Stem Cell Mobilization Research Literatures

Ma Hongbao *, Margaret Young **, Zhu Yucui ***, Yang Yan *, Zhu Huaijie ****

* Brookdale University Hospital and Medical Center, Brooklyn, New York 11212, USA, ma8080@gmail.com; ** Cambridge, MA 02138, USA; *** Department of Dermatology, Columbia University Medical Center, 630 West, 168th Street, New York, New York 10032, USA; **** The 2nd Affiliated Hospital of Zhengzhou University, 2 Jingba Road, Zhengzhou, Henan, China, yz81@columbia.edu

Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the stem cell mobilization related studies.
[Ma H, Young M, Zhu Y, Yang Y, Zhu H. **Stem Cell Mobilization Research Literatures**. Stem Cell. 2016;7(1):65-82] ISSN: 1945-4570 (print); ISSN: 1945-4732 (online)]. http://www.sciencepub.net/stem. 6. doi:10.7537/marsscj07011606.

Key words: stem cell; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Adamiak, M., A. Poniewierska-Baran, et al. "Evidence that a lipolytic enzyme-hematopoietic-specific phospholipase C-beta2-promotes mobilization of hematopoietic stem cells by decreasing their lipid raft-mediated bone marrow retention and increasing the promobilizing effects of granulocytes." Leukemia. 2016 Apr;30(4):919-28. doi: 10.1038/leu.2015.315. Epub 2015 Nov 19.

Hematopoietic stem/progenitor cells (HSPCs) reside in the bone marrow (BM) microenvironment and are retained there by the interaction of membrane lipid raft-associated receptors, such as the alpha-chemokine receptor CXCR4 and the alpha4beta1-integrin (VLA-4, very late antigen 4 receptor) receptor, with their respective specific ligands, stromal-derived factor 1 and vascular cell adhesion molecule 1, expressed in BM stem cell niches. The integrity of the lipid rafts containing these receptors is maintained by the glycolipid glycosylphosphatidylinositol anchor (GPI-A). It has been reported that a cleavage fragment of the fifth component of the activated complement cascade, C5a, has an important role in mobilizing HSPCs into the peripheral blood (PB) by (i) inducing degranulation of BM-residing granulocytes and (ii) promoting their egress from the BM into the PB so that they permeabilize the endothelial barrier for subsequent egress of HSPCs. We report here that hematopoietic cell-specific phospholipase C-beta2 (PLC-beta2) has a crucial role in pharmacological mobilization of HSPCs. On the one hand, when released during degranulation of granulocytes, it digests GPI-A, thereby disrupting membrane lipid rafts and impairing retention of HSPCs in BM niches. On the other hand, it is an intracellular enzyme required for degranulation of granulocytes and their egress from BM. In support of this dual role, we demonstrate that PLC-beta2-knockout mice are poor mobilizers and provide, for the first time, evidence for the involvement of this lipolytic enzyme in the mobilization of HSPCs.

Afifi, S., N. G. Adel, et al. "Upfront plerixafor plus G-CSF versus cyclophosphamide plus G-CSF for stem cell mobilization in multiple myeloma: efficacy and cost analysis study." Bone Marrow Transplant. 2016 Apr;51(4):546-52. doi: 10.1038/bmt.2015.322. Epub 2016 Jan 4.

Cyclophosphamide plus G-CSF (C+G-CSF) is one of the most widely used stem cell (SC)

mobilization regimens for patients with multiple myeloma (MM). Plerixafor plus G-CSF (P+G-CSF) has demonstrated superior SC mobilization efficacy when compared with G-CSF alone and has been shown to rescue patients who fail mobilization with G-CSF or C+G-CSF. Despite the proven efficacy of P+G-CSF in upfront SC mobilization, its use has been limited, mostly due to concerns of high price of the drug. However, a comprehensive comparison of the efficacy and cost effectiveness of SC mobilization using C+G-CSF versus P+G-CSF is not available. In this study, we compared 111 patients receiving C+G-CSF to 112 patients receiving P+G-CSF. The use of P+G-CSF was associated with a higher success rate of SC collection defined as 5 x 10(6) CD34+ cells/kg (94 versus 83%, P=0.013) and less toxicities. Thirteen patients in the C+G-CSF arm were hospitalized owing to complications while none in the P+G-CSF group. C+G-CSF was associated with higher financial burden as assessed using institutional-specific costs and charges (P<0.001) as well as using Medicare reimbursement rates (P=0.27). Higher rate of hospitalization, increased need for salvage mobilization, and increased G-CSF use account for these differences.

Al Tayeb, H., A. El Dorry, et al. "Autologous Stem Cells Transplantation in Egyptian Patients with Liver Cirrhosis on Top of Hepatitis C Virus." Int J Stem Cells. 2015 Nov;8(2):209-18. doi: 10.15283/ijsc.2015.8.2.209.

BACKGROUND AND OBJECTIVES: Use of pluripotent stem cells is an ideal solution for liver insufficiencies. This work aims is to evaluate the safety and feasibility of autologous stem cells transplantation (SCT) in Egyptian patients of liver cirrhosis on top of hepatitis C virus (HCV). SUBJECTS AND RESULTS: 20 patients with HCV induced liver cirrhosis were divided into 2 groups. Group I: included 10 patients with liver cirrhosis Child score >/=9, for whom autologous stem cell transplantation was done using granulocyte colony stimulating factor (G-CSF) for stem cells mobilization. Separation and collection of the peripheral blood stem cells was done by leukapheresis. G-CSF mobilized peripheral blood mononuclear cells (G-CSF PB-MNCs) were counted by flow cytometry. Stem cell injection into the hepatic artery was done. Group II: included 10 patients with HCV induced liver cirrhosis as a control group. Follow up and comparison between both groups were done over a follow up period of 6 months. The procedure was well tolerated. Mobilization was successful and the total number of G-CSF PB-MNCs in the harvests ranged from 25x10(6) to 191x10(6). There was improvement in the quality of life, serum albumin, total bilirubin, liver enzymes and the Child-Pugh score of group I over the first two-three months after the procedure. CONCLUSION: SCT in HCV induced liver cirrhosis is a safe procedure. It can improve the quality of life and hepatic functions transiently with no effect on the life expectancy or the fate of the liver cirrhosis.

Ali, N., S. N. Adil, et al. "Autologous Hematopoietic Stem Cell Transplantation-10 Years of Data From a Developing Country." Stem Cells Transl Med. 2015 Aug;4(8):873-7. doi: 10.5966/sctm.2015-0015. Epub 2015 Jun 1.

Intensive chemotherapy followed by autologous stem cell transplantation is the treatment of choice for patients with hematological malignancies. The objective of the present study was to evaluate the outcomes of patients with mainly lymphoma and multiple myeloma after autologous stem cell transplant. The pretransplant workup consisted of the complete blood count, an evaluation of the liver, kidney, lung, and infectious profile, chest radiographs, and a dental review. For lymphoma, all patients who achieved at least a 25% reduction in the disease after salvage therapy were included in the study. Mobilization was done with cyclophosphamide, followed by granulocyte colony-stimulating factor, 300 microg twice daily. The conditioning regimens included BEAM (carmustine, etoposide, cytarabine, melphalan) and high-dose melphalan. A total of 206 transplants were performed from April 2004 to December 2014. Of these, 137 were allogeneic transplants and 69 were autologous. Of the patients receiving an autologous transplant, 49 were male and 20 were female. Of the 69 patients, 26 underwent transplantation for Hodgkin's lymphoma, 23 for non-Hodgkin's lymphoma, and 15 for multiple myeloma and 4 and 1 for Ewing's sarcoma and neuroblastoma, respectively. The median age +/- SD was 34 +/- 13.1 years (range, 4-64). A mean of 4.7 x 10(8) +/- 1.7 mononuclear cells per kilogram were infused. The median time to white blood cell recovery was 18.2 +/- 5.34 days. Transplant-related mortality occurred in 10 patients. After a median follow-up period of 104 months, the overall survival rate was 86%. High-dose chemotherapy, followed by autologous stem cell transplant, is an effective treatment option for patients with hematological malignancies, allowing further consolidation of response.

Andreeva, E. R., M. V. Pogodina, et al. "[Hypoxic stress as a trigger of multipotent mesenchymal stromal cell activation]." Fiziol Cheloveka. 2015 Mar-Apr;41(2):123-9.

Multipotent mesenchymal stromal (stem) cells (MSCs) are a heterogeneous cell population of

different commitment and is actively involved in the physiological and regenerative tissue remodeling. MSC mobilization from local tissue depots and their activation in the tissue damage foci are the key issues in the study of mechanisms of MSC features. Short-term (up to 72 h) hypoxic stress that is considered as a constitutive feature of the damage foci, may contribute to the activation of MSC potential. This review is analyzed the data on the impact of short hypoxic stress ex vivo on the viability, functional activity of MSCs and possible molecular mechanisms of these effects.

Andreone, P., L. Catani, et al. "Reinfusion of highly purified CD133+ bone marrow-derived stem/progenitor cells in patients with end-stage liver disease: A phase I clinical trial." Dig Liver Dis. 2015 Dec;47(12):1059-66. doi: 10.1016/j.dld.2015.08.018. Epub 2015 Sep 10.

BACKGROUND: Bone marrow stem/progenitor cells seem to be effective in liver regeneration after tissue injury. AIM: To evaluate the feasibility and safety of the mobilization and reinfusion of CD133+ stem/progenitor cells in patients with end-stage liver disease. METHODS: Autologous CD133+ stem/progenitor cells, mobilized with granulocyte-colony stimulating factor, were collected by leukapheresis and reinfused at increasing doses through the hepatic artery starting from 5x10(4)/kg up to 1x10(6)/kg. RESULTS: 16 subjects with Model for End-stage Liver Disease (MELD) score between 17 and 25 were enrolled, 14 mobilized an adequate number of CD133+ stem/progenitor cells and 12 were reinfused. No severe adverse events related to the procedure were reported. MELD score significantly worsened during mobilization in Child Turcotte Pugh-C patients. A significant improvement of liver function was observed 2 months after reinfusion (MELD 19.5 vs. 16; P=0.045). Overall, 5 patients underwent liver transplantation within 12 months from reinfusion and 2 died because of progressive liver failure. CONCLUSIONS: CD133+ stem/progenitor cells reinfusion in patients with end-stage liver disease is feasible and safe. A worsening of liver function was observed during mobilization in Child Turcotte Pugh-C patients. The temporary improvement of MELD score after reinfusion suggests that stem cells therapy may be a "bridge to transplant" approach for these patients.

Bar-Or, D., G. W. Thomas, et al. "Low Molecular Weight Fraction of Commercial Human Serum Albumin Induces Morphologic and Transcriptional Changes of Bone Marrow-Derived Mesenchymal Stem Cells." Stem Cells Transl Med. 2015 Aug;4(8):945-55. doi: 10.5966/sctm.2014-0293. Epub 2015 Jun 3.

