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Stem Cell

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Stem Cell Immunology Research Literatures

Dr. Mark Herbert

World Development Institute
39 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

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 related studies.
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Key words: stem cell; immunology; 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.

Alexandersson, A., et al. (2019). "Viral infections and immune reconstitution interaction after pediatric allogenic hematopoietic stem cell transplantation." Infect Dis (Lond) **51**(10): 772-778.

Background: Viral infections are a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Although immune suppression plays a central role, the literature shows conflicting results on interplay between post-transplant immune reconstitution (IR) and viral infections. Methods: We prospectively studied viral infections and IR in 30 pediatric patients undergoing allogenic HSCT, with a follow-up time of 24 months. In total, 1337 blood (CMV, EBV, HHV-6, ADV and BKV) and urine (BKV and JCV) virus samples were analyzed. IR including B-cells (CD19+), T cells (CD3+, CD4+, CD8+) and NK-cells were measured. Clinical outcomes included overall survival (OS), non-relapse mortality (NRM), graft-versus-host disease (GVHD) and occurrence of blood culture positive bacterial infections. Results: We found BKV reactivation to be most frequent, 47% of the children had viremia and 77% viruria. The frequencies of CMV, HHV-6 and adeno viremia were 37%, 37% and 6%, respectively. Viremias beyond 3 months post-HSCT were uncommon. Factors such as GVHD, use of steroids, EBV and CMV infections and pre-transplant irradiation affected IR. No specific viral infection or IR related factor was associated to OS or NRM. Conclusions: Viral infections and IR interact in a bi-directional manner. Accordingly, close follow-up of both IR and viral loads is warranted.

Andre, I., et al. (2019). "Ex vivo generated human T-lymphoid progenitors as a tool to accelerate immune reconstitution after partially HLA compatible hematopoietic stem cell transplantation or after gene therapy." Bone Marrow Transplant **54**(Suppl 2): 749-755.

Prolonged T-cell immunodeficiency following HLA- incompatible hematopoietic stem cell transplantation (HSCT) represents a major obstacle hampering the more widespread use of this approach. Strategies to fasten T-cell reconstitution in this setting are highly warranted as opportunistic infections and an increased risk of relapse account for high rates of morbidity and mortality especially during early month following this type of HSCT. We have implemented a feeder free cell system based on the use of the notch ligand DL4 and cytokines allowing for the in vitro differentiation of human T-Lymphoid Progenitor cells

(HTLPs) from various sources of CD34+ hematopoietic stem and precursor cells (HSPCs). Co-transplantion of human T-lymphoid progenitors (HTLPs) and non- manipulated HSPCs into immunodeficient mice successfully accelerated the reconstitution of a polyclonal T-cell repertoire. This review summarizes preclinical data on the use of T-cell progenitors for treatment of post- transplantation immunodeficiency and gives insights into the development of GMP based protocols for potential clinical applications including gene therapy approaches. Future clinical trials implementing this protocol will aim at the acceleration of immune reconstitution in different clinical settings such as SCID and leukemia patients undergoing allogeneic transplantation. Apart from pure cell-therapy approaches, the combination of DL-4 culture with gene transduction protocols will open new perspectives in terms of gene therapy applications for primary immunodeficiencies.

Bertaina, A. and M. G. Roncarolo (2019). "Graft Engineering and Adoptive Immunotherapy: New Approaches to Promote Immune Tolerance After Hematopoietic Stem Cell Transplantation." Front Immunol **10**: 1342.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapeutic option for a wide range of immune and hematologic malignant and non-malignant disorders. Once transplanted, allogeneic cells have to support myeloid repopulation and immunological reconstitution, but also need to become tolerant to the host via central or peripheral mechanisms to achieve the desired therapeutic effect. Peripheral tolerance after allogeneic HSCT may be achieved by several mechanisms, though blocking alloreactivity to the host human leukocyte antigens while preserving immune responses to pathogens and tumor antigens remains a challenge. Recently uncovered evidence on the mechanisms of post-HSCT immune reconstitution and tolerance in transplanted patients has allowed for the development of novel cell-based therapeutic approaches. These therapies are aimed at inducing long-term peripheral tolerance and reducing the risk of graft-vs-host disease (GvHD), while sparing the graft-vs-leukemia (GvL) effect. Thus, ensuring effective long term remission in hematologic malignancies. Today, haploidentical stem cell transplants have become a widely used treatment for patients with hematological malignancies. A myriad of ex vivo and in vivo T-cell depletion strategies have been adopted, with the goal of preventing GvHD while preserving GvL in the context of immunogenetic disparity. alphabeta T-cell/CD19 B-cell depletion techniques, in particular, has gained significant momentum, because of the high rate of leukemia-free survival and the low risk of severe GvHD. Despite progress, better treatments are still needed in a portion of patients to further reduce the incidence of relapse and achieve long-term tolerance. Current post-HSCT cell therapy approaches designed to induce tolerance and minimizing GvHD occurrence include the use of (i) gammadelta T cells, (ii) regulatory Type 1 T (Tr1) cells, and (iii) engineered FOXP3(+) regulatory T cells. Future protocols may include post-HSCT infusion of allogeneic effector or regulatory T cells engineered with a chimeric antigen receptor (CAR). In the present review, we describe the most recent advances in graft engineering and post-HSCT adoptive immunotherapy.

Bi, Y., et al. (2020). "Human Adipose Tissue-Derived Mesenchymal Stem Cells in Parkinson's Disease: Inhibition of T Helper 17 Cell Differentiation and Regulation of Immune Balance Towards a Regulatory T Cell Phenotype." Clin Interv Aging **15**: 1383-1391.

Background: Parkinson's disease (PD) is a neurodegenerative disorder displaying a typical neuroinflammation pathology that may result from an imbalance between regulatory T cells (Treg) and T helper 17 (Th17) cells. Human adipose tissue-derived mesenchymal stem cells (Ad-MSCs) exert immunomodulatory effects by inhibiting effector T cell responses and have been used to treat diverse immune disorders. We aimed to investigate the modulating effect of human Ad-MSCs on peripheral blood mononuclear cells (PBMCs) of patients with PD, focusing on differentiation into Th17 and Treg cells. Methods: We isolated human peripheral blood CD4(+)T cells and co-cultured them with Ad-MSCs at a ratio of 4:1 under either Th17 or Treg cell polarizing conditions for 4 days to detect the proportions of IL-17-producing CD4(+)T (Th17) and CD4(+)CD25(+)Foxp3(+)regulatory T (Treg) cells by flow cytometry. We also determined the mRNA expression levels of the retinoid-related orphan nuclear receptor (RORgammat) transcription factor and those of interleukin-6 receptor (IL-6R), interleukin-23 receptor (IL-23R), leukemia inhibitory factor (LIF), and LIF receptor (LIFR) by quantitative reverse transcription PCR. We detected levels of cytokines in the supernatant (including LIF, IL-6, IL-23, IL-10, and TGF-beta) using ELISA. Results: Our results showed that Ad-MSCs specifically inhibited the differentiation of PBMCs of patients with PD into IL-17-producing CD4(+)T cells by decreasing expressions of IL-6R, IL-23R, and RORgammat (the key transcription factor for Th17 cells). Moreover, Ad-MSCs induced a functional CD4(+)CD25(+)Foxp3(+)T regulatory cell phenotype as evidenced by the secretion of IL-10. The levels of IL-6, IL-23, and TGF-beta remained constant after co-culture under either the Th17 or the Treg cell polarizing condition. In addition, levels of LIF protein and its receptor mRNA were significantly increased under both polarizing conditions. Conclusion: The

present in vitro study found that Ad-MSCs from healthy participants were able to correct the imbalance between Th17 and Treg found in PBMCs of PD patients, which were correlated with an increase in LIF secretion and a decrease in expression of IL-6R, IL-23R, and RORgammat. These findings should be confirmed by in vivo experiments.

Bialek-Waldmann, J. K., et al. (2019). "Monocytes reprogrammed with lentiviral vectors co-expressing GM-CSF, IFN-alpha2 and antigens for personalized immune therapy of acute leukemia pre- or post-stem cell transplantation." Cancer Immunol Immunother **68**(11): 1891-1899.

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and overall survival remains poor. Chemotherapy is the standard of care for intensive induction therapy. Patients who achieve a complete remission require post-remission therapies to prevent relapse. There is no standard of care for patients with minimal residual disease (MRD), and stem cell transplantation is a salvage therapy. Considering the AML genetic heterogeneity and the leukemia immune-suppressive properties, novel cellular immune therapies to effectively harness immunological responses to prevent relapse are needed. We developed a novel modality of immune therapy consisting of monocytes reprogrammed with lentiviral vectors expressing GM-CSF, IFN-alpha and antigens. Preclinical studies in humanized mice showed that the reprogrammed monocytes self-differentiated into highly viable induced dendritic cells (iDCs) in vivo which migrated effectively to lymph nodes, producing remarkable effects in the de novo regeneration of T and B cell responses. For the first-in-man clinical trial, the patient's monocytes will be transduced with an integrase-defective tricistronic lentiviral vector expressing GM-CSF, IFN-alpha and a truncated WT1 antigen. For transplanted patients, pre-clinical development of iDCs co-expressing cytomegalovirus antigens is ongoing. To simplify the product chain for a de-centralized supply model, we are currently exploring a closed automated system for a short two-day manufacturing of iDCs. A phase I clinical trial study is in preparation for immune therapy of AML patients with MRD. The proposed cell therapy can fill an important gap in the current and foreseeable future immunotherapies of AML.

Brettig, T., et al. (2019). "Use of TCR alpha(+)beta(+)/CD19(+)-Depleted Haploidentical Hematopoietic Stem Cell Transplant Is a Viable Option in Patients With Primary Immune Deficiency Without Matched Sibling Donor." J Clin Immunol **39**(5): 505-511.

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for many patients with primary immune deficiency (PID). Haploidentical donors have historically been associated with higher rates of graft-versus-host disease (GvHD) and graft failure. Use of T cell receptor (TCR) alpha(+)beta(+)/CD19(+)-depleted grafts has resulted in improved haploidentical HSCT outcomes. We sought to evaluate outcomes of TCR alpha(+)beta(+)/CD19(+)-depleted haploidentical HSCT in pediatric patients with PID at a single center in Australia. Specifically, we evaluated immune reconstitution, looking at time to T cell and B cell reconstitution, and B cell function post-HSCT. Eleven patients with a mean age of 7.92 years (range 0.33-17.17 years) were included. The median time to B cell recovery was 93 days (range 41-205 days), and the median time to cessation of immunoglobulin replacement was 281.5 days (range 41-205 days). All patients who had ceased immunoglobulin replacement had an adequate response to pneumococcal conjugate (Prevenar 13) vaccine. The median time to CD4(+) recovery was 132 days (range 30-296 days), and naive T cells were present in all surviving patients by 4 months post-HSCT. Eight of 11 patients are surviving, with six patients having whole blood chimerism greater than 95%, one patient with whole blood chimerism of 82.8%, and another with 76.0%. All of these patients clinically had no evidence of underlying immunodeficiency. Likelihood of overall survival at 2 years post-HSCT was 81.8%. Cumulative incidence of acute GvHD was 27.3%. Cumulative incidence of CMV viremia was 63.6%. All patients previously exposed to CMV had reactivation post-HSCT, but were controlled with pre-emptive CMV treatment. Assuming most children with PID have a haploidentical donor available, use of this technique is likely to result in good outcomes for patients who do not have a suitable matched sibling or matched unrelated donor.

Cao, J., et al. (2019). "Emerging role of stem cell memory-like T cell in immune thrombocytopenia." Scand J Immunol **89**(3): e12739.

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by autoantibody-mediated platelet destruction. Multiple factors have been implicated in ITP pathogenesis, including T-lymphocyte dysfunctions. Increasing studies have indicated that stem cell memory-like T cell (TSCM) plays an important role in the development of multiple autoimmune diseases. This study aimed to explore the clinical correlation between the TSCM subset and ITP. The percentages of peripheral blood naive T cells (TNs), TSCMs, central memory T cells (TCMs), effector memory T cells (TEMs) and effector T cells (TEs) among CD4(+) and CD8(+) T cells in 20 ITP patients before and after treatment were detected using flow cytometry. Our results showed that the percentages of peripheral blood

CD4(+) and CD8(+) T cells in ITP patients were imbalanced. The percentage of CD8(+) TSCMs in peripheral blood before treatment in ITP patients was significantly higher than that in healthy controls, whereas the percentages of the other T cell subsets did not exhibit significant differences. Our study further analysed the correlation between the change in the percentage of CD8(+) TSCMs and the treatment efficacy. The results showed that the percentage of peripheral blood CD8(+) TSCMs in ITP patients after glucocorticoid treatment significantly decreased and the changes of the percentages of CD8(+) TSCMs before and after treatment in complete response (CR) and response (R) patients were obvious. Our finding showed that the imbalance of the percentage of CD8(+) TSCMs might be involved in the development of ITP and might serve as a novel indicator of efficacy.

Chen, M., et al. (2019). "Chronic Inflammation Directs an Olfactory Stem Cell Functional Switch from Neuroregeneration to Immune Defense." Cell Stem Cell **25**(4): 501-513 e505.

Although olfactory mucosa possesses long-lived horizontal basal stem cells (HBCs) and remarkable regenerative capacity, the function of human olfactory neuroepithelium is significantly impaired in chronic inflammatory rhinosinusitis. Here, we show that, while inflammation initially damages olfactory neurons and activates HBC-mediated regeneration, continued inflammation locks HBCs in an undifferentiated state. Global gene expression in mouse HBCs reveals broad upregulation of NF-kappaB-regulated cytokines and chemokines including CCL19, CCL20, and CXCL10, accompanied by enhancement of "stemness"-related transcription factors. Loss-of-function studies identify an NF-kappaB-dependent role of HBCs in amplifying inflammatory signaling, contributing to macrophage and T cell local proliferation. Chronically activated HBCs signal macrophages to maintain immune defense and prevent Treg development. In diseased human olfactory tissue, activated HBCs in a P63(+) undifferentiated state similarly contribute to inflammation through chemokine production. These observations establish a mechanism of chronic rhinosinusitis-associated olfactory loss, caused by a functional switch of neuroepithelial stem cells from regeneration to immune defense.

Chen, Y., et al. (2018). "Continuous Immune Cell Differentiation Inferred From Single-Cell Measurements Following Allogeneic Stem Cell Transplantation." Front Mol Biosci **5**: 81.

The process of immune system regeneration after allogeneic stem cell transplantation is slow, complex, and insufficiently understood. An entire immune system with all of its cell populations must regenerate from infused donor hematopoietic stem cells over the course of weeks and months post-transplantation. Both innate and adaptive arms of the immune system differ in their capacity and speed to reconstitiute in the recipient, which contributes to inadequacy in global immunity during the delayed reconstitution period. Systems-level analyses of immune systems in human patients have been made possible by high-throughput and high-dimensional, state-of-the-art, single-cell methodologies such as mass cytometry. Mass cytometry has revolutionized our ability to comprehensively profile all immune cell populations simultaneously in blood or tissue samples, providing signatures of differentially regulated cells in a range of clinical conditions. Such kind of systems immunology analyses promise not only for more accurate descriptions of variation between patients but also within individual patients over time, inter-dependencies between cell populations and the inference of developmental trajectories for specific cell populations. Here, we took advantage of a recently performed longitudinal mass cytometry analysis in 26 patients with hematological malignancies followed during the first 12 months following allogeneic stem cell transplantation. We present a proof-of-principle analysis to understand the evolution of individual immune cell populations. By applying non-linear dimensionality reduction and feauture extraction algorithms, we infer trajectories for individual immune cell populations, and map continuous marker expression changes occuring during immune cell regeneration that add novel information about this developmental process.

Choi, Y. B., et al. (2019). "Safety and immune cell kinetics after donor natural killer cell infusion following haploidentical stem cell transplantation in children with recurrent neuroblastoma." PLoS One **14**(12): e0225998.

