Hematopoietic stem cells

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Abstract: Haematopoiesis is the formation of blood cellular components. All cellular blood components are derived from haematopoietic stem cells. Hematopoietic stem cells (HSCs) give rise to all lineages of blood cells. Because HSCs must persist for a lifetime, the balance between their proliferation and quiescence is suitably regulated to ensure blood homeostasis while limiting cellular damage. Cell cycle regulation therefore plays a important role to control the HSC function during both fetal life and in the adult.
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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 (Ma, et al, 2007). Stem cells play the key functions.

Hematopoietic stem cells (HSCs) are the blood cells that divide to all the other blood cells and are derived from mesoderm. They are located in the red bone marrow, which is contained in the core of most bones. They give rise to the myeloid (monocytes, macrophage, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes, platelets, dendritic cells, etc) and lymphoid lineages (T-cells, B-cells, NK-cells, etc). Hematopoietic tissue contains cells with long-term and short-term regeneration capacitiesand committed multipotent, oligopotent, and unipotent progenitors. HSCs are a heterogeneous. HSCs are found in the bone marrow of adults, specially in the pelvis, femur, sternum, umbilical cord blood and peripheral blood. Stem and progenitor cells can be taken from the pelvis at the iliac crest using a needle and syringe. The cells can be removed as liquid or they can be removed via a core biopsy. In order to harvest stem cells from the circulating peripheral, blood donors are injected with a cytokine, such as granulocyte-colony stimulating factor (G-CSF), that induce cells to leave the bone marrow and circulate in the blood vessels. HSCs can replenish all blood cell types and self-renew. A small number of HSCs can expand to generate a very large number of daughter HSCs. This can be used in bone marrow transplantation when a small number of HSCs reconstitute the hematopoietic system. HSCs have a higher potential than other immature blood cells to pass the bone marrow barrier and travel in the blood from the bone marrow in one bone to another bone. When settle in the thymus they may develop into T cells. In the case of fetuses and other extramedullary hematopoiesis, HSCs can settle in the liver or spleen and develop. This ability is the reason why HSCs may be harvested directly from the blood. With regard to morphology, hematopoietic stem cells resemble lymphocytes. They are non-adherent, and rounded, with a rounded nucleus and low cytoplasm-to-nucleus ratio. Since PHSC cannot be isolated as a pure population, it is not possible to identify them in a microscope. The above description is based on the morphological characteristics of a heterogeneous population, of which PHSC are a component. Many of these markers belong to the cluster of differentiation series, such as CD34, CD38, CD45, CD90, CD105, CD133 and c-kit, etc. There are many differences between the human and mice hematopoietic cell markers for the commonly accepted type of hematopoietic stem cells. HSC cannot be easily observed directly, and, therefore, their behaviors need to be inferred indirectly. Clonal studies are likely the closest technique for single cell in vivo studies of HSC. Here, sophisticated experimental and statistical methods are used to ascertain that, with a high probability, a single HSC is contained in a transplant administered to a lethally irradiated host. The clonal expansion of this stem cell can then be observed over time by monitoring the percent donor-type cells in blood as the host is reconstituted. The resulting time series is defined as the repopulation kinetic of the HSC (Wikipedia, 2015).

Mesoderm is one of the three primary *germ layers* in the early *embryo*. The other two layers are the *ectoderm* (outside layer) and *endoderm* (inside

layer), with the mesoderm as the *middle* layer between them. The mesoderm forms mesenchyme, mesothelium, non-epithelial blood cells and coelomocytes. Blood cells are responsible for maintenance and immune protection of every cell type of the body.

HSCs reside in the bone marrow and have the unique ability to give rise to all of the different mature blood cell types and tissues. HSCs are self-renewing cells: when they proliferate, at least some of their daughter cells remain as HSCs, so the pool of stem cells does not become depleted. This phenomenon is called asymmetric division. All blood cells are divided into three lineages.

Hematopoiesis is the lifelong process by which all the cells of the blood system are produced in a hierarchical manner from a small population of hematopoietic stem cells, which reside in the bone marrow cavity in adult mammals.

Bone marrow is a flexible tissue in the interior of bones. Red blood cells are produced by cores of bone marrow in the heads of long bones in a process. Bone marrow is a key component of the lymphatic system, producing the lymphocytes that support the animal's immune system.

Lymphatic system is part of the circulatory system, comprising a network of lymphatic vessels that carry lymph directionally towards the heart. Lymph is similar to blood plasma but contains lymphocytes and other white blood cells.