Osteoarthritis (OA) is the most common chronic disease of the joint; however, the therapeutic options for severe OA are limited. The low molecular weight fraction of commercial 5% human serum albumin (LMWF5A) has been shown to have anti-inflammatory properties that are mediated, in part, by a diketopiperazine that is present in the albumin preparation and that was demonstrated to be safe and effective in reducing pain and improving function when administered intra-articularly in a phase III clinical trial. In the present study, bone marrow-derived mesenchymal stem cells (BMMSCs) exposed to LMWF5A exhibited an elongated phenotype with diffuse intracellular F-actin, pronounced migratory leading edges, and filopodia-like projections. In addition, LMWF5A promoted chondrogenic condensation in "micromass" culture, concurrent with the upregulation of collagen 2alpha1 mRNA. Furthermore, the transcription of the CXCR4-CXCL12 axis was significantly regulated in a manner conducive to migration and homing. Several transcription factors involved in stem cell differentiation were also found to bind oligonucleotide response element probes following exposure to LMWF5A. Finally, a rapid increase in PRAS40 phosphorylation was observed following treatment, potentially resulting in the activation mTORC1. Proteomic analysis of synovial fluid taken from a preliminary set of patients indicated that at 12 weeks following administration of LMWF5A, a microenvironment exists in the knee conducive to stem cell infiltration, self-renewal, and differentiation, in addition to indications of remodeling with a reduction in inflammation. Taken together, these findings imply that LMWF5A treatment may prime stem cells for both mobilization and chondrogenic differentiation, potentially explaining some of the beneficial effects achieved in clinical trials.

Bilgin, Y. M. and G. E. de Greef "Plerixafor for stem cell mobilization: the current status." Curr Opin Hematol. 2016 Jan;23(1):67-71. doi: 10.1097/MOH.0000000000000200.

PURPOSE OF REVIEW: Nowadays, plerixafor is approved for patients who fail to mobilize sufficient CD34(+) cells for an autologous stem cell transplantation. Plerixafor is effective in the majority of these patients, who otherwise could not be treated adequately. We discussed in this review the current status of the optimal use of plerixafor in different clinical diagnoses and settings. RECENT FINDINGS: Plerixafor seems to be more effective in patients with multiple myeloma than in lymphoma. Even patients who had very low circulating CD34(+) cells before administration of plerixafor have an important benefit. Several strategies in different clinical settings showed

an effective response after administration of plerixafor, without the superiority of one strategy. Plerixafor is well tolerated with acceptable toxicity; however, it is an expensive drug. SUMMARY: Plerixafor is an effective drug in patients who fail to mobilize with conventional strategy. No strategy seems superior for the optimal use of plerixafor. More studies focusing on the kinetics and cost-effectiveness are needed.

Bitan, M., R. Eshel, et al. "Combined plerixafor and granulocyte colony-stimulating factor for harvesting high-dose hematopoietic stem cells: Possible niche for plerixafor use in pediatric patients." Pediatr Transplant. 2016 Mar 16. doi: 10.1111/petr.12692.

PB is a source of HSC, especially for autologous HCT in solid tumors. However, there is a risk of failing to achieve the target number of SC after mobilization with growth factors alone in patients who were heavily pretreated with chemotherapy or those in need for tandem transplants. SC were harvested from seven pediatric patients with solid tumors who were in need of autologous HCT following combination GCSF and plerixafor. Six of them received plerixafor after failing to achieve enough SC with GCSF only, while the seventh patient received the combined protocol upfront. All seven patients achieved the target number of SC according to their treatment protocol. There were no adverse events. All patients underwent autologous HCT using the harvested HSC and achieved full engraftment. A protocol for harvesting autologous HCT using GCSF and plerixafor is feasible and safe in children with solid tumors who had been heavily pretreated with chemotherapy or needed tandem transplants.

Bunse, C. E., S. Tischer, et al. "G-CSF impairs CD8+ T-cell functionality by interfering with central activation elements." Clin Exp Immunol. 2016 Mar 16. doi: 10.1111/cei.12794.

Besides mobilizing stem cells into the periphery, granulocyte-colony stimulating factor (G-CSF) has been shown to influence various types of innate and adaptive immune cells. For example, it impairs the effector function of cytotoxic T lymphocytes (CTLs). It is assumed that this effect is mediated indirectly by monocytes, regulatory T cells and immunomodulatory cytokines influenced by G-CSF. In this study, isolated G-CSF-treated CD8+ T cells were stimulated antigen-dependently with peptide-major histocompatibility complex (pMHC)-coupled artificial antigen-presenting cells (aAPCs) or stimulated antigen-independently with anti-CD3/CD28 stimulator beads. By measuring the changes in IFN-gamma and granzyme B expression at the mRNA and protein level, we showed for the first time that G-CSF has a direct effect on CD8+ CTLs, which was confirmed based on the reduced production of IFN-gamma and granzyme B by the cytotoxic T-cell line TALL-104 after G-CSF treatment. By investigating further elements affected by G-CSF in CTLs from stem cell donors and untreated controls, we found a decreased phosphorylation of ERK1/2, Lck and CD3zeta after G-CSF treatment. Additionally, miRNA-155 and activation marker expression levels were reduced. In summary, our results show that G-CSF directly influences the effector function of cytotoxic CD8+ T cells and affects various elements of T-cell activation. This article is protected by copyright. All rights reserved.

Cameron, A. M., R. Wesson, et al. "Chimeric Allografts Induced by Short-Term Treatment with Stem Cell Mobilizing Agents Result in Long-term Kidney Transplant Survival without Immunosuppression: II Study in Miniature Swine." Am J Transplant. 2016 Jan 8. doi: 10.1111/ajt.13703.

Transplantation is now lifesaving therapy for patients with end stage organ failure but requires lifelong immunosuppression with resultant morbidity. Current immunosuppressive strategies inhibit T cell activation and prevent donor-recipient engagement. Therefore, it is not surprising that few host cells are demonstrated in donor grafts. However, our recent small animal studies found large numbers of recipient stem cells present after transplant and pharmacological mobilization resulting in a chimeric, repopulated organ. We now confirm these findings in a well characterized large animal preclinical model. Here we show that AMD3100 (A) and FK506 (F) mobilization of endogenous stem cells immediately post kidney transplant combined with repeat therapy at 1, 2, and 3 months led to drug free long term survival in maximally immunologically mismatched swine. Three long term recipients have stable chimeric transplants, preserved anti-donor skin graft responses, and normal serum creatinine despite withdrawal of all medication for 3 years. This article is protected by copyright. All rights reserved.

Danylesko, I., R. Sareli, et al. "Plerixafor (Mozobil): A Stem Cell-Mobilizing Agent for Transplantation in Lymphoma Patients Predicted to Be Poor Mobilizers - A Pilot Study." Acta Haematol. 2016;135(1):29-36. doi: 10.1159/000435769. Epub 2015 Aug 22.

Autologous hematopoietic stem cell transplantation is the standard therapy for refractory/relapsed aggressive lymphoma. The initial step of the procedure involves mobilization and collection of hematopoietic stem cells. G-CSF fails to achieve mobilization in 15-25% of lymphoma patients. Plerixafor is a novel CXCR4 antagonist that

can promote mobilization. It has been used successfully in patients after the failure of G-CSF. It is reasonable to test whether plerixafor should become the mobilizing agent of choice in patients expected to exhibit difficulties in mobilization. We initiated a study to assess the use of plerixafor as a first-line stem cell mobilizer in 20 elderly or heavily pretreated patients with non-Hodgkin or Hodgkin lymphoma. The minimum defined CD34+ cell dose of >/=2 x 106 cells/kg was achieved by 90% of the patients, and for 83% of them with one apheresis procedure. The target CD34+ dose of >/=5 x 106 cells/kg was achieved by 70% of the patients. The median number of circulating CD34+ cells before and after plerixafor was 14.4 and 42.8 cells/mul, respectively. The post-plerixafor adverse events were mild. All patients promptly engrafted after high-dose chemotherapy treatment. We conclude that plerixafor administration is safe and efficient for upfront mobilization in lymphoma patients predicted to be poor mobilizers.

de Wit, R. H., S. M. de Munnik, et al. "Molecular Pharmacology of Chemokine Receptors." Methods Enzymol. 2016;570:457-515. doi: 10.1016/bs.mie.2015.12.002. Epub 2016 Jan 19.

Chemokine receptors are involved in various pathologies such as inflammatory diseases, cancer, and HIV infection. Small molecule and antibody-based antagonists have been developed to inhibit chemokine-induced receptor activity. Currently two small molecule inhibitors targeting CXCR4 and CCR5 are on the market for stem cell mobilization and the treatment of HIV infection, respectively. Antibody fragments (e.g., nanobodies) targeting chemokine receptors are primarily orthosteric ligands, competing for the chemokine binding site. This is opposed by most small molecules, which act as allosteric modulators and bind to the receptor at a topographically distinct site as compared to chemokines. Allosteric modulators can be distinguished from orthosteric ligands by unique features, such as a saturable effect and probe dependency. For successful drug development, it is essential to determine pharmacological parameters (i.e., affinity, potency, and efficacy) and the mode of action of potential drugs during early stages of research in order to predict the biological effect of chemokine receptor targeting drugs in the clinic. This chapter explains how the pharmacological profile of chemokine receptor targeting ligands can be determined and quantified using binding and functional experiments.

Debeurme, F., C. Lacout, et al. "JAK2 inhibition has different therapeutic effects according to myeloproliferative neoplasm development in mice." J Cell Mol Med. 2015 Nov;19(11):2564-74. doi: 10.1111/jcmm.12608. Epub 2015 Jul 14.

JAK2 inhibition therapy is used to treat patients suffering from myeloproliferative neoplasms (MPN). Conflicting data on this therapy are reported possibly linked to the types of inhibitors or disease type. Therefore, we decided to compare in mice the effect of a JAK2 inhibitor, Fedratinib, in MPN models of increasing severity: polycythemia vera (PV), post-PV myelofibrosis (PPMF) and rapid post-essential thrombocythemia MF (PTMF). The models were generated through JAK2 activation by the JAK2(V617F) mutation or MPL constant stimulation. JAK2 inhibition induced a correction of splenomegaly, leucocytosis and microcytosis in all three MPN models. However, the effects on fibrosis, osteosclerosis, granulocytosis, erythropoiesis or platelet counts varied according to the disease severity stage. Strikingly, complete blockade of fibrosis and osteosclerosis was observed in the PPMF model, linked to correction of MK hyper/dysplasia, but not in the PTMF model, suggesting that MF development may also become JAK2-independent. Interestingly, we originally found a decreased in the JAK2(V617F) allele burden in progenitor cells from the spleen but not in other cell types. Overall, this study shows that JAK2 inhibition has different effects according to disease phenotypes and can (i) normalize platelet counts, (ii) prevent the development of marrow fibrosis/osteosclerosis at an early stage and (iii) reduce splenomegaly through blockage of stem cell mobilization in the spleen.

DeLeve, L. D., X. Wang, et al. "VEGF-sdf1 RECRUITMENT OF CXCR7+ BONE MARROW PROGENITORS OF LIVER SINUSOIDAL ENDOTHELIAL CELLS PROMOTES RAT LIVER REGENERATION." Am J Physiol Gastrointest Liver Physiol. 2016 Mar 3:ajpgi.00056.2016. doi: 10.1152/ajpgi.00056.2016.

BACKGROUND AND AIMS: In liver injury, recruitment of bone marrow progenitors of liver sinusoidal endothelial cells (now named sprocs) is necessary for normal liver regeneration. Hepatic VEGF is a central regulator of the recruitment process. Here we examine whether stromal cell derived factor-1 (sdf-1 or CXCL-12) acts downstream from VEGF to mediate recruitment of bone marrow sprocs, what the sdf-1 receptor type (CXCR4 or CXCR7) is on sprocs, and whether sdf-1 signaling is required for normal liver regeneration. METHODS: Studies were performed in the rat partial hepatectomy model. Tracking studies of bone marrow sprocs were performed in wild type Lewis rats that had undergone bone marrow transplantation from transgenic EGFP+ Lewis rats. Knockdown studies were performed using

anti-sense oligonucleotides. RESULTS: Expression of sdf-1 doubles in liver and in LSECs after partial hepatectomy. The upregulation of sdf-1 expression increases proliferation of sprocs in the bone marrow, mobilization of CXCR7+ bone marrow sprocs to the circulation, and engraftment of CXCR7+ bone marrow sprocs in the liver, and promotes liver regeneration. Knockdown of hepatic VEGF with anti-sense oligonucleotides decreases hepatic sdf-1 expression and plasma sdf-1 levels. When the effect of VEGF knockdown on sdf-1 is offset by infusion of sdf-1, VEGF knockdown-induced impairment of BM sproc recruitment after partial hepatectomy is completely attenuated and liver regeneration is normalized. CONCLUSION: These data demonstrate that the VEGF-sdf-1 pathway regulates recruitment of CXCR7+ bone marrow sprocs to the hepatic sinusoid after partial hepatectomy and is required for normal liver regeneration.