INTRODUCTION: Under the hypothesis that early natural killer cell infusion (NKI) following haploidentical stem cell transplantation (haplo-SCT) will reduce relapse in the early post-transplant period, we conducted a pilot study to evaluate the safety and feasibility of NKI following haplo-SCT in children with recurrent neuroblastoma who failed previous tandem high-dose chemotherapy and autologous SCT. METHODS: We used the high-dose 131I-metaiodobenzylguanidine and cyclophosphamide/fludarabine/anti-thymocyte globulin regimen for conditioning and infused 3 x 107/kg of ex-vivo expanded NK cells derived from a haploidentical parent donor on days 2, 9, and 16 post-transplant. Interleukin-2 was administered (1 x 106 IU/m2/day) subcutaneously to activate infused donor NK cells on days 2, 4, 6, 9, 11, 13, 16, 18, and 20 post-transplant. RESULTS: Seven children received a total of 19 NKIs, and NKI-related acute toxicities were fever (n = 4)

followed by chills (n = 3) and hypertension (n = 3); all toxicities were tolerable. Grade >/=II acute GVHD and chronic GVHD developed in two and five patients, respectively. Higher amount of NK cell population was detected in peripheral blood until 60 days post-transplant than that in the reference cohort. Cytomegalovirus and BK virus reactivation occurred in all patients and Epstein-Barr virus in six patients. Six patients died of relapse/progression (n = 5) or treatment-related mortality (n = 1), and one patient remained alive. CONCLUSION: NKI following haplo-SCT was relatively safe and feasible in patients with recurrent neuroblastoma. Further studies to enhance the graft-versus-tumor effect without increasing GVHD are needed.

Cole, G., et al. (2019). "DNA vaccination via RALA nanoparticles in a microneedle delivery system induces a potent immune response against the endogenous prostate cancer stem cell antigen." Acta Biomater **96**: 480-490.

Castrate resistant prostate cancer (CRPC) remains a major challenge for healthcare professionals. Immunotherapeutic approaches, including DNA vaccination, hold the potential to harness the host's own immune system to mount a cell-mediated, anti-tumour response, capable of clearing disseminated tumour deposits. These anti-cancer vaccines represent a promising strategy for patients with advanced disease, however, to date DNA vaccines have demonstrated limited efficacy in clinical trials, owing to the lack of a suitable DNA delivery system. This study was designed to evaluate the efficacy of a two-tier delivery system incorporating cationic RALA/pDNA nanoparticles (NPs) into a dissolvable microneedle (MN) patch for the purposes of DNA vaccination against prostate cancer. Application of NP-loaded MN patches successfully resulted in endogenous production of the encoded Prostate Stem Cell Antigen (PSCA). Furthermore, immunisation with RALA/pPSCA loaded MNs elicited a tumour-specific immune response against TRAMP-C1 tumours ex vivo. Finally, vaccination with RALA/pPSCA loaded MNs demonstrated anti-tumour activity in both prophylactic and therapeutic prostate cancer models in vivo. This is further evidence that this two-tier MN delivery system is a robust platform for prostate cancer DNA vaccination. STATEMENT OF SIGNIFICANCE: This research describes the development and utilisation of our unique microneedle (MN) DNA delivery system, which enables penetration through the stratum corneum and deposition of the DNA within the highly immunogenic skin layers via a dissolvable MN matrix, and facilitates cellular uptake via complexation of pDNA cargo into nanoparticles (NPs) with the RALA delivery peptide. We report for the first time on using the NP-MN platform to immunise mice with encoded Prostate Stem Cell Antigen (mPSCA) for prostate cancer DNA vaccination. Application of the NP-MN system resulted in local mPSCA expression in vivo. Furthermore, immunisation with the NP-MN system induced a tumour-specific cellular immune response, and inhibited the growth of TRAMP-C1 prostate tumours in both prophylactic and therapeutic challenge models in vivo.

Conrad, A., et al. (2019). "VaccHemInf project: protocol for a prospective cohort study of efficacy, safety and characterisation of immune functional response to vaccinations in haematopoietic stem cell transplant recipients." BMJ Open **9**(2): e026093.

INTRODUCTION: Immune reconstitution after haematopoietic stem cell transplantation (HSCT) is a complex and dynamic process, varying from a state of nearly complete immunosuppression to an expected full immune recovery. Specific vaccination guidelines recommend reimmunisation after HSCT but data regarding vaccine efficacy in this unique population are scarce. New immune functional assays could enable prediction of vaccine response in the setting of HSCT. METHODS AND ANALYSIS: A prospective, longitudinal single-centre cohort study of autologous and allogeneic HSCT recipients was designed in order to determine the vaccine response to five vaccine targets (pneumococcus, hepatitis B virus, Haemophilus Influenzae type b, tetanus and diphtheria) and to correlate it to immune function parameters. A workflow was set up to study serological response to vaccines and to describe the functional immune status of 100 HSCT recipients (50 autologous and 50 allogeneic) before and 3, 12 and 24 months after primary immunisation. At each time point, 'basic' immune status recording (serology, immunophenotyping of lymphocyte subsets by flow cytometry) will be assessed. The immune response will furthermore be evaluated before and 3 months after primary vaccination by two ex vivo immune functional assays assessing: (1) tumour necrosis factor alpha, interferon gamma production and host messenger RNA expression on whole-blood stimulation by lipopolysaccharide or Staphylococcus aureus enterotoxin B and (2) T-lymphocyte proliferation in response to a standard mitogen (phytohaemagglutinin) or to selected recall antigens. Reference intervals will be determined from a cohort of 30 healthy volunteers. This translational study will provide data describing vaccine response, immune functionality of HSCT recipients over time and will allow mapping HSCT recipients with regard to their immune function. ETHICS AND DISSEMINATION: Ethical approval has been obtained from the institutional review board (no 69HCL17_0769). Results will be communicated at scientific meetings and submitted for publication in

peer-reviewed journals. TRIAL REGISTRATION NUMBER: NCT03659773; Pre-results.

Corraliza, A. M., et al. (2019). "Differences in Peripheral and Tissue Immune Cell Populations Following Haematopoietic Stem Cell Transplantation in Crohn's Disease Patients." J Crohns Colitis **13**(5): 634-647.

BACKGROUND AND AIMS: Recent studies have shown the efficacy of autologous haematopoietic stem cell transplantation [HSCT] in severely refractory Crohn's disease [CD] patients. HSCT is thought to eliminate auto-reactive cells; however, no specific studies of immune reconstitution in CD patients are available. METHODS: We followed a group of CD patients [n = 18] receiving autologous HSCT, with 50% of them achieving endoscopic drug-free remission. To elucidate the mechanisms driving efficacy, we monitored changes after HSCT in blood and intestine immune-cell composition. CD patients [n = 22] receiving anti-tumour necrosis factor [TNF]-alpha were included for comparison. RESULTS: Severe immune ablation followed by HSCT induced dramatic changes in both peripheral blood T and B cells in all patients regardless of the efficacy of the treatment. Endoscopic remission at week 52 following HSCT was associated with significant intestinal transcriptional changes. A comparison of the remission signature with that of anti-TNFalpha identified both common and unique genes in the HSCT-induced response. Based on deconvolution analysis of intestinal biopsy transcriptome data, we show that response to HSCT, but not to anti-TNFalpha, is associated with an expansion of naive B-cells, as seen in blood, and a decrease in the memory resting T-cell content. As expected, endoscopic remission, in response to both HSCT and anti-TNFalpha, led to a significant reduction in intestinal neutrophil and M1 macrophage content. CONCLUSIONS: Peripheral blood immune remodelling after HSCT does not predict efficacy. In contrast, a profound intestinal T-cell depletion that is maintained long after transplant is associated with mucosal healing following HSCT, but not anti-TNFalpha.

Cuvelier, G. D. E., et al. (2019). "Clinical presentation, immunologic features, and hematopoietic stem cell transplant outcomes for IKBKB immune deficiency." Clin Immunol **205**: 138-147.

IKBKB immune deficiency is a rare but life-threatening primary immunodeficiency disorder, involving activation defects in adaptive and innate immunity. We present sixteen cases of a homozygous IKBKB mutation (c.1292dupG) in infants characterized by early-onset bacterial, viral, fungal and Mycobacterial infections. In most cases, T- and B-cells were quantitatively normal, but phenotypically naive, with severe hypogammaglobulinemia. T-cell receptor excision circles were normal, meaning newborn screening by TREC analysis would miss IKBKB cases. Although IKBKB immune deficiency does not meet traditional laboratory based definitions for SCID, this combined immune deficiency appears to be at least as profound. Urgent HSCT, performed in eight patients, remains the only known curative therapy, although only three patients are survivors. Ongoing infections after transplant remain a concern, and may be due to combinations of poor social determinants of health, secondary graft failure, and failure of HSCT to replace non-hematopoietic cells important in immune function and dependent upon IKK/NF-kappaB pathways.

Ebrahim, N., et al. (2019). "Adipose Tissue-Derived Mesenchymal Stem Cell Modulates the Immune Response of Allergic Rhinitis in a Rat Model." Int J Mol Sci **20**(4).

This study was designed to investigate the potential effects and underlying mechanism of adipose tissue-derived mesenchymal stem cells (MSCs) on allergic inflammation compared to Montelukast as an antileukotriene drug in a rat model of allergic rhinitis (AR). The effect of MSCs was evaluated in albino rats that were randomly divided into four (control, AR, AR + Montelukast, and AR + MSCs) groups. Rats of AR group were sensitized by ovalbumin (OVA) and then challenged with daily nasal drops of OVA diluted in sterile physiological saline (50 muL/nostril, 100 mg/mL, 10% OVA) from day 15 to day 21 of treatment with/without Montelukast (1 h before each challenge) or MSCs I/P injection (1 x 10(6) MCSs; weekly for three constitutive weeks). Both Montelukast and MSCs treatment started from day 15 of the experiment. At the end of the 5th week, blood samples were collected from all rats for immunological assays, histological, and molecular biology examinations. Both oral Montelukast and intraperitoneal injection of MSCs significantly reduced allergic symptoms and OVA-specific immunoglobulin E (IgE), IgG1, IgG2a and histamine as well as increasing prostaglandin E2 (PGE2). Further analysis revealed that induction of nasal innate cytokines, such as interleukin (IL)-4 and TNF-alpha; and chemokines, such as CCL11 and vascular cell adhesion molecule-1 (VCAM-1), were suppressed; and transforming growth factor-beta (TGF-beta) was up-regulated in Montelukast and MSCs-treated groups with superior effect to MSCs, which explained their underlying mechanism. In addition, the adipose tissue-derived MSCs-treated group had more restoring effects on nasal mucosa structure demonstrated by electron microscopical examination.

Elfeky, R., et al. (2019). "Immune reconstitution following hematopoietic stem cell transplantation using different stem cell sources." Expert Rev Clin Immunol **15**(7): 735-751.

Introduction: Adequate immune reconstitution post-HSCT is crucial for the success of transplantation, and can be affected by both patient- and transplant-related factors. Areas covered: A systematic literature search in PubMed, Scopus, and abstracts of international congresses is performed to investigate immune recovery posttransplant. In this review, we discuss the pattern of immune recovery in the post-transplant period focusing on the impact of stem cell source (bone marrow, peripheral blood stem cells, and cord blood) on immune recovery and HSCT outcome. We examine the impact of serotherapy on immune reconstitution and the need to tailor dosing of serotherapy agents when using different stem cell sources. We discuss new techniques being used particularly with cord blood and haploidentical grafts to improve immune recovery in each scenario. Expert opinion: Cord blood T cells provide a unique CD4+ biased immune reconstitution. Initial studies using targeted serotherapy with cord grafts showed improved immune recovery with limited alloreactivity. Two competing haploidentical approaches have developed in recent years including TCRalphabeta/CD19 depleted grafts and post-cyclophosphamide haplo-HSCT. Both approaches have comparable survival rates with limited alloreactivity. However, delayed immune reconstitution is still an ongoing problem and could be improved by modified donor lymphocyte infusions from the same haploidentical donor.

Erbey, F., et al. (2019). "Successful treatment of BCG-related immune reconstitution inflammatory syndrome following ex vivo T-cell-depleted haploidentical hematopoietic stem cell transplantation: A case report." Pediatr Transplant **23**(5): e13464.

IRIS is a phenomenon describing localized inflammatory reactions at BCG vaccination site and development of lymphadenopathy as immune system recovers. It is a rare entity in children following haploidentical HSCT. We represent the successful treatment of a case with fluctuating lymphadenopathy due to BCG vaccine during immune reconstitution period following ex vivo T-cell-depleted haploidentical HSCT.

Felix, R. G., et al. (2020). "Adipose-derived stem cells and adipose-derived stem cell-conditioned medium modulate in situ imbalance between collagen I- and collagen V-mediated IL-17 immune response recovering bleomycin pulmonary fibrosis." Histol Histopathol **35**(3): 289-301.

The immunogenic collagen V (Col V) and the proinflammatory cytokine interleukin (IL)-17 have been implicated in the pathogenesis of multiple autoimmune diseases. Col V is also up-regulated during adipogenesis and can stimulate adipocyte differentiation in vitro. Conditioned medium (CM) generated from adipose-derived mesenchymal stem cells (MSCs) reduces bleomycin (BLM)-induced lung injury in rats, suggesting a crucial role in situ of immunomodulatory factors secreted by MSCs in these beneficial effects. In the present work, we investigated this hypothesis, analyzing levels of plasma inflammatory mediators and inflammatory and fibrotic mediators in the lung tissue of BLM-injured rats after treatment with MSCs and CM. Pulmonary fibrosis was intratracheally induced by BLM. After 10 days, BLM animals were further randomized into subgroups receiving saline, MSCs, or CM intravenously. On days 14 and 21, the animals were euthanized, and the lungs were examined through protein expression of nitric oxide synthase (NOS), IL-17, transforming growth factor-beta (TGF-beta), vascular endothelial growth factor, endothelin-1, and the immunogenic Col V through histological quantitative evaluation and plasma levels of fibrinogen, Von Willebrand factor, and platelet-derived growth factor (PDGF). Rats that had been injected with MSCs and CM showed a significant increase in weight and significant improvements at 14 and 21 days after intravenous injection at both time points of analysis of plasma fibrinogen, PDGF, and Von Willebrand factor and NOS-2 expression, supporting an early anti-inflammatory action, thus reducing TGF-beta and collagen I fibers. In contrast, intravenous injection of CM was able to significantly increase the deposition of Col V fibers and IL-17 on both day 14 and day 21 as compared with the amount observed in rats from the BLM group and MSC groups. In conclusion, this study reinforces previous observations on the therapeutic properties of MSCs and CM and is the first report to demonstrate the association of its actions with immunomodulatory biomarkers on lung tissue. We concluded that adipose-derived stem cells and adipose-derived stem cells-CM modulate an in situ imbalance between collagen I- and Col V-mediated IL-17 immune response, emerging as a promising therapeutic option for recovering from BLM pulmonary fibrosis.

Francois, S., et al. (2019). "Mesenchymal Stem Cell Administration Attenuates Colon Cancer Progression by Modulating the Immune Component within the Colorectal Tumor Microenvironment." Stem Cells Transl Med **8**(3): 285-300.

We here determine the influence of mesenchymal stem cell (MSC) therapy on the progression of solid tumors. The influence of MSCs was investigated in human colorectal cancer cells as well as in an immunocompetent rat model of colorectal carcinogenesis representative of the human pathology. Treatment with bone marrow (BM)-derived MSCs significantly reduced both cancer initiation and cancer progression by increasing the number of tumor-free animals as well as decreasing the number and the size of the tumors by half, thereby extending their lifespan.

The attenuation of cancer progression was mediated by the capacity of the MSCs to modulate the immune component. Specifically, in the adenocarcinomas (ADKs) of MSC-treated rats, the infiltration of CD68+ monocytes/macrophages was 50% less while the presence of CD3+ lymphocytes increased almost twofold. The MSCs reprogrammed the macrophages to become regulatory cells involved in phagocytosis thereby inhibiting the production of proinflammatory cytokines. Furthermore, the MSCs decreased NK (Natural Killer) and rTh17 cell activities, Treg recruitment, the presence of CD8+ lymphocytes and endothelial cells while restoring Th17 cell activity. The expression of miR-150 and miR-7 increased up to fivefold indicating a likely role for these miRNAs in the modulation of tumor growth. Importantly, MSC administration limited the damage of healthy tissues and attenuated tumor growth following radiotherapy. Taken together, we here show that that MSCs have durable action on colon cancer development by modulating the immune component of the tumor microenvironment. In addition, we identify two miRNAs associated with the capacity of MSCs to attenuate cancer growth. Stem Cells Translational Medicine 2019;8:285&300.

Fu, Y. Y., et al. (2019). "T Cell Recruitment to the Intestinal Stem Cell Compartment Drives Immune-Mediated Intestinal Damage after Allogeneic Transplantation." Immunity **51**(1): 90-103 e103.