Bone marrow stromal cells, also known as mesenchymal stem cells or fibroblastic colony-forming units, are multipotent non-hematopoietic stem cells adhering to culture plates (Abdallah and Kassem 2009). Mesenchymal stem cells of the bone marrow have the ability to renew and differentiate themselves into multiple lineages of conjunctive tissues, including bone, cartilage, adipose tissue, tendons, muscle, and bone marrow stroma. Those cells have been first described by Friedenstein et al., who found that mesenchymal stem cells adhere to culture plates, look like in vitro fibroblasts, and build up colonies (Friedenstein et al. 1987). The cell cycle activity of HSCs is carefully modulated by a complex interplay between cell-intrinsic mechanisms and cell-extrinsic factors produced by the microenvironment. This fine-tuned regulatory network may become altered with age, leading to aberrant HSC cell cycle regulation, degraded HSC function, and hematological malignancy.

Bone marrow is the site of hematopoiesis and bone marrow transplant has been successfully used for decades as a means of treating various hematological malignancies in which the recipient hematopoietic compartment is replaced by donor-derived stem cells. Progenitor cells in bone marrow are capable to differentiate into other tissues, such as cardiac tissue. Clinical trials have been conducted demonstrating beneficial effects of bone marrow infusion in cardiac patients. It is believed that injured tissue, whether neural tissue after a stroke, or injured cardiac tissue, has the ability to selectively attract bone marrow stem cells, perhaps to induce regeneration. Bone marrow has therapeutic effect in conditions ranging from liver failure, to peripheral artery disease, and the possibility of using bone marrow stem cells in kidney failure has been relatively understudied (Ma et al. 2009).

Mesenchymal stem cells have been brought to the attention of many researchers, because these cells are of great interest for treating various human diseases. Many studies have isolated mesenchymal stem cells and controlled, in vitro, its differentiation into cartilaginous tissue and bone using specific growth factors, with the objective of using this technology for repairing injured tissues of mesenchymal origin (Xian and Foster 2006; Kurdi and Booz 2007).

The umbilical cord is a conduit between the developing embryo or fetus and the placenta. During prenatal development, the umbilical cord is physiologically and genetically part of the fetus and normally contains two arteries and one vein. The umbilical vein supplies the fetus with oxygenated, nutrient-rich blood from the placenta. The blood within the umbilical cord, known as cord blood, is a rich and readily available source of primitive, undifferentiated stem cells. These cord blood cells can be used for bone marrow transplant.

Macrophages are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, and cancer cells in a process called phagocytosis. They play a critical role in non-specific defense (innate immunity), and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. In humans, dysfunctional macrophages cause severe diseases such as chronic granulomatous disease that result in frequent infections.

Basophils contain large cytoplasmic granules which obscure the cell nucleus under the microscope when stained. However, when unstained, the nucleus is visible and it usually has two lobes. The mast cell, another granulocyte, is similar in appearance and function. Both cell types store histamine, a chemical that is secreted by the cells when stimulated. However, they arise from different cell lines, and mast cells usually do not circulate in the blood stream, but instead are located in connective tissue. Like all circulating granulocytes, basophils can be recruited out of the blood into a tissue when needed.

Hematopoietic stem cell transplants can be used to treat patients with cancers and other diseases of the

blood and immune systems. Hematopoietic stem cells are able to form other kinds of cells, such as muscle, blood vessels, and bone, and hematopoietic stem cells can replace a wider array of cells and tissues. The stem cells that form blood and immune cells are known as hematopoietic stem cells, which are responsible for the constant renewal of blood—the production of billions of new blood cells every day. The hematopoietic stem cell is the cell isolated from the blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, mobilize out of the bone marrow into circulating blood and undergo programmed cell apoptosis.

If bone marrow cells from the transplanted animal are transplanted to another lethally irradiated animal and restore its hematopoietic system over some months, they are the long-term stem cells that are capable of self-renewal. Other cells from bone marrow can immediately regenerate all the different types of blood cells, but under normal condition they cannot renew themselves over the long term that are considered as the short-term progenitor or precursor cells. Progenitor or precursor cells are relatively immature cells that are precursors to a fully differentiated cell of the same tissue type, which can proliferate but only have a limited capacity to differentiate into more than one cell.