Dogu, M. H., A. H. Kaya, et al. "Does the preference of peripheral versus central venous access in peripheral blood stem cell collection/yield change stem cell kinetics in autologous stem cell transplantation?" Transfus Apher Sci. 2016 Feb;54(1):76-9. doi: 10.1016/j.transci.2016.01.017. Epub 2016 Jan 11.

Central venous access is often used during apheresis procedure in stem cell collection. The aim of the present study was to evaluate whether central or peripheral venous access has an effect on stem cell yield and the kinetics of the procedure and the product in patients undergoing ASCT after high dose therapy. A total of 327 patients were retrospectively reviewed. The use of peripheral venous access for stem cell yield was significantly more frequent in males compared to females (p = 0.005). Total volume of the product was significantly lower in central venous access group (p = 0.046). As being a less invasive procedure, peripheral venous access can be used for stem cell yield in eligible selected patients.

Elayan, M. M., J. G. Horowitz, et al. "Tbo-Filgrastim versus Filgrastim during Mobilization and Neutrophil Engraftment for Autologous Stem Cell Transplantation." Biol Blood Marrow Transplant. 2015 Nov;21(11):1921-5. doi: 10.1016/j.bbmt.2015.05.024. Epub 2015 May 30.

There are limited data available supporting the use of the recombinant granulocyte colony-stimulating factor (G-CSF), tbo-filgrastim, rather than traditionally used filgrastim to mobilize peripheral blood stem cells (PBSC) or to accelerate engraftment after autologous stem cell transplantation (ASCT). We sought to compare the efficacy and cost of tbo-filgrastim to filgrastim in these settings. Patients diagnosed with lymphoma or plasma cell disorders undergoing G-CSF mobilization, with or without plerixafor, were included in this retrospective analysis. The primary outcome was total collected CD34(+) cells/kg. Secondary mobilization endpoints included peripheral CD34(+) cells/muL on days 4 and 5 of mobilization, adjunctive use of plerixafor, CD34(+) cells/kg collected on day 5, number of collection days and volumes processed, number of collections reaching 5 million CD34(+) cells/kg, and percent reaching target collection goal in 1 day. Secondary engraftment endpoints included time to neutrophil and platelet engraftment, number of blood product transfusions required before engraftment, events of febrile neutropenia, and length of stay. A total of 185 patients were included in the final analysis. Patients receiving filgrastim (n = 86) collected a median of 5.56 x 10(6) CD34(+) cells/kg, compared with a median of 5.85 x 10(6) CD34(+) cells/kg in the tbo-filgrastim group (n = 99; P = .58). There were no statistically significant differences in all secondary endpoints with the exception of apheresis volumes processed (tbo-filgrastim, 17.0 liters versus filgrastim, 19.7 liters; P < .01) and mean platelet transfusions (tbo-filgrastim, 1.7 units versus filgrastim, 1.4 units; P = .04). In conclusion, tbo-filgrastim demonstrated similar CD34(+) yield compared with filgrastim in mobilization and post-transplantation settings, with no clinically meaningful differences in secondary efficacy and safety endpoints. Furthermore, tbo-filgrastim utilization was associated with cost savings of approximately $1406 per patient utilizing average wholesale price.

Elbana, A. M., S. Abdel-Salam, et al. "Role of Endogenous Bone Marrow Stem Cells Mobilization in Repair of Damaged Inner Ear in Rats." Int J Stem Cells. 2015 Nov;8(2):146-54. doi: 10.15283/ijsc.2015.8.2.146.

BACKGROUND AND OBJECTIVES: The utilization of the stem cells is widely used in the last few years in different fields of medicine, either by external transplantation or endogenous mobilization, most of these studies still experimental on animals; few were tried on human as in the spinal cord injury or myocardial infarction. As regard its use in the inner ear, stem cell transplantation was examined in many previous studies, while the mobilization idea is a new method to be experimented in inner ear hair cell regeneration. The present work assessed the possibility of mobilizing endogenous bone marrow derived stem cells (SCs) in rats using granulocyte colony stimulating factor (G-CSF) to induce regeneration and repair to experimentally damaged inner ear hair cells by Amikacin injection. METHODS: The study included thirty adult Sprague

Dawley male rats. Experimental induction of inner ear damage was done by repeated intratympanic injection of amikacin sulfate. Mobilization of bone marrow SCs was provoked by subcutaneous injection of GCSF. Cochlear integrity, induction of hearing loss and functional recovery of sensory hearing loss were assessed using Distortion Product Otoacoustic Emission (DPOAEs). The morphological alteration and recovery of the organ of Corti was assessed histologically using the light and scanning electron microscopes. RESULTS: After six month duration, there was improvement in 50% of the sensorineural DPOAE results. Functional recovery coincided with the repair of structural components of organ of Corti. CONCLUSIONS: SCs mobilization by G-CSF is a promising alternative method for replacement therapy in sensorineural hearing loss.

Elsaesser, A. F., S. Schwarz, et al. "Characterization of a migrative subpopulation of adult human nasoseptal chondrocytes with progenitor cell features and their potential for in vivo cartilage regeneration strategies." Cell Biosci. 2016 Feb 13;6:11. doi: 10.1186/s13578-016-0078-6. eCollection 2016.

BACKGROUND: Progenitor cells display interesting features for tissue repair and reconstruction. In the last years, such cells have been identified in different cartilage types. In this study, we isolated a migrative subpopulation of adult human nasoseptal chondrocytes with progenitor cell features by outgrowth from human nasal septum cartilage. These putative progenitor cells were comparatively characterized with mesenchymal stem cells (MSC) and human nasal septum chondrocytes with respect to their cellular characteristics as well as surface marker profile using flow cytometric analyses. Differentiation capacity was evaluated on protein and gene expression levels. RESULTS: The migrative subpopulation differentiated into osteogenic and chondrogenic lineages with distinct differences to chondrocytes and MSC. Cells of the migrative subpopulation showed an intermediate surface marker profile positioned between MSC and chondrocytes. Significant differences were found for CD9, CD29, CD44, CD90, CD105 and CD106. The cells possessed a high migratory ability in a Boyden chamber assay and responded to chemotactic stimulation. To evaluate their potential use in tissue engineering applications, a decellularized septal cartilage matrix was either seeded with cells from the migrative subpopulation or chondrocytes. Matrix production was demonstrated immunohistochemically and verified on gene expression level. Along with secretion of matrix metalloproteinases, cells of the migrative subpopulation migrated faster into the collagen matrix than chondrocytes, while synthesis of cartilage specific matrix was comparable. CONCLUSIONS: Cells of the migrative subpopulation, due to their migratory characteristics, are a potential cell source for in vivo regeneration of nasal cartilage. The in vivo mobilization of nasal cartilage progenitor cells is envisioned to be the basis for in situ tissue engineering procedures, aiming at the use of unseeded biomaterials which are able to recruit local progenitor cells for cartilage regeneration.

Gao, F., H. Hou, et al. "Bone marrow-derived cells in ocular neovascularization: contribution and mechanisms." Angiogenesis. 2016 Apr;19(2):107-18. doi: 10.1007/s10456-016-9497-6. Epub 2016 Feb 15.

Ocular neovascularization often leads to severe vision loss. The role of bone marrow-derived cells (BMCs) in the development of ocular neovascularization, and its significance, is increasingly being recognized. In this review, we discuss their contribution and the potential mechanisms that mediate the effect of BMCs on the progression of ocular neovascularization. The sequence of events by which BMCs participate in ocular neovascularization can be roughly divided into four phases, i.e., mobilization, migration, adhesion and differentiation. This process is delicately regulated and liable to be affected by multiple factors. Cytokines such as vascular endothelial growth factor, granulocyte colony-stimulating factor and erythropoietin are involved in the mobilization of BMCs. Studies have also demonstrated a key role of cytokines such as stromal cell-derived factor-1, tumor necrosis factor-alpha, as well as vascular endothelial growth factor, in regulating the migration of BMCs. The adhesion of BMCs is mainly regulated by vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and vascular endothelial cadherin. However, the mechanisms regulating the differentiation of BMCs are largely unknown at present. In addition, BMCs secrete cytokines that interact with the microenvironment of ocular neovascularization; their contribution to ocular neovascularization, especially choroidal neovascularization, can be aggravated by several risk factors. An extensive regulatory network is thought to modulate the role of BMCs in the development of ocular neovascularization. A comprehensive understanding of the involved mechanisms will help in the development of novel therapeutic strategies related to BMCs. In this review, we have limited the discussion to the recent progress in this field, especially the research conducted at our laboratory.

Gazendam, R. P., A. van de Geer, et al. "Impaired killing of Candida albicans by granulocytes mobilized for transfusion purposes: a role for granule

components." Haematologica. 2016 Jan 22. pii: haematol.2015.136630.

Granulocyte transfusions are used to treat neutropenic patients with life-threatening bacterial or fungal infections that do not respond to anti-microbial drugs. Donor neutrophils that have been mobilized with granulocyte-colony stimulating factor (G-CSF) and dexamethasone are functional in terms of antibacterial activity, but less is known about their fungal killing capacity. We investigated the neutrophil-mediated cytotoxic response against C. albicans and A. fumigatus in detail. Whereas G-CSF/dexamethasone-mobilized neutrophils appeared less mature as compared to neutrophils from untreated controls, these cells exhibited normal ROS production by the NADPH oxidase system and an unaltered granule mobilization capacity upon stimulation. G-CSF/dexamethasone-mobilized neutrophils efficiently inhibited A. fumigatus germination and killed Aspergillus and Candida hyphae, but the killing of C. albicans yeasts was distinctly impaired. Following normal Candida phagocytosis, analysis by mass spectrometry of purified phagosomes after fusion with granules demonstrated that major constituents of the antimicrobial granule components, including Major Basic Protein (MBP), were reduced. Purified MBP showed candidacidal activity, and neutrophil-like Crisp-Cas9 NB4-KO-MBP differentiated into phagocytes were impaired in Candida killing. Together, these findings indicate that G-CSF/dexamethasone-mobilized neutrophils for transfusion purposes have a selectively impaired capacity to kill Candida yeasts, as a consequence of an altered neutrophil granular content.

Goker, H., S. Etgul, et al. "Optimizing mobilization strategies in difficult-to-mobilize patients: The role of plerixafor." Transfus Apher Sci. 2015 Aug;53(1):23-9. doi: 10.1016/j.transci.2015.05.011. Epub 2015 Jun 9.

Peripheral blood stem cell collection is currently the most widely used source for hematopoietic autologous transplantation. Several factors such as advanced age, previous chemotherapy, disease and marrow infiltration at the time of mobilization influence the efficacy of CD34(+) progenitor cell mobilization. Despite the safety and efficiency of the standard mobilization protocols (G-CSF +/- chemotherapy), there is still a significant amount of mobilization failure rate (10-40%), which necessitate novel agents for effective mobilization. Plerixafor, is a novel agent, has been recently approved for mobilization of hematopoietic stem cells (HSCs). The combination of Plerixafor with G-CSF provides the collection of large numbers of stem cells in fewer apheresis sessions and can salvage those who fail with standard mobilization regimens. The development and optimization of practical algorithms for the use Plerixafor is crucial to make hematopoietic stem cell mobilization more efficient in a cost-effective way. This review is aimed at summarizing how to identify poor mobilizers, and define rational use of Plerixafor for planning mobilization in hard-to-mobilize patients.