The key sites within the gastrointestinal (GI) tract where T cells mediate effector responses and the impact of these responses on intestinal stem cells (ISCs) remain unclear. Using experimental bone marrow transplantation to model immune-mediated GI damage and 3D imaging to analyze T cell localization, we found that the ISC compartment is the primary intestinal site targeted by T cells after transplantation. Recruitment to the crypt base region resulted in direct T cell engagement with the stem cell compartment and loss of crypt base columnar ISCs, which expressed both MHC classes I and II. Vasculature expressing the adhesion molecule MAdCAM-1 clustered near the crypt base, preferentially regulating crypt compartment invasion and ISC reduction without affecting T cell migration to villi. These findings indicate that allogeneic T cells rapidly access the stem cell niche after transplantation, and this targeted recruitment to the stem cell compartment results in ISC loss during immune-mediated GI damage.

Gooptu, M., et al. (2018). "Effect of Antihuman T Lymphocyte Globulin on Immune Recovery after Myeloablative Allogeneic Stem Cell Transplantation with Matched Unrelated Donors: Analysis of Immune Reconstitution in a Double-Blind Randomized Controlled Trial." Biol Blood Marrow Transplant **24**(11): 2216-2223.

We recently conducted a randomized double-blind study in which we demonstrated that moderate/severe chronic graft-versus-host disease (cGVHD) but not cGVHD-free survival was reduced in patients receiving anti-T lymphocyte globulin (ATLG) versus placebo. In a companion study we performed immunophenotypic analysis to determine the impact of ATLG on immune reconstitution (IR) and to correlate IR with clinical outcomes. The randomized study (n=254) included patients (aged 18 to 65 years) who underwent myeloablative transplants for acute myeloid leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia from HLA-matched unrelated donors. Ninety-one patients consented for the companion IR study (ATLG=44, placebo=47). Blood samples were collected on days 30, 100, 180, and 360 after hematopoietic cell transplantation (HCT), and multiparameter flow cytometry was performed in a blinded fashion. Reconstitution of CD3(+) and CD4(+) T cells was delayed up to 6 months post-HCT in the ATLG arm, whereas absolute regulatory T cell (Treg) (CD4(+)25(+)127-) numbers were lower only in the first 100 days. Analysis of the CD4(+) Treg and conventional T cells (Tconv) (CD4(+)25(-)127(+)) compartments showed a profound absence of naive Tregs and Tconv in the first 100 days post-HCT, with very slow recovery for 1 year. B cell and natural killer cell recovery were similar in each arm. Higher absolute counts of CD3(+), CD4(+), CD8(+) T, Tregs, and Tconv were associated with improved overall survival, progression-free survival, and nonrelapse mortality but not moderate/severe cGVHD. Although ATLG delays CD3(+) and CD4(+) T cell recovery post-transplant, it has a relative Treg sparing effect after the early post-HCT period, with possible implications for protection from cGVHD. ATLG severely compromises the generation of naive CD4(+) cells (Treg and Tconv), potentially affecting the diversity of the TCR repertoire and T cell responses against malignancy and infection.

Gooptu, M., et al. (2019). "Effect of Sirolimus on Immune Reconstitution Following Myeloablative Allogeneic Stem Cell Transplantation: An Ancillary Analysis of a Randomized Controlled Trial Comparing Tacrolimus/Sirolimus and Tacrolimus/Methotrexate (Blood and Marrow Transplant Clinical Trials Network/BMT CTN 0402)." Biol Blood Marrow Transplant **25**(11): 2143-2151.

Although allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for hematologic neoplasms, one of its limiting toxicities continues to be graft-versus-host disease, both acute (aGVHD) and chronic (cGVHD). Sirolimus is a mammalian target of rapamycin inhibitor that has proven effective in GVHD prophylaxis in combination with a calcineurin inhibitor, such as tacrolimus. The impact of sirolimus on immune reconstitution has not

been comprehensively investigated in vivo thus far, however. Here we present an ancillary analysis of the randomized study BMT-CTN 0402 that examined the effect of sirolimus on immune subsets post-transplantation. We further examine the association between different lymphocyte subsets and outcomes post-transplantation in each arm. BMT-CTN 0402 was a randomized trial (n=304) comparing 2 GVHD prophylaxis regimens, tacrolimus/sirolimus (Tac/Sir) and tacrolimus/methotrexate (Tac/MTX), in patients with acute myelogenous leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome undergoing myeloablative HLA-matched HCT. There were no differences in 114-day GVHD-free survival (primary endpoint), aGVHD, cGVHD, relapse, or overall survival (OS) between the 2 arms. Of the 304 patients, 264 had available samples for the current immune reconstitution analysis. Blood samples were collected at 1, 3, 6, 12, and 24 months post-HCT. Multiparameter flow cytometry was performed at the project laboratory (Esoterix Clinical Trials Services) in a blinded fashion, and results for the 2 arms were compared. Multivariable Cox regression models, treating each phenotypic parameter as a time-dependent variable, were constructed to study the impact of reconstitution on clinical outcomes. There were no significant differences in patient and transplantation characteristics between the Tac/Sir and Tac/MTX arms in this analysis. Absolute lymphocyte count and CD3(+) cell, CD4(+) cell, and conventional T cell (Tcon) counts were significantly decreased in the Tac/Sir arm for up to 3 months post-HCT, whereas CD8(+) cells recovered even more slowly (up to 6 months) in this arm. Interestingly, there was no clear difference in the absolute number of regulatory T cells (Tregs, defined as CD4(+)CD25(+) cells) between the 2 arms at any point post-HCT; however, the Treg:Tcon ratio was significantly greater in the Tac/Sir arm in the first 3 months after HCT. B lymphocyte recovery was significantly compromised in the Tac/Sir arm from 1 month to 6 months after HCT, whereas natural killer cell reconstitution was not affected in the Tac/Sir arm. In the outcomes analysis, higher numbers of CD3(+) cells, CD4(+) cells, CD8(+) cells, and Tregs were associated with better OS. Neither Treg numbers nor the Treg:Tcon ratio was correlated with GVHD. Our findings indicate that Tac/Sir has a more profound T cell suppressive effect than the combination of Tac/MTX in the early post-transplantation period, and particularly compromises the recovery of CD8(+) T cells, which have been implicated in aGVHD. Sirolimus used in vivo with tacrolimus does not appear to result in increased absolute numbers of Tregs, but might have a beneficial effect on the Treg:Tcon balance in the first 3 months after transplantation. Nonetheless, no differences in aGVHD or cGVHD between the 2 arms were observed in the parent randomized trial. Calcineurin-inhibitor free, sirolimus-containing GVHD prophylaxis strategies, incorporating other novel agents, should be investigated further to maximize the potential favorable effect of sirolimus on Treg:Tcon balance in the post-transplantation immune repertoire. Sirolimus significantly compromises B cell recovery in the first 6 months post-HCT, with potential complex effects on cGVHD that merit further study.

Gugjoo, M. B., et al. (2020). "Mesenchymal Stem Cell-Mediated Immuno-Modulatory and Anti- Inflammatory Mechanisms in Immune and Allergic Disorders." Recent Pat Inflamm Allergy Drug Discov **14**(1): 3-14.

BACKGROUND: Mesenchymal Stem Cells (MSCs) are present in almost all the tissues of the body and act as the backbone of the internal tissue homeostasis. Among their various characteristic features, immuno-modulatory and/ anti-inflammatory properties play an important role in therapeutics. OBJECTIVE: The current topic focuses on the characterization and immuno-modulatory and/ antiinflammatory properties of MSCs. To present and discuss the current status of MSCs immunomodulatory properties. METHODS: Available literature on MSCs properties and patents have been detailed, critically interpreted, and discussed based upon available literature. The main focus has been on their characteristic immunomodulatory and anti-inflammatory properties though some of the basic characterization markers have also been detailed. The databases searched for the literature include PubMed, Med Line, PubMed Central, Science Direct and a few other scientific databases. RESULTS: MSCs are present in a very limited concentration in the tissues, and as such their culture expansion becomes imperative. MSCs immuno-modulatory and anti-inflammatory roles are achieved through direct cell-cell contact and / by the release of certain factors. Such properties are controlled by micro-environment upon which currently very limited control can be exerted. Besides, further insights in the xeno-protein free culture media as against the fetal bovine serum is required. CONCLUSION: MSCs have been well-isolated, cultured and characterized from numerous tissues of the body. The majority of the studies have shown MSCs as immuno-compromised with immunomodulatory and / or anti-inflammatory properties except some of the latest studies that have failed to achieve the desired results and thus, demand further research. Further research is required in the area to translate the results into clinical application.

Hakim, R., et al. (2019). "Mesenchymal stem cells transplanted into spinal cord injury adopt immune cell-like characteristics." Stem Cell Res Ther **10**(1): 115.

BACKGROUND: Mesenchymal stem cells (MSCs) and their cellular response to various stimuli

have been characterized in great detail in culture conditions. In contrast, the cellular response of MSCs in an in vivo setting is still uncharted territory. In this study, we investigated the cellular response of MSCs following transplantation into spinal cord injury (SCI). METHODS: Mouse bone marrow-derived MSCs were transplanted 24 h following severe contusion SCI in mice. As controls, MSCs transplanted to the uninjured spinal cord and non-transplanted MSCs were used. At 7 days post transplantation, the MSCs were isolated from the SCI, and their global transcriptional changes, survival, differentiation, proliferation, apoptosis, and phenotypes were investigated using RNA sequencing, immunohistochemistry, and flow cytometry. RESULTS: MSCs transplanted into SCI downregulated genes related to cell-cycle regulation/progression, DNA metabolic/biosynthetic process, and DNA repair and upregulated genes related to immune system response, cytokine production/response, response to stress/stimuli, signal transduction and signaling pathways, apoptosis, and phagocytosis/endocytosis. MSCs maintained their surface expression of Sca1 and CD29 but upregulated expression of CD45 following transplantation. Transplanted MSCs maintained their surface expression of MHC-I but upregulated surface expression of MHC-II. Transplanted MSCs survived and proliferated to a low extent, did not express Caspase-3, and did not differentiate into neurons or astrocytes. CONCLUSION: MSCs transplanted into SCI upregulate expression of CD45 and MHC-II and expression of genes related to cytokine production, phagocytosis/endocytosis, and immune cells/response and thereby adopt immune cell-like characteristics within the recipient.

Hilger, N., et al. (2018). "Incubation of Immune Cell Grafts With MAX.16H5 IgG1 Anti-Human CD4 Antibody Prolonged Survival After Hematopoietic Stem Cell Transplantation in a Mouse Model for Fms Like Tyrosine Kinase 3 Positive Acute Myeloid Leukemia." Front Immunol **9**: 2408.

Despite the constant development of innovative therapeutic options for hematological malignancies, the gold-standard therapy regimen for curative treatment often includes allogeneic hematopoietic stem cell transplantation (HSCT). The graft-vs.-leukemia effect (GVL) is one of the main therapeutic goals that arises from HSCT. On the other hand, graft-vs.-host disease (GVHD) is still one of the main and most serious complications following allogeneic HSCT. In acute myeloid leukemia (AML), HSCT together with high-dose chemotherapy is used as a treatment option. An aggressive progression of the disease, a decreased response to treatment, and a poor prognosis are connected to internal tandem duplication (ITD) mutations in the Fms like tyrosine kinase 3 (FLT3) gene, which affects around 30% of AML patients. In this study, C3H/HeN mice received an allogeneic graft together with 32D-FLT3(ITD) AML cells to induce acute GVHD and GVL. It was examined if pre-incubation of the graft with the anti-human cluster of differentiation (CD) 4 antibody MAX.16H5 IgG1 prevented the development of GVHD and whether the graft function was impaired. Animals receiving grafts pre-incubated with the antibody together with FLT3(ITD) AML cells survived significantly longer than mice receiving untreated grafts. The observed prolonged survival due to MAX.16H5 incubation of immune cell grafts prior to transplantation may allow an extended application of additional targeted strategies in the treatment of AML.

Hou, Q., et al. (2020). "Intestinal Stem Cells and Immune Cell Relationships: Potential Therapeutic Targets for Inflammatory Bowel Diseases." Front Immunol **11**: 623691.

The mammalian intestine is the largest immune organ that contains the intestinal stem cells (ISC), differentiated epithelial cells (enterocytes, Paneth cells, goblet cells, tuft cells, etc.), and gut resident-immune cells (T cells, B cells, dendritic cells, innate lymphoid cell, etc.). Inflammatory bowel disease (IBD), a chronic inflammatory disease characterized by mucosa damage and inflammation, threatens the integrity of the intestine. The continuous renewal and repair of intestinal mucosal epithelium after injury depend on ISCs. Inflamed mucosa healing could be a new target for the improvement of clinical symptoms, disease recurrence, and resection-free survival in IBD treated patients. The knowledge about the connections between ISC and immune cells is expanding with the development of in vitro intestinal organoid culture and single-cell RNA sequencing technology. Recent findings implicate that immune cells such as T cells, ILCs, dendritic cells, and macrophages and cytokines secreted by these cells are critical in the regeneration of ISCs and intestinal epithelium. Transplantation of ISC to the inflamed mucosa may be a new therapeutic approach to reconstruct the epithelial barrier in IBD. Considering the links between ISC and immune cells, we predict that the integration of biological agents and ISC transplantation will revolutionize the future therapy of IBD patients.

Ingham, A. C., et al. (2019). "Specific gut microbiome members are associated with distinct immune markers in pediatric allogeneic hematopoietic stem cell transplantation." Microbiome **7**(1): 131.

BACKGROUND: Increasing evidence reveals the importance of the microbiome in health and disease and inseparable host-microbial dependencies. Host-microbe interactions are highly relevant in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT), i.e., a replacement of the cellular components of the patients' immune system

with that of a foreign donor. HSCT is employed as curative immunotherapy for a number of non-malignant and malignant hematologic conditions, including cancers such as acute lymphoblastic leukemia. The procedure can be accompanied by severe side effects such as infections, acute graft-versus-host disease (aGvHD), and death. Here, we performed a longitudinal analysis of immunological markers, immune reconstitution and gut microbiota composition in relation to clinical outcomes in children undergoing HSCT. Such an analysis could reveal biomarkers, e.g., at the time point prior to HSCT, that in the future could be used to predict which patients are of high risk in relation to side effects and clinical outcomes and guide treatment strategies accordingly. RESULTS: In two multivariate analyses (sparse partial least squares regression and canonical correspondence analysis), we identified three consistent clusters: (1) high concentrations of the antimicrobial peptide human beta-defensin 2 (hBD2) prior to the transplantation in patients with high abundances of Lactobacillaceae, who later developed moderate or severe aGvHD and exhibited high mortality. (2) Rapid reconstitution of NK and B cells in patients with high abundances of obligate anaerobes such as Ruminococcaceae, who developed no or mild aGvHD and exhibited low mortality. (3) High inflammation, indicated by high levels of C-reactive protein, in patients with high abundances of facultative anaerobic bacteria such as Enterobacteriaceae. Furthermore, we observed that antibiotic treatment influenced the bacterial community state. CONCLUSIONS: We identify multivariate associations between specific microbial taxa, host immune markers, immune cell reconstitution, and clinical outcomes in relation to HSCT. Our findings encourage further investigations into establishing longitudinal surveillance of the intestinal microbiome and relevant immune markers, such as hBD2, in HSCT patients. Profiling of the microbiome may prove useful as a prognostic tool that could help identify patients at risk of poor immune reconstitution and adverse outcomes, such as aGvHD and death, upon HSCT, providing actionable information in guiding precision medicine.

Jafarzadeh, N., et al. (2019). "Alteration of cellular and immune-related properties of bone marrow mesenchymal stem cells and macrophages by K562 chronic myeloid leukemia cell derived exosomes." J Cell Physiol **234**(4): 3697-3710.

Leukemic cells can impact the bone marrow niche to create a tumor-favorable microenvironment using their secreted factors. Little knowledge is available about immunosuppressive and tumor-promoting properties of chronic myeloid leukemia derived exosomes in bone marrow stromal components. We report here that K562-derived exosomes can affect the gene expression, cytokine secretion, nitric oxide (NO) production, and redox potential of bone marrow mesenchymal stem cells (BM-MSCs) and macrophages. Human BM-MSCs and mouse macrophages were treated with K562-derived exosomes. Our results demonstrated that the expression of the genes involved in hematopoietic developmental pathways and immune responses, including C-X-C motif chemokine 12 (Cxcl12), Dickkopf-related protein 1 (DKK1), wnt5a, interleukin 6 (IL-6), transforming growth factor-beta, and tumor necrosis factor-alpha (TNF-alpha), changed with respect to time and exosome concentration in BM-MSCs. The TNF-alpha level was higher in exosome-treated BM-MSCs compared with the control. Exosome treatment of BM-MSCs led to an increased production of NO and a decreased production of reactive oxygen species (ROS) in a time- and concentration-dependent manner. We have shown that K562-derived exosomes induce overexpression of IL-10 and TNF-alpha and downregulation of iNOS transcript levels in macrophages. The enzyme-linked immunosorbent assay results showed that TNF-alpha and IL-10 secretions increased in macrophages. Treatment of macrophages with purified exosomes led to reduced NO and ROS levels. These results suggest that K562-derived exosomes may alter the local bone marrow niche toward a leukemia-reinforcing microenvironment. They can modulate the inflammatory molecules (TNF-alpha and NO) and the redox potential of BM-MSCs and macrophages and direct the polarization of macrophages toward tumor-associated macrophages.