The classic source of hematopoietic stem cells is bone marrow. Although quiescence is essential for the self-renewal of adult HSCs, they must nonetheless retain the capacity to proliferate rapidly, albeit transiently, in response to extrinsic cues that signal injury or infection.

In the late 1980s and early 1990s, it was known that blood from the human umbilical cord and placenta was a rich source of stem cells. The umbilical cord and placenta support the development of fetus during pregnancy and they are delivered along with the baby, and are usually discarded after the birth. Since the first successful umbilical cord blood transplants in children, the collection and therapeutic use of these cells has grown quickly. The New York Blood Center's Placental Blood Program in Manhattan of New York City is the largest U.S. public umbilical cord blood bank and has more that ten thousand donated samples for the transplantation purpose. Since it began to collect umbilical cord blood in 1992, New York Blood Center has provided thousands of cord blood units to patients. A lot of umbilical cord blood recipients have lived over eight years, relying on the stem cells from an umbilical cord blood transplant. Now, many countries have umbilical cord blood banks.

The number of blood cells in the bone marrow and blood is regulated by genetic and molecular mechanisms. Apoptosis is the process of programmed cell death that leads cells to self-destruct. If there are too few stem cells in the body, more cells divide and boost the numbers. If excess stem cells are injected into an animal, they simply wouldn't divide or would undergo apoptosis and be eliminated. Excess numbers of stem cells in the transplant will improve the engraftment. Stem cells transplantation can treat cancers (NIH, 2014). Hematopoietic stem cells are the paradigm for understanding the fundamental properties of adult stem cells, and for clinical stem cell therapy. Bone marrow transplantation is the standard of care treatment for a variety of malignant and benign hematological diseases.

T cells are a heterogeneous cell population comprising different subsets that exert distinct roles in cell-mediated immunity. Granulocytes are released from the bone marrow and make up the major group of leukocytes in the blood.

According to Symonds's opinions, CAL-USA-11 is a Phase I/II human study designed to assess the safety, feasibility, and tolerability of the Cal-1 product in HIV-infected individuals who have previously been on ART but are not currently taking any antiretroviral agent. Symonds gives an objective of the Cal-1 therapy is to increase the number of protected cells in the body of an individual infected with HIV to the point where the virus is incapable of causing harm. This would potentially reduce or eliminate the need for a lifetime of antiretroviral therapy. Symonds's study has three arms. All participants will receive the Cal-1 product. Participants in two of the three study arms will also receive different doses of a drug known as busulfan prior to the infusion, which has the potential to make the therapy more effective. Laboratory assessments performed throughout the course of the study will monitor: • the participants' general health and level of HIV infection; • the participants' level of CD4+ T cells; • the presence of Cal-1 modified cells in various cell types in the blood and lymphoid tissue; and • the safety of the approach. The primary objectives of the study are to evaluate: • The safety, feasibility, and tolerability of Cal-1 gene-transduced hematopoietic cell populations. • The safety and tolerability of low- and moderate-dose busulfan as a non-myeloablative conditioning agent as a means to improve engraftment of transduced HSPC. The study is open to men and women ages 18 to 65 who are HIV-infected but do not have any other serious medical conditions. Participants must have been well-controlled on ART in the past, but must not be taking ART currently. Treating stem cells along with T cells, it can create the potential for the progeny of the stem cells and exhibit genetic resistance to HIV, and therefore repopulate the participant's immune system (Symonds, 2015).

The first isolation of hematopoietic stem cells (HSC) required quantitative clonal assays for every

blood cell progenitor type and methods to sort cells based on their unique expression profiles, as determined by cell surface markers. All HSC activity in adult mouse bone marrow (BM) was shown to be contained in a population marked by the composite phenotype of c-Kit+, Thy-1.1lo, lineage marker-, and Sca-1+. In humans, the isolation of a lCD34+CD90+ progenitor cell resulted in the purification of a homogeneous HSC population. The test for HSCs is in their ability to rescue myelo-ablated hosts from hematopoietic failure, and establish long-term multi-hematopoietic lineage reconstitution. Clinical implantation of HSCs into cancer patients has led to stable grafts depleted of contaminating hematopoietic cells and resident or metastasized malignant cells. The continued identification of novel hematopoietic stem cell markers will enable improved efficiency in the purification of HSCs for the treatment of disease (eBioscience, 2014).