Grabmaier, U., B. C. Huber, et al. "Mobilisation of haemopoietic stem cells in teriparatide-treated patients." Intern Med J. 2015 Aug;45(8):872-6. doi: 10.1111/imj.12830.

Parathyroid hormone (PTH) is the predominant regulator of calcium/phosphate homeostasis in the human body. Beside this classical function, preclinical and clinical studies indicated a relevant role for PTH in mobilisation of bone marrow-derived cells into peripheral blood. In addition, recombinant PTH (teriparatide) was recently approved for the treatment of severe osteoporosis. Therefore, it was the aim of the present study to investigate the dynamics of haemopoietic stem cells and corresponding in peripheral blood of 13 patients with osteoporosis during treatment with teriparatide. We were able to show that administration of teriparatide is sufficient to mobilise haemopoietic stem cells into the bloodstream accompanied by an alteration of mobilising cytokines. In conclusion, teriparatide might be a useful tool in the context of stem cell mobilisation.

Griffiths, K., O. Dolezal, et al. "I-bodies: human single domain antibodies that antagonize chemokine receptor CXCR4." J Biol Chem. 2016 Apr 1. pii: jbc.M116.721050.

CXCR4 is a G protein-coupled receptor with excellent potential as a therapeutic target for a range of clinical conditions including stem cell mobilization, cancer prognosis and treatment, fibrosis therapy and HIV. We report here the development of a fully human single-domain antibody-like scaffold termed an i-body, the engineering of which produces an i-body library possessing a long complementarity determining region (CDR) binding loop, and the isolation and characterisation of a panel of i-bodies with activity against human CXCR4. The CXCR4-specific i-bodies show antagonistic activity in a range of in vitro and in vivo assays including inhibition of HIV infection, cell migration and leukocyte recruitment but, importantly, not mobilization of hematopoietic stem cells. Epitope mapping of three CXCR4 i-bodies AM3-114, AM4-272 and AM3-523 revealed binding deep in the binding pocket of the receptor.

Guner, S. I., M. T. Yanmaz, et al. "The High Effect of Chemomobilization with High-Dose Etopside + Granulocyte-Colony Stimulating Factor in Autologous Hematopoietic Peripheral Blood Stem Cell Transplantation: A Single Center Experience." Hematol Rep. 2016 Mar 18;8(1):6319. doi: 10.4081/hr.2016.6319. eCollection 2016 Mar 17.

Autologous hematopoietic stem cell transplantation (auto-HSCT) provides hematopoietic support after high-dose chemotherapy and is the standard of care for patients with multiple myeloma (MM), chemo sensitive relapsed high or intermediate grade non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). However, yields of hematopoietic stem cells vary greatly between patients, and the optimal strategy to mobilize hematopoietic stem cells into peripheral blood for collection has not been defined yet. We investigated the efficacy and safety of chemo mobilization with an intermediate dose etoposide (VP-16; 200 mg/m(2) on days 1-3) and granulocyte-colony stimulating factor (G-CSF)(5 microg/kg twice daily from day 4 through the final day of collection). We reviewed our institutional experience with 91 patients (71 MM, 12 HL, 8 NHL) mobilized with this regimen. VP-16 + G-CSF resulted in successful mobilization in 95.55% of the patients (on one patient stem cell collection with plerixafor was applied), including 76 patients (83.52%) whose stem cells were collected successfully in a single day. Collection was managed between min. D8 and max. D17. Patient age, gender, exposure to previous irradiation and chemotherapy, previous mobilization attempts, and disease characteristics were not considered during selection. Adverse effects of the regimen included supportive transfusions and fevers requiring hospitalization or intravenous antibiotics. VP-16 and G-CSF appears to be a safe and effective mobilization regimen for patients with multiple myeloma, non-Hodgkin's lymphoma and Hodgkin's lymphoma undergoing autologous stem cell transplantation, producing excellent stem cell yield with the majority of patients requiring 1 day of apheresis.

Gur-Cohen, S., T. Itkin, et al. "PAR1 signaling regulates the retention and recruitment of EPCR-expressing bone marrow hematopoietic stem cells." Nat Med. 2015 Nov;21(11):1307-17. doi: 10.1038/nm.3960. Epub 2015 Oct 12.

Retention of long-term repopulating hematopoietic stem cells (LT-HSCs) in the bone marrow is essential for hematopoiesis and for protection from myelotoxic injury. We report that signaling cascades that are traditionally viewed as coagulation related also control retention of endothelial protein C receptor-positive (EPCR(+)) LT-HSCs in the bone marrow and their recruitment to the blood via two pathways mediated by protease activated receptor 1 (PAR1). Thrombin-PAR1 signaling induces nitric oxide (NO) production, leading to EPCR shedding mediated by tumor necrosis factor-alpha-converting enzyme (TACE), enhanced CXCL12-CXCR4-induced motility and rapid stem and progenitor cell mobilization. Conversely, bone marrow blood vessels provide a microenvironment enriched with activated protein C (aPC) that retains EPCR(+) LT-HSCs by limiting NO generation, reducing Cdc42 activity and enhancing integrin VLA4 affinity and adhesion. Inhibition of NO production by aPC-EPCR-PAR1 signaling reduces progenitor cell egress from the bone marrow, increases retention of bone marrow NO(low) EPCR(+) LT-HSCs and protects mice from chemotherapy-induced hematological failure and death. Our study reveals new roles for PAR1 and EPCR in controlling NO production to balance maintenance and recruitment of bone marrow EPCR(+) LT-HSCs, with potential clinical relevance for stem cell transplantation.

Hadarits, O., A. Zoka, et al. "Increased Proportion of Hematopoietic Stem and Progenitor Cell Population in Cord Blood of Neonates Born to Mothers with Gestational Diabetes Mellitus." Stem Cells Dev. 2016 Jan 1;25(1):13-7. doi: 10.1089/scd.2015.0203. Epub 2015 Nov 24.

We assessed the hematopoietic stem and progenitor cell (HSPC) population in the cord blood of neonates born to mothers with gestational diabetes mellitus (GDM) in a hypothesis generating pilot study, due to that, neonatal polycythemia may be the consequence of GDM pregnancy. Forty-five pregnant women with GDM (last trimester mean HbA1C = 33.9 mmol/mol) and 42 (nondiabetic) control pregnant women were enrolled after their routine 75 g oral glucose tolerance test (OGTT) between the 24th and 28th gestational week (with expected differences in their mean routine clinical characteristics: plasma glucose at OGTT: 0' = 5.07 vs. 4.62 mM, 120' = 8.9 vs. 5.76 mM, age = 35.07 vs. 31.66 years, prepregnancy body mass index = 27.9 vs. 23.9 kg/m(2), GDM vs. control, respectively) on a voluntary basis after signing the informed consent. EDTA-treated cord blood samples were analyzed by flow cytometry and the software Kaluza1.2 using CD45 and CD34-specific fluorescent antibodies to identify the HSPC population (CD34(+) cells within the CD45(dim) blast gate). The proportion of CD34(+)CD45(dim) HSPCs among the nucleated cells was significantly ($P < 0.05$, statistical power = 60.8%) higher in the cord blood samples of neonates born to mothers with GDM (median 0.38%) compared to neonates born to nondiabetic mothers (median

0.32%) and according to treatment types (P < 0.05) median: control 0.32%, GDM-diet only 0.37%, GDM-on insulin 0.45%; control versus GDM on insulin (P < 0.05). The increased proportion of circulating CD34(+)CD45(dim) cells in the cord blood may possibly be related to altered fetal stem cell mobilization in GDM pregnancy, yet these results should be interpreted only as preliminary due to the small sample sizes.

Itkin, T., S. Gur-Cohen, et al. "Distinct bone marrow blood vessels differentially regulate haematopoiesis." Nature. 2016 Apr 21;532(7599):323-328. doi: 10.1038/nature17624. Epub 2016 Apr 13.

Bone marrow endothelial cells (BMECs) form a network of blood vessels that regulate both leukocyte trafficking and haematopoietic stem and progenitor cell (HSPC) maintenance. However, it is not clear how BMECs balance these dual roles, and whether these events occur at the same vascular site. We found that mammalian bone marrow stem cell maintenance and leukocyte trafficking are regulated by distinct blood vessel types with different permeability properties. Less permeable arterial blood vessels maintain haematopoietic stem cells in a low reactive oxygen species (ROS) state, whereas the more permeable sinusoids promote HSPC activation and are the exclusive site for immature and mature leukocyte trafficking to and from the bone marrow. A functional consequence of high permeability of blood vessels is that exposure to blood plasma increases bone marrow HSPC ROS levels, augmenting their migration and differentiation, while compromising their long-term repopulation and survival. These findings may have relevance for clinical haematopoietic stem cell transplantation and mobilization protocols.

Jagirdar, N., R. D. Harvey, et al. "Plerixafor in combination with granulocyte-colony-stimulating factor after chemotherapy increases mobilization efficiency in patients with lymphoma or myeloma: results of a Phase II clinical trial." Transfusion. 2015 Oct;55(10):2351-7. doi: 10.1111/trf.13186. Epub 2015 Sep 2.

BACKGROUND: We tested whether adding plerixafor to G-CSF mobilization after chemotherapy would increase the proportion of patients collecting the target number of CD34+ cells/kg in 1 day of apheresis to >75%. STUDY DESIGN AND METHODS: Autologous stem cell transplant-anticipated multiple myeloma or lymphoma patients were eligible. Patients were mobilized with cyclophosphamide (n=17); DCEP (n=1); R-ICE (n=20); CHOP (n=2); or R-HCVAD (n=5) and given 5 mg/kg/day GCSF starting on Day 2 and increasing to 10 mg/kg/day on Day 6. Plerixafor 240 mg/kg was injected subcutaneously on the day the neutrophil count was more than 1.5 x 10(9) cells/L with apheresis the folllowing day. G-CSF, plerixafor, and apheresis continued daily until 5 x 10(6) (lymphoma) or 10 x 10(6) (myeloma) CD34+ cells/kg were collected. RESULTS: Seventeen myeloma and 28 lymphoma patients enrolled, and 76% collected the target number of CD34+ cells in 1 day. Twelve subjects with median CD34+ counts of 142 x 10(6) cells/L began apheresis without plerixafor and collected 20 x 10(6) CD34+ cells/kg in 1 day. The remaining 33 subjects, with median 11.7 x 10(6) CD34+ cells/L and 5.4 x 10(9) WBC/L, received plerixafor. Plerixafor-treated subjects collected 7.8 x 10(6) CD34+ cells/kg; 22 (67%) collected in 1 day, while 11 (33%) required more than 1 day. Plerixafor was well tolerated, with no serious adverse events. CONCLUSIONS: Plerixafor administration after chemotherapy for autologous stem cell mobilization is feasible, well tolerated, and increases the proportion of subjects collected in a single day compared to mobilization with G-CSF after chemotherapy.

Karakurt, N., T. Aksu, et al. "Angiopoietins in the bone marrow microenvironment of acute lymphoblastic leukemia." Hematology. 2016 Mar 1:1-7.