Jain, S., et al. (2021). "The Cancer Stem Cell Niche in Ovarian Cancer and Its Impact on Immune Surveillance." Int J Mol Sci **22**(8).

Ovarian cancer is an aggressive gynaecological cancer with extremely poor prognosis, due to late diagnosis as well as the development of chemoresistance after first-line therapy. Research advances have found stem-like cells present in ovarian tumours, which exist in a dynamic niche and persist through therapy. The stem cell niche interacts extensively with the immune and non-immune components of the tumour microenvironment. Significant pathways associated with the cancer stem cell niche have been identified which interfere with the immune component of the tumour microenvironment, leading to immune surveillance evasion, dysfunction and suppression. This review aims to summarise current evidence-based knowledge on the cancer stem cell niche within the ovarian cancer tumour microenvironment and its effect on immune surveillance. Furthermore, the review seeks to understand the clinical consequences of this dynamic

interaction by highlighting current therapies which target these processes.

Kalavska, K., et al. (2020). "Cancer Stem Cell Niche and Immune-Active Tumor Microenvironment in Testicular Germ Cell Tumors." Adv Exp Med Biol **1226**: 111-121.

Testicular germ cell tumors (TGCTs) represent the most common neoplasia among young men. Management of TGCTs is an excellent example of curative outcomes in clinical oncology. The unique sensitivity to cisplatin-based chemotherapy regimens has led to establishing TGCTs as a "model of cancer cure." However, mechanisms and factors underlying pervasive growth of TGCTs are still poorly understood. It is suggested that unique cancer stem cell (CSC) niche exists in the testicular tumor microenvironment. CSC niche potentially contributes to the progression of germ cell tumors. Furthermore, rich infiltration of TGCTs with immune cells indicates involvement of immune system in biology of this cancer type. This review summarizes current knowledge regarding specific cancer microenvironment in TGCTs and discusses the role of cancer stem cells as well as immune mechanisms in these tumors.

Kashiyama, N., et al. (2019). "Vasculogenically conditioned peripheral blood mononuclear cells inhibit mouse immune response to induced pluripotent stem cell-derived allogeneic cardiac grafts." PLoS One **14**(5): e0217076.

Allogeneic transplantation of induced pluripotent stem cell (iPSC)-derived cardiomyocytes is apromising treatment for cardiac diseases, although immune rejection by the recipient poses a concern. In this study, we aimed to investigate whether concomitant transplantation of vasculogenically conditioned peripheral blood mononuclear cells, which are otherwise immunosuppressive, may enhance graft survival. Luciferase-transduced, iPSC-derived cardiomyocytes from C57BL/6 mice were transplanted to the dorsal subcutaneous space of syngeneic C57BL/6 mice (n = 19), allogeneic Balb/c mice treated with (n = 20) or without (n = 20) immunosuppressants, and those injected with vasculogenically conditioned peripheral blood mononuclear cells (n = 20). Although graft survival, assessed by bioluminescence, was comparable among the groups initially, it improved significantly at days 7 and 10 in allogeneic transplanted mice treated with vasculogenically conditioned peripheral blood mononuclear cells than in others ($P < 0.01$). Our results proved that cell-based immunosuppression may boost clinical outcomes from allogeneic cell therapy.

Kim, S. H., et al. (2018). "Immune inflammatory modulation as a potential therapeutic strategy of stem cell therapy for ALS and neurodegenerative diseases." BMB Rep **51**(11): 545-546.

With emerging evidence on the importance of non-cell autonomous toxicity in neurodegenerative diseases, therapeutic strategies targeting modulation of key immune cells. including microglia and Treg cells, have been designed for treatment of ALS and other neurodegenerative diseases. Strategy switching the patient's environment from a pro-inflammatory toxic to an anti-inflammatory, and neuroprotective condition, could be potential therapy for neurodegenerative diseases. Mesenchymal stem cells (MSCs) regulate innate and adaptive immune cells, through release of soluble factors such as TGF-beta and elevation of regulatory T cells (Tregs) and T helper-2 cells (Th2 cells), would play important roles, in the neuroprotective effect on motor neuronal cell death mechanisms in ALS. Single cycle of repeated intrathecal injections of BM-MSCs demonstrated a clinical benefit lasting at least 6 months, with safety, in ALS patients. Cytokine profiles of CSF provided evidence that BM-MSCs, have a role in switching from pro-inflammatory to anti-inflammatory conditions. Inverse correlation of TGF-beta1 and MCP-1 levels, could be a potential biomarker to responsiveness. Thus, additional cycles of BM-MSC treatment are required, to confirm long-term efficacy and safety. [BMB Reports 2018; 51(11): 545-546].

Kobayashi, T., et al. (2019). "Relationship between clinical course of nivolumab-related myositis and immune status in a patient with Hodgkin's lymphoma after allogeneic hematopoietic stem cell transplantation." Int J Hematol **109**(3): 356-360.

Although programmed cell death (PD)-1 blockade induces immune-related adverse events (irAEs), little is known about the safety of PD-1 blockade after allogeneic hematopoietic stem cell transplantation (HSCT). Here, we describe immune system changes during nivolumab-related myositis in a patient with Hodgkin's lymphoma after allogeneic HSCT; to our knowledge, this is the first such report in the literature. At the onset of myositis, the patient lost lower limb mobility against gravity, and had an activated immune profile with increased cytotoxic CD107a and granzyme B expression, as well as pro-inflammatory cytokines, interferon-gamma, tumor necrosis factor-alpha, interleukin-2 in T and NK cells compared to healthy donor. Pulse steroid therapy decreased creatine kinase levels and induced PD-1 expression and regulatory T cells, but did not improve myositis; previously activated markers remained high. Four-week corticosteroid therapy decreased previously activated markers and the myositis improved. These findings provide new insights into nivolumab-induced irAE pathogenesis and suggest possible optimal treatments for irAEs.

Kong, W., et al. (2020). "Prognostic model of patients with liver cancer based on tumor stem cell content and immune process." Aging (Albany NY) **12**(16): 16555-16578.

Globally, liver hepatocellular carcinoma (LIHC) has a high mortality and recurrence rate, leading to poor prognosis. The recurrence of LIHC is closely related to two aspects: degree of immune infiltration and content of tumor stem cells. Hence, this study aimed to used RNA-seq and clinical data of LIHC from The Cancer Genome Atlas, Estimation of Stromal and Immune cells in Malignant Tumours, mRNA stemness index score, and weighted gene correlation network analysis methods to find genes significantly linked to the aforementioned two aspects. Key genes and clinical factors were used as input. Lasso regression and multivariate Cox regression were conducted to build an effective prognostic model for patients with liver cancer. Finally, four key genes (KLHL30, PLN, LYVE1, and TIMD4) and four clinical factors (Asian, age, grade, and bilirubin) were included in the prognostic model, namely Immunity and Cancer-stem-cell Related Prognosis (ICRP) score. The ICRP score achieved a great performance in test set. The area under the curve value of the ICRP score in test set for 1, 3, and 5 years was 0.708, 0.723, and 0.765, respectively, which was better than that of other prognostic prediction methods for LIHC. The C-index evaluation method also reached the same conclusion.

Lawitschka, A., et al. (2019). "National Institutes of Health-Defined Chronic Graft-vs.-Host Disease in Pediatric Hematopoietic Stem Cell Transplantation Patients Correlates With Parameters of Long-Term Immune Reconstitution." Front Immunol **10**: 1879.

Recent data revealed the importance of immune reconstitution (IR) for the evaluation of possible biomarkers in National Institutes of Health (NIH)-defined chronic graft-vs.-host disease (cGVHD) and its clinical aspects. In this large pediatric study (n = 146), we have analyzed whether cellular and humoral parameters of IR in the long-term follow-up (FU) with a special emphasis on B-cell reconstitution correlate with NIH-defined cGVHD criteria. HYPOTHESIS: we were especially interested in whether meaningful cGVHD biomarkers could be defined in a large pediatric cohort. We here demonstrate for the first time in a highly homogenous pediatric patient cohort that both cGVHD (n = 38) and its activity were associated with the perturbation of the B-cell compartment, including low frequencies of CD19(+)CD27(+) memory B-cells and increased frequencies of circulating CD19(+)CD21(low) B-cells, a well-known hyperactivated B-cell subset frequently found elevated in chronic infection and autoimmunity. Notably, resolution of cGVHD correlated with expansion of CD19(+)CD27(+) memory B-cells and normalization of CD19(+)CD21(low) B-cell frequencies. Moreover, we found that the severity of cGVHD had an impact on parameters of IR and that severe cGVHD was associated with increased CD19(+)CD21(low) B-cell frequencies. When comparing the clinical characteristics of the active and non-active cGVHD patients (in detail at time of analyses), we found a correlation between activity and a higher overall severity of cGVHD, which means that in the active cGVHD patient group were more patients with a higher disease burden of cGVHD-despite similar risk profiles for cGVHD. Our data also provide solid evidence that the time point of analysis regarding both hematopoietic stem cell transplantation (HSCT) FU and cGVHD disease activity may be of critical importance for the detailed investigation of pediatric cohorts. Finally, we have proven that the differences in risk factors and patterns of IR, with cGVHD as its main confounding factor, between malignant and non-malignant diseases, are important to be considered in future studies aiming at identification of novel biomarkers for cGVHD.

Lee, L., et al. (2021). "Increased Immune-Regulatory Receptor Expression on Effector T Cells as Early Indicators of Relapse Following Autologous Stem Cell Transplantation for Multiple Myeloma." Front Immunol **12**: 618610.

The benefit of autologous stem cell transplantation (ASCT) in newly diagnosed myeloma patients, apart from supporting high dose chemotherapy, may include effects on T cell function in the bone marrow (BM). We report our exploratory findings on marrow infiltrating T cells early post-ASCT (day+100), examining phenotype and T cell receptor (TCR) repertoire, seeking correlations with timing of relapse. Compared to healthy donors (HD), we observed an increase in regulatory T cells (CD4+FoxP3+, Tregs) with reduction in CD4 T cells, leading to lower CD4:8 ratios. Compared to paired pre-treatment marrow, both CD4 and CD8 compartments showed a reduction in naive, and increase in effector memory subsets, suggestive of a more differentiated phenotype. This was supported by increased levels of several immune-regulatory and activation proteins (ICOS, PD-1, LAG-3, CTLA-4 and GzmB) when compared with HD. Unsupervised analysis identified a patient subgroup with shorter PFS (p=0.031) whose BM contained increased Tregs, and higher immune-regulatory markers (ICOS, PD-1, LAG-3) on effector T cells. Using single feature analysis, higher frequencies of marrow PD-1+ on CD4+FoxP3- cells and Ki67+ on CD8 cells were independently associated with early relapse. Finally, studying paired pre-treatment and post-ASCT BM (n=5), we note reduced abundance of TCR sequences at day+100, with a greater proportion of expanded sequences indicating a more focused persistent TCR repertoire. Our findings indicate that,

following induction chemotherapy and ASCT, marrow T cells demonstrate increased activation and differentiation, with TCR repertoire focusing. Pending confirmation in larger series, higher levels of immune-regulatory proteins on T cell effectors at day+100 may indicate early relapse.

Leung, C. S., et al. (2019). "Ectopic expression of recipient CD47 inhibits mouse macrophage-mediated immune rejection against human stem cell transplants." FASEB J **33**(1): 484-493.

Like conventional transplants, immunosuppression is required to facilitate survival and function of human embryonic stem cell (hESC) derivatives after implantation into xenogeneic recipients. We have previously reported that T cells alone are sufficient to reject allogeneic murine ESC derivatives; and strategies that inhibit T-cell activation, including coreceptor and costimulation blockade, prevent hESC derivatives from being rejected. This study aimed to investigate, in addition to T cells, whether macrophages contribute to transplant rejection of hESC xenografts with nonobese diabetic (NOD)/SCID mice that lack functional T and B cells but have macrophages. We show that acute rejection against hESC-derived endothelial cells (hESC-ECs) was mediated, to some degree, by infiltrating macrophages that phagocytosed them. Transgenic expression of murine CD47 on cell surface of hESC-ECs mitigates macrophage-mediated phagocytosis and improves their survival after transplantation. Our results highlight that innate immune cells, such as macrophages, can reject hESC derivatives, raising concern against the use of NOD/SCID as transplant recipients for testing in vivo function of hESC-derived tissues. Augmenting CD47 signaling promotes survival and function of hESC derivatives after xenogeneic transplantation.-Leung, C. S., Li, J., Xu, F., Wong, A. S. L., Lui, K. O. Ectopic expression of recipient CD47 inhibits mouse macrophage-mediated immune rejection against human stem cell transplants.

Levy, A., et al. (2020). "Innate immune receptor NOD2 mediates LGR5(+) intestinal stem cell protection against ROS cytotoxicity via mitophagy stimulation." Proc Natl Acad Sci U S A **117**(4): 1994-2003.

The nucleotide-binding oligomerization domain-containing protein 2 (NOD2) agonist muramyl dipeptide (MDP), a peptidoglycan motif common to all bacteria, supports leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5)(+) intestinal stem cell (ISC) survival through NOD2 activation upon an otherwise lethal oxidative stress-mediated signal. However, the underlying protective mechanisms remain unknown. Here, using irradiation as stressor and primarily murine-derived intestinal organoids as a model system, we show that MDP induced a significant reduction of total and mitochondrial reactive oxygen species (ROS) within ISCs, which was associated with mitophagy induction. ATG16L1 knockout (KO) and NOD2 KO organoids did not benefit from the MDP-induced cytoprotection. We confirmed the MDP-dependent induction of ISC mitophagy upon stress in vivo. These findings elucidate the NOD2-mediated mechanism of cytoprotection involving the clearance of the lethal excess of ROS molecules through mitophagy, triggered by the coordinated activation of NOD2 and ATG16L1 by a nuclear factor kappaB (NF-kappaB)-independent pathway.

Li, H., et al. (2020). "Role of bone marrow-derived mesenchymal stem cell defects in CD8(+) CD28(-) suppressor T-lymphocyte induction in patients with immune thrombocytopenia and associated mechanisms." Br J Haematol **191**(5): 852-862.

Many immune dysfunctions participate in immune thrombocytopenia (ITP) pathogenesis, including numeric and functional defects in suppressor T (Ts) cells and immune-regulation abnormalities in mesenchymal stem cells (MSCs). Recent studies showed that MSCs can promote Ts cell differentiation. Thus, we compared the Ts cell induction ability of bone marrow-derived MSCs (BM-MSCs) between patients with ITP and normal controls (NCs), and examined the mechanism of this difference. Co-culture of CD8(+) T cells with BM-MSCs revealed that BM-MSCs elevated Ts cell percentage and function, but the efficiency was lower in patients with ITP than in NCs. Blockade experiments showed that blockade of interleukin 6 (IL-6) partially reversed Ts cell induction by BM-MSCs. Addition of exogenous IL-6 down-regulated Ts cell apoptosis. Moreover, BM-MSCs enhanced IL-10 secretion and inhibition ability of Ts cells. IL-6 secretion, regulatory abilities of IL-10 expression in Ts cells, and the enhanced efficiency of Ts cells inhibition function by BM-MSCs were all decreased in patients with ITP. All-trans retinoic acid preconditioning promoted BM-MSC induction of Ts cell percentages and umbilical cord-derived (UC) MSCs efficiently improved ITP Ts cell numbers and dysfunction. In conclusion, defects of BM-MSCs in Ts cell induction are involved in ITP pathogenesis, and exogenous UC-MSCs may be useful for ITP therapy.

Li, Z., et al. (2020). "High-dimensional single-cell proteomics analysis reveals the landscape of immune cells and stem-like cells in renal tumors." J Clin Lab Anal **34**(5): e23155.