Turritopsis nutricula is capable of rejuvenating itself due to a process called transdifferentiation. Transdifferentiation occurs when a non-stem cell turns itself into another type of cell. But, it is not clear if stem cells are involved in this immortality or not. As my opinion, the transdifferentiation in *Turritopsis nutricula* has related mechanism to stem cell when the life cycle reverted. It is important to reveal the relationship of this *Turritopsis nutricula* transdifferentiation and stem cell (Ma and Yang, 2010).

The following are recent reports in the hemotopoietic stem cell studies:

Ahmed, I., J. Teruya, et al. "The incidence of autoimmune hemolytic anemia in pediatric hematopoietic stem cell recipients post-first and post-second hematopoietic stem cell transplant." Pediatr Transplant. 2015 Mar 23. doi: 10.1111/petr.12455.

According the this study, the reported incidence of post-allogeneic HSCT AIHA was between 4.4% and 6% following a single stem cell transplant. Cord blood transplantation, T-cell depletion, and chronic GvHD are significantly associated with post-transplant AIHA.

Chang, Y. I., X. You, et al. "Loss of Dnmt3a and endogenous Kras cooperate to regulate hematopoietic stem and progenitor cell functions in leukemogenesis." Leukemia. 2015 Mar 24. doi: 10.1038/leu.2015.85.

Oncogenic NRAS and KRAS mutations are prevalent in human juvenile and chronic myelomonocytic leukemia (JMML/CMML). However, additional genetic mutations cooperating with oncogenic RAS in JMML/ CMML progression and/or their transformation to acute myeloid leukemia (AML) remain largely unknown. RAS cooperate to regulate hematopoietic stem and progenitor cells and promote myeloid malignancies.Leukemia accepted article preview online, 24 March 2015. doi:10.1038/leu.2015.85.

Chen, G., L. Chen, et al. "Systemic mastocytosis with recurrent anaphylactic shock and multiple organ dysfunction failure." Clin Lab. 2015;61(1-2):179-82.

The patient was rescued with positive treatment, administered on prednisolone and H1/H2-receptor blocking agents. Corticosteroid and IFN-alpha treatment have no significant effect on tumor burden, but no more anaphylactic shock occurred. Cladribine and imatinib are recommended to treat SM patients to obtain a better therapeutic effect. Maybe allogeneic hematopoietic stem cell transplantation is a cure for SM.

Jaskula, E., D. Dlubek, et al. "Anti-CMV-IgG Positivity of Donors Is Beneficial for alloHSCT Recipients with Respect to the Better Short-Term Immunological Recovery and High Level of CD4+CD25high Lymphocytes." Viruses. 2015 Mar 23;7(3):1391-408. doi: 10.3390/v7031391.

Hematopoietic stem cell transplantation from anti-cytomegalovirus immunoglobulin G (anti-CMV-IgG) positive donors facilitated immunological recovery post-transplant, which may indicate that chronic CMV infection has an effect on the immune system. High levels ((3)0.4%) of CD4+CD25high lymphocytes were significantly associated with better post-transplant survival (56% vs. 38%, four-year survival, p = 0.040). Donors who experience CMV infection/reactivation provide the recipients with lymphocytes, which readily reinforce the recovery of the transplanted patients' immune system.

Kajaste-Rudnitski, A. and L. Naldini "Cellular innate immunity and restriction of viral infection - implications for lentiviral gene therapy in human hematopoietic cells." Hum Gene Ther. 2015 Mar 26.

Hematopoietic gene therapy has tremendous potential to treat human disease. Nevertheless, for gene therapy to be efficacious, effective gene transfer into target cells must be reached without inducing detrimental effects on their biological properties. This remains a great challenge for the field as high vector doses and prolonged ex-vivo culture conditions are still required to reach significant transduction levels of clinically relevant human hematopoietic stem and progenitor cells (HSPC) while other potential target cells such as primary macrophages can hardly be transduced. The better understanding of the vector-host interactions in the context of hematopoietic gene

transfer is important for the development of safer and more efficient gene therapy strategies.

Kurita, T., K. Sato, et al. "Origin of Vocal Fold Stellate Cells in the Human Macula Flava." Ann Otol Rhinol Laryngol. 2015 Mar 23. pii: 0003489415578710.

The vocal fold stellate cells (VFSCs) in the human maculae flavae are tissue stem cells of the human vocal fold and that the maculae flavae are a stem cell niche. The cells in the human maculae flavae (CHMF) are undifferentiated cells derived from the differentiation of bone marrow cells. The results of this study are consistent with the hypothesis that the VFSCs are tissue stem cells or progenitor cells of the human vocal fold mucosa.