OBJECTIVE: Angiogenesis have implications in leukemia biology. Angiopoietin 1 (Ang 1) is an angiogenic cytokine which is essential in survival and proliferation of endothelial cells. Angiopoietin 2 (Ang 2) promotes dissociation of pericytes and increases vascular permeability and stromal derived factor 1 alpha (SDF 1alpha) which is a key player in stem cell traffic in the bone marrow (BM), has stimulating effects on angiogenesis as well. Here, we investigated the role of the leukemic BM microenvironment and specifically, the role of SDF 1alpha-CXCR4 and Ang 1/Ang 2-Tie 2 axes. METHODS: Here, Ang 1, Ang 2, and SDF 1alpha levels were measured in the BM plasma and in supernatants of mesenchymal stem/stromal cells (MSCs) of patients with ALL and compared with those of healthy controls. RESULTS: The results showed that at diagnosis, BM plasma levels of Ang 1 and SDF 1alpha were significantly low and Ang 2 was high when compared to control values. Remission induction was associated with an increase in Ang 1/Ang 2 ratio and SDF levels in BM plasma. DISCUSSION: The results suggest that BM microenvironment and leukemic cell-stroma interaction influences the secretion of Ang 1, 2 and SDF 1alpha, thus, may affect both angiogenesis, homing and mobilization of leukemic blasts.

Kyrcz-Krzemien, S., G. Helbig, et al. "Safety and efficacy of hematopoietic stem cells mobilization in patients with multiple sclerosis." Hematology. 2016 Feb 24:1-4.

INTRODUCTION: Multiple sclerosis (MS) is a T-cell-mediated chronic inflammatory disorder of the central nervous system. Several agents have been approved for treatment of MS, however their efficacy is limited and short term. Autologous hematopoietic stem cell (HSC) transplantation may remain an encouraging option for some MS patients who failed prior conventional treatment. OBJECTIVE: To assess the safety and effectiveness of HSCs mobilization in patients with MS. MATERIAL AND METHODS: Thirty-nine patients (20 females, 19 males) with relapsing-remitting MS at median age of 40 years (range 25-63) were included in this study. As a stem cell mobilization they received either granulocyte colony-stimulating factor (G-CSF) alone (10 mug/kg s.c. daily; n = 1) or cyclophosphamide (CY; 2.0 g/m2 i.v. on days 1-2) followed by G-CSF (n = 38). RESULTS: The median number of mobilized HSCs per kilogram was 6.32 x 106 (range 2.64-26.3 x 106). One apheresis was sufficient for collection of HSCs in 30 out of 39 MS patients (77%). Two aphereses were required for seven patients, three for one patient, and four for one patient (17, 3, and 3%, respectively). Side effects of HSCs mobilization have been reported for eight patients (30%) and they were as follows: Staphylococcus epidermidis bacteremia (n = 1), fever of unknown origin (n = 3), diarrhea (n = 3), and headache (n = 1). CONCLUSIONS: Mobilization using CY and/or G-CSF resulted in effective mobilization in all MS patients. This procedure was found to be safe. No fatal outcome has been reported.

Lisenko, K., M. Cremer, et al. "Efficient stem cell collection after modified cisplatin-based mobilization chemotherapy in patients with DLBCL." Biol Blood Marrow Transplant. 2016 Apr 6. pii: S1083-8791(16)30015-5. doi: 10.1016/j.bbmt.2016.03.030.

In patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) is commonly used as salvage therapy and for mobilization of peripheral blood stem cells (PBSC). At our center a modified regimen with administration of 25 mg/m2 cisplatin as a 3-hour infusion over 4 consecutive days instead of a single infusion of 100 mg/m2 over 24 hours has been established. The aim of this study was to analyze the efficiency of this modified R-DHAP scheme plus G-CSF as a mobilization regimen. We analyzed retrospectively clinical characteristics, PBSC collection and autologous stem cell transplantation (ASCT) parameters, as well as hematological reconstitution data of 65 patients with relapsed or refractory DLBCL who underwent PBSC collection after mobilization with the modified R-DHAP protocol at our institution between 2002 and 2013. Data were evaluated for the overall cohort and with regard to the number of R-DHAP cycles received prior to PBSC collection. PBSC collection was performed after the first, second or third R-DHAP course in 32 (49%), 30 (46%) and 3 (5%) patients, respectively. 63 (97%) patients reached the collection goal of >/=2.0x106 CD34+ cells/kg body weight (bw). A significantly higher median CD34+ collection yield was reached when cells were collected after the first compared to the second R-DHAP course ($p<0.01$). A peripheral blood leukocyte increase of >/=1.0 x109/l and platelets increase >/=20 x109/l was observed 11 days after ASCT. We conclude that the modified R-DHAP regimen proofed safe and feasible, showed an overall response rate (complete response, complete response unconfirmed, partial remission) of 66% and allowed efficient mobilization of CD34+ cells for PBSC collection.

Mangialardi, G. and P. Madeddu "Bone Marrow-Derived Stem Cells: a Mixed Blessing in the Multifaceted World of Diabetic Complications." Curr Diab Rep. 2016 May;16(5):43. doi: 10.1007/s11892-016-0730-x.

Diabetes is one of the main economic burdens in health care, which threatens to worsen dramatically if prevalence forecasts are correct. What makes diabetes harmful is the multi-organ distribution of its microvascular and macrovascular complications. Regenerative medicine with cellular therapy could be the dam against life-threatening or life-altering complications. Bone marrow-derived stem cells are putative candidates to achieve this goal. Unfortunately, the bone marrow itself is affected by diabetes, as it can develop a microangiopathy and neuropathy similar to other body tissues. Neuropathy leads to impaired stem cell mobilization from marrow, the so-called mobilopathy. Here, we review the role of bone marrow-derived stem cells in diabetes: how they are affected by compromised bone marrow integrity, how they contribute to other diabetic complications, and how they can be used as a treatment for these. Eventually, we suggest new tactics to optimize stem cell therapy.

Mansilla-Soto, J., I. Riviere, et al. "Cell and Gene Therapy for the Beta-Thalassemias: Advances and Prospects." Hum Gene Ther. 2016 Apr;27(4):295-304. doi: 10.1089/hum.2016.037.

The beta-thalassemias are inherited anemias caused by mutations that severely reduce or abolish expression of the beta-globin gene. Like sickle cell disease, a related beta-globin gene disorder, they are

ideal candidates for performing a genetic correction in patient hematopoietic stem cells (HSCs). The most advanced approach utilizes complex lentiviral vectors encoding the human beta-globin gene, as first reported by May et al. in 2000. Considerable progress toward the clinical implementation of this approach has been made in the past five years, based on effective CD34+ cell mobilization and improved lentiviral vector manufacturing. Four trials have been initiated in the United States and Europe. Of 16 evaluable subjects, 6 have achieved transfusion independence. One of them developed a durable clonal expansion, which regressed after several years without transformation. Although globin lentiviral vectors have so far proven to be safe, this occurrence suggests that powerful insulators with robust enhancer-blocking activity will further enhance this approach. The combined discovery of Bcl11a-mediated gamma-globin gene silencing and advances in gene editing are the foundations for another gene therapy approach, which aims to reactivate fetal hemoglobin (HbF) production. Its clinical translation will hinge on the safety and efficiency of gene targeting in true HSCs and the induction of sufficient levels of HbF to achieve transfusion independence.

Martino, M., A. G. Recchia, et al. "Efficacy of biosimilar granulocyte colony-stimulating factor versus originator granulocyte colony-stimulating factor in peripheral blood stem cell mobilization in de novo multiple myeloma patients." Cytotherapy. 2015 Oct;17(10):1485-93. doi: 10.1016/j.jcyt.2015.05.010. Epub 2015 Jul 15.

BACKGROUND AIMS: Filgrastim and lenograstim are the standard granulocyte colony-stimulating factor (G-CSF) agents for peripheral blood stem cell mobilization (PBSC) in patients who undergo autologous stem cell transplantation. METHODS: To assess whether biosimilars are effective, we conducted a single-center, prospective study that included 40 consecutive de novo multiple myeloma patients who received cyclophosphamide 4 g/m(2) per day plus biosimilar filgrastim G-CSF to mobilize PBSC. These patients were compared with a group of 37 patients matched for age, diagnosis, previous chemotherapy and mobilization who had been treated with originator G-CSF. The mean number of CD34+ cells/muL in the peripheral blood was 199.6 +/- 207.4 in the biosimilar and 192.8 +/- 154.7 in the originator group (P = 0.87). The median number of CD34+ cells/kg recipient collected was 11.5 +/- 5.8 and 12.3 +/- 5.3 in the biosimilar and originator groups, respectively (P = 0.51). The mobilization failure rate was 2.5% and 2.7% in the biosimilar filgrastim and originator filgrastim cohorts (P = NS), respectively. RESULTS: Twenty-nine patients in the biosimilar group and 28 patients in the originator group underwent autologous transplantation. There were no statistically significant differences between the biosimilar and originator G-CSF cohorts in terms of hematopoietic recovery parameters and transplant-related toxicities. CONCLUSIONS: The efficacy of biosimilar G-CSF appears to be equivalent to the reference G-CSF.

Matsumoto, T., T. Takami, et al. "Cell transplantation as a non-invasive strategy for treating liver fibrosis." Expert Rev Gastroenterol Hepatol. 2016 May;10(5):639-48. doi: 10.1586/17474124.2016.1134313. Epub 2016 Jan 11.

Advancements in antiviral drugs have enabled control of viral hepatitis; yet, many patients with liver cirrhosis (LC) are awaiting liver transplants. Liver transplantation yields dramatic therapeutic effects, but problems such as shortage of donors, surgical invasiveness, immunological rejection and costs, limit the number of transplantations. Advances in liver regeneration therapy through cell transplantation as a non-invasive treatment for cirrhosis will supplement these restrictions to the number of liver transplants. Clinical trials for LC have included hematopoietic stem cell mobilization by administration of granulocyte colony-stimulating factor, infusion of autologous bone marrow cells, and administration of autologous mesenchymal stem cells derived from bone marrow or umbilical cord. Several recently reported randomized controlled studies have shown the effectiveness of these approaches.

McCabe, A. and K. C. MacNamara "Macrophages: Key regulators of steady-state and demand-adapted hematopoiesis." Exp Hematol. 2016 Apr;44(4):213-22. doi: 10.1016/j.exphem.2016.01.003. Epub 2016 Jan 22.

Hematopoietic stem cell (HSC) function is required for balanced blood production throughout life; it is thus essential to understand the mechanisms regulating this highly dynamic process. Bone marrow-resident macrophages (Mvarphis) have recently emerged as an important component of the HSC niche, where they contribute to regulating HSC and progenitor cell (HSPC) mobilization and function. Here we review the role of macrophages (Mvarphis) on immune cell production, HSPC pool size, and mobilization at steady state and under inflammatory conditions. Inflammation induces marked changes in hematopoiesis to restrict or promote generation of specific cell lineages, and this often has a negative impact on HSC function. Cytokines and growth factors induced during inflammation influence hematopoiesis by acting directly on HSPCs and/or by modulating niche cell function. We focus particular

attention on the opposing effects of two key inflammatory proteins, interferon-gamma and granulocyte-colony stimulating factor, in regulating bone marrow-resident macrophages (Mvarphis) and HSPCs. Macrophages (Mvarphis) are essential for tissue homeostasis, and here we highlight their emerging role as a central regulator of both steady-state and demand-adapted hematopoiesis.

Mohammadi, M., M. Vaezi, et al. "Effects of short-term pretreatment with atorvastatin on mobilization of hematopoietic progenitor cells: A double-blind, randomized, controlled trial." Int J Hematol Oncol Stem Cell Res. 2015 Oct 1;9(4):173-9.

