures were the amount of MSCs per millilitre of bone marrow (BM), clusters of differentiation (CD), proliferation and differentiation capacities of the MSC. A volume reduction protocol was compared to the traditional laboratory methods of isolation using a Ficoll gradient and native BM. Fifty millilitres of BM were obtained from haematologically healthy male Caucasians (n=10, age 8 to 49 years). The number of colony forming units-fibroblast (CFU-F)/ml BM was highest in the centrifuge volume reduction protocol, followed by the native BM (not significant), the centrifuge Ficoll (p=0.042) and the manual Ficoll procedure (p=0.001). The MSC of all groups could differentiate into the mesenchymal lineages without significant differences between the groups. The CD pattern was identical for all groups: CD13+; CD 44+; CD73 +; CD90+; CD105+; HLA-A,B,C+; CD14-; CD34-; CD45-; CD271-; HLA-DR-. In a further clinical pilot study (n=5) with 297 ml BM (SD 18.6), the volume reduction protocol concentrated the MSC by a factor of 14: there were 1.08 x 10(2) MSC/ml BM (standard deviation (SD) 1.02 x 10(2)) before concentration, 14.8 x 10(2) MSC/ ml BM (SD 12.4 x 10(2)) after concentration, and on average 296 x 10(2) MSC (SD 248.9 x 10(2), range 86.4-691.5 x 10(2)) were available for MSC therapy. The volume reduction protocol of the closed centrifuge allows for the highest concentration of the MSC, and therefore, is a promising candidate for instant stem cell therapy.

Kennedy-Nasser, A. A. and M. K. Brenner (2007). "T-cell therapy after hematopoietic stem cell transplantation." Curr Opin Hematol **14**(6): 616-24.

PURPOSE OF REVIEW: The separation of graft versus host disease from graft versus leukaemia reactivity and the reconstitution of immunity to infectious agents are the main goals of T-cell therapy after allogeneic hematopoietic stem cell transplantation. We describe how an improved understanding of T-cell mediated graft versus leukemia and of antiviral responses is providing effective approaches to T-cell immunotherapy. RECENT FINDINGS: Over the past several years, researchers have developed strategies to eliminate alloreactive T cells from the graft, to expand naturally occurring regulatory T cells, and to select and expand antigen-specific T cells specific for tumor-associated or viral antigens. Incorporation of suicide genes allows the selective destruction of allodepleted or antigen-selected cells after infusion, further increasing the safety and potential applicability of these approaches. SUMMARY: In this review we describe current strategies for adoptive T-cell immunotherapy after hematopoietic stem cell transplantation.

Kewalramani, T., A. D. Zelenetz, et al. (2004). "Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or

primary refractory diffuse large B-cell lymphoma." Blood **103**(10): 3684-8.

Patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) who achieve complete response (CR) before autologous stem cell transplantation (ASCT) generally have better outcomes than those who achieve only partial response (PR). We investigated whether adding rituximab to the ifosfamide-carboplatin-etoposide (ICE) chemotherapy regimen (RICE) could increase the CR rate of patients with DLBCL under consideration for ASCT. Thirty-six eligible patients were treated with RICE, and 34 received all 3 planned cycles. The CR rate was 53%, significantly better than the 27% CR rate (P =.01) achieved among 147 similar consecutive historical control patients with DLBCL treated with ICE; the PR rate was 25%. Febrile neutropenia was the most frequent grade 3 or 4 nonhematologic toxicity; it occurred in 7.5% of delivered cycles. No patient had RICE-related toxicity that precluded ASCT. The median number of CD34(+) cells per kilogram mobilized was 6.3 x 10(6). Progression-free survival rates of patients who underwent transplantation after RICE were marginally better than those of 95 consecutive historical control patients who underwent transplantation after ICE (54% vs 43% at 2 years; P =.25). RICE appears to induce very high CR rates in patients with relapsed and refractory DLBCL; however, further studies are necessary to determine whether this treatment regimen will improve outcomes after ASCT.

Khan, M., V. K. Kutala, et al. (2008). "Measurement of oxygenation at the site of stem cell therapy in a murine model of myocardial infarction." Adv Exp Med Biol **614**: 45-52.

We have developed a noninvasive EPR (electron paramagnetic resonance) oximetry, based on a new class of oxygen-sensing nano-particulate probe (LiNc-BuO), for simultaneous monitoring of stem-cell therapy and in situ oxygenation (partial pressure of oxygen, pO2) in a mouse model of acute myocardial infarction (AMI). AMI was induced by a permanent occlusion of left-anterior-descending (LAD) coronary artery. Skeletal myoblast (SM) cells were used for therapy. The oximetry probe was implanted in the mid-ventricular region using a needle. Tissue histological studies after 3 weeks of implantation of the probe revealed significant fibrosis, which was solely due to the needle track and not due to the probe particles. The feasibility of long-term monitoring of pO2 was established in control (non-infarct) group of hearts (> 3 months; pO2 = 15.0 +/- 1.2 mmHg,). A mixture of the probe with/without SM cells (1 x 10(5)) was implanted as a single injection in the infarcted region and the myocardial tissue pO2 at the site of cell therapy was measured for 4 weeks. The pO2 was significantly higher in infarcted hearts treated with SM cells (pO2 = 3.5 +/- 0.9 mmHg) compared to untreated hearts (pO2 = 1.6 +/- 0.7 mmHg). We have demonstrated, for the first time, the feasibility of monitoring pO2 in mouse hearts after stem cell therapy.

Kim, B. G., D. H. Hwang, et al. (2007). "Stem cell-based cell therapy for spinal cord injury." Cell Transplant **16**(4): 355-64.

Traumatic injuries to the spinal cord lead to severe and permanent neurological deficits. Although no effective therapeutic option is currently available, recent animal studies have shown that cellular transplantation strategies hold promise to enhance functional recovery after spinal cord injury (SCI). This review is to analyze the experiments where transplantation of stem/progenitor cells produced successful functional outcome in animal models of SCI. There is no consensus yet on what kind of stem/progenitor cells is an ideal source for cellular grafts. Three kinds of stem/progenitor cells have been utilized in cell therapy in animal models of SCI: embryonic stem cells, bone marrow mesenchymal stem cells, and neural stem cells. Neural stem cells or fate-restricted neuronal or glial progenitor cells were preferably used because they have clear capacity to become neurons or glial cells after transplantation into the injured spinal cord. At least a part of functional deficits after SCI is attributable to chronic progressive demyelination. Therefore, several studies transplanted glial-restricted progenitors or oligodendrocyte precursors to target the demyelination process. Directed differentiation of stem/progenitor cells to oligodendrocyte lineage prior to transplantation or modulation of microenvironment in the injured spinal cord to promote oligodendroglial differentiation seems to be an effective strategy to increase the extent of remyelination. Transplanted stem/progenitor cells can also contribute to promoting axonal regeneration by functioning as cellular scaffolds for growing axons. Combinatorial approaches using polymer scaffolds to fill the lesion cavity or introducing regeneration-promoting genes will greatly increase the efficacy of cellular transplantation strategies for SCI.

Kim, H., H. J. Sohn, et al. (2006). "New staging systems can predict prognosis of multiple myeloma patients undergoing autologous peripheral blood stem cell transplantation as first-line therapy." Biol Blood Marrow Transplant **12**(8): 837-44.

Staging systems for multiple myeloma (MM) include the Southwest Oncology Group (SWOG) staging system, the International Staging System (ISS), and the Durie-Salmon (DS) staging system. We

evaluated whether staging at the time of diagnosis could predict survival in MM patients undergoing autologous peripheral blood stem cell transplantation (APBSCT) as first-line treatment. Between November 1996 and June 2005, 152 MM patients were treated with induction VAD (vincristine, adriamycin, dexamethasone) chemotherapy, followed by APBSCT at 6 institutions in Korea. Median follow-up times were 22.6 months (range, 5.4-101.9 months) from the day of diagnosis and 14.1 months (range, 0.4-96.1 months) from the day of APBSCT. Progression-free survival (PFS) from the day of diagnosis was predicted by the SWOG staging system (P = .0129) and ISS (P = .0299), but not by the DS staging system at diagnosis (P = .1074). In addition, overall survival (OS) from the day of diagnosis could be predicted by the SWOG staging system (P = .0207) and ISS (P = .0105), but not by the DS staging system (P = .2542). PFS from day of APBSCT was not predicted by the DS staging system (P = .5731), SWOG staging system (P = .2817), or ISS (P = .1167). OS from day of APBSCT could be predicted by the SWOG staging system (P = .0392) and ISS (P = .0198), but not by the DS staging system (P = .5426). Our findings indicate that PFS and OS in association with APBSCT can be predicted by stages assessed by the SWOG and ISS systems, but not by the DS system. Moreover, staging by the SWOG and ISS systems at the time of diagnosis was better correlated with survival than was staging at the time of APBSCT.

Kim, M., S. T. Lee, et al. (2008). "Stem cell-based cell therapy for Huntington disease: a review." Neuropathology **28**(1): 1-9.

Huntington disease (HD) is a devastating neurodegenerative disorder and no proven medical therapy is currently available to mitigate its clinical manifestations. Although fetal neural transplantation has been tried in both preclinical and clinical investigations, the efficacy is not satisfactory. With the recent explosive progress of stem cell biology, application of stem cell-based therapy in HD is an exciting prospect. Three kinds of stem cells, embryonic stem cells, bone marrow mesenchymal stem cells and neural stem cells, have previously been utilized in cell therapy in animal models of neurological disorders. However, neural stem cells were preferably used by investigators in experimental HD studies, since they have a clear capacity to become neurons or glial cells after intracerebral or intravenous transplantation, and they induce functional recovery. In this review, we summarize the current state of cell therapy utilizing stem cells in experimental HD animal models, and discuss the future considerations for developing new therapeutic strategies using neural stem cells.

Kim, S. U. and J. de Vellis (2009). "Stem cell-based cell therapy in neurological diseases: a review." J Neurosci Res **87**(10): 2183-200.

Human neurological disorders such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, multiple sclerosis (MS), stroke, and spinal cord injury are caused by a loss of neurons and glial cells in the brain or spinal cord. Cell replacement therapy and gene transfer to the diseased or injured brain have provided the basis for the development of potentially powerful new therapeutic strategies for a broad spectrum of human neurological diseases. However, the paucity of suitable cell types for cell replacement therapy in patients suffering from neurological disorders has hampered the development of this promising therapeutic approach. In recent years, neurons and glial cells have successfully been generated from stem cells such as embryonic stem cells, mesenchymal stem cells, and neural stem cells, and extensive efforts by investigators to develop stem cell-based brain transplantation therapies have been carried out. We review here notable experimental and preclinical studies previously published involving stem cell-based cell and gene therapies for Parkinson's disease, Huntington's disease, ALS, Alzheimer's disease, MS, stroke, spinal cord injury, brain tumor, and lysosomal storage diseases and discuss the future prospects for stem cell therapy of neurological disorders in the clinical setting. There are still many obstacles to be overcome before clinical application of cell therapy in neurological disease patients is adopted: 1) it is still uncertain what kind of stem cells would be an ideal source for cellular grafts, and 2) the mechanism by which transplantation of stem cells leads to an enhanced functional recovery and structural reorganization must to be better understood. Steady and solid progress in stem cell research in both basic and preclinical settings should support the hope for development of stem cell-based cell therapies for neurological diseases.

Kletzel, M., H. M. Katzenstein, et al. (2002). "Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago Pilot II Study." J Clin Oncol **20**(9): 2284-92.

PURPOSE: To investigate whether intensive induction therapy followed by triple-tandem cycles of high-dose therapy with peripheral-blood stem-cell rescue and local irradiation will improve event-free survival for patients with high-risk neuroblastoma. PATIENTS AND METHODS: From August 1995 to January 2000, 25 consecutive newly diagnosed high-risk neuroblastoma patients and one child with

recurrent MYCN-amplified disease were enrolled onto the Chicago Pilot II Protocol. After induction therapy and surgery, peripheral-blood stem cells were mobilized with three cycles of high-dose cyclophosphamide and granulocyte colony-stimulating factor. Patients then underwent triple-tandem cycles of high-dose therapy with peripheral-blood stem-cell rescue followed by radiation to the primary site. RESULTS: Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Sufficient numbers of peripheral-blood stem cells were collected in all but one patient. Seventeen patients were able to complete all three cycles of high-dose therapy and peripheral-blood stem-cell rescue, two patients completed two cycles, and three patients completed one cycle. There was one toxic death, and one patient died from complications of treatment for graft failure. With a median follow-up of 38 months, the 3-year event-free survival and survival rates are 57% +/- 11% and 79% +/- 10%, respectively. CONCLUSION: The results of this pilot study demonstrate that it is feasible to intensify consolidation with triple-tandem high-dose chemotherapy and peripheral-blood stem-cell rescue and local irradiation, and suggest that this treatment strategy may lead to improved survival for patients with high-risk neuroblastoma.

Kuittinen, T., E. Jantunen, et al. (2006). "Cardiac effects within 3 months of BEAC high-dose therapy in non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation." Eur J Haematol **77**(2): 120-7.

OBJECTIVES: Limited data are available on the cardiac effects of high-dose cyclophosphamide (CY) in patients with non-Hodgkin's lymphoma (NHL). We prospectively assessed the cardiac effects of high-dose CY in 30 adult NHL patients receiving CY 6 g/m(2) as part of BEAC high-dose therapy (HDT). METHODS: Radionuclide ventriculography (RVG) and plasma natriuretic peptide (NT-proANP, NT-proBNP) measurements were performed simultaneously prior to BEAC at baseline (d - 7), 12 days (d + 12) and 3 months (m + 3) after stem cell infusion (D0). In addition to these time points, natriuretic peptides were measured 2 days before (d - 2) and 1 week (d + 7) after stem cell infusion. RESULTS: Left ventricular ejection fraction (LVEF) decreased from d - 7 (53% +/- 2%) to d + 12 (49% +/- 2%, P = 0.009). However, no significant change in cardiac diastolic function was observed. The LVEF returned towards baseline by m + 3. Plasma NT-proANP and NT-proBNP increased significantly from baseline (445 +/- 65 pmol/L and 129 +/- 33 pmol/L) to d - 2 (1,127 +/- 142 pmol/L, P < 0.001 and 624 +/- 148 pmol/L, P < 0.001, respectively). Thereafter, they started to decrease, but on d + 7 NT-proANP (404 +/- 157 pmol/L, P = 0.048) and NT-proBNP (648 +/- 125 pmol/L, P = 0.015) were still significantly higher than at baseline. On d + 12 and m + 3 they no longer differed from baseline. CONCLUSIONS: Our findings suggest that high-dose CY results in acute, subclinical systolic dysfunction in NHL patients previously treated with anthracyclines. Natriuretic peptides seem to be more sensitive than LVEF to reflect this transient cardiac effect. Serial measurements of natriuretic peptides might be a useful tool to assess cardiac effects of high-dose CY.

Kumar, S., S. Giralt, et al. (2009). "Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens." Blood **114**(9): 1729-35.

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib, leading to improved outcomes. High-dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Before the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given its potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group (IMWG) was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferably within the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

Kumar, S., M. Q. Lacy, et al. (2004). "High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy." Bone Marrow Transplant **34**(2): 161-7.