Liu, F., D. Li, et al. "Induction of hematopoietic and endothelial cell program orchestrated by ETS transcription factor ER71/ETV2." EMBO Rep. 2015 Mar 23. pii: e201439939.

The ETS factor ETV2 (aka ER71) is essential for the generation of the blood and vascular system, as ETV2 deficiency leads to a complete block in blood and endothelial cell formation and embryonic lethality in the mouse. However, the ETV2-mediated gene regulatory network and signaling governing hematopoietic and endothelial cell development are poorly understood. The critical role that transient ETV2 expression plays in the regulation of hematopoietic and endothelial cell lineage specification and stability.

Liu, J., D. Y. Jia, et al. "Mitochondria Defects are Involved in Lead-acetate-induced Adult Hematopoietic Stem Cell Decline." Toxicol Lett. 2015 Mar 20. pii: S0378-4274(15)00110-1. doi: 10.1016/j.toxlet.2015.03.007.

Occupational high-grade lead exposure has been reduced in recent decades as a result of increased regulation. The lead acetate perturbs the hematopoietic balance of adult HSCs, associated with cellular mitochondria defects, increased intracellular ROS generation.

Margaix-Munoz, M., J. V. Bagan, et al. "Graft-versus-host disease affecting oral cavity. A review." J Clin Exp Dent. 2015 Feb 1;7(1):e138-45. doi: 10.4317/jced.51975. eCollection 2015 Feb.

Graft versus host disease (GVHD) is one of the most frequent and serious complications of hematopoietic stem cell transplantation, and is regarded as the leading cause of late mortality unrelated to the underlying malignant disease. GVHD is an autoimmune and alloimmune disorder that usually affects multiple organs and tissues, and exhibits a variable clinical course. It can manifest in either acute or chronic form. The acute presentation of GVHD is potentially fatal and typically affects the skin, gastrointestinal tract and liver. The chronic form is characterized by the involvement of a number of organs, including the oral cavity. Oral chronic GVHD is not considered a determinant factor for patient survival, which is close to 52% five years after diagnosis of the condition. Key words:Chronic graft-versus-host disease, oral chronic graft-versus-host disease, pathogenics, management, survival.

McDonald-Hyman, C., L. A. Turka, et al. Advances and challenges in immunotherapy for solid organ and hematopoietic stem cell transplantation, Sci Transl Med. 2015 Mar 25;7(280):280rv2.

Although major advances have been made in solid organ and hematopoietic stem cell transplantation in the last 50 years, big challenges remain. This review outlines the current immunological limitations for hematopoietic stem cell and solid organ transplantation and discusses new immune-modulating therapies in preclinical development and in clinical trials that may allow these obstacles to be overcome.

Nel, I., U. Jehn, et al. "Individual profiling of circulating tumor cell composition in patients with non-small cell lung cancer receiving platinum based treatment." Transl Lung Cancer Res. 2014 Apr;3(2):100-6. doi: 10.3978/j.issn.2218-6751.2014.03.05.

Circulating tumor cells (CTC) could serve as a "liquid biopsy" for individualizing and monitoring treatment in patients with solid tumors as recently shown by our group. This study assessed which non-hematopoietic cell types are identifiable in the peripheral blood of patients with non-small cell lung cancer (NSCLC) and correlated those to clinical characteristics. The data suggest that different CTC populations are identifiable in peripheral blood and that these individual cell type profiles might be used to predict outcome to platinum based systemic therapies in lung cancer patients.

Niavarani, A., E. Currie, et al. "APOBEC3A Is Implicated in a Novel Class of G-to-A mRNA Editing in WT1 Transcripts." PLoS One. 2015 Mar 25;10(3):e0120089. doi: 10.1371/journal.pone.0120089. eCollection 2015.

Classic deamination mRNA changes, including cytidine to uridine (C-to-U) and adenosine to inosine (A-to-I), are important exceptions to the central dogma and lead to significant alterations in gene transcripts and products. Although there are a few reports of non-classic mRNA alterations, as yet

there is no molecular explanation for these alternative changes. Wilms Tumor 1 (WT1) mutations and variants are implicated in several diseases, including Wilms tumor and acute myeloid leukemia (AML). This study observed two alternative G-to-A changes, namely c.1303G>A and c.1586G>A in cDNA clones and found them to be recurrent in a series of 21 umbilical cord blood mononuclear cell (CBMC) samples studied. Two less conserved U-to-C changes were also observed. These alternative changes were found to be significantly higher in non-progenitor as compared to progenitor CBMCs, while they were found to be absent in a series of AML samples studied, indicating they are targeted, cell type-specific mRNA editing modifications. These findings open the way to further investigations into the mechanisms of other potential mRNA changes, which will help to redefine the RNA editing paradigm in both health and disease.