BACKGROUND: Despite recent advances in mobilization techniques, a considerable portion of patients fail to mobilize sufficient number of cells for successful autologous stem cell transplantation. There are several studies available that have demonstrated enhanced mobilization of endothelial progenitor cells with atorvastatin. Therefore, this prospective trial was conducted to evaluate the mobilizing effect of atorvastatin on hematopoietic progenitor cells. SUBJECTS AND METHODS: Forty-four autologous HSCT candidates were randomized in a double-blind controlled trial to receive atorvastatin 40 mg daily or placebo plus standard G-CSF regimen. Treatment was initiated at the time of hospitalization and continued until the day of cell harvest. Independent-samples T-Test, Repeated Measures ANOVA and Mann-Whitney U test were performed to compare means. Categorical variables were analyzed using Chi-square and Fisher's exact test. RESULTS: Mean number of hematopoietic progenitor cells per microL of peripheral blood at the time of cell harvest did not differ significantly between the two groups. There was no statistically significant difference in secondary outcomes like time of platelet or PMN engraftment, occurrence of bleeding or infectious episode, duration of hospitalization and etc.

Ozkan, M. C., F. Sahin, et al. "Peripheral blood stem cell mobilization from healthy donors." Transfus Apher Sci. 2015 Aug;53(1):13-6. doi: 10.1016/j.transci.2015.05.008. Epub 2015 May 19.

Most frequently used graft of hematopoietic stem cells (HSCs) for allogeneic transplantation is peripheral blood stem cells (PBSCs) that are collected after mobilization with frequently granulocyte colony-stimulating factor (G-CSF). Administration of the optimal dose of G-CSF while preserving the donor health is one of the most important points for sufficient PBSC mobilization and harvest. We hereby tried to summarize characteristic features, potential side effects and main topics in peripheral blood stem cell mobilization from healthy donors.

Panaroni, C., K. Fulzele, et al. "PTH Signaling in Osteoprogenitors Is Essential for B-Lymphocyte Differentiation and Mobilization." J Bone Miner Res. 2015 Dec;30(12):2273-86. doi: 10.1002/jbmr.2581. Epub 2015 Jul 20.

Cells of the osteoblast lineage provide critical support for B lymphopoiesis in the bone marrow (BM). Parathyroid hormone (PTH) signaling in osteoblastic cells through its receptor (PPR) is an important regulator of hematopoietic stem cells; however, its role in regulation of B lymphopoiesis is not clear. Here we demonstrate that deletion of PPR in osteoprogenitors results in a significant loss of trabecular and cortical bone. PPR signaling in osteoprogenitors, but not in mature osteoblasts or osteocytes, is critical for B-cell precursor differentiation via IL-7 production. Interestingly, despite a severe reduction in B-cell progenitors in BM, mature B-lymphocytes were increased 3.5-fold in the BM of mice lacking PPR in osteoprogenitors. This retention of mature IgD(+) B cells in the BM was associated with increased expression of vascular cell adhesion molecule 1 (VCAM1) by PPR-deficient osteoprogenitors, and treatment with VCAM1 neutralizing antibody increased mobilization of B lymphocytes from mutant BM. Our results demonstrate that PPR signaling in early osteoblasts is necessary for B-cell differentiation via IL-7 secretion and for B-lymphocyte mobilization via VCAM1. (c) 2015 American Society for Bone and Mineral Research.

Peruzzi, M., E. De Falco, et al. "State of the Art on the Evidence Base in Cardiac Regenerative Therapy: Overview of 41 Systematic Reviews." Biomed Res Int. 2015;2015:613782. doi: 10.1155/2015/613782. Epub 2015 Jun 15.

OBJECTIVES: To provide a comprehensive appraisal of the evidence from secondary research on cardiac regenerative therapy. STUDY DESIGN AND SETTING: Overview of systematic reviews of controlled clinical trials concerning stem cell administration or mobilization in patients with cardiovascular disease. RESULTS: After a systematic database search, we short-listed 41 reviews (660 patients). Twenty-two (54%) reviews focused on acute myocardial infarction (AMI), 19 (46%) on chronic ischemic heart disease (IHD) or heart failure (HF), 29 (71%) on bone marrow-derived stem-cells (BMSC), and 36 (88%) to randomized trials only. Substantial variability among reviews was found for validity (AMSTAR score: median 9 [minimum 3]; 1st quartile 9; 3rd quartile 10; maximum 11), effect estimates (change in ejection fraction from baseline to follow-up: 3.47% [0.02%; 2.90%; 4.22%; 6.11%]), and

citations (Web of Science yearly citations: 4.1 [0; 2.2; 6.5; 68.9]). No significant association was found between these three features. However, reviews focusing on BMSC therapy had higher validity scores (P = 0.008) and showed more pronounced effect estimates (P = 0.002).

Pham, T., S. Patil, et al. "Comparison of biosimilar filgrastim with originator filgrastim for peripheral blood stem cell mobilization and engraftment in patients with multiple myeloma undergoing autologous stem cell transplantation." Transfusion. 2015 Nov;55(11):2709-13. doi: 10.1111/trf.13233. Epub 2015 Jul 14.

BACKGROUND: Nivestim is a biosimilar approved for the same indications as Neupogen including the mobilization of autologous peripheral blood stem cells (PBSCs). The clinical efficacy and safety of Nivestim for this use have not been formally assessed in clinical trials. STUDY DESIGN AND METHODS: In our retrospective single-center study we compared variables of PBSC mobilization and engraftment of 60 patients mobilized with Nivestim to that of 38 patients mobilized with Neupogen. RESULTS: We found no difference between Nivestim and Neupogen in peripheral blood CD34+ at first leukapheresis (47 x 10(6) cells/L vs. 60 x 10(6) cells/L, p = 0.48) nor the total CD34+ collected (5.37 x 10(6)/kg vs. 4.59 x 10(6) /kg, p = 0.22). However, a difference in the median number of leukapheresis procedures (one vs. two, p = 0.0007) was observed. Eighty-one patients (51 Nivestim and 30 Neupogen mobilized) went on to transplantation. Median time to neutrophil engraftment (15 days vs. 13.5 days, p = 0.09) and platelet (PLT) engraftment (20 days vs. 18 days, p = 0.01) was longer in the Nivestim group. The significant delay in PLT engraftment did not, however, translate to increased PLT transfusions (two vs. three, p = 0.2) or impact significantly on hospitalization time for admissions within 30 days posttransplant (20 days vs. 18 days, p = .17).

Phinney, D. G., M. Di Giuseppe, et al. "Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs." Nat Commun. 2015 Oct 7;6:8472. doi: 10.1038/ncomms9472.

Mesenchymal stem cells (MSCs) and macrophages are fundamental components of the stem cell niche and function coordinately to regulate haematopoietic stem cell self-renewal and mobilization. Recent studies indicate that mitophagy and healthy mitochondrial function are critical to the survival of stem cells, but how these processes are regulated in MSCs is unknown. Here we show that MSCs manage intracellular oxidative stress by targeting depolarized mitochondria to the plasma membrane via arrestin domain-containing protein 1-mediated microvesicles. The vesicles are then engulfed and re-utilized via a process involving fusion by macrophages, resulting in enhanced bioenergetics. Furthermore, we show that MSCs simultaneously shed micro RNA-containing exosomes that inhibit macrophage activation by suppressing Toll-like receptor signalling, thereby de-sensitizing macrophages to the ingested mitochondria. Collectively, these studies mechanistically link mitophagy and MSC survival with macrophage function, thereby providing a physiologically relevant context for the innate immunomodulatory activity of MSCs.

Piscaglia, A. C., S. Rutella, et al. "Circulating hematopoietic stem cells and putative intestinal stem cells in coeliac disease." J Transl Med. 2015 Jul 11;13:220. doi: 10.1186/s12967-015-0591-0.

BACKGROUND: The intestinal stem cells (ISC) modulation and the role of circulating hematopoietic stem cells (HSC) in coeliac disease (CD) are poorly understood. Our aim was to investigate the longitudinal modifications in peripheral blood HSC traffic and putative ISC density induced by gluten-free diet (GFD) in CD. METHODS: Thirty-one CD patients and 7 controls were enrolled. Circulating CD133(+) and CD34(+) HSC were measured by flow cytometry, at enrolment and after 7 days and 1, 3, 6, 12, and 24 months of GFD. Endoscopy was performed at diagnosis and repeated at 6, 12, and 24 months following GFD. We used the Marsh-Oberhuber score to evaluate the histological severity of duodenal damage; immunohistochemistry was employed to measure the intraepithelial lymphoid infiltrate (IEL, CD3(+) lymphoid cells) and the putative ISC compartment (CD133(+) and Lgr5(+) epithelial cells). RESULTS: At enrolment, circulating HSCs were significantly increased in CD patients and they further augmented during the first week of GFD, but progressively decreased afterwards. CD patients presented with villous atrophy, abundant IEL and rare ISC residing at the crypt base. Upon GFD, IEL progressively decreased, while ISC density increased, peaking at 12 months. After 24 months of GFD, all patients were asymptomatic and their duodenal mucosa was macroscopically and histologically normal.

Sawen, P., S. Lang, et al. "Mitotic History Reveals Distinct Stem Cell Populations and Their Contributions to Hematopoiesis." Cell Rep. 2016 Mar 29;14(12):2809-18. doi: 10.1016/j.celrep.2016.02.073. Epub 2016 Mar 17.

Homeostasis of short-lived blood cells is dependent on rapid proliferation of immature

precursors. Using a conditional histone 2B-mCherry-labeling mouse model, we characterize hematopoietic stem cell (HSC) and progenitor proliferation dynamics in steady state and following several types of induced stress. HSC proliferation following HSC transplantation into lethally irradiated mice is fundamentally different not only from native hematopoiesis but also from other stress contexts. Whereas transplantation promoted sustained, long-term proliferation of HSCs, both cytokine-induced mobilization and acute depletion of selected blood cell lineages elicited very limited recruitment of HSCs to the proliferative pool. By coupling mCherry-based analysis of proliferation history with multiplex gene expression analyses on single cells, we have found that HSCs can be stratified into four distinct subtypes. These subtypes have distinct molecular signatures and differ significantly in their reconstitution potentials, showcasing the power of tracking proliferation history when resolving functional heterogeneity of HSCs.

Scala, S. "Molecular Pathways: Targeting the CXCR4-CXCL12 Axis--Untapped Potential in the Tumor Microenvironment." Clin Cancer Res. 2015 Oct 1;21(19):4278-85. doi: 10.1158/1078-0432.CCR-14-0914. Epub 2015 Jul 21.

Evidence suggests that the CXC-chemokine receptor-4 pathway plays a role in cancer cell homing and metastasis, and thus represents a potential target for cancer therapy. The homeostatic microenvironment chemokine CXCL12 binds the CXCR4 and CXCR7 receptors, activating divergent signals on multiple pathways, such as ERK1/2, p38, SAPK/JNK, AKT, mTOR, and the Bruton tyrosine kinase (BTK). An activating mutation in CXCR4 is responsible for a rare disease, WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), and dominant CXCR4 mutations have also been reported in Waldenstrom macroglobulinemia. The CXCR4-CXCL12 axis regulates the hematopoietic stem cell niche--a property that has led to the approval of the CXCR4 antagonist plerixafor (AMD3100) for mobilization of hematopoietic precursors.

Severson, C. C. "The role of biosimilar granulocyte colony stimulating factor (GCSF) Zarzio for progenitor cell mobilization and the treatment of therapy-induced neutropenia in adult hematopoietic stem cell transplantation." Can Oncol Nurs J. 2015 Fall;25(4):443-54.

Originator GCSF (Neupogen) has been used to mobilize progenitor stem cells and treat therapy-induced neutropenia in Canadian stem cell transplant settings for years. Although its benefit is not in question, viable alternatives are available. Biosimilar GCSF (Zarzio) is widely in use in Europe since 2009 and was recently approved in the U.S.for the same five indications as Neupogen. Zarzio is reported as safe, equally efficacious, more accessible and cost effective without negatively impacting patient outcomes. This paper summarizes the supporting evidence.