Autologous stem cell transplant (SCT) improves survival in multiple myeloma (MM) and remains the standard of care for eligible patients. Nearly a third of patients with newly diagnosed MM fail initial therapy aimed at reducing tumor burden

preceding SCT (primary refractory). It is unclear if an initial response is important for successful SCT. We evaluated our experience with SCT in 50 patients with primary refractory MM and compared it to 101 patients with chemosensitive disease receiving SCT. The study cohort had a median age of 56 years (range 29-72) consisting of 87 males (58%). A total of 46 patients (92%) in the refractory group and 100 (99%) in the chemosensitive group had a response to transplant (50% or greater reduction in the M-protein). In all, 10 refractory patients (20%) and 35 (35%) in the chemosensitive group achieved a CR (P=0.06). The 1-year estimated progression-free survival from the time of transplant for the refractory group was 70% compared to 83% for the chemosensitive group (P=0.65). The lack of response to initial induction therapy does not appear to preclude a good response to SCT. We recommend that patients with primary refractory MM be offered early SCT.

Kumar, S., M. Q. Lacy, et al. (2004). "Single agent dexamethasone for pre-stem cell transplant induction therapy for multiple myeloma." Bone Marrow Transplant **34**(6): 485-90.

Given the survival advantage, high-dose therapy (HDT) remains the standard of care for patients with multiple myeloma eligible for the procedure. For those undergoing HDT, initial therapy aimed at reducing tumor burden is given prior to stem cell harvest. Various regimens, mostly variations of VAD (vincristine, doxorubicin, dexamethasone), are used for induction therapy. We retrospectively evaluated if single agent dexamethasone would be an effective induction therapy, given that it is the most active drug in these combinations. A total of 35 patients who received induction therapy with dexamethasone alone were compared to a similar group of 72 patients who received VAD as the initial therapy. We found a 63% response rate with dexamethasone compared to 74% with VAD (P=0.25). Including minimal responses, the overall response rate for Dex and VAD was 74 and 86%, respectively (P=0.13). The overall and complete response rates to transplant, respectively, were 97 and 26% for the dexamethasone group and 100 and 39% for the VAD group; P=0.33 and 0.18. No significant differences were observed in the progression-free and overall survival at 1 year post transplant. Single agent dexamethasone appears to be an effective alternative to VAD for induction therapy prior to HDT in myeloma.

Kume, A., Y. Hanazono, et al. (2002). "Selective expansion of transduced cells for hematopoietic stem cell gene therapy." Int J Hematol **76**(4): 299-304.

Although gene transfer into hematopoietic stem cells holds a considerable therapeutic potential, clinical trials targeting this cell compartment have achieved limited success. Poor transduction efficiency with gene transfer vectors used in human studies has hindered delivering therapeutic genes to clinically relevant numbers of target cells. One way to overcome the low-efficiency problem is by selecting or expanding the number of genetically modified cells to a suprathreshold level to achieve clinical efficacy. This approach may be further classified into 2 categories: one is to transfer a drug resistance gene and eliminate unmodified cells with cytotoxic drugs, and the other is to confer a direct growth advantage on target cells. This review aims at an overview of recent advances involving these strategies, with some details of "selective amplifier genes," a novel system that we have developed for specific expansion of genetically modified hematopoietic cells.

LaPar, D. J., I. L. Kron, et al. (2009). "Stem cell therapy for ischemic heart disease: where are we?" Curr Opin Organ Transplant **14**(1): 79-84.

PURPOSE OF REVIEW: Stem cell transplantation is currently generating a great deal of interest in the treatment of ischemic heart disease (IHD) as the replacement of akinetic scar tissue by viable myocardium should improve cardiac function, impede progressive left ventricular remodeling, and revascularize ischemic areas. Substantial work in stem cell therapy for ischemic heart disease has recently been reported. RECENT FINDINGS: Stem cell populations have been expanding. Most recently, induced pluripotent stem (iPS) cells have been discovered that have the potential to revolutionize stem cell therapy. Many of the efforts in stem cell therapy for ischemic heart disease have been inconclusive and often contradicting. Transdifferentiation of stem cells into cardiomyocytes remains controversial. The therapeutic effect of the stem cell seems consistent with paracrine function rather than transdifferentiation. Systemic and micromilieu factors appear to dictate the fate of implanted stem cells. SUMMARY: Although animal studies produce controversial results, and many basic questions remain unanswered, more and more clinical trials are underway. Consequently, researchers must begin to focus upon a few basic critical issues: the modulation of the systemic and microenvironment for stem cells in order to augment stem cell survival and transdifferentiation; the underlying mechanisms of stem cell therapy and the fate of stem cells; differentiation into myocytes or other terminal cell populations with favorable paracrine functions.

Lee, B. C., H. C. Hsu, et al. (2009). "Cell therapy generates a favourable chemokine gradient for stem cell recruitment into the infarcted heart in rabbits." Eur J Heart Fail **11**(3): 238-45.

AIMS: Stem cell recruitment into the heart is determined by a concentration gradient of stromal-derived factor 1 (SDF-1) from bone marrow to peripheral blood and from blood to injured myocardium. However, this gradient is decreased in chronic myocardial infarction (MI). This study evaluated the effect of cell therapy using bone marrow stromal cells (BMSCs) on an SDF-1 gradient in post-infarction rabbits. METHODS AND RESULTS: Myocardial infarction was induced in male New Zealand white rabbits (2.5-3 kg) by ligation of the left anterior descending coronary artery. Two months later, the rabbits were randomized to either saline or BMSC (2 x 10(6) autologous BMSCs injected into the left ventricular cavity) treatment. Four weeks after therapy, the SDF-1 gradients from bone marrow to blood and from blood to myocardium increased in the BMSC group compared with the saline group. This was accompanied by an increase in cells positive for CD34, CD117, and STRO-1 in the myocardium, resulting in more capillary density, better cardiac function, and a decrease in infarct size. CONCLUSION: Generation of an SDF-1 gradient towards the heart is a novel effect of BMSC-based cell therapy. This effect facilitates stem cell recruitment into remodelled myocardium and supports improvement in cardiac function.

Lee, S., D. W. Kim, et al. (2003). "Minimal residual disease-based role of imatinib as a first-line interim therapy prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia." Blood **102**(8): 3068-70.

Fourteen adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) were studied to evaluate the role of imatinib prior to allogeneic stem cell transplantation (SCT). Of these, 12 patients were in complete hematologic response (CHR), and 2 were refractory. Imatinib was administered as an interim schedule after each chemotherapy course. After the first imatinib cycle, 11 patients remained in sustained CHR with a decrease in the BCR-ABL/ABL ratios (0.89 logs), and one refractory patient achieved CHR. Meanwhile, 2 patients were resistant to imatinib. Ten patients receiving a second imatinib cycle following consolidation showed sustained CHR, including 2 molecular CR, with a further decrease in the BCR-ABL/ABL ratios (0.19 logs). Twelve patients underwent SCT in a favorable status, and of these, 11 are still alive in a leukemia-free status at 9 to 28+ months after SCT. First-line imatinib interim therapy appears to be a useful strategy to bridge the time to SCT for patients with Ph+ ALL.

Leen, A. M., A. Christin, et al. (2009). "Cytotoxic T lymphocyte therapy with donor T cells prevents and treats adenovirus and Epstein-Barr virus infections after haploidentical and matched unrelated stem cell transplantation." Blood **114**(19): 4283-92.

Viral infection or reactivation remains a major cause of morbidity and mortality after allogeneic stem cell transplantation. We now show that infusions of single cytotoxic T lymphocyte (CTL) lines (5 x 10(6)-1.35 x 10(8) cells/m(2)) with specificity for 2 commonly detected viruses, Epstein-Barr virus (EBV) and adenovirus, can be safely administered to pediatric transplantation recipients receiving partially human leukocyte antigen-matched and haploidentical stem cell grafts (n = 13), without inducing graft-versus-host disease. The EBV-specific component of the CTLs expanded in vivo and persisted for more than 12 weeks, but the adenovirus-specific component only expanded in vivo in the presence of concomitant adenoviral infection. Nevertheless, adenovirus-specific T cells could be detected for at least 8 weeks in peripheral blood, even in CTL recipients without viral infection, provided the adenovirus-specific component of their circulating lymphocytes was first expanded by exposure to adenoviral antigens ex vivo. After infusion, none of these 13 high-risk recipients developed EBV-associated lymphoproliferative disease, while 2 of the subjects had resolution of their adenoviral disease. Hence, bispecific CTLs containing both EBV- and adenovirus-specific T cells can safely reconstitute an antigen responsive "memory" population of CTLs after human leukocyte antigen-mismatched stem cell transplantation and may provide antiviral activity. This trial was registered at www.clinicaltrials.gov as #NCT00590083.

Li, Z., Y. Liu, et al. (2009). "Toward a stem cell gene therapy for breast cancer." Blood **113**(22): 5423-33.

Current approaches for treatment of late-stage breast cancer rarely result in a long-term cure. In part this is due to tumor stroma that prevents access of systemically or intratumorally applied therapeutics. We propose a stem cell gene therapy approach for controlled tumor stroma degradation that uses the pathophysiologic process of recruitment of inflammatory cells into the tumor. This approach involves genetic modification of hematopoietic stem cells (HSCs) and their subsequent transplantation into tumor-bearing mice. We show that inducible, intratumoral expression of relaxin (Rlx) either by transplanting tumor cells that contained the Rlx gene or by transplantation of mouse HSCs transduced with

an Rlx-expressing lentivirus vector delays tumor growth in a mouse model of breast cancer. The antitumor effect of Rlx was mediated through degradation of tumor stroma, which provided increased access of infiltrating antitumor immune cells to their target tumor cells. Furthermore, we have shown in a human/mouse chimeric model that genetically modified HSCs expressing a transgene can access the tumor site. Our findings are relevant for cancer gene therapy and immunotherapy.

Lim, Z. Y., G. Cook, et al. (2009). "Results of a phase I/II British Society of Bone Marrow Transplantation study on PCR-based pre-emptive therapy with valganciclovir or ganciclovir for active CMV infection following alemtuzumab-based reduced intensity allogeneic stem cell transplantation." Leuk Res **33**(2): 244-9.

This multi-centre randomized study assessed the bioavailability of ganciclovir in patients undergoing alemtuzumab-based reduced intensity conditioning (RIC) haematopoietic stem cell transplantation (HSCT) after oral administration of valganciclovir. Patients were randomized to 2 groups receiving either oral valganciclovir (900 mg twice daily) or intravenous ganciclovir (5mg/kg twice daily) for 14 days. Twenty-seven patients were recruited and 18 patients (67%) completed allocated treatment resulting in clearance of cytomegolovirus (CMV) DNA load at a median of 14 days. The bioavailability of ganciclovir from valganciclovir was 73% (95% CI: 34-112%). The average exposure in the valganciclovir group (36.9+/-14.9 microg h/ml) was higher than the ganciclovir cohort (27.9+/-7.5 microg h/ml). When compared with intravenous ganciclovir, oral valganciclovir had high bioavailability in patients undergoing alemtuzumab-based RIC HSCT.

Lin, D. P., M. Y. Chang, et al. (2003). "Male germ line stem cells: from cell biology to cell therapy." Reprod Fertil Dev **15**(6): 323-31.

Research using stem cells has several applications in basic biology and clinical medicine. Recent advances in the establishment of male germ line stem cells provided researchers with the ability to identify, isolate, maintain, expand and differentiate the spermatogonia, the primitive male germ cells, as cell lines under in vitro conditions. The ability to culture and manipulate stem cell lines from male germ cells has gradually facilitated research into spermatogenesis and male infertility, to an extent beyond that facilitated by the use of somatic stem cells. After the introduction of exogenous genes, the spermatogonial cells can be transplanted into the seminiferous tubules of recipients, where the transplanted cells can contribute to the offspring. The present review concentrates on the origin, life cycle and establishment of stem cell lines from male germ cells, as well as the current status of transplantation techniques and the application of spermatogonial stem cell lines.

Liu, J. J., J. H. Shin, et al. (2006). "Stem cell therapy for hearing loss: Math1 overexpression in VOT-E36 cells." Otol Neurotol **27**(3): 414-21.

HYPOTHESIS: VOT-E36 cells acquire mechanosensitivity after mammalian atonal homolog 1 (Math1) overexpression. BACKGROUND: VOT-E36 cells are derived from a population of epithelial cells in the ventral region of the otocyst at embryonic Day 10.5, before hair cell differentiation. These cells express a number of specific molecular markers for hair cells under both proliferation and differentiation states. Overexpression of Math1 can convert nonsensory epithelial cells into hair cells in the cochlea. Based on this information, we tested whether VOT-E36 cells can be converted into hair cells by Math1 overexpression. METHODS: Using reverse transcriptase-polymerase chain reaction-based analysis, we first compared the expression patterns of various molecular markers for hair cell development in VOT-E36 cells between proliferation and differentiation states, and also before and after overexpression of Math1. Subsequently, with a standard calcium imaging method, we examined whether VOT-E36 cells overexpressing Math1 could detect mechanical vibrations and activate spiral ganglion neurons in a coculture model. In addition, using confocal and scanning electron microscopes, we examined morphologic changes of VOT-E36 cells after Math1 overexpression. RESULTS: Consistent with previous reports, this study has shown that VOT-E36 cells express a number of specific molecular markers for hair cells in both proliferation and differentiation states. Under appropriate culture conditions, Math1 is transiently expressed in this cell line during conditional differentiation. In VOT-E36 cells overexpressing Math1, the normal expression pattern of certain molecular markers for mature hair cells is partially restored. Interestingly, after coculture with spiral ganglion neurons, VOT-E36 cells overexpressing Math1 are able to respond to mechanical vibrations and activate spiral ganglion neurons. Possible molecular mechanisms underlying this novel finding have been explored. CONCLUSION: Math1 overexpression can partially restore presumably downstream signaling cascades for normal hair cell differentiation in VOT-E36 cells, which are able to detect mechanical vibrations after being cocultured with spiral ganglion neurons.

Lovell, K. L., S. A. Kraemer, et al. (2001). "In utero hematopoietic stem cell transplantation: a caprine model for prenatal therapy in inherited metabolic diseases." Fetal Diagn Ther **16**(1): 13-7.

OBJECTIVES: We explored the feasibility and efficacy of in utero hematopoietic stem cell transplantation in the caprine animal model system with the objectives of determining procedures for transplantation and establishing methods for detecting engraftment. METHODS: Male fetal liver hematopoietic stem cells were injected into female fetuses during the immunotolerant period, using either hysterotomy or ultrasound-guided injections. RESULTS: The rate of fetal death was much lower for the ultrasound-guided injections. Donor cells were observed in the peritoneal fluid of 4 fetuses 3 days after injection, but no donor cells were detected in tissues at longer time periods. CONCLUSIONS: Ultrasound-guided injection of hematopoietic stem cells into the abdomen of a developing fetus is safe and feasible. The parameters required for successful engraftment have not yet been identified.

Mader, E. K., Y. Maeyama, et al. (2009). "Mesenchymal stem cell carriers protect oncolytic measles viruses from antibody neutralization in an orthotopic ovarian cancer therapy model." Clin Cancer Res **15**(23): 7246-55.