BACKGROUND: Renal tumors are highly heterogeneous, and identification of tumor heterogeneity is an urgent clinical need for effective treatment. Mass cytometry (MC) can be used to perform high-dimensional single-cell proteomics analysis of heterogeneous samples via cytometry by time-of-flight (CyTOF), in order to achieve more accurate observation and classification of phenotypes

within a cell population. This study aimed to develop a high-dimensional MC method for the detection and analysis of heterogeneity in renal tumors. MATERIALS AND METHODS: We collected tissue samples from 8 patients with different types of renal tumors. Single-cell suspensions were prepared and stained using a panel of 28 immune cell-centric antibodies and a panel of 21 stem-like cell-centric antibodies. The stained cells were detected using CyTOF. RESULT: Renal tumors were divided into 25 immune cell subsets (4 CD4+ T cells, 7 CD8+ T cells, 1 B cells, 8 macrophages, 1 dendritic cells, 2 natural killer (NK) cells, 1 granulocyte, and 1 other subset) and 7 stem-like cells subsets (based on positivity of vimentin, CD326, CD34, CD90, CD13, CD44, and CD47). Different types of renal tumors have different cell subsets with significantly different characteristics. CONCLUSION: High-dimensional single-cell proteomics analysis using MC aids in the discovery and analysis of renal tumors heterogeneity. Additionally, it can be used to accurately classify the immune cell population and analyze the expression of stem cell-related markers in renal tumors. Our findings provide a valuable resource for deciphering tumor heterogeneity and might improve the clinical management of patients with renal tumors.

Lin, Y. H., et al. (2019). "USP44 is dispensable for normal hematopoietic stem cell function, lymphocyte development, and B-cell-mediated immune response in a mouse model." Exp Hematol **72**: 1-8.

Ubiquitin-specific protease 44 (USP44) is a nuclear protein with deubiquitinase (DUB) catalytic activity that has been implicated as an important regulator of cell cycle progression, gene expression, and genomic stability. Dysregulation in the molecular machinery controlling cell proliferation, gene expression, and genomic stability in human or mouse is commonly linked to hematopoietic dysfunction, immunodeficiency, and cancer. We therefore set out to explore the role of USP44 in hematopoietic and immune systems through characterization of a Usp44-deficient mouse model. We report that USP44 is dispensable for the maintenance of hematopoietic stem cell numbers and function under homeostatic conditions, and also after irradiation or serial transplantation. USP44 is also not required for normal lymphocyte development. Usp44-deficient B cells show normal activation, proliferation, and immunoglobulin class switching in response to in vitro stimulation, and Usp44-deficient mice mount normal antibody response to immunization. We also tested the effects of USP44 deficiency on disease progression and survival in the Emu-myc model of mouse B-cell lymphoma and observed a trend toward earlier lethality of Usp44(-/-) Emu-myc mice; however, this did not reach statistical significance. Overall, we conclude that USP44 is dispensable for the normal physiology of hematopoietic and immune systems, and its functions in these systems are likely redundant with other USP family proteins.

Liu, Q., et al. (2021). "Mesenchymal stem cells alleviate experimental immune-mediated liver injury via chitinase 3-like protein 1-mediated T cell suppression." Cell Death Dis **12**(3): 240.

Liver diseases with different pathogenesis share common pathways of immune-mediated injury. Chitinase-3-like protein 1 (CHI3L1) was induced in both acute and chronic liver injuries, and recent studies reported that it possesses an immunosuppressive ability. CHI3L1 was also expressed in mesenchymal stem cells (MSCs), thus we investigates the role of CHI3L1 in MSC-based therapy for immune-mediated liver injury here. We found that CHI3L1 was highly expressed in human umbilical cord MSCs (hUC-MSCs). Downregulating CHI3L1 mitigated the ability of hUC-MSCs to inhibit T cell activation, proliferation and inflammatory cytokine secretion in vitro. Using Concanavalin A (Con A)-induced liver injury mouse model, we found that silencing CHI3L1 significantly abrogated the hUC-MSCs-mediated alleviation of liver injury, accompanying by weakened suppressive effects on infiltration and activation of hepatic T cells, and secretion of pro-inflammatory cytokines. In addition, recombinant CHI3L1 (rCHI3L1) administration inhibited the proliferation and function of activated T cells, and alleviated the Con A-induced liver injury in mice. Mechanistically, gene set enrichment analysis showed that JAK/STAT signalling pathway was one of the most significantly enriched gene pathways in T cells co-cultured with hUC-MSCs with CHI3L1 knockdown, and further study revealed that CHI3L1 secreted by hUC-MSCs inhibited the STAT1/3 signalling in T cells by upregulating peroxisome proliferator-activated receptor delta (PPARdelta). Collectively, our data showed that CHI3L1 was a novel MSC-secreted immunosuppressive factor and provided new insights into therapeutic treatment of immune-mediated liver injury.

Liu, Z., et al. (2021). "Bone marrow-derived mesenchymal stem cells inhibit CD8(+) T cell immune responses via PD-1/PD-L1 pathway in multiple myeloma." Clin Exp Immunol **205**(1): 53-62.

High expression of the inhibitory receptor programmed cell death ligand 1 (PD-L1) on tumor cells and tumor stromal cells have been found to play a key role in tumor immune evasion in several human malignancies. However, the expression of PD-L1 on bone marrow mesenchymal stem cells (BMSCs) and whether the programmed cell death 1 (PD-1)/PD-L1 signal pathway is involved in the BMSCs versus T cell immune response in multiple myeloma (MM) remains poorly defined. In this study, we explored the

expression of PD-L1 on BMSCs from newly diagnosed MM (NDMM) patients and the role of PD-1/PD-L1 pathway in BMSC-mediated regulation of CD8(+) T cells. The data showed that the expression of PD-L1 on BMSCs in NDMM patients was significantly increased compared to that in normal controls (NC) (18.81 +/- 1.61 versus 2.78+/- 0.70%; P < 0.001). Furthermore, the PD-1 expression on CD8(+) T cells with NDMM patients was significantly higher than that in normal controls (43.22 +/- 2.98 versus 20.71 +/- 1.08%; P < 0.001). However, there was no significant difference in PD-1 expression of CD4(+) T cells and natural killer (NK) cells between the NDMM and NC groups. Additionally, the co-culture assays revealed that BMSCs significantly suppressed CD8(+) T cell function. However, the PD-L1 inhibitor effectively reversed BMSC-mediated suppression in CD8(+) T cells. We also found that the combination of PD-L1 inhibitor and pomalidomide can further enhance the killing effect of CD8(+) T cells on MM cells. In summary, our findings demonstrated that BMSCs in patients with MM may induce apoptosis of CD8(+) T cells through the PD-1/PD-L1 axis and inhibit the release of perforin and granzyme B from CD8(+) T cells to promote the immune escape of MM.

Lopez-Santalla, M., et al. (2020). "Cell Therapy With Mesenchymal Stem Cells Induces an Innate Immune Memory Response That Attenuates Experimental Colitis in the Long Term." J Crohns Colitis **14**(10): 1424-1435.

BACKGROUND AND AIMS: Mesenchymal stem cells [MSCs] are used in preclinical and clinical studies for treatment of immune-mediated disorders, thanks to their immunomodulatory properties. Cell therapy with MSCs induces multiple effects in the immune system which ultimately lead to increase in the number of immune cells with regulatory phenotype. In this study, we investigated whether the beneficial effects of MSC therapy are maintained in the long term in a clinically relevant mouse model of colitis. METHODS: A single dose of adipose-derived MSCs [aMSCs] was infused into dextran sulphate sodium [DSS]-induced colitic mice during the induction phase of the disease. Following a latency period of 12 weeks, mice were re-challenged with a second 7-day cycle of DSS. RESULTS: DSS-induced colitic mice treated with aMSCs showed significant reduction in their colitic disease activity index during the second DSS challenge when compared with non-aMSC treated DSS-induced colitic mice. Strikingly, the long-term protection induced by aMSC therapy was also observed in Rag-1-/- mice where no adaptive immune memory cell responses take place. Increased percentages of Ly6G+CD11b+ myeloid cells were observed 12 weeks after the first inflammatory challenge in the peritoneal cavity, spleen, and bone marrow of DSS-induced colitic mice that were infused with aMSCs. Interestingly, upon re-challenge with DSS, these animals showed a concomitant increase in the regulatory/inflammatory macrophage ratio in the colon lamina propria. CONCLUSIONS: Our findings demonstrate for the first time that MSC therapy can imprint an innate immune memory-like response in mice which confers sustained protection against acute inflammation in the long term.

Lu, Z., et al. (2019). "Mesenchymal stem cells induce dendritic cell immune tolerance via paracrine hepatocyte growth factor to alleviate acute lung injury." Stem Cell Res Ther **10**(1): 372.

BACKGROUND: Mesenchymal stem cells (MSCs) have been shown to alleviate acute lung injury (ALI) via paracrine hepatocyte growth factor (HGF) and to induce the differentiation of dendritic cells (DCs) into tolerogenic dendritic cells (DCregs) and participate in the immune response. However, whether MSCs induce the production of DCregs by secreting HGF to alleviate early ALI remains unclear. We observed that the protective effect of mouse bone marrow-derived MSCs against lipopolysaccharide (LPS)-induced ALI was achieved by inducing mature DCs (mDCs) to differentiate into DCregs, and its mechanism is related to the activation of the HGF/Akt pathway. METHODS: MSCs or MSCs with overexpression or knockdown of HGF were cocultured with DCs derived from mouse bone marrow using a Transwell system for 3 days. Moreover, we used MSCs or MSCs with overexpression or knockdown of HGF to treat LPS-induced ALI mice for 24 h. Flow cytometry was performed to measure the phagocytosis, accumulation, and maturation of DCs, as well as proliferation of T cells. Lung injury was estimated by lung wet weight to body weight ratio (LWW/BW) and histopathological analysis. Furthermore, we used the Akt inhibitor MK-2206 in a coculture system to elucidate the role of the HGF/Akt pathway in regulating the differentiation of DCs into regulatory DCs and relieving lung injury in early ALI mice. RESULTS: Immature DCs (imDCs) were induced to mature after 24 h of LPS (50 ng/ml) stimulation. MSCs or HGF induced the differentiation of mDCs into regulatory DCs characterized by low expression of MHCII, CD86, and CD40 molecules, strong phagocytic function, and the ability to inhibit T cell proliferation. The effect of MSCs on DCregs was enhanced with the increase in HGF secretion and was weakened with the decrease in HGF secretion. DCregs induced by recombinant HGF were attenuated by the Akt inhibitor MK-2206. Lung DC aggregation and mDC ratio increased in LPS-induced ALI mice, while treatment with MSCs decreased lung DC aggregation and maturation and alleviated lung pathological injury. High expression of the HGF gene enhanced the above

effect of MSCs, while decreased expression of HGF weakened the above effect of MSCs. CONCLUSIONS: MSCs alleviate early ALI via paracrine HGF by inducing mDCs to differentiate into regulatory DCs. Furthermore, the mechanism of HGF-induced differentiation of mDCs into DCregs is related to the activation of the Akt pathway.

Maeda, Y. (2021). "Immune reconstitution after T-cell replete HLA haploidentical hematopoietic stem cell transplantation using high-dose post-transplant cyclophosphamide." J Clin Exp Hematop **61**(1): 1-9.

As HLA haploidentical related donors are quickly available, HLA haploidentical hematopoietic stem cell transplantation (haploHSCT) using high-dose post-transplant cyclophosphamide (PTCy) is now widely used. Recent basic and clinical studies revealed the details of immune reconstitution after T-cell replete haploHSCT using PTCy. T cells and NK cells in the graft proliferate abundantly at day 3 post-haploHSCT, and the PTCy eliminates these proliferating cells. After ablation of proliferating mature cells, donor-derived NK cell reconstitution occurs after the second week; however, recovering NK cells remain functionally impaired for at least several months after haploHSCT. PTCy depletes proliferating cells, resulting in the preferential accumulation of Treg and CD4+ T cells, especially the memory stem T cell (T(SCM)) phenotype. T(SCM) capable of both self-renewal and differentiation into effector T cells may play an important role in the first month of immune reconstitution. Subsequently, de novo T cells progressively recover but their levels remain well below those of donor CD4+ T cells at the first year after haploHSCT. The phenotype of recovering T cells after HSCT is predominantly effector memory, whereas B cells are predominantly phenotypically naive throughout the first year after haploHSCT. B cell recovery depends on de novo generation and they are not detected until week 4 after haploHSCT. At week 5, recovering B cells mostly exhibit an unconventional transitional cell phenotype and the cell subset undergoes maturation. Recent advances in immune reconstitution have improved our understanding of the relationship between haploHSCT with PTCy and the clinical outcome.

Malmegrim, K. C. R., et al. (2019). "Editorial: Immune Profile After Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases: Where Do We Stand?" Front Immunol **10**: 3044.

Martin Gonzalez, J., et al. (2018). "A new genetic tool to improve immune-compromised mouse models: Derivation and CRISPR/Cas9-mediated targeting of NRG embryonic stem cell lines." Genesis **56**(9): e23238.

Development of human hematopoietic stem cells and differentiation of embryonic stem (ES) cells/induced pluripotent stem (iPS) cells to hematopoietic stem cells are poorly understood. NOD (Non-obese diabetic)-derived mouse strains, such as NSG (NOD-Scid-il2Rg) or NRG (NOD-Rag1-il2Rg), are the best available models for studying the function of fetal and adult human hematopoietic cells as well as ES/iPS cell-derived hematopoietic stem cells. Unfortunately, engraftment of human hematopoietic stem cells is very variable in these models. Introduction of additional permissive mutations into these complex genetic backgrounds of the NRG/NSG mice by natural breeding is a very demanding task in terms of time and resources. Specifically, since the genetic elements defining the NSG/NRG phenotypes have not yet been fully characterized, intense backcrossing is required to ensure transmission of the full phenotype. Here we describe the derivation of embryonic stem cell (ESC) lines from NRG pre-implantation embryos generated by in vitro fertilization followed by the CRISPR/CAS9 targeting of the Gata-2 locus. After injection into morula stage embryos, cells from three tested lines gave rise to chimeric adult mice showing high contribution of the ESCs (70%-100%), assessed by coat color. Moreover, these lines have been successfully targeted using Cas9/CRISPR technology, and the mutant cells have been shown to remain germ line competent. Therefore, these new NRG ESC lines combined with genome editing nucleases bring a powerful genetic tool that facilitates the generation of new NOD-based mouse models with the aim to improve the existing xenograft models.

McClellan, A., et al. (2019). "Equine Fetal, Adult, and Embryonic Stem Cell-Derived Tenocytes Are All Immune Privileged but Exhibit Different Immune Suppressive Properties In Vitro." Stem Cells Dev **28**(21): 1413-1423.

In horses and humans, tendon injuries are a significant problem. Not only can they occur in both athletes and nonathletes, they require lengthy periods of recuperation and undergo poor natural regeneration, which leads to high reinjury rates. Embryonic stem cells (ESCs) may provide a renewable source of allogeneic cells to use in clinical applications to aid tissue regeneration. Equine ESCs can undergo tenocyte differentiation in vivo and in vitro, but the immune properties of tenocytes isolated from either ESCs or tissues have not previously been characterized. Here, we demonstrate that equine tenocytes derived from fetal and adult tendon tissue and ESCs express robust levels of major histocompatibility complex (MHC) I but no MHC II in response to inflammatory cytokine interferon gamma (IFNgamma). However, MHC expression does not affect their allorecognition by peripheral blood mononuclear cells in vitro. Adult and fetal tenocytes remain immune privileged and strongly immune suppressive in both the presence and absence

of exogenously applied IFNgamma. In contrast, ESC-derived tenocytes are immune privileged even in the presence of IFNgamma, but they are only weakly immune suppressive in the presence but not in the absence of exogenously applied IFNgamma. This is despite ESC-tenocytes expressing a number of genes involved in immune modulation at significantly higher levels than those expressed by adult and fetal tenocytes when in standard, nonstimulated monolayer culture. Together, this work suggests that, similar to other fibroblasts, tenocytes have immune modulatory properties, and that culture-expanded tenocytes derived from primary tissues or ESCs may be safe to use in clinical transplantations to injured tendons of unrelated animals.

Mellgren, K., et al. (2019). "Use of Multivariate Immune Reconstitution Patterns to Describe Immune Reconstitution after Allogeneic Stem Cell Transplantation in Children." Biol Blood Marrow Transplant **25**(10): 2045-2053.