Shaw, B. E., B. R. Logan, et al. "Analysis of the Effect of Race, Socioeconomic Status, and Center Size on Unrelated National Marrow Donor Program Donor Outcomes: Donor Toxicities Are More Common at Low-Volume Bone Marrow Collection Centers." Biol Blood Marrow Transplant. 2015 Oct;21(10):1830-8. doi: 10.1016/j.bbmt.2015.06.013. Epub 2015 Jun 23.

Previous studies have shown that risks of collection-related pain and symptoms are associated with sex, body mass index, and age in unrelated donors undergoing collection at National Marrow Donor Program centers. We hypothesized that other important factors (race, socioeconomic status [SES], and number of procedures at the collection center) might affect symptoms in donors. We assessed outcomes in 2726 bone marrow (BM) and 6768 peripheral blood stem cell (PBSC) donors collected between 2004 and 2009. Pain/symptoms are reported as maximum levels over mobilization and collection (PBSC) or within 2 days of collection (BM) and at 1 week after collection. For PBSC donors, race and center volumes were not associated with differences in pain/symptoms at any time. PBSC donors with high SES levels reported higher maximum symptom levels 1 week after donation (P = .017).

Sivgin, S., E. Karakus, et al. "Evaluation of the efficacy and safety of original filgrastim (Neupogen(R)), biosimilar filgrastim (Leucostim(R)) and Lenograstim (Granocyte(R)) in CD34 peripheral hematopoietic stem cell mobilization procedures for allogeneic hematopoietic stem cell transplant donors." Transfus Apher Sci. 2016 Mar 24. pii: S1473-0502(16)00049-5. doi: 10.1016/j.transci.2016.03.003.

OBJECTIVES AND AIM: In this study, we aimed to compare the potency of different G-CSF agents including original filgrastim (Neupogen(R)), biosimilar filgrastim (Leucostim(R)) and Lenograstim (Granocyte(R)) on CD34+ cell mobilization in patients that underwent allogeneic hematopoietic stem cell transplantation (alloHSCT). PATIENTS AND METHODS: The data of 243 donors for alloHSCT recipients diagnosed with mostly acute leukemia and myelodsyplastic syndromes (MDS) were analyzed, retrospectively. Data for stem cell mobilization have been recorded from patients' files. Donors who received Filgrastim (Neupogen(R), Group I),

biosimilar Filgrastim (Leucostim(R), Group II) and Lenograstim (Granocyte(R), Group III) were analyzed for total CD34+ cell count at the end of mobilization procedures. RESULTS: A total of 243 donors and patients for alloHSCT were analyzed retrospectively. The diagnosis of the patients were; acute myeloid leukemia (AML) (110 patients, 45.2%), acute lymphoid leukemia (ALL) (61 patients, 25.1%), aplastic anemia (AA) (38 patients, 15.6%), lymphomas (14 patients, 5.7%) and others (20 patients, 8.4%). The median number of total collected PB CD34+ cells (x106/kg) was 7.12 (min-max: 5.38-7.90) in the Neupogen(R) group, 7.27 (min-max: 6.79-7.55) in the Leucostim(R) group and 7.15 (min-max: 5.34-7.58) in the Granocyte(R) group. There was no statistically significant difference among groups in terms of total collected PB CD34+ cells ($p = 0.919$). The median doses of G-CSF agents (microg/kg/day) in PBSC collection in Neupogen(R) group was; 11.00 (10.00-12.00) in Leucostim(R) group10.35 (min-max: 10.00-11.10) and in Granocyte(R) group11.00 (min-max: 10.00-11.00). There was no statistical significance among groups ($p = 0.215$). CONCLUSION: Biosimilar filgrastim (Leucostim(R)) was found comparable to original Filgrastim (Neupogen(R)) and Lenograstim (Granocyte(R)) for PBSC mobilization in donors of the patients that underwent alloHSCT.

Sugiyama, A., T. Yujiri, et al. "Altered expression of circadian clock genes during peripheral blood stem cell mobilization induced by granulocyte colony-stimulating factor." Chronobiol Int. 2015 Aug;32(7):934-41. doi: 10.3109/07420528.2015.1053910.

Circulating hematopoietic stem cells exhibit robust circadian fluctuations, which influence the mobilized cell yield, even during enforced stem cell mobilization. However, alterations in the expression of circadian clock genes during granulocyte colony-stimulating factor (G-CSF)-induced peripheral blood stem cell (PBSC) mobilization are not fully elucidated. Therefore, we measured the expression of these genes in human peripheral blood leukocytes from 21 healthy donors. While CRY1 mRNA expression significantly increased by 3.9-fold ($p < 0.01$), the expression of PER3, CRY2 and BMAL1 mRNAs significantly decreased (by 0.2-fold, 0.2-fold, and 0.6-fold, respectively; $p < 0.001$) after G-CSF administration. Moreover, CRY1 mRNA expression was inversely correlated with the plasma level of noradrenaline ($r = -0.36$, $p < 0.05$), while PER3, CRY2, and BMAL1 mRNA expression directly correlated with the plasma level of noradrenaline ($r = 0.55$, $r = 0.66$, and $r = 0.57$, respectively; $p < 0.001$). Thus, significant correlations between the levels of circadian clock gene mRNAs and the plasma level of noradrenaline, a sympathetic nervous system neurotransmitter, were established. The modulation of sympathetic activation and of the circadian clock may be novel therapeutic targets for increasing stem cell yields in PBSC donors.

Timuragaoglu, A. "The role of the nurses and technicians for stem cell mobilisation and collection." Transfus Apher Sci. 2015 Aug;53(1):30-3. doi: 10.1016/j.transci.2015.05.012. Epub 2015 Jun 29.

Stem Cell Transplantation is last chance for some patients and they enter the unit highly hopeful for their life. Although the physicians, medical director of unit are the observable part of iceberg, which is on the surface, nurses and the other members of team are like the huge invisible part of iceberg. If they are not educated well increased mortality rates are inevitable. This article summarises the role of nurses well to the fore and technicians.

Werner, J. K. and R. D. Stevens "Traumatic brain injury: recent advances in plasticity and regeneration." Curr Opin Neurol. 2015 Dec;28(6):565-73. doi: 10.1097/WCO.0000000000000265.

PURPOSE OF REVIEW: There is an urgent need for effective therapies to restore neurologic function and decrease disability following traumatic brain injury (TBI). Here, emerging findings on the mechanisms of post-TBI neural repair and regeneration, as well as therapeutic implications, are selectively reviewed. RECENT FINDINGS: Recent discoveries include the characterization of the inhibitory signaling systems within the injury site, postinjury stem cell niche activation, the role of serotonin signaling in repair, and environment enrichment. A potentially transformative finding has been the identification of exosomes, nano-sized extracellular vesicles which have key roles in cell signaling, and might serve as novel biomarkers and as vehicles for targeted delivery of repair-inducing molecules. SUMMARY: In the experimental setting, post-TBI repair can be promoted by modulation of inhibitory signaling, neurotrophic factor administration, and amplified serotonin signaling; additional strategies include mobilization of endogenous stem cell populations, exogenous cell-based therapies, and environmental enhancement. Feasibility, safety, and efficacy of these approaches need further investigation in humans. Studies are also needed to evaluate biomarkers based on molecular traces of neural repair and regeneration, which could transform prognostic and predictive modeling of post-TBI recovery trajectories.