PURPOSE: Preexisting antiviral antibodies in cancer patients can quickly neutralize oncolytic measles virus (MV) and decrease its antitumor potency. In contrast to "naked" viruses, cell-associated viruses are protected from antibody neutralization. Hence, we hypothesized that measles virotherapy of ovarian cancer in measles-immune mice might be superior if MV-infected mesenchymal stem cell (MSC) carriers are used. EXPERIMENTAL DESIGN: Antimeasles antibodies titers in ovarian cancer patients were determined. The protection of MV by MSC from antimeasles antibodies, the in vivo biodistribution profiles, and tumor infiltration capability of MSC were determined. Measles-naive or immune tumor-bearing mice were treated with naked virus or MSC-associated virus and mice survivals were compared. RESULTS: MSC transferred MV infection to target cells via cell-to-cell heterofusion and induced syncytia formation in the presence of high titers of antimeasles antibody, at levels that completely inactivated naked virus. Athymic mice bearing i.p. human SKOV3ip.1 ovarian tumor xenografts passively immunized with measles-immune human serum were treated with saline, naked MV, or MV-infected MSC. Bioluminescent and fluorescent imaging data indicated that i.p. administered MSC localized to peritoneal tumors, infiltrated into the tumor parenchyma, and transferred virus infection to tumors in measles naive and passively immunized mice. Survival of the measles-immune mice was significantly enhanced by treatment with MV-infected MSC. In contrast, survivals of passively immunized mice were not prolonged by treatment with naked virus or uninfected MSC. CONCLUSIONS: MSC should be used as carriers of MV for intraperitoneal virotherapy in measles-immune ovarian cancer patients.

Mak, Y. K., C. H. Chan, et al. (2003). "Consolidation therapy with autologous blood stem cell transplantation in a patient with primary plasma cell leukaemia." Clin Lab Haematol **25**(1): 55-8.

Primary plasma cell leukaemia (PPCL) is a rare form of plasma cell dyscrasia. Conventional melphalan-based treatment is often ineffective, with a reported median survival of 2-7 months only. We report a 53-year-old man with PPCL who was treated with four cycles of combination chemotherapy including vincristine, adriamycin and dexamethasone that resulted in a good partial remission. High-dose melphalan 200 mg/m2 and autologous peripheral blood stem cell (PBSC) rescue was then given 6 months after diagnosis. Maintenance interferon-alpha was started 8 weeks after transplantation with good drug compliance. Complete remission was achieved and molecular remission was documented 11 months after autologous PBSC transplantation. In conclusion, high-dose therapy followed by autologous stem cell rescue is a feasible option for PPCL that can result in a reasonably sustained remission.

Masson, S., D. J. Harrison, et al. (2004). "Potential of hematopoietic stem cell therapy in hepatology: a critical review." Stem Cells **22**(6): 897-907.

Adult stem cell plasticity raised expectations regarding novel cellular therapies of regenerative medicine after findings of unexpected plasticity were reported. In this review, reports of hematopoietic stem cells (HSCs) contributing to hepatocytic lineages are critically discussed with reference to rodent and human models. In particular, the role of liver injury and the potential contribution HSCs make to hepatic regeneration in both injury and physiological maintenance is reviewed. The relative contributions of genomic plasticity and cell fusion are studied across different model systems, highlighting possible factors that may explain differences between often conflicting reports. Insights from experimental studies will be described that shed light on the mechanisms underlying the migration, engraftment, and transdifferentiation of HSCs in liver injury. Although it appears that under differing circumstances, macrophage fusion, HSC fusion, and HSC transdifferentiation can all contribute to hepatic

epithelial lineages, a much greater understanding of the factors that regulate the long-term efficacy of such cells is needed before this phenomenon can be used clinically.

Mathieu, M., J. Bartunek, et al. (2009). "Cell therapy with autologous bone marrow mononuclear stem cells is associated with superior cardiac recovery compared with use of nonmodified mesenchymal stem cells in a canine model of chronic myocardial infarction." J Thorac Cardiovasc Surg **138**(3): 646-53.

OBJECTIVE: Stem cell therapy can facilitate cardiac repair in infarcted myocardium, but the optimal cell type remains uncertain. We conducted a randomized, blind, and placebo-controlled comparison of autologous bone marrow mononuclear cell and mesenchymal stem cell therapy in a large-animal model of chronic myocardial infarction. METHODS: Eleven weeks after coronary ligation, 24 dogs received intramyocardial injections of mononuclear cells (227.106 +/- 32.106 cells), mesenchymal stem cells (232.106 +/- 40.106 cells), or placebo (n = 8 per group). Cardiac performance and remodeling were assessed up to 16 weeks' follow-up. RESULTS: At echocardiographic analysis, the wall motion score index showed a sustained improvement after mononuclear cell transfer (from 1.8 +/- 0.1 to 1.5 +/- 0.07) and a moderate late improvement after mesenchymal stem cell transfer (from 1.9 +/- 0.08 to 1.7 +/- 0.1). After mononuclear cell transfer, end-systolic elastance increased (from 2.23 +/- 0.25 to 4.42 +/- 0.55 mm Hg/mL), infarct size decreased (from 13% +/- 0.67% to 10% +/- 1.17%), N-terminal B-type natriuretic propeptide level decreased (from 608 +/- 146 to 353 +/- 118 pmol/L), and relative wall area and arterial density increased. Vascular endothelial growth factor receptor 2 expression was upregulated in the border zone. No change in cardiac contractility or histologic parameters was noted in the mesenchymal stem cell group. CONCLUSION: In a canine model of chronic myocardial infarction, bone marrow mononuclear cell transfer is superior to mesenchymal stem cell transfer in improvement of cardiac contractility and regional systolic function and reduction in infarct size and plasma N-terminal B-type natriuretic propeptide level. Functional improvement is associated with a favorable angiogenic environment and neovascularization.

Matthay, K. K., J. C. Tan, et al. (2006). "Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study." J Clin Oncol **24**(3): 500-6.

PURPOSE: To determine the maximum-tolerated dose (MTD) and toxicity of iodine-131-metaiodobenzylguanidine ((131)I-MIBG) with carboplatin, etoposide, melphalan (CEM) and autologous stem-cell transplantation (ASCT) in refractory neuroblastoma. PATIENTS AND METHODS: Twenty-four children with primary refractory neuroblastoma and no prior ASCT were entered; 22 were assessable for toxicity and response. (131)I-MIBG was administered on day -21, CEM was administered on days -7 to -4, and ASCT was performed on day 0, followed by 13-cis-retinoic acid. (131)I-MIBG was escalated in groups of three to six patients, stratified by corrected glomerular filtration rate (GFR). RESULTS: The MTD for patients with normal GFR (> or = 100 mL/min/1.73 m2) was 131I-MIBG 12 mCi/kg, carboplatin 1,500 mg/m2, etoposide 1,200 mg/m2, and melphalan 210 mg/m2. In the low-GFR cohort, at the initial dose level using 12 mCi/kg of 131I-MIBG and reduced chemotherapy, one in six patients had dose limiting toxicity (DLT), including veno-occlusive disease (VOD). Three more patients in this group had grade 3 or 4 hepatotoxicity, and two had VOD, without meeting DLT criteria. There was only one death as a result of toxicity among all 24 patients. All assessable patients engrafted, with median time for neutrophils > or = 500/microL of 10 days and median time for platelets > or = 20,000/microL of 26 days. Six of 22 assessable patients had complete or partial response, and 15 patients had mixed response or stable disease. The estimated probability of event-free survival and survival from the day of MIBG infusion for all patients at 3 years was 0.31 +/- 0.10 and 0.58 +/- 0.10, respectively. CONCLUSION: 131I-MIBG with myeloablative chemotherapy is feasible and effective for patients with neuroblastoma exhibiting de novo resistance to chemotherapy.

Mattson, M. P. (2000). "Emerging neuroprotective strategies for Alzheimer's disease: dietary restriction, telomerase activation, and stem cell therapy." Exp Gerontol **35**(4): 489-502.

The molecular, biochemical and cellular events that result in synaptic dysfunction and neuronal degeneration in the brain in Alzheimer's disease (AD) are becoming known. Age-related increases in cellular oxidative stress, and impairment of energy metabolism, result in disruption of neuronal calcium homeostasis and increased vulnerability of neurons to excitotoxicity and apoptosis. Inherited forms of AD that result from mutations in the beta-amyloid precursor protein (APP) and presenilins accelerate the neurodegenerative cascade by increasing production and deposition of neurotoxic forms of amyloid beta-peptide and by perturbing calcium homeostasis.

Dietary restriction (DR; reduced calorie intake with maintained nutrition) extends life span of rodents and (probably) humans. DR increases resistance of neurons to dysfunction and degeneration, and improves behavioral outcome, in experimental models of AD and other age-related neurodegenerative disorders by a mechanism involving a mild stress response. Telomerase, a specialized reverse transcriptase, has been proposed to possess anti-aging properties. The catalytic subunit of telomerase (TERT) is expressed in neurons throughout the brain during development, but is absent from neurons in the adult brain. TERT exhibits neuroprotective properties in experimental models of neurodegenerative disorders suggesting that manipulations that induce telomerase in neurons may protect against age-related neurodegeneration. Finally, the exciting and exploding field of stem cell research suggests methods for replacing damaged or lost brain cells in an array of neurological disorders.

Min, C. K., D. W. Kim, et al. (2000). "Additional stem cell therapy for graft failure after allogeneic bone marrow transplantation." Acta Haematol **104**(4): 185-92.

In this study we retrospectively evaluated the effect and outcome of a boost dose of donor stem cells without additional chemotherapy or total body irradiation. Between March 1983 and August 1999, 20 of 788 (2.5%) patients receiving allogeneic bone marrow transplantation (BMT) were treated with an additional boost dose of donor cells. The reasons for the use of the boost treatment were primary graft failure (early rejection; n = 7), secondary graft failure including late rejection (n = 10), refractory pure red cell aplasia caused by the remaining recipient cells producing anti-erythrocyte antibodies (n = 2), and donor lymphocyte infusion induced pancytopenia (n = 1). The patients were aged from 17 to 48 years (median age 31 years). The underlying diseases of the patients were severe aplastic anemia in 12 patients, acute myelogenous leukemia in 3, acute lymphocytic leukemia in 3, and chronic myelogenous leukemia in 2. The donors were human leukocyte antigen-identical siblings in 18 cases, 1 mismatched related donor, and 1 unrelated donor. The cell source was bone marrow in 6 cases and peripheral blood progenitor cells in 14. The median interval between BMT and the boost treatment was 7 weeks (range 1-124). No conditioning regimen was given prior to the boost treatment for 11 patients, while 4 received total nodal irradiation (TNI) plus antithymocyte globulin (ATG), 3 ATG alone, and 2 TNI plus steroid. The median infused booster mononuclear cell dose was 2.55 x 10(8)/kg (range 0.28-37.0). Fifteen (75%) patients achieved a hematological recovery. After the boost treatment, 6 of 20 (30%) patients developed acute graft-versus-host disease (GVHD) > or = grade II, 3 of whom had had prior GVHD. Five (31.3%) of the evaluable 16 patients developed chronic GVHD. The GVHDs were easily controlled using immunosuppressive agents except in the case of 1 patient. Five patients died after the boost treatment; 2 within 30 days, 2 within 60 days, and 1 after 32 months. The causes of death were: 3 engraftment failures, 1 late rejection, and 1 infection following GVHD. With a median follow-up of 31.5 months (range 6-92), the Kaplan-Meier method estimated that the overall survival rate 1 and 3 years after the boost treatment was 80 and 71%, respectively. The survival of patients with primary graft failure was determined to be significantly lower compared to that of patients with secondary graft failure, using the log rank test (p = 0.0176). Disease category, stem cell source, conditioning prior to a boost treatment, and year of boost treatment did not have an influence on survival. We conclude that the reinfusion of donor stem cells is frequently successful in achieving engraftment with rare occurrence of fatal GVHD. Furthermore, relatively good long-term survival was demonstrated.

Miranda, S. R., S. Erlich, et al. (2000). "Hematopoietic stem cell gene therapy leads to marked visceral organ improvements and a delayed onset of neurological abnormalities in the acid sphingomyelinase deficient mouse model of Niemann-Pick disease." Gene Ther **7**(20): 1768-76.

Types A and B Niemann-Pick disease (NPD) result from the deficient activity of acid sphingomyelinase (ASM). Currently, no treatment is available for either form of NPD. Using the ASM knockout (ASMKO) mouse model, we evaluated the effects of ex vivo hematopoietic stem cell gene therapy on the NPD phenotype. Thirty-two newborn ASMKO mice were preconditioned with low dose radiation (200 cGy) and transplanted with ASMKO bone marrow cells which had been transduced with an ecotropic retroviral vector encoding human ASM. Engraftment of donor-derived cells ranged from 15 to 60% based on Y-chromosome in situ hybridization analysis of peripheral white blood cells, and was achieved in 92% of the transplanted animals. High levels of ASM activity (up to five-fold above normal) were found in the engrafted animals for up to 10 months after transplantation, and their life-span was extended from a mean of 5 to 9 months by the gene therapy procedure. Biochemical and histological analysis of tissues obtained 4-5 months after transplantation indicated that the ASM activities were increased and the sphingomyelin storage was significantly reduced in the spleens, livers and lungs of the treated mice, major sites of pathology in type B

NPD. The presence of Purkinje cell neurons was also markedly increased in the treatment group as compared with non-treated animals at 5 months after transplantation, and a reduction of storage in spinal cord neurons was observed. However, all of the transplanted mice eventually developed ataxia and died earlier than normal mice. Overall, these results indicated that hematopoietic stem cell gene therapy should be effective for the treatment of non-neurological type B NPD, but improved techniques for targeting the transplanted cells and/or expressed enzyme to specific sites of pathology in the central nervous system must be developed in order to achieve effective treatment for type A NPD.

Misaghian, N., G. Ligresti, et al. (2009). "Targeting the leukemic stem cell: the Holy Grail of leukemia therapy." Leukemia **23**(1): 25-42.

Since the discovery of leukemic stem cells (LSCs) over a decade ago, many of their critical biological properties have been elucidated, including their distinct replicative properties, cell surface phenotypes, their increased resistance to chemotherapeutic drugs and the involvement of growth-promoting chromosomal translocations. Of particular importance is their ability to transfer malignancy to non-obese diabetic-severe combined immunodeficient (NOD-SCID) mice. Furthermore, numerous studies demonstrate that acute myeloid leukemia arises from mutations at the level of stem cell, and chronic myeloid leukemia is also a stem cell disease. In this review, we will evaluate the main characteristics of LSCs elucidated in several well-documented leukemias. In addition, we will discuss points of therapeutic intervention. Promising therapeutic approaches include the targeting of key signal transduction pathways (for example, PI3K, Rac and Wnt) with small-molecule inhibitors and specific cell surface molecules (for example, CD33, CD44 and CD123), with effective cytotoxic antibodies. Also, statins, which are already widely therapeutically used for a variety of diseases, show potential in targeting LSCs. In addition, drugs that inhibit ATP-binding cassette transporter proteins are being extensively studied, as they are important in drug resistance-a frequent characteristic of LSCs. Although the specific targeting of LSCs is a relatively new field, it is a highly promising battleground that may reveal the Holy Grail of cancer therapy.

Mollura, D. J., J. M. Hare, et al. (2003). "Stem-cell therapy for renal diseases." Am J Kidney Dis **42**(5): 891-905.