Immune reconstitution after hematopoietic stem cell transplantation (HSCT) is a complex process. Impacts of the reconstitution of different immune cells over time are complex and difficult to understand. New mathematical models are needed to better understand this process. In this study, we used principal component analysis to better analyze the process of immune reconstitution after HSCT. Forty-six consecutive patients receiving HSCT for malignant and nonmalignant disorders were included in the study. All patients were followed for at least 24 months after transplantation with regular blood sampling for analysis of lymphocyte subset numbers and function. Exponentially transformed lymphocyte subset counts and lymphocyte functional markers were analyzed to identify major trends in the reconstitution process. Using our multivariate model for mapping immune reconstitution after HSCT, we showed that dysfunctional reconstitution patterns precede severe complications, such as chronic graft-versus-host disease, relapse, and death.

Merli, P., et al. (2020). "Immune Modulation Properties of Zoledronic Acid on TcRgammadelta T-Lymphocytes After TcRalphabeta/CD19-Depleted Haploidentical Stem Cell Transplantation: An analysis on 46 Pediatric Patients Affected by Acute Leukemia." Front Immunol **11**: 699.

TcRalphabeta/CD19-cell depleted HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT) represents a promising new platform for children affected by acute leukemia in need of an allograft and lacking a matched donor, disease recurrence being the main cause of treatment failure. The use of zoledronic acid to enhance TcRgammadelta+ lymphocyte function after TcRalphabeta/CD19-cell depleted haplo-HSCT was tested in an open-label, feasibility, proof-of-principle study. Forty-six children affected by high-risk acute leukemia underwent haplo-HSCT after removal of TcRalphabeta+ and CD19+ B lymphocytes. No post-transplant pharmacological graft-versus-host disease (GvHD) prophylaxis was given. Zoledronic acid was administered monthly at a dose of 0.05 mg/kg/dose (maximum dose 4 mg), starting from day +20 after transplantation. A total of 139 infusions were administered, with a mean of 3 infusions per patient. No severe adverse event was observed. Common side effects were represented by asymptomatic hypocalcemia and acute phase reactions (including fever, chills, malaise, and/or arthralgia) within 24-48 h from zoledronic acid infusion. The cumulative incidence of acute and chronic GvHD was 17.3% (all grade I-II) and 4.8% (all limited), respectively. Patients given 3 or more infusions of zoledronic acid had a lower incidence of both acute GvHD (8.8 vs. 41.6%, p = 0.015) and chronic GvHD (0 vs. 22.2%, p = 0.006). Transplant-related mortality (TRM) and relapse incidence at 3 years were 4.3 and 30.4%, respectively. Patients receiving repeated infusions of zoledronic acid had a lower TRM as compared to those receiving 1 or 2 administration of the drug (0 vs. 16.7%, p = 0.01). Five-year overall survival (OS) and disease-free survival (DFS) for the whole cohort were 67.2 and 65.2%, respectively, with a trend toward a better OS for patients receiving 3 or more infusions (73.1 vs. 50.0%, p = 0.05). The probability of GvHD/relapse-free survival was significantly worse in patients receiving 1-2 infusions of zoledonic acid than in those given >/=3 infusions (33.3 vs. 70.6%, respectively, p = 0.006). Multivariable analysis showed an independent positive effect on outcome given by repeated infusions of zoledronic acid (HR 0.27, p = 0.03). These data indicate that the use of zoledronic acid after TcRalphabeta/CD19-cell depleted haploHSCT is safe and may result in a lower incidence of acute GvHD, chronic GvHD, and TRM.

Merli, P., et al. (2019). "Role of interferon-gamma in immune-mediated graft failure after allogeneic hematopoietic stem cell transplantation." Haematologica **104**(11): 2314-2323.

Pathophysiology of graft failure (GF) occurring after allogeneic hematopoietic stem cell transplantation (HSCT) still remains elusive. We measured serum levels of several different cytokines/chemokines in 15 children experiencing GF, comparing their values with those of 15 controls who had sustained donor cell engraftment. Already at day +3 after transplantation, patients developing GF had serum levels of interferon (IFN)-gamma and CXCL9 (a chemokine specifically induced by IFNgamma) significantly higher than those of controls (8859+/-7502 vs. 0 pg/mL, P=0.03, and 1514.0+/-773 vs.

233.6+/-50.1 pg/mlL, P=0.0006, respectively). The role played by IFNgamma in HSCT-related GF was further supported by the observation that a rat anti-mouse IFNgamma-neutralizing monoclonal antibody promotes donor cell engraftment in Ifngr1(-/-)mice receiving an allograft. In comparison to controls, analysis of bone marrow-infiltrating T lymphocytes in patients experiencing GF documented a predominance of effector memory CD8(+) cells, which showed markers of activation (overexpression of CD95 and downregulation of CD127) and exhaustion (CD57, CD279, CD223 and CD366). Finally, we obtained successful donor engraftment in 2 out of 3 children with primary hemophagocytic lymphohistiocytosis who, after experiencing GF, were re-transplanted from the same HLA-haploidentical donor under the compassionate use coverage of emapalumab, an anti-IFNgamma monoclonal antibody recently approved by the US Food and Drug Administration for treatment of patients with primary hemophagocytic lymphohistiocytosis. Altogether, these results suggest that the IFNgamma pathway plays a major role in GF occurring after HSCT. Increased serum levels of IFNgamma and CXCL9 represent potential biomarkers useful for early diagnosis of GF and provide the rationale for exploring the therapeutic/preventive role of targeted neutralization of IFNgamma.

Minculescu, L., et al. (2020). "Improved Relapse-Free Survival in Patients With High Natural Killer Cell Doses in Grafts and During Early Immune Reconstitution After Allogeneic Stem Cell Transplantation." Front Immunol **11**: 1068.

Mature immunocompetent cells from the stem cell graft as well as early robust immune reconstitution are essential for the graft-vs. -tumor (GVT) effect to eliminate residual malignant cells after allogeneic hematopoietic stem cell transplantation (HSCT). In this prospective study we characterized graft composition of T- and NK cell subsets in 88 recipients of peripheral blood stem cell grafts with multicolor flowcytometry. Our primary aim was to analyze the impact of graft composition on immune reconstitution and clinical outcomes after transplantation. Patients transplanted with graft NK cell doses above the median value of 27 x 10(6)/kg had significantly increased relapse-free-survival compared to patients transplanted with lower doses, HR 2.12 (95% CI 1.01-4.45, p = 0.04) Peripheral blood concentrations of NK cells obtained from donors before G-CSF mobilization were significantly correlated to graft NK cell doses (Spearman's rho 0.53, p = 0.03). The dose of transplanted NK cells/kg correlated significantly with NK cell concentrations in patients early after transplantation (Spearman's rho 0.26, p = 0.02, and rho = 0.35, p = 0.001 for days 28 and 56, respectively). Early immune reconstitution above median values of NK cells was significantly associated with improved relapse-free survival (HR 2.84 [95% CI 1.29-6.28], p = 0.01, and HR 4.19 [95% CI 1.68-10.4], p = 0.002, for day 28 and 56, respectively). Early concentrations above the median value of the mature effector CD56dim NK cell subset were significantly associated with decreased relapse incidences at 1 year, 7% (95% CI 1.8-17) vs. 28% (95% CI 15-42), p = 0.04, and 7% (95% CI 1.8-18) vs. 26% (95% CI 14-40) %, p = 0.03, for days 28 and 56, respectively. The results suggest a protective effect of high doses of NK cells in grafts and during early immune reconstitution and support the perception of NK cells as innate effector cells with anti-tumor effects in the setting of allogeneic stem cell transplantation.

Minculescu, L., et al. (2019). "Improved Overall Survival, Relapse-Free-Survival, and Less Graft-vs.-Host-Disease in Patients With High Immune Reconstitution of TCR Gamma Delta Cells 2 Months After Allogeneic Stem Cell Transplantation." Front Immunol **10**: 1997.

T-cell receptor (TCR) gammadelta cells are perceived as innate-like effector cells with the possibility of mediating graft-vs. -tumor (GVT) without causing graft-vs.-host disease (GVHD) in the setting of hematopoietic allogeneic stem cell transplantation (HSCT). We conducted a prospective study to assess the clinical impact of TCR gammadelta cell immune reconstitution on overall survival, relapse-free-survival, relapse and GVHD. The impact of CD3, CD4, and CD8 T cells together with NK cells including subtypes were analyzed in parallel. A total of 108 patients with hematological malignancies transplanted with HLA-matched, T cell replete stem cell grafts were included for analyses of absolute concentrations of CD3, CD4, and CD8 positive T cells and NK cells together with a multi-color flow cytometry panel with staining for TCRalphabeta, TCRgammadelta, Vdelta1, Vdelta2, CD3, CD4, CD8, HLA-DR, CD196, CD45RO, CD45RA, CD16, CD56, CD337, and CD314 at 28, 56, 91, 180, and 365 days after transplantation. Immune reconstitution data including subsets and differentiation markers of T and NK cells during the first year after transplantation was provided. Patients with TCR gammadelta cell concentrations above the median value of 21 (0-416) x 10(6) cells/L 56 days after transplantation had significantly improved overall survival (p = 0.001) and relapse-free survival (p = 0.007) compared to patients with concentrations below this value. When day 56 cell subset concentrations were included as continuous variables, TCR gammadelta cells were the only T cell subsets with a significant impact on OS and RFS; the impact of TCR gammadelta cells remained statistically significant in multivariate analyses adjusted for pre-transplant risk factors. The risk of death from relapse was

significantly decreased in patients with high concentrations of TCR gammadelta cells 56 days after transplantation (p = 0.003). Also, the risk of acute GVHD was significantly lower in patients with day 28 TCR gammadelta cell concentrations above the median of 18 x 10(6) cells/L compared to patients with low concentrations (p = 0.01). These results suggest a protective role of TCR gammadelta cells in relapse and GVHD and encourage further research in developing adaptive TCR gammadelta cell therapy for improving outcomes after HSCT.

Mizuhashi, S., et al. (2021). "Immune cell therapy against disseminated melanoma by utilizing induced pluripotent stem cell-derived myeloid cell lines producing interferon-beta or interleukin-15/interleukin-15 receptor alpha." J Dermatol Sci **102**(2): 133-136.

Morales-Molina, A., et al. (2018). "Antitumor virotherapy using syngeneic or allogeneic mesenchymal stem cell carriers induces systemic immune response and intratumoral leukocyte infiltration in mice." Cancer Immunol Immunother **67**(10): 1589-1602.

Oncolytic virotherapy uses oncolytic viruses that selectively replicate in cancer cells. The use of cellular vehicles with migration ability to tumors has been considered to increase their delivery to target sites. Following this approach, the antitumor efficacy of the treatment Celyvir (mesenchymal stem cells infected with the oncolytic adenovirus ICOVIR-5) has been demonstrated in patients with neuroblastoma. However, the better efficacy of syngeneic or allogeneic mesenchymal stem cells as cell carriers and the specific role of the immune system in this therapy are still unknown. In this study we use our virotherapy Celyvir with syngeneic and allogeneic mouse mesenchymal stem cells to determine their antitumor efficacy in a C57BL/6 murine adenocarcinoma model. Adoptive transfer of splenocytes from treated mice to new tumor-bearing mice followed by a secondary adoptive transfer to a third group was performed. Similar reduction of tumor growth and systemic activation of the innate and adaptive immune system was observed in groups treated with syngeneic or allogeneic mesenchymal stem cells loaded with ICOVIR-5. Moreover, a different pattern of infiltration was observed by immunofluorescence in Celyvir-treated groups. While non-treated tumors presented higher density of infiltrating immune cells in the periphery of the tumor, both syngeneic and allogeneic Celyvir-treated groups presented higher infiltration of CD45+ cells in the core of the tumor. Therefore, these results suggest that syngeneic and allogeneic Celyvir induce systemic activation of the immune system, similar antitumor effect and a higher intratumoral infiltration of leukocytes.

Moskorz, W., et al. (2021). "Myelodysplastic syndrome patients display alterations in their immune status reflected by increased PD-L1-expressing stem cells and highly dynamic exhausted T-cell frequencies." Br J Haematol **193**(5): 941-945.

Little data are available for the expression of immune checkpoint (IC) molecules within myelodysplastic syndrome (MDS). Here, we report increased PD-L1(+) CD34(+) CD38(-) and PD-L1(+) CD34(+) CD38(+) stem cell frequencies within MDS patients compared to stem cell recipients in remission. Additionally, we observed exceedingly similar PD1(+) and Tim-3(+) T-cell frequencies between acute myeloid leukaemia (AML) and MDS samples that were elevated compared to patients in remission. Furthermore, we found highly dynamic Tim-3(+) and PD1(+) T-cell frequencies within serial samples of relapsing MDS with excess blasts (MDS-EB II) patients, correlating with further disease markers. These findings support the idea of a potential successful implementation of IC inhibitor treatment in suitable MDS patients.

Muller, L., et al. (2020). "Bidirectional Crosstalk Between Cancer Stem Cells and Immune Cell Subsets." Front Immunol **11**: 140.

Cancer stem cells (CSCs), also known as tumor-initiating cells, are characterized by an increased capacity for self-renewal, multipotency, and tumor initiation. While CSCs represent only a small proportion of the tumor mass, they significantly account for metastatic dissemination and tumor recurrence, thus making them attractive targets for therapy. Due to their ability to sustain in dormancy, chemo- and radiotherapy often fail to eliminate cancer cells with stemness properties. Recent advances in the understanding of the tumor microenvironment (TME) illustrated the importance of the immune contexture, determining the response to therapy and clinical outcome of patients. In this context, CSCs exhibit special properties to escape the recognition by innate and adaptive immunity and shape the TME into an immunosuppressive, pro-tumorigenic landscape. As CSCs sculpt the immune contexture, the phenotype and functional properties of the tumor-infiltrating immune cells in turn influence the differentiation and phenotype of tumor cells. In this review, we summarize recent studies investigating main immunomodulatory properties of CSCs and their underlying molecular mechanisms as well as the impact of immune cells on cancer cells with stemness properties. A deeper understanding of this bidirectional crosstalk shaping the immunological landscape and determining therapeutic responses will facilitate the improvement of current treatment modalities and the design of innovative strategies to precisely target CSCs.

Qin, F., et al. (2019). "Immune recovery after in vivo T-cell depletion myeloablative conditioning hematopoietic stem cell transplantation in severe beta-thalassemia children." Eur J Haematol **103**(4): 342-350.

BACKGROUND: The clinical outcome of hematopoietic stem cell transplantation (HSCT) in those with severe beta-thalassemia (beta-TM) is closely related to post-transplantation immune reconstitution (IR). However, the data on the IR in these settings are scarce. METHODS: A prospective analysis of the clinical outcome and IR in 47 children with severe beta-TM who underwent in vivo T-cell depletion myeloablative conditioning and matched sibling donor HSCT was performed. Immune reconstitution, including immune cell subset counts, as well as the generation of new T and B cells assays after HSCT, was measured. RESULTS: In the first year after HSCT, bacterial infections and cytomegalovirus (CMV) reactivation were observed in 70.2% and 36.2% of the patients, respectively. In the same period, poor CD4(+) T-cell recovery was observed. The B cells recovered within 6 months. Natural killer (NK) cells recovered as early as 1 month, but their function was defective. Cord blood and bone marrow (CB + BM) group had slower T-cell recovery, and higher B cells and NK cells in comparison with peripheral blood and bone marrow (PB + BM) group. CONCLUSIONS: The high incidence of infection within 1 year after in vivo T-cell depletion myeloablative conditioning HSCT in severe beta-TM was consistent with poor IR.

Raj, R., et al. (2020). "Multicenter Outcome of Hematopoietic Stem Cell Transplantation for Primary Immune Deficiency Disorders in India." Front Immunol **11**: 606930.