Pathak, V., J. Kuhn, et al. "Use of Activated Factor VII in Patients with Diffuse Alveolar Hemorrhage: A 10 Years Institutional Experience." Lung. 2015 Mar 24.

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition with an obscure etiology and pathogenesis. It is associated with many drugs and diseases including chemotherapy, hematopoietic stem cell transplantation, and autoimmune disorders. This retrospective study reports our experience with 23 patients who had DAH and received intravenous recombinant activated Factor VIIa (rFVIIa). METHODS: Activated Factor VII can achieve hemostasis in patients with diffuse alveolar hemorrhage.

Schinke, C., O. Giricz, et al. "IL8-CXCR2 pathway inhibition as a therapeutic strategy against MDS and AML stem cells." Blood. 2015 Mar 25. pii: blood-2015-01-621631.

AML and MDS are associated with disease initiating stem cells that are not eliminated by conventional therapies. Novel therapeutic targets against pre-leukemic stem cells need to be identified for potentially curative strategies. We conducted parallel transcriptional analysis of highly fractionated stem and progenitor populations in MDS, AML and control samples and found Interleukin 8 (IL8) to be consistently overexpressed in patient samples. The receptor for IL8, CXCR2, was also significantly increased in MDS CD34+ cells from a large clinical cohort and was predictive of increased transfusion dependence. High CXCR2 expression was also an adverse prognostic factor in the TCGA AML cohort, further pointing to the critical role of IL8-CXCR2 axis in AML/MDS. Functionally, CXCR2 inhibition by knockdown and pharmacologic approaches led to significant reduction in proliferation in several leukemic cell lines and primary MDS / AML samples via induction of G0/G1 cell cycle arrest. Importantly, inhibition of CXCR2 selectively inhibited immature hematopoietic stem cells from MDS/AML samples without an effect on healthy controls. CXCR2 knockdown also impaired leukemic growth in vivo. Together, these studies demonstrate that the IL8 receptor CXCR2 is an adverse prognostic factor in MDS/AML and is a potential therapeutic target against immature, LSC-enriched cell fractions in MDS and AML.

Schulz, M., D. Karpova, et al. "Variant rs1801157 in the 3'UTR of SDF-1ss Does Not Explain Variability of Healthy-Donor G-CSF Responsiveness." PLoS One. 2015 Mar 24;10(3):e0121859. doi: 10.1371/journal.pone.0121859. eCollection 2015.

The genetics responsible for the inter-individually variable G-CSF responsiveness remain elusive. A single nucleotide polymorphism (SNP) in the 3'UTR of CXCL12, rs1801157, was implicated in X4-tropic HiV susceptibility and later, in two small studies, in G-CSR responsiveness in patients and donors. The position of the SNP in the 3'UTR together with in-silico predictions suggested differential binding of micro-RNA941 as an underlying mechanism. In a cohort of 515 healthy stem cell donors we attempted to reproduce the correlation of the CXCL12 3'UTR SNP and mobilization responses and tested the role of miR941 in this context. The SNP was distributed with the expected frequency. Mobilization efficiency for CD34+ cells in WT, heterozygous and homozygous SNP individuals was indistinguishable, even after controlling for gender. miR941 expression in non-hematopoietic bone marrow cells was undetectable and miR941 did not interact with the 3' UTR of CXCL12. Proposed effects of the SNP rs1801157 on G-CSF responsiveness cannot be confirmed in a larger cohort.

Storch, E., T. Mark, et al. "A novel hematopoietic progenitor cell mobilization and collection algorithm based on preemptive CD34 enumeration." Transfusion. 2015 Mar 21. doi: 10.1111/trf.13076.

The collection of autologous peripheral blood (PB) stem cells can be challenging in the subgroup of patients deemed "poor mobilizers" with granulocyte-colony-stimulating factor. Plerixafor, a CXCR-4 antagonist, is an alternative mobilizing agent, but is costly, and the optimal mobilization algorithm has yet to be determined. Use of a protocol to assess PB CD34 1 day before collection allows for preemptive administration of plerixafor to augment mobilization. Subsequently, days of collection and processed blood volume are reduced while there is

less RBC and granulocyte contamination in the collected stem cell product.