Significant attention is currently directed to the biological and therapeutic capabilities of stem cells for developing novel treatments for acute and chronic kidney diseases. To date, viable sources of stem cells for renal therapies include adult bone marrow and embryonic tissues, including the metanephric mesenchyme and mesonephros. Native adult kidney stem cells have yet to be identified. Systemically introduced stem cells can engraft in sites of renal disease and injury to show donor phenotypes. Stem cells can differentiate into cells similar to glomeruli, mesangium, and tubules in the kidneys. The impact of stem-cell engraftment and differentiation on renal function presently is unknown. Identification of renal diseases treatable with stem-cell therapies is expected to evolve as stem-cell technologies advance. Methods of modifying stem cells to improve homing, differentiation, and integration into host tissues need further characterization. Ethical and legal controversies about embryonic research and cloning are shaping the regulation and funding of stem-cell research for kidney diseases. Scientific and clinical understanding of stem cells and their potential for renal treatments are in the early stage of development. This field offers great promise, and there are significant opportunities for future investigation in clinical, biological, and ethical aspects of stem-cell therapy for kidney diseases.

Mori, T., S. Okamoto, et al. (2002). "Dose-adjusted preemptive therapy for cytomegalovirus disease based on real-time polymerase chain reaction after allogeneic hematopoietic stem cell transplantation." Bone Marrow Transplant **29**(9): 777-82.

We have prospectively evaluated the efficacy of real-time PCR-guided preemptive therapy for CMV diseases in allogeneic hematopoietic stem cell transplant recipients with grades II-IV acute GVHD. The dose of ganciclovir was adjusted according to the viral load determined by real-time polymerase chain reaction (PCR). On detecting CMV reactivation in the plasma, ganciclovir was initiated at a dose of 5 mg/kg body weight once daily, and the dose was increased to twice daily if viral load continued to increase after initiating ganciclovir. In 39 evaluable patients, CMV reactivation assessed by real-time PCR became positive in 30 (77%). One developed CMV gastroenteritis before PCR became positive. Thus the remaining 29 patients were treated preemptively with ganciclovir. The dose of ganciclovir was increased in 12 patients (41%) of preemptively treated patients for increasing viral load. CMV diseases were diagnosed in two patients (one gastroenteritis and one retinitis), and late CMV disease was diagnosed in one patient (gastritis). The treatment was generally well-tolerated, but three patients (10%) developed neutropenia (neutrophil count less than 1.0 x 10(9)/l). In conclusion, real-time PCR-guided preemptive therapy

with decreased dose of ganciclovir is feasible and does not increase the frequency of CMV diseases if the dose is adjusted according to the viral load.

Morse, M. A. (1999). "Technology evaluation: Stem-cell therapy, Aastrom Biosciences Inc." Curr Opin Mol Ther **1**(6): 745-52.

The expansion of human stem cells and their genetic manipulation represent areas of increasing interest in the field of stem cell transplantation. Previously, stem cell transplantation has been accomplished by using cellular products obtained by large volume bone marrow or peripheral blood harvest. Difficulties with this approach include inadequate cell numbers and tumor cell contamination. Furthermore, for gene transfer modalities requiring proliferating progenitor cells, low gene expression would be expected in these products. To address these difficulties, the AastromReplicell System has been developed as a fully closed and automated system for expanding hematopoietic cells. Investigators at Aastrom have evaluated the conditions needed for optimal growth including the need for unpurified bone marrow or cord blood mononuclear cells, high cell densities, serum-containing medium and certain types of plastic surfaces. Studies have now been initiated to demonstrate the feasibility of generating enough cells to fully reconstitute hematopoiesis from small volumes of cellular progenitors. It has also been demonstrated that tumor cell contamination passively decreases during the culture period. It now remains to be shown in a direct comparison that this approach yields greater efficacy and a lower cost than transplantation with unmanipulated large volume marrow or peripheral blood stem cell products.

Nehlin, J. O. and T. Barington (2009). "Strategies for future histocompatible stem cell therapy." Biogerontology **10**(4): 339-76.

Stem cell therapy based on the safe and unlimited self-renewal of human pluripotent stem cells is envisioned for future use in tissue or organ replacement after injury or disease. A gradual decline of regenerative capacity has been documented among the adult stem cell population in some body organs during the aging process. Recent progress in human somatic cell nuclear transfer and inducible pluripotent stem cell technologies has shown that patient-derived nuclei or somatic cells can be reprogrammed in vitro to become pluripotent stem cells, from which the three germ layer lineages can be generated, genetically identical to the recipient. Once differentiation protocols and culture conditions can be defined and optimized, patient-histocompatible pluripotent stem cells could be directed towards virtually every cell type in the human body. Harnessing this capability to enrich for given cells within a developmental lineage, would facilitate the transplantation of organ/tissue-specific adult stem cells or terminally differentiated somatic cells to improve the function of diseased organs or tissues in an individual. Here, we present an overview of various experimental cell therapy technologies based on the use of patient-histocompatible stem cells, the pending issues needed to be dealt with before clinical trials can be initiated, evidence for the loss and/or aging of the stem cell pool and some of the possible uses of human pluripotent stem cell-derivatives aimed at curing disease and improving health.

Neofytos, D., D. Horn, et al. (2009). "Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry." Clin Infect Dis **48**(3): 265-73.

BACKGROUND: With use of data from the Prospective Antifungal Therapy (PATH) Alliance registry, we performed this multicenter, prospective, observational study to assess the epidemiologic characters and outcomes of invasive fungal infection (IFI) in hematopoietic stem cell transplant (HSCT) recipients. METHODS: Sixteen medical centers from North America reported data on adult HSCT recipients with proven or probable IFI during the period July 2004 through September 2007. The distribution of IFIs and rates of survival at 6 and 12 weeks after diagnosis were studied. We used logistic regression models to determine risk factors associated with 6-week mortality for allogeneic HSCT recipients with invasive aspergillosis (IA). RESULTS: Two hundred thirty-four adult HSCT recipients with a total of 250 IFIs were included in this study. IA (59.2%) was the most frequent IFI, followed by invasive candidiasis (24.8%), zygomycosis (7.2%), and IFI due to other molds (6.8%). Voriconazole was the most frequently administered agent (68.4%); amphotericin B deoxycholate was administered to a few patients (2.1%). Ninety-three (46.7%) of 199 HSCT recipients with known outcome had died by week 12. The 6-week survival rate was significantly greater for patients with IA than for those with invasive candidiasis and for those with IFI due to the Zygomycetes or other molds ($P < .07$). The 6-week mortality rate for HSCT recipients with IA was 21.5%. At 6 weeks, there was a trend toward a worse outcome among allogeneic HSCT recipients with IA who received myeloablative conditioning ($P = .07$); absence of mechanical ventilation or/and hemodialysis ($P = .01$) were associated with improved survival. CONCLUSIONS: IA remains the most commonly

identified IFI among HSCT recipients, but rates of survival in persons with IA appear to have improved, compared with previously reported data. Invasive candidiasis and IFI due to molds other than Aspergillus species remain a significant problem in HSCT recipients.

Nichols, G., K. de Castro, et al. (2002). "Therapy-related myelodysplastic syndrome after autologous stem cell transplantation for breast cancer." Leukemia **16**(9): 1673-9.

Therapy-related myelodysplastic syndrome and acute myelogenous leukemia (t-MDS/AML) are serious complications of chemotherapy and radiotherapy for cancer. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) may be associated with an increased incidence of these complications. The frequency of t-MDS/AML after ASCT for breast cancer is uncertain. We reviewed our database of 379 consecutive breast cancer ASCT patients treated with alkylator-based chemotherapy, followed for a median of 1.52 years (range 0-8.97), with a median survival of 6.16 years. Three patients have developed tMDS/AML. The probability of developing this complication at 5 years is 0.032 in our series. We have used pathologic, cytogenetic and molecular methods to evaluate which portions of therapy may have predisposed to the development of this complication. Cytogenetic abnormalities were not found in the stem cell harvests of these patients by metaphase analysis or by fluorescence in situ hybridization (FISH). One patient demonstrated a clonal X chromosome inactivation pattern in her stem cell harvest, indicating pre-transplant chemotherapy may have been responsible for the development of her leukemia. As two of our patients developed this complication at greater than 4 years post-transplant, the number of cases may increase with longer follow-up. While the incidence appears to be low, further prospective and retrospective analysis will be necessary to determine which portions of therapy predispose to the development of t-MDS/AML in patients undergoing ASCT for treatment of breast cancer.

Nikolic, B., S. Faintuch, et al. (2009). "Stem cell therapy: a primer for interventionalists and imagers." J Vasc Interv Radiol **20**(8): 999-1012.

In recent years, research advancement in stem cell therapy has been rapid. Accordingly, general clinical, scientific, and public attention to the application of stem cell therapy has been substantial. Promises are great, most notably with regard to the application of stem cell therapy for diseases that are currently difficult to treat or incurable such as Parkinson disease or diabetes mellitus. It is in the best interest of patient care for diagnostic and interventional radiologists to be actively involved in the development of these therapies, both at the bench and at the bedside in clinical studies. Specifically, the diagnostic radiologist can become an expert in imaging, tracking, and monitoring of stem cells and in the assessment of engraftment efficiency, whereas the interventionalist is a natural expert in targeted stem cell delivery by means of different routes (percutaneous, selective intravenous, or intraarterial). In addition, there is a potential role for the interventionalist to create engraftment territory and increase engraftment bed fertility with controlled intentional tissue destruction (eg, by means of thermal ablation) that might precede stem cell administration.

Nishikawa, S., A. Okamura, et al. (2009). "Extended mycophenolate mofetil administration beyond day 30 in allogeneic hematopoietic stem cell transplantation as preemptive therapy for severe graft-versus-host disease." Transplant Proc **41**(9): 3873-6.

To prevent acute graft-versus-host disease (GVHD), mycophenolate mofetil (MMF) combined with calcineurin inhibitors have been used in allogeneic hematopoietic stem cell transplantation (allo-SCT). Previous studies commonly utilize MMF treatment until day 30 after allo-SCT. However, the feasibility of continuous administration after day 30 has not been well evaluated. We retrospectively assessed the safety and efficacy of extended drug administration. Twenty-five patients ceased MMF at day 30 (group A); whereas, 16 patients (group B) received extended regimens depending on individual risk factors for GVHD. No severe adverse events were observed in either group. Although the cumulative incidence (CI) of grade I to IV GVHD at day 100 was comparable between the 2 groups, the CI of grade II to IV GVHD was less among group B (12.5%) compared with group A (42.3%). Extended MMF administration may be safe and beneficial as preemptive therapy to reduce the development of moderate-to-severe acute GVHD.

Oelmann, E., M. Thomas, et al. (2002). "Early tandem high-dose ifosfamide, carboplatin, etoposide therapy with stem cell rescue for small-cell lung cancer: brief report on the results of a phase-I/II trial." Oncology **63**(3): 248-53.

OBJECTIVE: High-dose therapy (HDT) for small-cell lung cancer is experimental. Late intensification HDT for chemosensitive disease can increase the number and quality of remissions and prolong relapse-free survival, but has not yet shown impact on overall survival. This is possibly due to resistant residual disease. To overcome the development of resistance, we have tested early

intensification tandem HDT. METHODS: We performed a phase-I/II trial using 1 conventional cycle of ifosfamide, carboplatin, etoposide (ICE) plus granulocyte colony-stimulating factor for stem cell recruitment followed by 2 cycles of high-dose ICE with rescue by CD34+ cell-enriched peripheral blood mononuclear cells. Dose escalation was performed for the 2 high-dose ICE cycles. Radiotherapy for limited disease was according to standard protocols. RESULTS: 17 patients were entered: 2 female patients; 15 male patients; median age 53 (range 36-65) years; 2 patients with limited disease, and 15 patients with extensive disease. We treated 4 patients at dose level 1, 11 patients at level 2, and 2 patients at level 3. The maximum tolerable dose was at level 2 with neuropathy being dose-limiting. Overall, toxicity was < or = grade 2 for all patients up to dose level 2 with hematotoxicity being grade 4 for all patients. There were 15 partial remissions (88%), 1 no change (6%), and 1 progressive disease (6%). Median time to progression was 7.9 months. Overall survival was 12.9 months (median). CONCLUSIONS: Early intensification with this protocol is feasible. Although a comparatively good response rate and median time to progression have been observed in this group dominated by patients with extensive disease, overall survival is short and no substantial long-term survival was found.

Ogata, M., T. Satou, et al. (2008). "Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation." Bone Marrow Transplant **41**(3): 279-85.

Human herpesvirus 6 (HHV-6) causes life-threatening encephalopathy in recipients of allogeneic SCT, but no consensus has been reached regarding appropriate preventive methods. This study evaluated a plasma HHV-6 viral load-guided preemptive approach against HHV-6-associated encephalopathy. Plasma real-time PCR assay was performed once a week. Among 29 patients, 19 developed positive plasma HHV-6 DNA. Median maximum plasma HHV-6 DNA was 4593.5 copies/ml plasma (range, 150.0-127 891.0 copies/ml plasma). In one of eight events with low-level HHV-6 DNA (defined as <1000 copies/ml plasma) and four of seven events with mid-level HHV-6 DNA (1000-9999.5 copies/ml plasma), HHV-6 loads in plasma subsequently continued increasing. Ganciclovir was administered against six of nine patients with high-level HHV-6 DNA (> or =10,000 copies/ml plasma). High-level HHV-6 DNA resolved similarly in both groups with or without ganciclovir therapy. Among the nine patients with high-level HHV-6 DNA two developed encephalopathy. As encephalopathy developed before the detection of high-level HHV-6 DNA in plasma, these two patients had not received preemptive ganciclovir therapy. In conclusion, our preemptive approach against HHV-6-associated encephalopathy cannot prevent all cases of HHV-6 encephalopathy in SCT recipients due to the dynamic kinetics of plasma HHV-6 viral load.

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.

Olafsen, T., Z. Gu, et al. (2007). "Targeting, imaging, and therapy using a humanized antiprostate stem cell antigen (PSCA) antibody." J Immunother **30**(4): 396-405.

The murine 1G8 (micro1G8) monoclonal antibody directed against prostate stem cell antigen (PSCA) prevents prostate tumor establishment, growth, and metastasis in murine models. To further

delineate in vivo targeting properties, micro1G8 was radiolabeled with In-111 and evaluated in nude mice bearing PC3-PSCA xenografts. Tumor activity ranged from 11.8% to 17.1% injected dose per gram (ID/g) at 24 to 96 hours postinjection. To extend the clinical applicability of micro1G8, a chimeric 1G8 antibody was produced that exhibited specific binding to PSCA and significant antitumor effect over micro1G8 in established LAPC-9 prostate cancer xenografts (P=0.0014). However, low expression yields and instability prompted us to humanize 1G8 by grafting the complementary determining regions onto the stable, human Fv framework of anti-p185 4D5v8 (trastuzumab). Two humanized 1G8 (hu1G8) versions (A and B) that differed in the number of murine residues present in the C-terminal half of CDR-H2, were produced. Biacore binding studies demonstrated affinities of 1.47 nM for micro1G8 and 3.74 nM for hu2B3-B, representing a 2.5-fold reduction. Tumor targeting of version B radioiodinated with I was evaluated by serial microPET imaging. Specific tumor targeting of I-hu1G8-B to PC3-PSCA [12.7 (+/-1.6)% ID/g at 94 h] and LAPC-9 [6.6 (+/-0.9)% ID/g at 168 h) xenografts was observed. Inhibition of tumor growth by hu1G8-B was demonstrated in mice bearing low-expressing SW-780-PSCA bladder carcinoma xenografts. In this model, the micro1G8 was ineffective, whereas the hu1G8-B exhibited approximately 50% inhibitory effect. These data support further development of hu1G8 anti-PSCA antibody for targeted imaging and therapy for tumors of urogenital origin.