The above contents are the collected information

from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Adamiak, M., A. Poniewierska-Baran, et al. "Evidence that a lipolytic enzyme-hematopoietic-specific phospholipase C-beta2-promotes mobilization of hematopoietic stem cells by decreasing their lipid raft-mediated bone marrow retention and increasing the promobilizing effects of granulocytes." Leukemia. 2016 Apr;30(4):919-28. doi: 10.1038/leu.2015.315. Epub 2015 Nov 19.
2. Afifi, S., N. G. Adel, et al. "Upfront plerixafor plus G-CSF versus cyclophosphamide plus G-CSF for stem cell mobilization in multiple myeloma: efficacy and cost analysis study." Bone Marrow Transplant. 2016 Apr;51(4):546-52. doi: 10.1038/bmt.2015.322. Epub 2016 Jan 4.
3. Al Tayeb, H., A. El Dorry, et al. "Autologous Stem Cells Transplantation in Egyptian Patients with Liver Cirrhosis on Top of Hepatitis C Virus." Int J Stem Cells. 2015 Nov;8(2):209-18. doi: 10.15283/ijsc.2015.8.2.209.
4. Ali, N., S. N. Adil, et al. "Autologous Hematopoietic Stem Cell Transplantation-10 Years of Data From a Developing Country." Stem Cells Transl Med. 2015 Aug;4(8):873-7. doi: 10.5966/sctm.2015-0015. Epub 2015 Jun 1.
5. Andreeva, E. R., M. V. Pogodina, et al. "[Hypoxic stress as a trigger of multipotent mesenchymal stromal cell activation]." Fiziol Cheloveka. 2015 Mar-Apr;41(2):123-9.
6. Andreone, P., L. Catani, et al. "Reinfusion of highly purified CD133+ bone marrow-derived stem/progenitor cells in patients with end-stage liver disease: A phase I clinical trial." Dig Liver Dis. 2015 Dec;47(12):1059-66. doi: 10.1016/j.dld.2015.08.018. Epub 2015 Sep 10.
7. Baidu. http://www.baidu.com. 2016
8. Bar-Or, D., G. W. Thomas, et al. "Low Molecular Weight Fraction of Commercial Human Serum Albumin Induces Morphologic and Transcriptional Changes of Bone Marrow-Derived Mesenchymal Stem Cells." Stem Cells Transl Med. 2015 Aug;4(8):945-55. doi: 10.5966/sctm.2014-0293. Epub 2015 Jun 3.
9. Bilgin, Y. M. and G. E. de Greef "Plerixafor for stem cell mobilization: the current status." Curr Opin Hematol. 2016 Jan;23(1):67-71. doi: 10.1097/MOH.0000000000000200.
10. Bitan, M., R. Eshel, et al. "Combined plerixafor and granulocyte colony-stimulating factor for harvesting high-dose hematopoietic stem cells: Possible niche for plerixafor use in pediatric patients." Pediatr Transplant. 2016 Mar 16. doi: 10.1111/petr.12692.
11. Bunse, C. E., S. Tischer, et al. "G-CSF impairs CD8+ T-cell functionality by interfering with central activation elements." Clin Exp Immunol. 2016 Mar 16. doi: 10.1111/cei.12794.
12. Cameron, A. M., R. Wesson, et al. "Chimeric Allografts Induced by Short-Term Treatment with Stem Cell Mobilizing Agents Result in Long-term Kidney Transplant Survival without Immunosuppression: II Study in Miniature Swine." Am J Transplant. 2016 Jan 8. doi: 10.1111/ajt.13703.
13. Danylesko, I., R. Sareli, et al. "Plerixafor (Mozobil): A Stem Cell-Mobilizing Agent for Transplantation in Lymphoma Patients Predicted to Be Poor Mobilizers - A Pilot Study." Acta Haematol. 2016;135(1):29-36. doi: 10.1159/000435769. Epub 2015 Aug 22.
14. de Wit, R. H., S. M. de Munnik, et al. "Molecular Pharmacology of Chemokine Receptors." Methods Enzymol. 2016;570:457-515. doi: 10.1016/bs.mie.2015.12.002. Epub 2016 Jan 19.
15. Debeurme, F., C. Lacout, et al. "JAK2 inhibition has different therapeutic effects according to myeloproliferative neoplasm development in mice." J Cell Mol Med. 2015 Nov;19(11):2564-74. doi: 10.1111/jcmm.12608. Epub 2015 Jul 14.
16. DeLeve, L. D., X. Wang, et al. "VEGF-sdf1 RECRUITMENT OF CXCR7+ BONE MARROW PROGENITORS OF LIVER SINUSOIDAL ENDOTHELIAL CELLS PROMOTES RAT LIVER REGENERATION." Am J Physiol Gastrointest Liver Physiol. 2016 Mar 3:ajpgi.00056.2016. doi: 10.1152/ajpgi.00056.2016.
17. Dogu, M. H., A. H. Kaya, et al. "Does the preference of peripheral versus central venous access in peripheral blood stem cell collection/yield change stem cell kinetics in autologous stem cell transplantation?" Transfus Apher Sci. 2016 Feb;54(1):76-9. doi: 10.1016/j.transci.2016.01.017. Epub 2016 Jan 11.
18. Elayan, M. M., J. G. Horowitz, et al. "Tbo-Filgrastim versus Filgrastim during Mobilization and Neutrophil Engraftment for Autologous Stem Cell Transplantation." Biol Blood Marrow Transplant. 2015 Nov;21(11):1921-5. doi: 10.1016/j.bbmt.2015.05.024. Epub 2015 May 30.
19. Elbana, A. M., S. Abdel-Salam, et al. "Role of Endogenous Bone Marrow Stem Cells Mobilization in Repair of Damaged Inner Ear in Rats." Int J Stem Cells. 2015 Nov;8(2):146-54. doi: 10.15283/ijsc.2015.8.2.146.
20. Elsaesser, A. F., S. Schwarz, et al. "Characterization of a migrative subpopulation of adult human nasoseptal chondrocytes with progenitor cell features and their potential for in vivo cartilage regeneration strategies." Cell Biosci. 2016 Feb 13;6:11. doi: 10.1186/s13578-016-0078-6. eCollection 2016.
21. Gao, F., H. Hou, et al. "Bone marrow-derived cells in ocular neovascularization: contribution and mechanisms." Angiogenesis. 2016 Apr;19(2):107-18. doi: 10.1007/s10456-016-9497-6. Epub 2016 Feb 15.
22. Gazendam, R. P., A. van de Geer, et al. "Impaired killing of Candida albicans by granulocytes mobilized for transfusion purposes: a role for granule components." Haematologica. 2016 Jan 22. pii: haematol.2015.136630.
23. Goker, H., S. Etgul, et al. "Optimizing mobilization strategies in difficult-to-mobilize patients: The role of plerixafor." Transfus Apher Sci. 2015 Aug;53(1):23-9. doi: 10.1016/j.transci.2015.05.011. Epub 2015 Jun 9.
24. Google. http://www.google.com. 2016
25. Grabmaier, U., B. C. Huber, et al. "Mobilisation of haemopoietic stem cells in teriparatide-treated patients." Intern Med J. 2015 Aug;45(8):872-6. doi: 10.1111/imj.12830.
26. Griffiths, K., O. Dolezal, et al. "I-bodies: human single domain antibodies that antagonize chemokine receptor CXCR4." J Biol Chem. 2016 Apr 1. pii: jbc.M116.721050.
27. Guner, S. I., M. T. Yanmaz, et al. "The High Effect of Chemomobilization with High-Dose Etopside + Granulocyte-Colony Stimulating Factor in Autologous Hematopoietic Peripheral Blood Stem Cell Transplantation: A Single Center Experience." Hematol Rep. 2016 Mar 18;8(1):6319. doi: 10.4081/hr.2016.6319. eCollection 2016 Mar 17.
28. Gur-Cohen, S., T. Itkin, et al. "PAR1 signaling regulates the retention and recruitment of EPCR-expressing bone marrow hematopoietic stem cells." Nat Med. 2015 Nov;21(11):1307-17. doi: 10.1038/nm.3960. Epub 2015 Oct 12.
29. Hadarits, O., A. Zoka, et al. "Increased Proportion of Hematopoietic Stem and Progenitor Cell Population in Cord Blood of Neonates Born to Mothers with Gestational Diabetes Mellitus." Stem Cells Dev. 2016 Jan 1;25(1):13-7. doi: 10.1089/scd.2015.0203. Epub 2015 Nov 24.
30. Itkin, T., S. Gur-Cohen, et al. "Distinct bone marrow blood vessels differentially regulate haematopoiesis." Nature. 2016 Apr 21;532(7599):323-328. doi: 10.1038/nature17624. Epub 2016 Apr 13.
31. Jagirdar, N., R. D. Harvey, et al. "Plerixafor in combination with granulocyte-colony-stimulating factor after chemotherapy increases mobilization efficiency in patients

with lymphoma or myeloma: results of a Phase II clinical trial." Transfusion. 2015 Oct;55(10):2351-7. doi: 10.1111/trf.13186. Epub 2015 Sep 2.
32. Karakurt, N., T. Aksu, et al. "Angiopoietins in the bone marrow microenvironment of acute lymphoblastic leukemia." Hematology. 2016 Mar 1:1-7.
33. Kyrcz-Krzemien, S., G. Helbig, et al. "Safety and efficacy of hematopoietic stem cells mobilization in patients with multiple sclerosis." Hematology. 2016 Feb 24:1-4.
34. Lisenko, K., M. Cremer, et al. "Efficient stem cell collection after modified cisplatin-based mobilization chemotherapy in patients with DLBCL." Biol Blood Marrow Transplant. 2016 Apr 6. pii: S1083-8791(16)30015-5. doi: 10.1016/j.bbmt.2016.03.030.
35. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
36. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
37. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
38. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
39. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
40. Mangialardi, G. and P. Madeddu "Bone Marrow-Derived Stem Cells: a Mixed Blessing in the Multifaceted World of Diabetic Complications." Curr Diab Rep. 2016 May;16(5):43. doi: 10.1007/s11892-016-0730-x.
41. Mansilla-Soto, J., I. Riviere, et al. "Cell and Gene Therapy for the Beta-Thalassemias: Advances and Prospects." Hum Gene Ther. 2016 Apr;27(4):295-304. doi: 10.1089/hum.2016.037.
42. Martino, M., A. G. Recchia, et al. "Efficacy of biosimilar granulocyte colony-stimulating factor versus originator granulocyte colony-stimulating factor in peripheral blood stem cell mobilization in de novo multiple myeloma patients." Cytotherapy. 2015 Oct;17(10):1485-93. doi: 10.1016/j.jcyt.2015.05.010. Epub 2015 Jul 15.
43. Matsumoto, T., T. Takami, et al. "Cell transplantation as a non-invasive strategy for treating liver fibrosis." Expert Rev Gastroenterol Hepatol. 2016 May;10(5):639-48. doi: 10.1586/17474124.2016.1134313. Epub 2016 Jan 11.
44. McCabe, A. and K. C. MacNamara "Macrophages: Key regulators of steady-state and demand-adapted hematopoiesis." Exp Hematol. 2016 Apr;44(4):213-22. doi: 10.1016/j.exphem.2016.01.003. Epub 2016 Jan 22.
45. Mohammadi, M., M. Vaezi, et al. "Effects of short-term pretreatment with atorvastatin on mobilization of hematopoietic progenitor cells: A double-blind, randomized, controlled trial." Int J Hematol Oncol Stem Cell Res. 2015 Oct 1;9(4):173-9.
46. National Center for Biotechnology Information, U.S. National Library of Medicine**.** http://www.ncbi.nlm.nih.gov/pubmed. 2015.
47. Ozkan, M. C., F. Sahin, et al. "Peripheral blood stem cell mobilization from healthy donors." Transfus Apher Sci. 2015 Aug;53(1):13-6. doi: 10.1016/j.transci.2015.05.008. Epub 2015 May 19.
48. Panaroni, C., K. Fulzele, et al. "PTH Signaling in Osteoprogenitors Is Essential for B-Lymphocyte Differentiation and Mobilization." J Bone Miner Res. 2015 Dec;30(12):2273-86. doi: 10.1002/jbmr.2581. Epub 2015 Jul 20.
49. Peruzzi, M., E. De Falco, et al. "State of the Art on the Evidence Base in Cardiac Regenerative Therapy: Overview of 41 Systematic Reviews." Biomed Res Int. 2015;2015:613782. doi: 10.1155/2015/613782. Epub 2015 Jun 15.
50. Pham, T., S. Patil, et al. "Comparison of biosimilar filgrastim with originator filgrastim for peripheral blood stem cell mobilization and engraftment in patients with multiple myeloma undergoing autologous stem cell transplantation." Transfusion. 2015 Nov;55(11):2709-13. doi: 10.1111/trf.13233. Epub 2015 Jul 14.
51. Phinney, D. G., M. Di Giuseppe, et al. "Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs." Nat Commun. 2015 Oct 7;6:8472. doi: 10.1038/ncomms9472.
52. Piscaglia, A. C., S. Rutella, et al. "Circulating hematopoietic stem cells and putative intestinal stem cells in coeliac disease." J Transl Med. 2015 Jul 11;13:220. doi: 10.1186/s12967-015-0591-0.
53. Sawen, P., S. Lang, et al. "Mitotic History Reveals Distinct Stem Cell Populations and Their Contributions to Hematopoiesis." Cell Rep. 2016 Mar 29;14(12):2809-18. doi: 10.1016/j.celrep.2016.02.073. Epub 2016 Mar 17.
54. Scala, S. "Molecular Pathways: Targeting the CXCR4-CXCL12 Axis--Untapped Potential in the Tumor Microenvironment." Clin Cancer Res. 2015 Oct 1;21(19):4278-85. doi: 10.1158/1078-0432.CCR-14-0914. Epub 2015 Jul 21.
55. Severson, C. C. "The role of biosimilar granulocyte colony stimulating factor (GCSF) Zarzio for progenitor cell mobilization and the treatment of therapy-induced neutropenia in adult hematopoietic stem cell transplantation." Can Oncol Nurs J. 2015 Fall;25(4):443-54.
56. Shaw, B. E., B. R. Logan, et al. "Analysis of the Effect of Race, Socioeconomic Status, and Center Size on Unrelated National Marrow Donor Program Donor Outcomes: Donor Toxicities Are More Common at Low-Volume Bone Marrow Collection Centers." Biol Blood Marrow Transplant. 2015 Oct;21(10):1830-8. doi: 10.1016/j.bbmt.2015.06.013. Epub 2015 Jun 23.
57. Sivgin, S., E. Karakus, et al. "Evaluation of the efficacy and safety of original filgrastim (Neupogen(R)), biosimilar filgrastim (Leucostim(R)) and Lenograstim (Granocyte(R)) in CD34 peripheral hematopoietic stem cell mobilization procedures for allogeneic hematopoietic stem cell transplant donors." Transfus Apher Sci. 2016 Mar 24. pii: S1473-0502(16)00049-5. doi: 10.1016/j.transci.2016.03.003.
58. Sugiyama, A., T. Yujiri, et al. "Altered expression of circadian clock genes during peripheral blood stem cell mobilization induced by granulocyte colony-stimulating factor." Chronobiol Int. 2015 Aug;32(7):934-41. doi: 10.3109/07420528.2015.1053910.
59. Timuragaoglu, A. "The role of the nurses and technicians for stem cell mobilisation and collection." Transfus Apher Sci. 2015 Aug;53(1):30-3. doi: 10.1016/j.transci.2015.05.012. Epub 2015 Jun 29.
60. Werner, J. K. and R. D. Stevens "Traumatic brain injury: recent advances in plasticity and regeneration." Curr Opin Neurol. 2015 Dec;28(6):565-73. doi: 10.1097/WCO.0000000000000265.
61. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.