Tabatabaei-Qomi, R., M. Sheykh-Hasan, et al. "Development of a PCR assay to detect mycoplasma contamination in cord blood hematopoietic stem cells." Iran J Microbiol. 2014 Aug;6(4):281-4.

Contamination of cell lines and biological products is one of the major problems of cell culture techniques. Rapid detection of mycoplasma contamination in cell culture is an important part of quality control standards in related laboratories. The aim of this study was to evaluate the efficacy of PCR in detection of myroplasma as contaminants in cell cultures and other biological products. In this study, PCR assays were optimized for 16 S rRNA target gene. Also the utilized PCR method was evaluated in terms of sensitivity and specificity. Finally, a simple DNA extraction and PCR analysis of 164 cell culture of adipose tissue derived mesenchymal stem cells were performed. The results showed that a 715 bp product was amplified and subsequently was confirmed by sequencing. The technique could detect 10 copies of the target DNA. No cross-reactivity with genomic DNA of other microorganisms was observed. CONCLUSIONS: The PCR technique in this study was based on 16S rRNA gene. It was highly sensitive and specific since it was able to detected Mycoplasma contamination in cell cultures.

Toth, K., B. Ying, et al. "Valganciclovir inhibits human adenovirus replication and pathology in permissive immunosuppressed female and male Syrian hamsters." Viruses. 2015 Mar 23;7(3):1409-28. doi: 10.3390/v7031409.

Adenovirus infections of immunocompromised pediatric hematopoietic stem cell transplant patients can develop into serious and often deadly multi-organ disease. There are no drugs approved for adenovirus infections. Cidofovir (an analog of 2-deoxycytidine monophosphate) is used at times but it can be nephrotoxic and its efficacy has not been proven in clinical trials. Brincidofovir, a promising lipid-linked derivative of cidofovir, is in clinical trials. Ganciclovir, an analog of 2-deoxyguanosine, has been employed occasionally but with unknown efficacy in the clinic. In this study, we evaluated valganciclovir against disseminated adenovirus type 5 (Ad5) infection in our permissive immunosuppressed Syrian hamster model. We administered valganciclovir prophylactically, beginning 12 h pre-infection or therapeutically starting at Day 1, 2, 3, or 4 post-infection. Valganciclovir significantly increased survival, reduced viral replication in the liver, and mitigated the pathology associated with Ad5 infection. In cultured cells, valganciclovir inhibited Ad5 DNA replication and blocked the transition from early to late stage of infection. Valganciclovir directly inhibited Ad5 DNA polymerase in vitro, which may explain, at least in part, its mechanism of action. Ganciclovir and valganciclovir are approved to treat infections by certain herpesviruses. Our results support the use of valganciclovir to treat disseminated adenovirus infections in immunosuppressed patients.

Williams-Hooker, R., M. Adams, et al. "Caregiver and health care provider preferences of nutritional support in a hematopoietic stem cell transplant unit." Pediatr Blood Cancer. 2015 Mar 21. doi: 10.1002/pbc.25473.

Many pediatric oncology patients undergoing hematopoietic stem cell transplantation (HSCT) require nutritional support (NS) because of their inability to consume adequate caloric intake enough calories orally. Although NS can be provided either enteraly (EN) or parenteraly (PN), EN is the preferred method of NS as long as if the gastrointestinal tract is functioning.

Yamada, E., R. Yoshikawa, et al. Impacts of Humanized Mouse Models on the Investigation of HIV-1 Infection: Illuminating the Roles of Viral Accessory Proteins in Vivo, Viruses. 2015 Mar 23;7(3):1373-1390.

Human immunodeficiency virus type 1 (HIV-1) encodes four accessory genes: vif, vpu, vpr, and nef. Recent investigations using in vitro cell culture systems have shed light on the roles of these HIV-1 accessory proteins, Vif, Vpr, Vpu, and Nef, in counteracting, modulating, and evading various cellular factors that are responsible for anti-HIV-1 intrinsic immunity. However, since humans are the exclusive target for HIV-1 infection, conventional animal models are incapable of mimicking the dynamics of HIV-1 infection in vivo. Moreover, the effects of HIV-1 accessory proteins on viral infection in vivo remain unclear. To elucidate the roles of HIV-1 accessory proteins in the dynamics of viral infection in vivo, humanized mouse models, in which the mice are xenotransplanted with human hematopoietic stem cells, has been utilized. This review describes the current knowledge of the roles of HIV-1 accessory proteins in viral infection, replication, and pathogenicity in vivo, which are revealed by the studies using humanized mouse models.