Oliansky, D. M., J. H. Antin, et al. (2009). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review." Biol Blood Marrow Transplant **15**(2): 137-72.

Clinical research examining the role of hematopoietic stem cell transplantation (SCT) in the therapy of myelodysplastic syndromes (MDS) in adults is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations based on the evidence are presented in Table 3, and were reached unanimously by a panel of MDS experts. The identified priority areas of needed future research in MDS include: (1) the benefit of using alternative donor sources (eg, cord blood; haploidentical family donors) for patients without matched sibling or unrelated donors; (2) the role and appropriate timing of allogeneic SCT in combination with hypomethylating and immunomodulatory treatment regimens; (3) randomized trials comparing the safety and efficacy of various novel agents for treating MDS; and (4) the influence of the various MDS treatment modalities on patient-reported quality-of-life outcomes.

Oliansky, D. M., F. Appelbaum, et al. (2008). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review." Biol Blood Marrow Transplant **14**(2): 137-80.

Clinical research examining the role of hematopoietic stem cell transplantation (HSCT) in the therapy of acute myelogenous leukemia (AML) in adults is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations based on the evidence are presented in Table 3, entitled Summary of Treatment Recommendations Made by the Expert Panel for Adult Acute Myelogenous Leukemia, and were reached unanimously by a panel of AML experts. The identified priority areas of needed future research in adult AML include: (1) What is the role of HSCT in treating patients with specific molecular markers (eg, FLT3, NPM1, CEBPA, BAALC, MLL, NRAS, etc.) especially in patients with normal cytogenetics? (2) What is the benefit of using HSCT to treat different cytogenetic subgroups? (3) What is the impact on survival outcomes of reduced intensity or nonmyeloablative versus conventional conditioning in older (>60 years) and intermediate (40-60 years) aged adults? (4) What is the impact on survival outcomes of unrelated donor HSCT vesus chemotherapy in younger (<40 years) adults with high risk disease?

Oliansky, D. M., J. D. Rizzo, et al. (2007). "The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children: an evidence-based review." Biol Blood Marrow Transplant **13**(1): 1-25.

Clinical research examining the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute myeloid leukemia (AML) in children is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations based on the evidence are presented in the table entitled "Summary of Treatment Recommendations Made by the Expert Panel for Pediatric Acute Myeloid Leukemia" and were reached

unanimously by a panel of experts in AML. The identified priority areas of needed future research in pediatric AML include: What is the role of risk group stratification, including the role of cytogenetics, in selection of patients for allogeneic SCT, especially those in first CR? What is the appropriate timing and use of alternative donor SCT, given that matched unrelated donor SCT appears to yield outcomes equivalent to matched related donor SCT? What is the role of reduced intensity SCT (including the use of fludarabine-based preparative regimens) and/or other immunomodulatory approaches to maximize the graft-versus-leukemic effect? and What is the role of biologically targeted agents (ie, tyrosine kinase inhibitors, farnesyl transferase inhibitors, Flt-3 inhibitors, etc) in the treatment of AML, including induction, consolidation, conditioning regimens, and after SCT?

Pal, R. (2009). "Embryonic stem (ES) cell-derived cardiomyocytes: a good candidate for cell therapy applications." Cell Biol Int **33**(3): 325-36.

During the last decade, embryonic stem cells (ESC) have unleashed new avenues in the field of developmental biology and emerged as a potential tool to understand the molecular mechanisms taking place during the process of differentiation from the embryonic stage to adult phenotype. Their uniqueness lies in retaining the capacity of unlimited proliferation and to differentiate into all somatic cells. Together with promising results from rodent models, ESC has raised great hope among for human ESC-based cell replacement therapy. ESC could potentially revolutionize medicine by providing a powerful and renewable cell source capable of replacing or repairing tissues that have been damaged in almost all degenerative diseases such as Parkinson's disease, myocardial infarction (MI) and diabetes. Somatic stem cells are an attractive option to explore for transplantation because they are autologous, but their differentiation potential is very limited. Currently, the major sources of somatic cells used for basic research and clinical trials come from bone marrow. But their widespread acceptability has not been gained because many of the results are confusing and inconsistent. The focus here is on human embryonic stem cells (hESCs), using methods to induce their differentiation to cardiomyocytes in vitro. Their properties in relation to primary human cardiomyocytes and their ability to integrate into host myocardium have been investigated into how they can enhance cardiac function. However, important aspects of stem cell biology and the transplantation process remain unresolved. In summary, this review updates the recent progress of ES cell research in cell therapy, discusses the problems in the practical utility of ESC, and evaluates how far this adjunctive experimental approach can be successful.

Park, K. I., B. T. Himes, et al. (2006). "Neural stem cells may be uniquely suited for combined gene therapy and cell replacement: Evidence from engraftment of Neurotrophin-3-expressing stem cells in hypoxic-ischemic brain injury." Exp Neurol **199**(1): 179-90.

Previously, we reported that, when clonal neural stem cells (NSCs) were transplanted into brains of postnatal mice subjected to unilateral hypoxic-ischemic (HI) injury (optimally 3-7 days following infarction), donor-derived cells homed preferentially (from even distant locations) to and integrated extensively within the large ischemic areas that spanned the hemisphere. A subpopulation of NSCs and host cells, particularly in the penumbra, "shifted" their differentiation towards neurons and oligodendrocytes, the cell types typically damaged following asphyxia and least likely to regenerate spontaneously and in sufficient quantity in the "post-developmental" CNS. That no neurons and few oligodendrocytes were generated from the NSCs in intact postnatal cortex suggested that novel signals are transiently elaborated following HI to which NSCs might respond. The proportion of "replacement" neurons was approximately 5%. Neurotrophin-3 (NT-3) is known to play a role in inducing neuronal differentiation during development and perhaps following injury. We demonstrated that NSCs express functional TrkC receptors. Furthermore, the donor cells continued to express a foreign reporter transgene robustly within the damaged brain. Therefore, it appeared feasible that neuronal differentiation of exogenous NSCs (as well as endogenous progenitors) might be enhanced if donor NSCs were engineered prior to transplantation to (over)express a bioactive gene such as NT-3. A subclone of NSCs transduced with a retrovirus encoding NT-3 (yielding >90% neurons in vitro) was implanted into unilaterally asphyxiated postnatal day 7 mouse brain (emulating one of the common causes of cerebral palsy). The subclone expressed NT-3 efficiently in vivo. The proportion of NSC-derived neurons increased to approximately 20% in the infarction cavity and >80% in the penumbra. The neurons variously differentiated further into cholinergic, GABAergic, or glutamatergic subtypes, appropriate to the cortex. Donor-derived glia were rare, and astroglial scarring was blunted. NT-3 likely functioned not only on donor cells in an autocrine/paracrine fashion but also on host cells to enhance neuronal differentiation of both. Taken together, these observations suggest (1) the feasibility of taking a fundamental biological response to injury and augmenting it for repair purposes and (2) the

potential use of migratory NSCs in some degenerative conditions for simultaneous combined gene therapy and cell replacement during the same procedure in the same recipient using the same cell (a unique property of cells with stem-like attributes).

Perez-Simon, J. A., C. Encinas, et al. (2008). "Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the national institutes health scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy." Biol Blood Marrow Transplant **14**(10): 1163-71.

Several grading systems have been developed in the bone marrow transplantation setting in attempts to predict survival in patients with chronic graft-versus-host disease (cGVHD). In this study, we evaluated the prognostic value of the National Institutes of Health (NIH) scoring system and investigated for any additional prognostic factors in a series of 171 patients undergoing peripheral blood stem cell transplantation (PBSCT) from matched related donors. The cumulative incidence of cGVHD was 70%; cumulative incidences of mild, moderate, and severe cGVHD were 29%, 42% and 28%, respectively. Overall, 68% of patients were free from immunosuppression 5 years after transplantation. Absence of previous acute GVHD (aGVHD; hazard ratio [HR] = 2; P = .004) and mild cGVHD (HR = 4.2; P = .007) increased the probability of being off immunosuppressive treatment by the last follow-up. Overall survival (OS) at 5 years was 52%. Severe cGVHD, according to the NIH scoring system (HR = 13.27; P = .001) adversely influenced outcome, whereas de novo onset (HR = 0.094; P = .003) had a more favorable impact on survival. The combination of both variables allowed us to identify 4 different subgroups of patients with OS of 82%, 70%, 50%, and 25%. Our findings indicate that the NIH scoring system has some prognostic value in patients undergoing PBSCT and, together with the type of onset, must be considered to predict the possible outcome of patients who develop cGVHD.

Piscaglia, A. C., C. Di Campli, et al. (2005). "Human cordonal stem cell intraperitoneal injection can represent a rescue therapy after an acute hepatic damage in immunocompetent rats." Transplant Proc **37**(6): 2711-4.

BACKGROUND AND AIM: Tissue homeostasis and turnover require reserve stem proliferating cells. Several studies performed on immunodeficient animals have suggested a degree of plasticity by the hematopoietic stem cell compartment that may represent source for liver regeneration. We sought to explore the hepatic differentiation potential of hematopoietic stem cells from human cord blood, after toxic liver damage induced by allyl-alcohol in immunocompetent rats. MATERIALS AND METHODS: Wistar rats were divided into groups (A) allyl-alcohol intraperitoneal injection with hematopoietic stem cell intraperitoneal infusion at 1 day and sacrifice 3 days later; (B) stem cell injection and sacrifice 3 days later; (C) allyl-alcohol infusion and sacrifice 4 days later; and (D) sacrifice without any treatment. Livers, spleens, and bone marrows were analysed for human stem cells using flow-cytometry; livers were also tested by histology and immunohistochemistry to study the pattern of hepatic regeneration after damage and human stem cell conversion into hepatocyte-like cells, respectively. RESULTS: Flow-cytometry revealed selective recruitment of human hematopoietic stem cells by damaged livers (group A) compared with control group B. In addition, liver damage was reduced in animals treated with stem cells. Immunohistochemistry demonstrated that human stem cells could convert hepatic cells. CONCLUSIONS: Our study demonstrated that hematopoietic stem cells selectively recruited by injured livers can contribute to hepatic regeneration after acute toxic damage in immunocompetent recipients.

Piscaglia, A. C., M. A. Zocco, et al. (2005). "How does human stem cell therapy influence gene expression after liver injury? Microarray evaluation on a rat model." Dig Liver Dis **37**(12): 952-63.

BACKGROUND: Tissue homeostasis is guaranteed by stem proliferating reserve, depending on dynamic changes in gene expression. A high plasticity is shown by the haematopoietic stem cells, potential source for liver regeneration. AIM: We aimed to evaluate the gene expression modifications induced by human haematopoietic stem cell therapy after liver injury in rats. SUBJECTS: Rats were sorted as follows: (A) human-haematopoietic stem cell injection after allyl alcohol liver damage; (B) only haematopoietic stem cell injection; (C) only allyl alcohol injection; and (D) sacrifice without any treatment. METHODS: Livers, spleens and bone marrows were analysed with flow-cytometry. Livers were also studied by reverse-transcription PCR, histology, immunohistochemistry and microarray analysis; selected genes were confirmed by real-time PCR. RESULTS: In subset A, haematopoietic stem cells were selectively recruited by liver, with respect to the group B, and they improved the liver regeneration process compared to group C. As regards microarrays, haematopoietic stem cell infusion upregulates 265 genes and downregulates 149 genes. Differentially regulated genes belong to a broad range of functional pathways, including proliferation,

differentiation, adhesion/migration and transcripts related to oval-cell activation. Real-time PCR validated array results. CONCLUSIONS: Our study confirmed the capacity of haematopoietic stem cells to contribute to liver regeneration. Moreover, microarray analysis led to the identification of genes whose regulation strongly correlates with a more efficient process of liver repair after haematopoietic stem cell injection.

Pradhan, K. R., C. S. Johnson, et al. (2006). "A novel intensive induction therapy for high-risk neuroblastoma utilizing sequential peripheral blood stem cell collection and infusion as hematopoietic support." Pediatr Blood Cancer **46**(7): 793-802.

OBJECTIVE: To determine the feasibility, toxicities, and the response rate (RR) of a dose intensive, submyeloablative, induction chemotherapy protocol termed EPiC (etoposide, carboplatin, and intensive cyclophosphamide) utilizing sequential peripheral blood stem cell (PBSC) collection and infusion as hematopoietic support in children with newly diagnosed Stage 4 neuroblastoma. PATIENTS AND METHODS: Twenty-five children (age >1 year) with Stage 4 neuroblastoma were enrolled. First and third cycles consisted of cyclophosphamide (4 gm/m2) and carboplatin (400 mg/m2). Second and fourth cycles consisted of carboplatin (1 gm/m2), and etoposide (450 mg/m2). PBSC were collected following Cycles 1, 2, and 3 and reinfused in each subsequent cycle. Following EPiC and surgical resection of the primary tumor, patients proceeded to various consolidation therapies. RR was scored using the International Neuroblastoma Response Criteria. RESULTS: Using PBSC infusion following EPiC chemotherapy resulted in a dose intensity averaging 85% of intended dose intensity; and in early neutrophil but not platelet recovery. PBSC were adequately collected in all, but one patient. The protocol had minimal non-hematological toxicities. There was one toxic death. The overall RR was 78%, which included PR (partial response) and VGPR (very good partial response). The 5-year event-free survival and overall survival were 44% and 54%, respectively at a median follow-up of 58.6 months. CONCLUSION: EPiC is a feasible, well-tolerated, sub-myeloablative, induction chemotherapy protocol for children with high-risk neuroblastoma. RR is equivalent to prior published studies, however, with minimal toxicities. Sequential PBSC collection and infusion is feasible even in very young children.

Price, M. J., C. C. Chou, et al. (2006). "Intravenous mesenchymal stem cell therapy early after reperfused acute myocardial infarction improves left ventricular function and alters electrophysiologic properties." Int J Cardiol **111**(2): 231-9.

Direct intramyocardial injection of mesenchymal stem cells (MSCs) improves left ventricular ejection fraction (LVEF) and may increase ventricular arrhythmia in hearts with myocardial infarction (MI). We hypothesized that intravenous MSCs given early after acute MI would engraft in injured myocardium, improve LV function, and result in pro-arrhythmic electrical remodeling. We created an apical infarction in swine by balloon occlusion/reperfusion, administered diI-labeled allogeneic bone marrow derived MSCs intravenously 30 min post-reperfusion and measured LVEF and wall thickness at baseline, 1 month, and 3 months. Epicardial effective refractory periods (ERPs) were determined before sacrifice. At 3 months, treated pigs [n=7] had significantly higher LVEF than controls [n=8] (49+/-2% vs. 44+/-3%, P=0.015) and significantly less wall thickening of non-infarcted myocardium. ERPs were significantly shorter than controls at all pacing cycle lengths (P<or=0.002), suggesting a pro-arrhythmic potential. DiI was found in the lungs, in infarct, and peri-infarct myocardium. Conclusion: IV infusion of MSCs soon after acute MI in swine improves LVEF and limits wall thickening in the remote non-infarcted myocardium, consistent with a beneficial effect on post-MI ventricular remodeling. Since there is no need for immune suppression or clinical expertise, IV infusion of MSCs may expand the potential clinical application of stem cell therapy.

Rottenburger, C., K. Kiel, et al. (1999). "Clonotypic CD20+ and CD19+ B cells in peripheral blood of patients with multiple myeloma post high-dose therapy and peripheral blood stem cell transplantation." Br J Haematol **106**(2): 545-52.