Background: Hematopoietic stem cell transplantation (HSCT) is the curative option for many primary immune deficiency disorders (PID). In the last 5 years, increased awareness, availability of diagnostics based on flow cytometry, genetic testing, improved supportive care, use of reduced toxicity conditioning, and success of haploidentical donor HSCT have improved access to HSCT for children with PID in India. We present results on children with PID who underwent HSCT across India and the factors that influenced outcome. Patients and Methods: We collected retrospective data on the outcome of HSCT for PID from seven centers. We analyzed the impact of the type of PID, conditioning regimen, time period of HSCT- before or after January 2016, graft versus host disease prophylaxis, cause of mortality and overall survival. Results: A total of 228 children underwent HSCT for PID at a median age of 12 months (range, 1 to 220 months) with a median follow up of 14.4 months. Infants accounted for 51.3% of the cohort and the male female ratio was 3:1. SCID (25%) and HLH (25%) were the more frequent diagnoses. Matched family donor was available in 36.4% and 44.3% children had a haploidentical HSCT. Reduced and myeloablative conditioning regimens were used with 64% children receiving a treosulfan based conditioning regimen. Peripheral blood stem cells were the predominant graft source at 69.3%. The survival in infants (60.2%) was inferior to children aged over 1 year (75.7% p value = 0.01). Children with Wiskott Aldrich syndrome (74.3%) and chronic granulomatous disease (82.6%) had the best outcomes. The survival was superior in children receiving HSCT from a matched sibling (78%) versus an alternate donor HSCT (61% p value = 0.04). In the cohort transplanted after January 2016 survival improved from 26.8% to 77.5% (p value = 0.00). Infection remains the main cause of mortality at in over 50% children. The 5-year overall survival rate was 68%. Conclusion: Survival of children with PID undergoing HSCT in India has improved dramatically in last 5 years. Alternate donor HSCT is now feasible and has made a therapeutic option accessible to all children with PID.

Roex, M. C. J., et al. (2021). "Effect of alemtuzumab-based T-cell depletion on graft compositional change in vitro and immune reconstitution early after allogeneic stem cell transplantation." Cytotherapy **23**(1): 46-56.

BACKGROUND AIMS: To reduce the risk of graft-versus-host disease (GVHD) after allogeneic stem cell transplantation (alloSCT), T-cell depletion (TCD) of grafts can be performed by the addition of alemtuzumab (ALT) "to the bag" (in vitro) before transplantation. In this prospective study, the authors analyzed the effect of in vitro incubation with 20 mg ALT on the composition of grafts prior to graft infusion. Furthermore, the authors assessed whether graft composition at the moment of infusion was predictive for T-cell reconstitution and development of GVHD early after TCD alloSCT. METHODS: Sixty granulocyte colony-stimulating factor-mobilized stem cell grafts were obtained from >/=9/10 HLA-matched related and unrelated donors. The composition of the grafts was analyzed by flow cytometry before and after in vitro incubation with ALT. T-cell reconstitution and incidence of severe GVHD were monitored until 12 weeks after transplantation. RESULTS: In vitro incubation of grafts with 20 mg ALT resulted in an initial median depletion efficiency of T-cell receptor (TCR) alpha/beta T cells of 96.7% (range, 63.5-99.8%), followed by subsequent depletion in vivo. Graft volumes and absolute leukocyte counts of grafts before the addition of ALT were not predictive for the efficiency of TCR alpha/beta T-cell depletion. CD4(pos) T cells were depleted more efficiently than CD8(pos) T cells, and naive and regulatory T cells were depleted more efficiently than memory and effector T cells. This differential depletion of T-cell

subsets was in line with their reported differential CD52 expression. In vitro depletion efficiencies and absolute numbers of (naive) TCR alpha/beta T cells in the grafts after ALT incubation were not predictive for T-cell reconstitution or development of GVHD post-alloSCT. CONCLUSIONS: The addition of ALT to the bag is an easy, fast and generally applicable strategy to prevent GVHD in patients receiving alloSCT after myeloablative or non-myeloablative conditioning because of the efficient differential depletion of donor-derived lymphocytes and T cells.

Saberian, C., et al. (2021). "Post-transplantation cyclophosphamide reduces the incidence of acute graft-versus-host disease in patients with acute myeloid leukemia/myelodysplastic syndromes who receive immune checkpoint inhibitors after allogeneic hematopoietic stem cell transplantation." J Immunother Cancer **9**(2).

BACKGROUND: Immune checkpoint inhibitors (ICIs) are being used after allogeneic hematopoietic stem cell transplantation (alloHCT) to reverse immune dysfunction. However, a major concern for the use of ICIs after alloHCT is the increased risk of graft-versus-host disease (GVHD). We analyzed the association between GVHD prophylaxis and frequency of GVHD in patients who had received ICI therapy after alloHCT. METHODS: A retrospective study was performed in 21 patients with acute myeloid leukemia (n=16) or myelodysplastic syndromes (n=5) who were treated with antiprogrammed cell death protein 1 (16 patients) or anticytotoxic T lymphocyte-associated antigen 4 (5 patients) therapy for disease relapse after alloHCT. Associations between the type of GVHD prophylaxis and incidence of GVHD were analyzed. RESULTS: Four patients (19%) developed acute GVHD. The incidence of acute GVHD was associated only with the type of post-transplantation GVHD prophylaxis; none of the other variables included (stem cell source, donor type, age at alloHCT, conditioning regimen and prior history of GVHD) were associated with the frequency of acute GVHD. Twelve patients received post-transplantation cyclophosphamide (PTCy) for GVHD prophylaxis. Patients who received PTCy had a significantly shorter median time to initiation of ICI therapy after alloHCT compared with patients who did not receive PTCy (median 5.1 months compared with 26.6 months). Despite early ICI therapy initiation, patients who received PTCy had a lower observed cumulative incidence of grades 2-4 acute GVHD compared with patients who did not receive PTCy (16% compared with 22%; p=0.7). After controlling for comorbidities and time from alloHCT to ICI therapy initiation, the analysis showed that PTCy was associated with a 90% reduced risk of acute GVHD (HR 0.1, 95% CI 0.02 to 0.6, p=0.01). CONCLUSIONS: ICI therapy for relapsed acute myeloid leukemia/myelodysplastic syndromes after alloHCT may be a safe and feasible option. PTCy appears to decrease the incidence of acute GVHD in this cohort of patients.

Salzmann-Manrique, E., et al. (2018). "Joint Modeling of Immune Reconstitution Post Haploidentical Stem Cell Transplantation in Pediatric Patients With Acute Leukemia Comparing CD34(+)-Selected to CD3/CD19-Depleted Grafts in a Retrospective Multicenter Study." Front Immunol **9**: 1841.

Rapid immune reconstitution (IR) following stem cell transplantation (SCT) is essential for a favorable outcome. The optimization of graft composition should not only enable a sufficient IR but also improve graft vs. leukemia/tumor effects, overcome infectious complications and, finally, improve patient survival. Especially in haploidentical SCT, the optimization of graft composition is controversial. Therefore, we analyzed the influence of graft manipulation on IR in 40 patients with acute leukemia in remission. We examined the cell recovery post haploidentical SCT in patients receiving a CD34(+)-selected or CD3/CD19-depleted graft, considering the applied conditioning regimen. We used joint model analysis for overall survival (OS) and analyzed the dynamics of age-adjusted leukocytes; lymphocytes; monocytes; CD3(+), CD3(+)CD4(+), and CD3(+)CD8(+) T cells; natural killer (NK) cells; and B cells over the course of time after SCT. Lymphocytes, NK cells, and B cells expanded more rapidly after SCT with CD34(+)-selected grafts ($P = 0.036$, $P = 0.002$, and $P < 0.001$, respectively). Contrarily, CD3(+)CD4(+) helper T cells recovered delayer in the CD34 selected group ($P = 0.026$). Furthermore, reduced intensity conditioning facilitated faster immune recovery of lymphocytes and T cells and their subsets ($P < 0.001$). However, the immune recovery for NK cells and B cells was comparable for patients who received reduced-intensity or full preparative regimens. Dynamics of all cell types had a significant influence on OS, which did not differ between patients receiving CD34(+)-selected and those receiving CD3/CD19-depleted grafts. In conclusion, cell reconstitution dynamics showed complex diversity with regard to the graft manufacturing procedure and conditioning regimen.

Seo, E., et al. (2021). "Immunologic monitoring of cytomegalovirus (CMV) enzyme-linked immune absorbent spot (ELISPOT) for controlling clinically significant CMV infection in pediatric allogeneic hematopoietic stem cell transplant recipients." PLoS One **16**(2): e0246191.

The dynamics of recovery of cytomegalovirus (CMV)-specific cell-mediated immunity (CMI) and its impact on controlling clinically significant CMV

infections following hematopoietic stem cell transplant (HSCT) are rarely reported in pediatric HSCT recipients. In this study, dynamics of recovery of CMV-specific CMI and its clinical significance in controlling CMV viremia and clinically significant CMV infections were assessed in pediatric allogeneic HSCT recipients. All subjects underwent CMV pp65- and IE1-specific enzyme-linked immune absorbent spot (ELISPOT) assays just before transplantation and then monthly until the detection of CMV-specific CMI with >/= 5 spot-forming cells (SFC) / 2.0 x 105 cells. Clinically significant CMV infections were defined as CMV diseases, prolonged CMV infections, recurrent CMV infections or late onset CMV infections. Among 52 recipients, 88.5% of recipients recovered CMV-specific CMI with >/= 5 SFC/ 2.0 x 105 cells at a median of 34 days (interquartile range [IQR]: 29-95 days) following HSCT, 55.8% at 30 days following HSCT, and 73.1% at 90 days following HSCT. The presence of CMV-specific CMI before HSCT was the significant factors for the reconstitution of CMV specific CMI after HSCT (adjusted odds ratio [aOR] = 13.33; 95% confidence interval [CI] = 1.21-142.86). After HSCT, 30 recipients experienced CMV viremia, of which 20 were clinically significant CMV infections. The full recovery of CMV-specific CMI with >/= 50 SFC / 2.0 x 105 cells after HSCT was the protective factor for the development of clinically significant CMV infections (aOR = 0.13; 95% CI = 0.22-0.71). In the haploidentical HSCT recipients, 82.1% recovered CMV-specific CMI at a median of 65 days after HSCT (IQR: 34-118 days) with a tendency to recover their CMV-specific CMI later than did those from non-haploidentical donors (65 days vs. 30 days; P = 0.001). Clinically significant CMV infections tended to occur more frequently in the haploidentical HSCT recipients compared to those with matched donor HSCT (46.4% vs. 29.2%; P = 0.205). The full recovery of CMV-specific CMI with >/= 50 SFC/2.0 x 105 cells after HSCT also lowered the risk of development of clinically significant CMV infections (aOR = 0.08; 95% CI = 0.01-0.90). However, transplantation from haploidentical donors was a significant risk factor hampering recovery of CMV-specific CMI (aOR = 0.08; 95% CI = 0.01-0.86) and full recovery of CMV-specific CMI (aOR = 0.05; 95% CI = 0.01-0.50). Pre-transplant CMV-specific CMI influenced the recovery of CMV-specific CMI, and the full recovery of CMV-specific CMI could be a surrogate marker for preventing clinically significant CMV infections in pediatric HSCT recipients. Immunologic monitoring using ELISPOT assay before and after HSCT helps in identifying patients with a high risk of CMV infection and in controlling CMV infection.

Servaas, N. H., et al. (2020). "The role of innate immune cells in systemic sclerosis in the context of autologous hematopoietic stem cell transplantation." Clin Exp Immunol **201**(1): 34-39.

Systemic sclerosis (SSc) is a complex, heterogeneous autoimmune connective tissue disease. Autologous hematopoietic stem-cell transplantation (AHSCT) has emerged as a valuable treatment option for rapidly progressive diffuse cutaneous SSc (dcSSc) patients, and thus far is the only treatment that has been shown to have a long-term clinical benefit. AHSCT is thought to reintroduce immune homeostasis through elimination of pathogenic self-reactive immune cells and reconstitution of a new, tolerant immune system. However, the mechanism of action underlying this reset to tolerance remains largely unknown. In this study we review the immune mechanisms underlying AHSCT for SSc, with a focus on the role of the innate immune cells, including monocytes and natural killer (NK) cells, in restoring immune balance after AHSCT.

Shao, L., et al. (2020). "Knockout of beta-2 microglobulin enhances cardiac repair by modulating exosome imprinting and inhibiting stem cell-induced immune rejection." Cell Mol Life Sci **77**(5): 937-952.

BACKGROUND AND AIMS: Allogeneic human umbilical mesenchymal stem cells (alloUMSC) are convenient cell source for stem cell-based therapy. However, immune rejection is a major obstacle for clinical application of alloUMSC for cardiac repair after myocardial infarction (MI). The immune rejection is due to the presence of human leukocyte antigen (HLA) class I molecule which is increased during MI. The aim of this study was to knockout HLA light chain beta2-microglobulin (B2M) in UMSC to enhance stem cell engraftment and survival after transplantation. METHODS AND RESULTS: We developed an innovative strategy using CRISPR/Cas9 to generate UMSC with B2M deletion (B2M(-)UMSC). AlloUMSC injection induced CD8(+) T cell-mediated immune rejection in immune competent rats, whereas no CD8(+) T cell-mediated killing against B2M(-)UMSC was observed even when the cells were treated with IFN-gamma. Moreover, we demonstrate that UMSC-derived exosomes can inhibit cardiac fibrosis and restore cardiac function, and exosomes derived from B2M(-)UMSC are more efficient than those derived from UMSC, indicating that the beneficial effect of exosomes can be enhanced by modulating exosome's imprinting. Mechanistically, microRNA sequencing identifies miR-24 as a major component of the exosomes from B2M(-)UMSCs. Bioinformatics analysis identifies Bim as a putative target of miR-24. Loss-of-function studies at the cellular level and gain-of-function approaches in exosomes show that the beneficial effects of B2M(-)UMSCs are mediated by the exosome/miR-24/Bim pathway. CONCLUSION: Our findings demonstrate that modulation of exosome's imprinting via B2M knockout is an efficient strategy to

prevent the immune rejection of alloUMSCs. This study paved the way to the development of new strategies for tissue repair and regeneration without the need for HLA matching.

Shen, Y., et al. (2019). "Effects of Gastric Cancer Cell-Derived Exosomes on the Immune Regulation of Mesenchymal Stem Cells by the NF-kB Signaling Pathway." Stem Cells Dev **28**(7): 464-476.

Mesenchymal stem cells (MSCs) are important components of the tumor microenvironment, which play an important role in tumor development. Exosomes derived from tumor cells can affect the biological characteristics of MSCs. Our study examined the effects of exosomes derived from gastric cancer cells on MSC immunomodulatory functions. Exosomes were extracted from gastric cancer cell line AGS (AGS-Exos) and cultured with MSCs. MSCs were then cocultured with both human peripheral blood mononuclear cells and macrophages [phorbol-12-myristate-13-acetate (PMA)-stimulated THP1 cells]. The activation levels of T cells and macrophages were detected by flow cytometry and real-time quantitative polymerase chain reaction (RT-PCR). Changes in the MSC signaling pathway after AGS-Exos stimulation were studied using RNA Chip, and the molecular mechanisms of functional change in MSCs were studied by inhibiting the signaling pathway. MSCs treated with AGS-Exos could promote macrophage phagocytosis and upregulate the secretion of proinflammatory factor, and promote the activation of CD69 and CD25 on the surface of T cells. RNA Chip results indicated the abnormal activation of the NF-kB signaling pathway in MSCs after AGS-Exos stimulation, and this was verified by the identification of key proteins in the pathway using western blot analysis. After NF-kB signaling pathway inhibition, the effect of MSCs stimulated by AGS-Exos on T cells and macrophages was markedly weakened. Therefore, AGS-Exos affected the immunomodulation function of MSCs through the NF-kB signaling pathway, which enhanced the ability of MSCs to activate immune cells, maintain the inflammatory environment, and support tumor growth.

Sterling, C. and J. Webster (2020). "Harnessing the immune system after allogeneic stem cell transplant in acute myeloid leukemia." Am J Hematol **95**(5): 529-547.

Allogeneic stem cell transplantation (allo-SCT) is the most successful and widely used immunotherapy for the treatment of acute myeloid leukemia (AML), as a result of its anti-leukemic properties driven by T cells and natural killer (NK) cells, leading to a graft-vs-leukemia (GVL) effect. Despite its essential role in AML treatment, relapse after allo-SCT is common and associated with a poor prognosis. There is longstanding interest in developing immunologic strategies to augment the GVL effect post-transplant to prevent relapse and improve outcomes. In addition to prophylactic maintenance strategies, the GVL effect can also be used in relapsed patients to reinduce remission. While immune checkpoint inhibitors and other novel immune-targeted agents have been successfully used in the post-transplant setting to augment the GVL effect and induce remission in small clinical trials of relapsed patients, exacerbations of graft-vs-host disease (GVHD) have limited their broader use. Here we review advances in three areas of immunotherapy that have been studied in post-transplant AML: donor lymphocyte infusion (DLI), immune checkpoint inhibitors, and other monoclonal antibodies (mAbs), including antibody-drug conjugates (ADCs) and ligand receptor antagonists. We also discuss additional therapies with proposed immunologic mechanisms, such as hypomethylating agents, histone deacetylase inhibitors, and the FLT3 inhibitor sorafenib.