Yamamoto, S., M. Otsu, et al. "Screening of Drugs to Treat 8p11 Myeloproliferative Syndrome Using Patient-Derived Induced Pluripotent Stem Cells with Fusion Gene CEP110-FGFR1." PLoS One. 2015 Mar 24;10(3):e0120841. doi: 10.1371/journal.pone.0120841. eCollection 2015.

Induced pluripotent stem (iPS) cells provide powerful tools for studying disease mechanisms and developing therapies for diseases. The 8p11 myeloproliferative syndrome (EMS) is an aggressive chronic myeloproliferative disorder (MPD) that is caused by constitutive activation of fibroblast growth factor receptor 1. EMS is rare and, consequently, effective treatment for this disease has not been established. Here, iPS cells were generated from an EMS patient (EMS-iPS cells) to assist the development of effective therapies for EMS. When iPS cells were co-cultured with murine embryonic stromal cells, EMS-iPS cells produced more hematopoietic progenitor and hematopoietic cells, and CD34+ cells derived from EMS-iPS cells exhibited 3.2-7.2-fold more macrophage and erythroid colony forming units (CFUs) than those derived from control iPS cells. These data indicate that EMS-iPS cells have an increased hematopoietic differentiation capacity, which is characteristic of MPDs.

Ye, L., L. R. Morse, et al. "Osteopetrorickets due to Snx10 Deficiency in Mice Results from Both Failed Osteoclast Activity and Loss of Gastric Acid-Dependent Calcium Absorption." PLoS Genet. 2015 Mar 26;11(3):e1005057. doi: 10.1371/journal.pgen.1005057. eCollection 2015 Mar.

Mutations in sorting nexin 10 (Snx10) have recently been found to account for roughly 4% of all human malignant osteopetrosis, some of them fatal. To study the disease pathogenesis, we investigated the expression of Snx10 and created mouse models in which Snx10 was knocked down globally or knocked out in osteoclasts. Endocytosis is severely defective in Snx10-deficent osteoclasts, as is extracellular acidification, ruffled border formation, and bone resorption. We also discovered that Snx10 is highly expressed in stomach epithelium, with mutations leading to high stomach pH and low calcium solubilization. Global Snx10-deficiency in mice results in a combined phenotype: osteopetrosis (due to osteoclast defect) and rickets (due to high stomach pH and low calcium availability, resulting in impaired bone mineralization). Osteopetrorickets, the paradoxical association of insufficient mineralization in the context of a positive total body calcium balance, is thought to occur due to the inability of the osteoclasts to maintain normal calcium-phosphorus homeostasis.

Yeral, M., C. Boga, et al. "Tunnelled Central Venous Catheter-Related Problems in the Early Phase of Haematopoietic Stem Cell Transplantation and Effects on Transplant Outcome." Turk J Haematol. 2015 Mar 5;32(1):51-57. doi: 10.4274/tjh.2013.0278.

Haematopoietic stem cell recipients need central venous catheters (CVCs) for easy administration of intravenous fluid, medications, apheresis, or dialysis procedures. However, CVCs may lead to infectious or non-infectious complications such as thrombosis. The effect of these complications on transplantation outcome is not clear. This manuscript presents the complication rates of double-lumen tunnelled CVCs and their effect on transplantation outcome. Data from 111 consecutive patients, of whom 75 received autologous and 36 received allogeneic peripheral blood stem cell transplantations, were collected retrospectively. The data were validated by the Record Inspection Group of the related JACIE-accredited transplantation centre. Thrombosis developed in 2.7% of recipients (0.9 per 1000 catheter days). Catheter-related infection was identified in 14 (12.6%) patients (3.6 per 1000 catheter days). Coagulase-negative Staphylococcus was the most common causative agent. Engraftment time, rate of 100-day mortality, and development of grade II-IV graft-versus-host disease were not found to be associated with catheter-related complications. CONCLUSION: These results indicate that adverse events related with tunnelled CVCs are manageable and have no negative effects on transplant outcome.

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