The number of circulating clonotypic B cells in patients with multiple myeloma (MM) after high-dose therapy (HDT) with peripheral blood stem cell transplantation (PBSCT) was investigated. Peripheral CD19+ B cells have been reported to persist throughout conventional and HDT and might resemble a source of relapse in patients with MM. We assessed the proportion of malignant cells in CD20+ and CD19+ cell fractions of 14 peripheral blood (PB) samples from 12 patients after HDT and PBSCT. Nine samples were obtained from patients in continuous remission, and five patients were in progressive disease or beginning relapse. The CD20+ fractions obtained had a mean purity of 96.8%. The percentages of tumour cells were determined using a quantitative allele-specific oligonucleotide PCR assay based on the method of limiting dilutions. In the group of patients in continuous remission the median number of tumour cells in the CD20+ cell fractions was 1.9/ml (range 0-

7.2 tumour cells/ml PB) higher than in the CD20- fractions (median 0; range 0-29 tumour cells/ml PB). Higher tumour cell numbers in both fractions, particularly pronounced in the negative ones, were found in patients with progressive disease or beginning relapse (CD20+: range 3.8-585; median 32 tumour cells/ml PB; CD20-: range 25-25527; median 334 tumour cells/ml PB). Enrichment with the anti-CD19 antibody as a second pan B-cell marker revealed comparable tumour cell numbers. In conclusion, an anti-CD20 antibody treatment could be a promising approach for the eradication of malignant cells in the PB of patients in continuous remission after HDT and PBSCT with low amounts of tumour cells in the B-cell compartment and an almost complete absence of tumour cells in the CD20- fractions.

Rouskova, L., I. Hruska, et al. (2008). "Issues and ethical problems of stem cell therapy--where is Hippocrates?" Acta Medica (Hradec Kralove) **51**(2): 121-6.

Stem cells and their therapeutic use present many questions associated with ethical problems in medicine. There is great effort on the part of physicians to help millions of patients while there are ethical problems with the use of new methods and technologies and all of these are affected by economic and political influences. How will the current generation deal with these problems? Medicine, in this begard, is experiencing a stormy evolution of human culture in the relationships between disease, patient and doctor. Philosophy approaches the same juncture of human culture, but seemingly from the other side. Both disciplines are facing a great problem: How to unite the content of current human morality and the desire for health? Both philosophers and physicians perceive this deficit in human culture as it does not provide immediately usable normatives, which the living generation of healthy and ill is waiting for. It may be said that medicine, as many times before, has reached a stage where it cannot rely only on the proved axiologic values from the past, ethical normatives or cultivated moral sense of its subjects. Medicine has no other alternative than to take an active part in resolution of interdisciplinary problems originating from philosophic-biologic or philosophic-medical inquiries of axiologic, ethical, and moral issues. Our paper indicates some ways of the search in forming ethical principles of the stem-cell therapy from the view of biologists and physicians. New ways are recommended in theoretical-methodological interdisciplinary research, especially, in theoretical and experimental biology, and theoretical and clinical medicine, as well as philosophy. In this paper important ethical problems are pointed out in order to find answers to some key problems connected with cell therapy and the use of stem cells.

Sakai, D., J. Mochida, et al. (2005). "Differentiation of mesenchymal stem cells transplanted to a rabbit degenerative disc model: potential and limitations for stem cell therapy in disc regeneration." Spine (Phila Pa 1976) **30**(21): 2379-87.

STUDY DESIGN: An in vivo study to assess the differentiation status of mesenchymal stem cells (MSCs) transplanted to the nucleus pulposus of degenerative discs in a rabbit model. OBJECTIVES: To evaluate the fate of MSCs transplanted to the nucleus pulposus of degenerative discs in a rabbit and to determine whether they are a suitable alternative for cell transplantation therapy for disc degeneration. SUMMARY OF BACKGROUND DATA: Although MSCs have been proposed as candidate donor cells for transplantation to treat intervertebral disc degeneration, their differentiation after transplantation has not been adequately investigated. METHODS: Autologous MSCs, labeled with green fluorescent protein, were transplanted into mature rabbits. Consecutive counts of transplanted MSCs in the nucleus area were performed for 48 weeks after transplantation. Differentiation of transplanted cells was determined by immunohistochemical analysis. The proteoglycan content of discs was measured quantitatively using a dimethylmethylene blue assay, and mRNA expression of Type I and II collagen, aggrecan and versican was measured semi-quantitatively using reverse transcription polymerase chain reaction. RESULTS: Many cells that were positive for green fluorescent protein were observed in the nucleus pulposus of cell-transplanted rabbit discs 2 weeks after transplantation. Their number increased significantly by 48 weeks. Some GFP-positive cells were positive for cell-associated matrix molecules, such as Type II collagen, keratan sulfate, chondroitin sulfate, aggrecan, and the nucleus pulposus phenotypic markers, hypoxia inducible factor 1 alpha, glutamine transporter 1, and matrix metalloproteinase 2. MSCs did not show significant expression of these molecules before transplantation. Biochemical and gene expression analyses showed significant restoration of total proteoglycan content and matrix-related genes compared with nontransplanted discs. CONCLUSIONS: MSCs transplanted to degenerative discs in rabbits proliferated and differentiated into cells expressing some of the major phenotypic characteristics of nucleus pulposus cells, suggesting that these MSCs may have undergone site-dependent differentiation. Further studies are needed to evaluate their functional role.

Sanchorawala, V., D. G. Wright, et al. (2004). "High-dose intravenous melphalan and autologous stem cell transplantation as initial therapy or following two cycles of oral chemotherapy for the treatment of AL amyloidosis: results of a prospective randomized trial." Bone Marrow Transplant **33**(4): 381-8.

Summary:A prospective randomized trial was conducted to study the timing of high-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) in AL amyloidosis. In all, 100 newly diagnosed patients were randomized to receive HDM/SCT, either as initial therapy (Arm-1) or following two cycles of oral melphalan and prednisone (Arm-2). The objectives of the trial were to compare survival and hematologic and clinical responses. With a median follow-up of 45 months (range 24-70), the overall survival was not significantly different between the two treatment arms (P=0.39). The hematologic response and organ system improvements after treatment did not differ between the two groups. Fewer patients received HDM/SCT in Arm-2 because of disease progression during the oral chemotherapy phase of the study, rendering them ineligible for subsequent high-dose therapy. This affected patients with cardiac involvement particularly, and led to a trend for an early survival disadvantage in Arm-2. Hence, newly diagnosed patients with AL amyloidosis eligible for HDM/SCT did not benefit from initial treatment with oral melphalan and prednisone, and there was a survival disadvantage for patients with cardiac involvement if HDM/SCT was delayed by initial oral chemotherapy.

Shields, L. E., L. Gaur, et al. (2004). "Fetal immune suppression as adjunctive therapy for in utero hematopoietic stem cell transplantation in nonhuman primates." Stem Cells **22**(5): 759-69.

In utero hematopoietic stem cell transplantation could potentially be used to treat many genetic diseases but rarely has been successful except in severe immunodeficiency syndromes. We explored two ways to potentially increase chimerism in a nonhuman primate model: (a) fetal immune suppression at the time of transplantation and (b) postnatal donor stem cell infusion. Fetal Macaca nemestrina treated with a combination of the corticosteroid betamethasone (0.9 mg/kg) and rabbit thymoglobulin (ATG; 50 mg/kg) were given haploidentical, marrow-derived, CD34+ -enriched donor cells. Animals treated postnatally received either donor-derived T cell-depleted or CD34+ -enriched marrow cells. Chimerism was determined by traditional and real-time polymerase chain reaction from marrow, marrow progenitors, peripheral blood, and mature peripheral blood progeny. After birth, the level of chimerism in the progenitor population was higher in the immune-suppressed animals relative to controls (11.3% +/- 2.7% and 5.1% +/- 1.5%, respectively; p = .057). Chimerism remained significantly elevated in both marrow (p = .02) and fluorescence-activated cell sorted and purified CD34+ cells (p = .01) relative to control animals at > or = 14 months of age. Peripheral blood chimerism, both at birth and long term, was similar in immune-suppressed and control animals. In the animals receiving postnatal donor cell infusions, there was an initial increase in progenitor chimerism; however, at 6-month follow-up, the level of chimerism was unchanged from the preinfusion values. Although fetal immune suppression was associated with an increase in the level of progenitor and marrow chimerism, the total contribution to marrow and the levels of mature donor progeny in the peripheral blood remained low. The level of long-term chimerism also was not improved with postnatal donor cell infusion.

Skapova, D., Z. Racil, et al. (2005). "Significance of qualitative PCR detection method for preemptive therapy of cytomegalovirus infection in patients after allogeneic hematopoietic stem cell transplantation -- single-centre experience." Neoplasma **52**(2): 137-42.

Both early cytomegalovirus (CMV) monitoring and prophylactic antiviral therapy can decrease clinical complications or can prevent them in patients after allogeneic hematopoietic stem cell transplantation (HSCT). Presented paper summarizes experiences with using regular monitoring of reactivation of CMV after allogeneic HSCT by qualitative polymerase chain reaction (PCR) method to prevent the development of symptomatic CMV disease. Samples of peripheral blood leukocytes (PBL) in 71 patients were monitored. Because of retransplantation in two patients, 73 transplantations, each followed by the monitoring, were performed. Patients were monitored weekly after the transplantation for CMV DNA-emia in PBL. An episode of CMV infection representing an indication for preemptive ganciclovir (GCV) or foscarnet (FOS) therapy was defined as two consecutive positive PCR results in 4-7 days. Median time of monitoring was 313 days. The CMV infection was found in 28/73 monitorings (38.4%) and always was followed by preemptive therapy. One recurrence of CMV infection was observed in 4/28 (14.3%) monitorings and two recurrences in 1/28 (3.6%) monitorings. Presented approach resulted in complete prevention of overt CMV disease and this study enable to show that qualitative PCR method for determination of incipient CMV infection followed by preemptive therapy is suitable for preventing patients after allogeneic transplantation from CMV disease.

Smaldone, M. C. and M. B. Chancellor (2008). "Muscle derived stem cell therapy for stress urinary incontinence." World J Urol **26**(4): 327-32.

AIM: The aim of this article is to discuss the potential of muscle-derived stem cells (MDSCs) for rhabdosphincter regeneration and to review the early clinical experiences with its application in patients with stress urinary incontinence. RESULTS: In anatomical and functional studies of the human and animal urethra, the middle urethral contained rhabdosphincter is critical for maintaining continence. Transplanted stem cells have the ability to undergo self-renewal and multipotent differentiation, leading to sphincter regeneration. In addition, such cells may release, or be engineered to release, neurotrophins with subsequent paracrine recruitment of endogenous host cells to concomitantly promote a regenerative response of nerve-integrated muscle. CONCLUSION: Cell-based therapies are most often associated with the use of autologous multipotent stem cells, such as bone marrow stromal cells. However, harvesting bone marrow stromal stem cells requires a general anesthetic, can be painful, and has variable yield of stem cells upon processing. In contrast, with appropriate experience, alternative autologous adult stem cells such as muscle-derived stem cells and adipose-derived stem cells can be obtained in large quantities and with minimal discomfort.

Smaldone, M. C., M. L. Chen, et al. (2009). "Stem cell therapy for urethral sphincter regeneration." Minerva Urol Nefrol **61**(1): 27-40.

In anatomical and functional studies of the human and animal urethra, the middle urethral contained rhabdosphincter is critical for maintaining continence. Transplanted stem cells may have the ability to undergo self renewal and multipotent differentiation, leading to sphincter regeneration. In addition, such cells may release, or be engineered to release, neurotrophins with subsequent paracrine recruitment of endogenous host cells to concomitantly promote a regenerative response of nerve-integrated muscle. Cell-based therapies are most often associated with the use of autologous multipotent stem cells, such as the bone marrow stromal cells. However, harvesting bone marrow stromal stem cells is difficult, painful, and may yield low numbers of stem cells upon processing. In contrast, alternative autologous adult stem cells such as muscle derived stem cells (MDSCs) and adipose-derived stem cells (ADSCs) can be easily obtained in large quantities and with minimal discomfort. This chapter aims to discuss the neurophysiology of stress urinary incontinence (highlighting the importance of the middle urethra); current injectable cell sources for endoscopic treatment; and the potential of MDSCs for the delivery of neurotrophic factors.

Sobajima, S., G. Vadala, et al. (2008). "Feasibility of a stem cell therapy for intervertebral disc degeneration." Spine J **8**(6): 888-96.

BACKGROUND CONTEXT: Different strategies to supplement/replenish the disc cell population have been proposed. Recently, adult stem cells have shown promise as a cell source for a variety of tissue engineering and cell therapy applications. A stem cell can renew itself through cell division and can be induced to develop into many different specialized cell types. Moreover, stem cells have shown ability to migrate and engraft within various tissues, as well as to exert stimulatory effects on other cell types through various mechanisms (eg, paracrine effects, cell-cell interactions). These characteristics make stem cells worthy of investigation as a source of cells for intervertebral disc (IVD) tissue engineering and cell therapy. PURPOSE: To determine feasibility of a stem cell therapy of IVD degeneration. STUDY DESIGN: In vitro studies of adult human cells to examine interactions between nucleus pulposus cells (NPCs) and mesenchymal stem cells (MSCs) at different ratios in 3-D pellet culture. In vivo studies of healthy adult rabbit discs injected with allogenic adult rabbit MSCs to examine stem cell survival and engraftment in living disc tissue. METHODS: In vitro study: Human NPCs were cocultured with human MSCs in different ratios (75:25, 50:50, 25:75) for 2 weeks in pellet culture, for comparison with pure NPC (100:0) and pure MSC (0:100) pellet cultures. Proteoglycan synthesis rate and glycosaminoglycan (GAG) content were measured by radioactive sulfate incorporation and dimethylmethylene blue assay, respectively. In vivo study: MSCs were isolated from the bone marrow of a New Zealand White (NZW) rabbit, retrovirally transduced with the lacZ marker gene, and injected into the nucleus pulposi of the L2-3, L3-4, and L4-5 lumbar discs of 12 other NZW rabbits. Three rabbits each were sacrificed at 3, 6, 12, or 24 weeks after cell implantation, and X-Gal staining was done to assess survival and localization of MSCs in the disc tissues. RESULTS: In vitro study: the 75:25 and 50:50 NPC:MSC cocultures yielded the greatest increases in extracellular matrix (ECM) production. In vivo study: MSCs were detected in histological sections of rabbit discs up to 24 weeks after allogenic stem cell implantation, without evidence of systemic illness in the recipient rabbits. The 24-week results in particular suggested the possibility of stem cell migration and engraftment into the inner annulus fibrosus. CONCLUSIONS: These encouraging results support feasibility of a stem cell therapy approach toward

supplementation/replenishment of IVD cells and synthesis/maintenance of a more functional ECM in a degenerated disc. Moreover, the in vivo results demonstrate that transplanted MSCs survive and successfully engraft into the IVD tissue, and are effective vehicles for exogenous gene delivery to the IVD--thus there appear to be multiple mechanisms whereby stem cells might able to confer therapeutic effects in a stem cell therapy of IVD degeneration.

Steingrimsdottir, H., A. Gruber, et al. (2000). "Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications." Haematologica **85**(8): 832-8.

BACKGROUND AND OBJECTIVES: Autologous peripheral stem cell transplantation (APSCT) is increasingly used for various hematologic malignancies and solid tumors. The objective of this study was to analyze the immune reconstitution after APSCT and see if there was any correlation with diagnosis, age, type of high-dose therapy, CD34(+) selection of the autograft and double vs single APSCT. DESIGN AND METHODS: Lymphocyte subset recovery was studied in 46 consecutive patients with hematologic malignancies and breast cancer, who underwent APSCT. Eleven patients with multiple myeloma received tandem autografts. Thirty-one patients were given total body irradiation (TBI) as part of the high-dose treatment. Eighteen patients received a CD34(+) selected graft. The percentage and absolute numbers of lymphocyte populations, T-cells (CD2(+), CD3(+)), B-cells (CD19(+)), NK cells (CD56(+)CD3(-) and CD16(+)CD3(-)) and T-cell subpopulations (CD4(+), CD8(+), CD4(+)CD45RA(+), CD4(+)CD45RO(+), CD4(+)DR(+), CD8(+)CD45RO(+), CD8(+)DR(+)), were monitored with flow cytometry during the first year after APSCT. RESULTS: The total B-cell (CD19(+)) and T-cell (CD3(+)) counts were reconstituted to normal levels 2-4 months after APSCT. All patients had a low CD4/CD8 ratio during the observation period, related to both a low number of CD4(+) cells and elevated numbers of CD8(+) cells. The low number of CD4(+) cells was due to a persistently low level of naive CD4(+)CD45RA(+) cells. A high proportion of the CD8+ cells displayed a phenotype compatible with activated T-cells (CD8(+)DR(+)) up to 10 months after autografting. The number of NK cells (CD56(+)3(-) or CD16(+)3(-)) reached normal values within one month post-transplant. No single variable, such as diagnoses, age, TBI as part of the high-dose treatment, tandem autografting or CD34(+) selection of the graft, influenced the immune or hematopoietic reconstitution and no correlation with documented infectious complications was found. INTERPRETATION AND CONCLUSIONS: Despite heterogeneity of diseases, age, initial treatment and high-dose regimens, lymphocyte subset analysis did not reveal any differences in hematopoietic or immune reconstitution. All patients had a low CD4(+)/CD8(+) ratio during at least the first year post-transplant, caused by a persistent increase of CD8(+) lymphocytes and a constant reduction of CD4(+) lymphocytes, making the patients susceptible to infections for a prolonged period of time post-transplant.

Stewart, D. A., D. Guo, et al. (2000). "Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation." Bone Marrow Transplant **26**(4): 383-8.

We previously reported a 50% (95% CI = 33-76%) 5 year event-free survival (EFS) rate for 23 patients with Hodgkin's disease (HD) who received salvage therapy with single agent high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT). Predictors of poor outcome included bulky disease and initial remission <1 year. Since 1995, similar poor prognosis patients have been treated with double high-dose therapy consisting of dose-intensive cyclophosphamide 5.25 g/m2, etoposide 1.05 g/m2, cisplatin 105 mg/m2 (DICEP) for tumor cytoreduction and stem cell mobilization followed by HDM/ASCT. The purpose of the present study is to determine if the use of DICEP is associated with improved event-free (EFS) and overall survival (OAS) for patients treated with HDM/ASCT. From February 1981 to June 1999, 46 consecutive patients received HDM/ASCT for relapsed (n = 35) or refractory (n = 11) HD. DICEP re-induction and blood stem cell mobilization was used for 21 patients. Factors considered for univariate and multivariate analyses included age at transplant, number of failed chemotherapy regimens, prior radiotherapy, length of initial remission, relapsed or refractory disease status, extranodal relapse, B symptoms at relapse, bulk, post-ASCT radiotherapy, and DICEP re-induction therapy. Cox proportional hazards models were constructed for both event and death. DICEP and HDM were well tolerated with no early treatment-related mortality or toxicity requiring life-sustaining measures. For all 46 patients, the projected 5 year EFS was 52% (95% CI = 38-72%) and OAS was 57% (95% CI = 40-82). Factors independently associated with relapse in multivariate analysis included bulk >5 cm (RR = 6.38, P = 0.002), prior radiotherapy (RR = 3.59, P = 0.027), and not using DICEP (RR = 5.29, P = 0.005). Factors

independently associated with death included bulk >5 cm (RR = 5.13, P = 0.009), > or =3 prior chemotherapy regimens (RR = 4.72, P = 0.019), and not using DICEP (RR = 7.49, P = 0.015). This study demonstrates that DICEP re-induction prior to HDM/ASCT is feasible. The preliminary data are sufficiently encouraging to warrant a multicenter phase II or a phase III trial evaluating DICEP followed by HDM/ASCT as salvage therapy for HD.

Stewart, D. A., J. M. Vose, et al. (1995). "The role of high-dose therapy and autologous hematopoietic stem cell transplantation for mantle cell lymphoma." Ann Oncol **6**(3): 263-6.

BACKGROUND: Although mantle cell lymphoma (MCL) is a distinct disease entity with well described clinical and pathological features, little information exists regarding its therapy. This paper will evaluate patients with MCL receiving either induction therapy with an anthracycline or high-dose chemotherapy and autologous hematopoietic stem cell transplantation for relapsed disease. PATIENTS AND METHODS: The cases of 14 previously untreated patients with MCL who received an anthracycline-containing combination chemotherapy regimen on Nebraska Lymphoma Study Group protocols from 3/83 to 2/92 were reviewed. During the same time period, a different set of nine patients with recurrent MCL were referred for high-dose chemoradiotherapy and autologous stem cell rescue as salvage therapy. RESULTS: The five year overall (OS) and failure-free (FFS) survivals from the initiation of chemotherapy for the patients receiving an induction therapy with an anthracycline containing regimen were 23% and 8%, respectively. At the time of this analysis, three of the nine transplant patients remain progression-free 7, 12, and 25 months post-transplant. Two year overall and FFS for all nine patients was 34%. CONCLUSIONS: Longer follow-up of greater patient numbers is required to determine whether high-dose therapy can overcome the chemoresistance and increase the cure rate of MCL. Since most patients with this disease have minimal chance of cure with standard chemotherapy, the optimal timing for high dose therapy may be as part of front-line treatment. Further clinical trials are required to investigate the potential benefits of high-dose therapy for patients with MCL.

Strunk, D., E. Rohde, et al. (2005). "Phenotypic characterization and preclinical production of human lineage-negative cells for regenerative stem cell therapy." Transfusion **45**(3): 315-26.

BACKGROUND: Regenerative stem cell therapy (SCT) is currently being tested in clinical trials. The ideal type and source of cells have not yet been defined. Lineage (Lin) depletion is an experimental procedure capable of enriching all recently recognized SC types with regenerative potency. This study was performed to define a practicable monoclonal antibody (MoAb) cocktail for Lin depletion and to test whether clinical-scale Lin depletion is possible. STUDY DESIGN AND METHODS: MoAbs (CD2/14/15/19/41/56/glycophorin A) were selected to mark seven mature hematopoietic lineages. Lin7-negative (Lin7NEG) cells were analyzed in peripheral blood (PB, n = 9), mobilized PB (MPB, n = 5), umbilical cord blood (UCB, n = 5), and marrow aspirates (BM, n = 4) by flow cytometry. Preclinical Lin depletion was tested with leukapheresis products from PB following good manufacturing practice (GMP) principles. RESULTS: Lin7NEG cells comprised 0.23 +/- 0.04, 0.27 +/- 0.03, 0.53 +/- 0.07, and 0.49 +/- 0.03 percent of PB, MPB, UCB, and BM, respectively. Basophils, CD34+, and dendritic cells constituted the major Lin7NEG subpopulations (84 +/- 2, 90 +/- 3, 40 +/- 3, and 80 +/- 3% in PB, MPB, UCB, and BM, respectively). Minor populations included CD7- and CD45- cells. Preclinical CD2/14/15/19/56 (Lin5) depletion after automated red blood cell and platelet reduction resulted in up to a 16.7-fold enrichment of CD34+ and CD34-/Lin5NEG cells. CONCLUSIONS: A seven-MoAb cocktail is sufficient to label more than 99 percent of nucleated cells in PB, MPB, UCB, and BM. Preclinical Lin depletion can be performed under GMP conditions from PB apheresis procedures.

Sueblinvong, V., B. T. Suratt, et al. (2007). "Novel therapies for the treatment of cystic fibrosis: new developments in gene and stem cell therapy." Clin Chest Med **28**(2): 361-79.

Cystic fibrosis (CF) was one of the first target diseases for lung gene therapy. Studies of lung gene transfer for CF have provided many insights into the necessary components of successful gene therapy for lung diseases. Many advancements have been achieved with promising results in vitro and in small animal models. However, studies in primate models and patients have been discouraging despite a large number of clinical trials. This reflects a number of obstacles to successful, sustained, and repeatable gene transfer in the lung. Cell-based therapy with embryonic stem cells and adult stem cells (bone marrow or cord blood), have been investigated recently and may provide a viable therapeutic approach in the future. In this article, the authors review CF pathophysiology with a focus on specific targets in the lung epithelium for gene transfer and summarize the current status and future directions of gene- and cell-based therapies.

Takenaka, K., T. Eto, et al. (2009). "Oral valganciclovir as preemptive therapy is effective for cytomegalovirus infection in allogeneic hematopoietic stem cell transplant recipients." Int J Hematol **89**(2): 231-7.

Between March 2007 and January 2008, the safety and efficacy of oral valganciclovir (VGC) preemptive therapy for cytomegalovirus (CMV) infection was evaluated in ten consecutive patients who received allogeneic hematopoietic stem cell transplantation (HSCT). Patients were screened once or twice per week after engraftment using CMV pp65 antigenemia assay. When more than 2 CMV antigen-positive cells per 50,000 leukocytes were detected, preemptive therapy with oral VGC was initiated at a dose of 900 mg twice daily for 3 weeks. Nine patients (90%) completed the 3-week VGC treatment except for one patient who developed febrile neutropenia. There was no other significant toxicity. CMV antigen-positive cells were rapidly decreased in all nine patients and became undetectable by the end of the VGC treatment. None of the patients developed CMV disease. CMV infection relapsed in four of the ten patients (40%) after the VGC treatment. These observations suggest that preemptive therapy with VGC is effective for preventing CMV disease in allogeneic HSCT patients. Further studies with a large number of patients will be necessary to determine the optimal initial- and maintenance-dose of VGC.

Tan, B. H., N. L. Chlebicka, et al. (2008). "Use of the cytomegalovirus pp65 antigenemia assay for preemptive therapy in allogeneic hematopoietic stem cell transplantation: a real-world review." Transpl Infect Dis **10**(5): 325-32.

Despite advances in surveillance strategies and antivirals, cytomegalovirus (CMV) infection continues to pose problems to patients receiving hematopoietic stem cell transplants (HSCTs). The bone marrow transplant (BMT) unit at the Singapore General Hospital embraced the preemptive strategy in late 2003. Although several studies have demonstrated its usefulness, we conducted this review to document CMV-related events at our institution. Forty-six patients underwent CMV surveillance using the CMV pp65 antigenemia (CMV Ag) assay from January 2004 to December 2005. Twenty-seven patients had CMV infection, and 19 remained antigenemia-negative. No differences were found between the 2 groups for the following potential risk factors for CMV infection: age, total number of co-morbidities, duration of neutropenia after conditioning, baseline creatinine, type of conditioning regimen (conventional vs. reduced intensity), type of transplant (matched sibling vs. others), recipient CMV status, donor CMV status, and use of total body irradiation. Two patients received alemtuzumab; both developed CMV Ag. Twelve episodes of CMV infection occurred after the 100th post-HSCT day. Two patients developed CMV disease. One of them could be considered a failure of the preemptive strategy, as she had CMV gastritis diagnosed on the same day that she became pp65-positive. The other developed CMV disease despite prompt institution of ganciclovir, although she had multiple post-HSCT complications requiring enhanced immunosuppression, as well as relapsed disease. One-year disease-free survival was 55.5% in those with CMV infection and 52.3% in those without infection. Survival was not affected by CMV infection.

Tse, H. F., K. H. Yiu, et al. (2007). "Bone marrow stem cell therapy for myocardial angiogenesis." Curr Vasc Pharmacol **5**(2): 103-12.

Despite the recent advances in medical therapy and coronary revascularization procedures, coronary artery disease (CAD) remains the major cause of morbidity and mortality in the developing countries. In patients with severe CAD, persistent myocardial ischemia in hibernated myocardium resulted in progressive loss of cardiomyocytes with development of heart failure. As a result, therapeutic approaches to enhance neovascularization are being underwent intensive investigation. Recent experimental studies have demonstrated adult bone marrow (BM) can induce neovascularization in ischemic myocardium can improve heart function. These findings have prompted the development of different cellular transplantation approaches for heart diseases refractory to conventional therapy after myocardial infarction. Although the initial pilot clinical trials have shown potential clinical benefit of BM therapy for therapeutic angiogenesis, the long-term safety, the optimal timing and treatment strategy remains unclear. Furthermore, in order to acquire more optimized quality and quantity of BM derived stem cell for myocardial regeneration, several issues remain to be addressed, such as the development of a more efficient method of stem cells identification, purification and expansion. Emerging, rationally designed, randomized clinical trials are required to assess the clinical implication of BM derived stem cells therapy in treatment of CAD.

Ueda, Y., Y. Sonoda, et al. (2004). "Mobilization of peripheral blood stem cells (PBSCs) after etoposide, adriamycin and cisplatin therapy, and a multimodal cell therapy approach with PBSCs in advanced gastric cancer." Oncol Rep **12**(2): 323-32.

The EAP combination of etoposide (ETP), doxorubicin (ADM) and cisplatin (CDDP) has been reported to be highly active for advanced gastric cancer. However, it is associated with severe

myelotoxicity, and its use has declined. We examined whether peripheral blood stem cells (PBSCs) could be mobilized during hematopoietic recovery after EAP, and assessed the possibility of using multimodal cell therapy with PBSCs for the treatment of advanced gastric cancer. Five men with advanced gastric adenocarcinoma were enrolled. All patients were chemotherapy-naive. EAP (ETP, 360 mg/m2; ADM, 40 mg/m2; CDDP, 80 mg/m2) was given to each patient, and myelotoxicity was carefully monitored. Granulocyte colony-stimulating factor was administered after the neutrophil nadir, and PBSCs were collected by leukapheresis during hematopoietic recovery. The median nadir of the neutrophil count after EAP was 225/ml, occurring between day 17 and 20. Sufficient numbers of PBSCs [CD34(+) cells, CFU-GM] could be mobilized in 4/5 patients. A 45-year-old patient with extended lymph node metastasis received high-dose EAP with peripheral blood stem cell transplantation (PBSCT), followed by cancer vaccine therapy with dendritic cells (DCs), induced from cryopreserved PBSCs. Both high-dose EAP with PBSCT and DC-based immunotherapy was safely performed for the first time against gastric cancer. Although associated with severe myelotoxicity, EAP can mobilize sufficient numbers of PBSCs during hematopoietic recovery. Multimodal cell therapy combining high-dose chemotherapy with PBSCT and DC-based immunotherapy is feasible and can be a reasonable approach in advanced gastric cancer.

Usui, N., N. Dobashi, et al. (2002). "Intensified daunorubicin in induction therapy and autologous peripheral blood stem cell transplantation in postremission therapy (Double-7 protocol) for adult acute myeloid leukemia." Int J Hematol **76**(5): 436-45.

To investigate whether an intensified dose of daunorubicin (DNR) in induction therapy and autologous peripheral blood stem cell transplantation (PBSCT) in the postremission period are effective treatments, we used a Double-7 protocol to treat adult patients with de novo acute myeloid leukemia (excluding M0 and M3). Induction therapy consisted of 40 mg/m2 of DNR intravenous drip infusion for 7 days and 200 mg/m2 of ara-C by continuous infusion for 7 days (7 + 7 DC regimen). Patients who achieved complete remission (CR) were given high-dose chemotherapy with autologous PBSCT in postremission therapy. Of the 22 assessable patients, 16 attained CR (73%). Disease-free survival (DFS) and overall survival (OS) at 3 years were 61.2% and 48.1%, respectively. Nine of the CR patients underwent PBSCT without therapy-related mortality. Patients in a favorable cytogenetic group (n = 7) attained 100% CR and long-term survival (71.4% DFS and 85.7% OS at 3 years). Thus, intensified DNR administration of 280 mg/m2 (40 mg/m2 per day for 7 days) in induction therapy for adult patients younger than 60 years of age might be optimal or at least comparable with the new anthracyclines such as idarubicin. In addition, autologous PBSCT in postremission therapy might improve DFS and OS, at least for patients in a favorable cytogenetic group, such as those with a t(8;21) abnormality.

Uzzaman, M., R. J. Benveniste, et al. (2005). "Embryonic stem cell-derived astrocytes: a novel gene therapy vector for brain tumors." Neurosurg Focus **19**(3): E6.

OBJECT: For gene therapy strategies currently in clinical trials, viral vectors are used to deliver transgenes directly to normal and tumor cells within the central nervous system (CNS). The use of viral vectors is limited by several factors. The aim of this study was to assess whether embryonic stem cell (ESC)-derived astrocytes expressing a doxycyclineinducible transgene can be used as a vector for gene therapy. METHODS: The authors generated a pure population of ESC-derived astrocytes carrying a transgene, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), inserted in the chromosome under the control of a highly regulated doxycycline-inducible expression system. Fully differentiated ESC-derived astrocytes were stereotactically transplanted in the mouse brain, and then cell migration and transgene expression were studied. RESULTS: The ESC-derived astrocytes started to migrate from the transplant site 48 hours after the procedure. They were found to have migrated throughout the brain tissue by 6 weeks. Transplanted ESC-derived astrocytes expressed the TRAIL transgene after doxycycline induction throughout the duration of the experiment. Teratoma formation was not observed in long-term experiments (12 weeks). CONCLUSIONS: These data show that ESC-derived astrocytes can be used as delivery vectors for CNS tumors. This technique might have a major impact on the treatment of patients with malignant gliomas and a wide spectrum of other neurological diseases.

Verkruyse, L. A., G. A. Storch, et al. (2006). "Once daily ganciclovir as initial pre-emptive therapy delayed until threshold CMV load > or =10000 copies/ml: a safe and effective strategy for allogeneic stem cell transplant patients." Bone Marrow Transplant **37**(1): 51-6.

Quantitative polymerase chain reaction (QPCR) for cytomegalovirus (CMV) is emerging as the preferred screening method for detection of CMV viremia in patients following allogeneic bone marrow and peripheral blood stem cell transplant. However, there are currently no universally accepted QPCR

treatment thresholds at which to start pre-emptive therapy. We report here results of a pre-emptive therapy strategy using ganciclovir (GCV) 5 mg/kg initiated once daily (ODG) delayed till a threshold CMV load of > or =10 000 copies/ml whole blood in clinically stable patients. Sixty-nine at risk patients underwent allogeneic stem cell transplant. 48/69 (70%) patients had an initial episode of CMV viremia. 5/48 (10%) cleared viremia without requiring treatment. 28/43 (65%) patients requiring treatment initiated treatment with ODG. 17/28 (61%) patients successfully cleared CMV viremia on ODG, 10/28 (36%) patients required dose escalation to twice daily GCV for increasing viral loads. There were two cases of CMV disease (colitis) and no deaths due to CMV disease in patients initiating treatment with ODG. We conclude delaying pre-emptive therapy with ODG until whole blood QPCR> or =10 000 copies/ml is a safe and effective strategy for CMV viremia after allogeneic stem cell transplant in clinically stable patients.

Vollweiler, J. L., S. P. Zielske, et al. (2003). "Hematopoietic stem cell gene therapy: progress toward therapeutic targets." Bone Marrow Transplant **32**(1): 1-7.

The concept of hematopoietic stem cell gene therapy is as exciting as that of stem cell transplantation itself. The past 20 years of research have led to improved techniques for transferring and expressing genes in hematopoietic stem cells and preclinical models now routinely indicate the ease with which new genes can be expressed in repopulating stem cells of multiple species. Both modified murine oncoretroviruses and lentiviruses transmit genes into the genome of hematopoietic stem cells and allow expression in the host following transplantation. Using oncoretroviruses, therapeutic genes for severe combined immunodeficiency, common variable gamma chain immunodeficiency, chronic granulomatous disease, Hurler's and Gaucher's Disease have all been used clinically with only modest success except for the patients with immunodeficiency in whom a partial T-cell chimerism has been dramatic. Since stem cell selection in vivo appears important to the therapeutic success of gene transfer, drug resistance selection, most recently using the MGMT gene, has been developed and appears to be safe. Future trials combining a drug resistance and therapeutic gene are planned, as are trials using safety-modified lentiviruses. The therapeutic potential of hematopoietic stem cell gene therapy, particularly given recent advances in stem cell plasticity, remains an exceptionally exciting area of clinical research.

Williams, S. F., T. Gilewski, et al. (1992). "High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report." J Clin Oncol **10**(11): 1743-7.

PURPOSE: Fifty-nine patients with newly diagnosed metastatic breast cancer were treated with induction chemotherapy followed by high-dose intensification and autologous stem-cell rescue (ASCR) to determine therapeutic efficacy. PATIENTS AND METHODS: Induction consisted of cyclophosphamide, doxorubicin, vincristine, and methotrexate with leucovorin rescue (LOMAC) in 27 patients, or fluorouracil, cisplatin, doxorubicin, and cyclophosphamide (FCAP) in 32 patients. Intensification after LOMAC was cyclophosphamide and thiotepa (CyTepa) with ASCR, and after FCAP it was cyclophosphamide, thiotepa, and carmustine (BCNU) in all but eight patients who received CyTepa. RESULTS: Median survival from study entry for the entire group was 13.3 months. Median time to progression from reinfusion for the 45 patients who underwent intensification was 7.5 months. After LOMAC and intensification, there were 12 complete responses (CR) (nine partial responses [PRs] after induction converted to CRs). Responses after FCAP and intensification were eight CRs (two PRs after induction converted to CRs). Median time to treatment failure from reinfusion was 5.4 months for LOMAC and intensification, and was 10.5 months for FCAP and intensification. Median survival from study entry was 15.1 months for all 27 LOMAC patients and 9.3 months for all 32 FCAP patients. Median time to treatment failure from reinfusion for 11 patients who were CRs at intensification has not been reached and is more than 13 months compared with a median of 5.5 months for the 23 patients in partial remission at intensification. CONCLUSIONS: High-dose intensification therapy has led to increased CR rates in metastatic breast cancer. The role of such therapy in the treatment of stage IV breast cancer requires further refinement.

Wiskemann, J. and G. Huber (2008). "Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation." Bone Marrow Transplant **41**(4): 321-9.

Even when the procedures are successful, patients experience considerable physical, psychological and psychosocial stress before, during and after hematopoietic stem cell transplantation (HSCT). Physical exercise therapy constitutes a potentially promising intervention to reduce such stress within the framework of HSCT because of its multidimensional effectiveness. Up to May 2007, fifteen published studies have examined physical exercise interventions in the context of HSCT, with no

study reporting any unexpected or negative effects. The most common intervention involved isolated aerobic exercise programs and occurred during or after the transplantation process; strength training programs and combined intervention strategies are being examined more rarely. Significant benefits from the exercise interventions have been predominantly reported for physical performance, quality of life and fatigue status of the patients. Several other benefits like a faster recurrence of immune cells or reduced severity of therapy-related side effects can be estimated. Future research is needed for the purpose of evidence-based medicine/therapy to provide more rigorous examinations of these interventions, to address existing methodological problems and to identify further effect levels of physical exercise therapy in the context of HSCT.

Xing, F., Z. Fang, et al. (2009). "Parthenogenetic embryonic stem cells derived from cryopreserved newborn mouse ovaries: a new approach to autologous stem cell therapy." Fertil Steril **91**(4): 1238-44.

OBJECTIVE: To evaluate whether cryopreserved newborn mouse ovaries can generate sufficient numbers of parthenogenetic mouse embryonic stem (pmES) cells for autologous stem cell therapy. DESIGN: Prospective study. SETTING: Reproductive clinic of Xinhua Hospital in Shanghai. ANIMAL(S): Kunming, C57BL/6J, BALB/c, and NOD-SCID mice. INTERVENTION(S): Cryopreserved newborn mouse ovaries were thawed, grafted into immunodeficient mice, treated with pregnant mare serum gonadotropin to promote follicular maturation, and collected oocytes activated in vitro to generate parthenogenetic embryonic stem cells. MAIN OUTCOME MEASURE(S): Preimplantation development and stem cell characterization. RESULT(S): This new protocol yielded a large number of oocytes from cryopreserved ovaries over a long period. These oocytes were used to derive pmES cell lines, which expressed embryonic stem cell-specific markers and differentiated into embryoid bodies in vitro and teratomas in vivo. The pmES cell line was propagated in an undifferentiated state for more than 30 passages and maintained a diploid karyotype. CONCLUSION(S): The pmES cells lines established by our protocol exhibited the same degree of pluripotency as standard embryonic stem cell lines. This approach may be used for exploring autologous stem cell therapies.

Xu, J., J. Qu, et al. (2008). "Mesenchymal stem cell-based angiopoietin-1 gene therapy for acute lung injury induced by lipopolysaccharide in mice." J Pathol **214**(4): 472-81.

Bone marrow-derived mesenchymal stem cells (MSCs) can serve as a vehicle for gene therapy. Angiopoietin-1 (Ang1) is a critical factor for endothelial survival and vascular stabilization via the inhibition of endothelial permeability and leukocyte-endothelium interactions. We hypothesized that MSC-based Ang1 gene therapy might be a potential therapeutic approach for lipopolysaccharide (LPS)-induced lung injury. MSCs were isolated from 6 week-old inbred male mice and transduced with the Ang1 gene, using a lentivirus vector. The MSCs showed no significant phenotypic changes after transduction. In the in vivo mouse model, the LPS-induced lung injury was markedly alleviated in the group treated with MSCs carrying Ang1 (MSCs-Ang1), compared with groups treated with MSCs or Ang1 alone. The expression of Ang1 protein in the recipient lungs was increased after MSCs-Ang1 administration. The histopathological and biochemical indices of LPS-induced lung injury were improved after MSCs-based Ang1 gene treatment. MSCs-Ang1 administration also reduced pulmonary vascular endothelial permeability and the recruitment of inflammatory cells into the lung. Cells of MSC origin could be detected in the recipient lungs for 2 weeks after injection with MSCs. These results suggest that MSCs and Ang1 have a synergistic role in the treatment of LPS-induced lung injury. MSC-based Ang1 gene therapy may be developed as a potential novel strategy for the treatment of acute lung injury.

Yamada, Y., A. Fujimoto, et al. (2006). "Cluster analysis and gene expression profiles: a cDNA microarray system-based comparison between human dental pulp stem cells (hDPSCs) and human mesenchymal stem cells (hMSCs) for tissue engineering cell therapy." Biomaterials **27**(20): 3766-81.

We investigated gene expression patterns and functional classifications regarding the clusters of human dental pulp stem cells (hDPSCs) and human mesenchymal stem cells (hMSCs)--which possess a multipotent ability--because little is known about the precise moleculobiological clues by which these cells activate their differentiating ability or functionality to eventually form dentin and bone, respectively. We first verified the expressions of the alkaline phosphatase (ALP) gene, dentin matrix protein 1 (DMP-1), and dentinsialophosphoprotein (DSPP) by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and consequently discovered the high expressions of these genes. Total RNA was also followed by hybridization with a human microarray system consisting of 12,814 genes. Analyses of gene expression patterns indicated several genes which encode extracellular matrix components, cell adhesion

molecules, growth factors, and transcription regulators. Functional and clustering analyses of differences in gene expression levels revealed cell signaling, cell communication, or cell metabolism. In the future, information on the gene expression patterns of hDPSCs and hMSCs might be useful in determining the detailed functional roles of the relevant genes and applicable to stem cell therapies, and these cells could also be used as multipotent cell sources for gene technology and tissue engineering technology.

Yamashita, T., K. Deguchi, et al. (2009). "Gene and stem cell therapy in ischemic stroke." Cell Transplant **18**(9): 999-1002.

Possible strategies for treating ischemic stroke include neuroprotection (preventing injured neurons from undergoing apoptosis in the acute phase of cerebral ischemia) and stem cell therapy (the repair of disrupted neuronal networks with newly born neurons in the chronic phase of cerebral ischemia). First, we estimated the neuroprotective effect of glial cell line-derived neurotrophic factor (GDNF) by administration of GFNF protein. GDNF protein showed a direct protective effect against ischemic brain damage. Pretreatment of animals with adenoviral vector containing GDNF gene (Ad-GDNF) 24 h before the subsequent transient middle cerebral artery occlusion (MCAO) effectively reduced infarcted volume. Secondly, we studied the neuroprotective effect of a calcium channel blocker, azelnidipine, or a by-product of heme degradation, biliverdin. Both azelnidipine and biliverdin had a neuroprotective effect in the ischemic brain through their antioxidative property. Lastly, we developed a restorative stroke therapy with a bioaffinitive scaffold, which is able to provide an appropriate platform for newly born neurons. In the future, we will combine these strategies to develop more effective therapies for treatment of strokes.

Yanada, M., K. Matsuo, et al. (2006). "Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis." Cancer **106**(12): 2657-63.

BACKGROUND: The prognosis for adult patients with acute lymphoblastic leukemia (ALL) remains unsatisfactory primarily because of the high incidence of recurrence. Therefore, optimal postremission therapy is a matter of vital concern. In particular, the clinical efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) should be clarified. METHODS: Rigorous criteria were used to select 7 studies of adult ALL that prospectively assessed overall survival (OS) using natural randomization based on donor availability combined with intention-to-treat analyses. The authors then performed a metaanalysis to evaluate the role of allogeneic HSCT. RESULTS: Seven studies that included 1274 patients were selected. A metaanalysis demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups (hazard ratio [HR], 1.29; 95% confidence interval [95% CI], 1.02-1.63 [P = .037]). When only high-risk patients were included in the analysis, the superiority of the survival advantage was even greater (HR, 1.42; 95% CI, 1.06-1.90 [P = .019]). A meta-regression analysis revealed that compliance with allogeneic HSCT showed a significant and positive correlation with survival (coefficient, 0.022; P < .01), suggesting that the greater the proportion of patients who actually received allogeneic HSCT, the better the survival of the donor group. No beneficial effects of autologous HSCT were observed. CONCLUSIONS: The current findings demonstrated that allogeneic HSCT improves the outcome of adult patients with high-risk ALL. Although these analyses were based on abstracted data, the results indicated that allogeneic HSCT should be considered for such patients if a suitable donor is available.

Zubko, R. and W. Frishman (2009). "Stem cell therapy for the kidney?" Am J Ther **16**(3): 247-56.

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

exploration of stem cell therapy in renal patients with multiple comorbidities.

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