Stern, L., et al. (2018). "Mass Cytometry for the Assessment of Immune Reconstitution After Hematopoietic Stem Cell Transplantation." Front Immunol **9**: 1672.

Mass cytometry, or Cytometry by Time-Of-Flight, is a powerful new platform for high-dimensional single-cell analysis of the immune system. It enables the simultaneous measurement of over 40 markers on individual cells through the use of monoclonal antibodies conjugated to rare-earth heavy-metal isotopes. In contrast to the fluorochromes used in conventional flow cytometry, metal isotopes display minimal signal overlap when resolved by single-cell mass spectrometry. This review focuses on the potential of mass cytometry as a novel technology for studying immune reconstitution in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Reconstitution of a healthy donor-derived immune system after HSCT involves the coordinated regeneration of innate and adaptive immune cell subsets in the recipient. Mass cytometry presents an opportunity to investigate immune reconstitution post-HSCT from a systems-level perspective, by allowing the phenotypic and functional features of multiple cell populations to be assessed simultaneously. This review explores the current knowledge of immune reconstitution in HSCT recipients and highlights recent mass cytometry studies contributing to the field.

Stratton, P., et al. (2020). "Immune Response Following Quadrivalent Human Papillomavirus Vaccination in Women After Hematopoietic Allogeneic Stem Cell Transplant: A Nonrandomized Clinical Trial." JAMA Oncol **6**(5): 696-705.

Importance: Human papillomavirus (HPV) infection is found in about 40% of women who survive allogeneic hematopoietic stem cell transplant and can

induce subsequent neoplasms. Objective: To determine the safety and immunogenicity of the quadrivalent HPV vaccine (HPV-6, -11, -16, and -18) in clinically stable women post-allogeneic transplant compared with female healthy volunteers. Interventions: Participants received the quadrivalent HPV vaccine in intramuscular injections on days 1 and 2 and then 6 months later. Design, Setting, and Participants: This prospective, open-label phase-1 study was conducted in a government clinical research hospital and included clinically stable women posttransplant who were or were not receiving immunosuppressive therapy compared with healthy female volunteers age 18 to 50 years who were followed up or a year after first receiving quadrivalent HPV vaccination. The study was conducted from June 2, 2010, until July 19, 2016. After all of the results of the study assays were completed and available in early 2018, the analysis took place from February 2018 to May 2019. Main Outcomes and Measures: Anti-HPV-6, -11, -16, and -18-specific antibody responses using L1 virus-like particle enzyme-linked immunosorbent assay were measured in serum before (day 1) and at months 7 and 12 postvaccination. Anti-HPV-16 and -18 neutralization titers were determined using a pseudovirion-based neutralization assay. Results: Of 64 vaccinated women, 23 (35.9%) were receiving immunosuppressive therapy (median age, 34 years [range, 18-48 years]; median 1.2 years posttransplant), 21 (32.8%) were not receiving immunosuppression (median age, 32 years [range, 18-49 years]; median 2.5 years posttransplant), and 20 (31.3%) were healthy volunteers (median age, 32 years [range, 23-45 years]). After vaccine series completion, 18 of 23 patients receiving immunosuppression (78.3%), 20 of 21 not receiving immunosuppression (95.2%), and all 20 volunteers developed antibody responses to all quadrivalent HPV vaccine types (P = .04, comparing the 3 groups). Geometric mean antibody levels for each HPV type were higher at months 7 and 12 than at baseline in each group (all geometric mean ratios >1; P < .001) but not significantly different across groups. Antibody and neutralization titers for anti-HPV-16 and anti-HPV-18 correlated at month 7 (Spearman rho = 0.92; P < .001 for both). Adverse events were mild and not different across groups. Conclusions and Relevance: Treatment with the HPV vaccination was followed by strong, functionally active antibody responses against vaccine-related HPV types and no serious adverse events. These findings suggest that HPV vaccination may be safely administered to women posttransplant to potentially reduce HPV infection and related neoplasia. Trial Registration: ClinicalTrials.gov Identifier: NCT01092195.

Sugiyama, T., et al. (2019). "Niches for hematopoietic stem cells and immune cell progenitors." Int Immunol **31**(1): 5-11.

The special microenvironments, termed niches, with which hematopoietic stem cells (HSCs) are in contact, have been thought to be required for the maintenance of HSCs and the generation of immune cells in bone marrow. Although the identity of the HSC niche has been a subject of long-standing debate, recent findings demonstrate that a population of mesenchymal stem cells, termed CXC chemokine ligand (CXCL)12-abundant reticular (CAR) cells or leptin receptor-expressing (LepR+) cells, are the major cellular components of niches for HSCs and lymphoid progenitors, which express specific transcription factors, including Foxc1 and Ebf3, and cytokines, including CXCL12 and stem cell factor (SCF), essential for their niche functions. The identity and functions of other types of cells, including osteoblasts, sinusoidal endothelial cells, periarteriolar cells, megakaryocytes and a population of macrophages in HSC maintenance, have also been shown.

Takashima, S., et al. (2019). "T cell-derived interferon-gamma programs stem cell death in immune-mediated intestinal damage." Sci Immunol **4**(42).

Despite the importance of intestinal stem cells (ISCs) for epithelial maintenance, there is limited understanding of how immune-mediated damage affects ISCs and their niche. We found that stem cell compartment injury is a shared feature of both alloreactive and autoreactive intestinal immunopathology, reducing ISCs and impairing their recovery in T cell-mediated injury models. Although imaging revealed few T cells near the stem cell compartment in healthy mice, donor T cells infiltrating the intestinal mucosa after allogeneic bone marrow transplantation (BMT) primarily localized to the crypt region lamina propria. Further modeling with ex vivo epithelial cultures indicated ISC depletion and impaired human as well as murine organoid survival upon coculture with activated T cells, and screening of effector pathways identified interferon-gamma (IFNgamma) as a principal mediator of ISC compartment damage. IFNgamma induced JAK1- and STAT1-dependent toxicity, initiating a proapoptotic gene expression program and stem cell death. BMT with IFNgamma-deficient donor T cells, with recipients lacking the IFNgamma receptor (IFNgammaR) specifically in the intestinal epithelium, and with pharmacologic inhibition of JAK signaling all resulted in protection of the stem cell compartment. In addition, epithelial cultures with Paneth cell-deficient organoids, IFNgammaR-deficient Paneth cells, IFNgammaR-deficient ISCs, and purified stem cell colonies all indicated direct targeting of the ISCs that was not dependent on injury to the Paneth cell niche.

Dysregulated T cell activation and IFNgamma production are thus potent mediators of ISC injury, and blockade of JAK/STAT signaling within target tissue stem cells can prevent this T cell-mediated pathology.
Waller, E. K., et al. (2019). "Kinetics of immune cell reconstitution predict survival in allogeneic bone marrow and G-CSF-mobilized stem cell transplantation." Blood Adv **3**(15): 2250-2263.

The clinical utility of monitoring immune reconstitution after allotransplant was evaluated using data from Blood and Marrow Transplant Clinical Trials Network BMT CTN 0201 (NCT00075816), a multicenter randomized study of unrelated donor bone marrow (BM) vs granulocyte colony-stimulating factor (G-CSF)-mobilized blood stem cell (G-PB) grafts. Among 410 patients with posttransplant flow cytometry measurements of immune cell subsets, recipients of G-PB grafts had faster T-cell reconstitution than BM recipients, including more naive CD4(+) T cells and T-cell receptor excision circle-positive CD4(+) and CD8(+) T cells at 3 months, consistent with better thymic function. Faster reconstitution of CD4(+) T cells and naive CD4(+) T cells at 1 month and CD8(+) T cells at 3 months predicted more chronic graft-versus-host disease (GVHD) but better survival in G-PB recipients, but consistent associations of T-cell amounts with GVHD or survival were not seen in BM recipients. In contrast, a higher number of classical dendritic cells (cDCs) in blood samples at 3 months predicted better survival in BM recipients. Functional T-cell immunity measured in vitro by cytokine secretion in response to stimulation with cytomegalovirus peptides was similar when comparing blood samples from BM and G-PB recipients, but the degree to which acute GVHD suppressed immune reconstitution varied according to graft source. BM, but not G-PB, recipients with a history of grades 2-4 acute GVHD had lower numbers of B cells, plasmacytoid dendritic cells, and cDCs at 3 months. Thus, early measurements of T-cell reconstitution are predictive cellular biomarkers for long-term survival and response to GVHD therapy in G-PB recipients, whereas more robust DC reconstitution predicted better survival in BM recipients.
Wang, Y., et al. (2019). "Aging of the immune system causes reductions in muscle stem cell populations, promotes their shift to a fibrogenic phenotype, and modulates sarcopenia." FASEB J **33**(1): 1415-1427.

Aging is associated with diminished muscle mass, reductions in muscle stem cell functions, and increased muscle fibrosis. The immune system, especially macrophages, can have important roles in modulating muscle growth and regeneration, suggesting that the immune system may also have significant influences on muscle aging. Moreover, the immune system experiences changes in function during senescence, suggesting that regulatory interaction between muscle cells and the immune system may also change during aging. In this study, we performed bone marrow transplantations between age-mismatched donor and recipient mice to test the influence of the age of the immune system on muscle aging. Transplantation of young bone marrow cells into old recipients prevented sarcopenia and prevented age-related change in muscle fiber phenotype. Transplantation of old bone marrow cells into young animals reduced satellite cell numbers and promoted satellite cells to switch toward a fibrogenic phenotype. We also demonstrated that conditioned media from young, but not old, bone marrow cells promoted myoblast proliferation in vitro, and we found that factors released by young bone marrow cells were more supportive of myotube differentiation in vitro. Together, our results demonstrate that aging of bone marrow cells promotes the age-related reduction of satellite cell number and function and contributes to sarcopenia.-Wang, Y., Wehling-Henricks, M., Welc, S. S., Fisher, A. L., Zuo, Q., Tidball, J. G. Aging of the immune system causes reductions in muscle stem cell populations, promotes their shift to a fibrogenic phenotype, and modulates sarcopenia.
Wen, T., et al. (2018). "Early immune response regulated by a bone marrow mesenchymal stem cell model of multiple trauma in rats." Immunotherapy **10**(12): 1053-1064.

AIM: To explore whether transplantation of bone marrow mesenchymal stem cells (BMSCs) would reduce the immune response and protect vital organs in a rat model of femur shaft fracture combined with craniocerebral injury. METHODS: The rats were divided into an experimental group (multiple traumas and receiving BMSCs injection, n = 25), a positive control group (only received the combination injuries, n = 25) and a negative group (n = 5). RESULTS: Compared with the positive control group, plasma IL-6 and IL-8 were significantly lower at the early stage, and IL-10 was higher at the late period in the experimental group ($p < 0.05$). TNF-alpha ex-vivo synthesis descended quickly after trauma. CONCLUSION: BMSCs reduced the inflammatory response and were effective in immunomodulations during severe trauma.
Wiegering, V., et al. (2019). "Differences of Immune Reconstitution of Dendritic Cells in Pediatric GvHD Patients After Allogenic Stem Cell Transplantation." J Pediatr Hematol Oncol **41**(2): e101-e107.

BACKGROUND: Hematopoietic stem cell transplantation (HSCT) is a life-saving procedure for children with a variety of (non) malignant conditions. GvHD is a severe complication with high morbidity and mortality. The pathogenesis remains unclear. We

studied dendritic cell (DC) reconstitution to detect potential differences, which may improve our knowledge in the development of chronic GvHD (cGvHD). PROCEDURE: We examined immune reconstitution (T, B, and NK cells and dendritic cells) at defined time points in a pediatric cohort who underwent 61 allogeneic HSCTs. RESULTS: Regarding DC reconstitution we found a fast reconstitution of the DC compartment negatively correlated with age. After HSCT, both myeloid DC (mDC) and plasmacytoid DC (pDC) counts recover to pre-HSCT levels within 2 months. Higher CCR7 positive cell counts were found in patients receiving TBI during engraftment and during the whole posttransplant period we found a correlation with an improved outcome. In cGVHD patients decreased total DC counts and increased pDCs were found after day+100. No relevant correlation was achieved regarding to HLA-matching, stem cell manipulation of the graft as well as HSCT-indication compared with different DC counts. DISCUSSION: Pathogenesis of cGvHD remains complex. Our data suggest an influence of dendritic cells, which may contribute to the clinical picture and should be further investigated in future studies.

Wurschi, G. W., et al. (2019). "MRI as an alternative to serum ferritin for diagnosis of iron overload in children in the context of immune response after stem cell transplantation." Pediatr Transplant **23**(8): e13583.

Multiple blood cell transfusions may cause iron overload or even liver fibrosis, requiring early diagnosis and intervention. SF is the standard for estimating iron levels in the body, but it also increases with inflammation. We hypothesized that T2 * magnetic resonance (MR) relaxometry is a more accurate alternative for follow-up in pediatric patients before and after allogenic SCT. Twenty-three children (mean age 10.2 years, 10 female, 13 male) were evaluated prospectively before SCT as well as at least 1 year after SCT with T2 * relaxometry on a 1.5 T MR-scanner to estimate liver iron concentrations from the T2 * values ("MR-Fe"). The results were compared with SF, while also considering CRP, and correlated with the number of transfusions. Overall, 24.3 transfusions were administered in average, mainly within 100 days of SCT (mean 10.5 units). Both MR-Fe and SF increased after SCT and decreased in the absence of new transfusions 1 year later without chelate therapy. This suggests regeneration of LP and iron loss, although the original states were not reached. Additionally, simultaneous peaks of CRP and SF were observed directly after SCT. MR-Fe did neither reveal these peaks nor was it associated with CRP (P = .39). We postulate that these early CRP and SF peaks after SCT are probably related to inflammatory reactions and not to iron overload. Thus, SF is not reliable for iron overload diagnosis after SCT in every condition. Beside this interaction, SF and MR-Fe revealed similar accuracy. MRI, however, has practical and economical disadvantages in routine estimation of iron.

Xie, M., et al. (2020). "Immunoregulatory Effects of Stem Cell-Derived Extracellular Vesicles on Immune Cells." Front Immunol **11**: 13.

Recent investigations on the regulatory action of extracellular vesicles (EVs) on immune cells in vitro and in vivo have sparked interest on the subject. As commonly known, EVs are subcellular components secreted by a paracellular mechanism and are essentially a group of nanoparticles containing exosomes, microvesicles, and apoptotic bodies. They are double-layer membrane-bound vesicles enriched with proteins, nucleic acids, and other active compounds. EVs are recognized as a novel apparatus for intercellular communication that acts through delivery of signal molecules. EVs are secreted by almost all cell types, including stem/progenitor cells. The EVs derived from stem/progenitor cells are analogous to the parental cells and inhibit or enhance immune response. This review aims to provide its readers a comprehensive overview of the possible mechanisms underlying the immunomodulatory effects exerted by stem/progenitor cell-derived EVs upon natural killer (NK) cells, dendritic cells (DCs), monocytes/macrophages, microglia, T cells, and B cells.

Yang, T., et al. (2018). "Co-culture of dendritic cells and cytokine-induced killer cells effectively suppresses liver cancer stem cell growth by inhibiting pathways in the immune system." BMC Cancer **18**(1): 984.

BACKGROUND: Application of dendritic cells (DC) for cancer immunotherapy involves tumor-associated immunogenic antigens for effective therapeutic strategies. The present study investigated whether DC co-cultured with autologous cytokine-induced killer cells (CIK) could induce a more specific immune response against liver cancer stem cells (LCSC) generated from human hepatocellular carcinoma (HCC) cells in vitro and in vivo. METHODS: Human DC and CIK were generated from peripheral blood mononuclear cells (PBMCs) taken from consenting liver cancer patients. Flow cytometry was used to determine the phenotypes of DC and CIK, and cell proliferation. The tumor growth and anti-tumor activity of these cells were further evaluated using a nude mouse tumor model. RESULTS: We demonstrated that DC and CIK significantly enhanced the apoptosis ratio, depending on DC-CIK cell numbers, by increasing caspase-3 protein expression and reducing proliferating cell nuclear antigen (PCNA) protein expression against LCSC. The in vivo data indicated that DC-CIK exhibited significant LCSC cell-induced tumor growth inhibition in nude mice, which

was most significant with LCSC antigen loaded DCs. CONCLUSIONS: The results showed, that DC-CIK cells could inhibit HCC and LCSC growths in vitro and in vivo and the most successful DC triggering of cell cytotoxic activity could be achieved by their LCSC antigen loading.

Yang, X., et al. (2018). "An Immune System-Modified Rat Model for Human Stem Cell Transplantation Research." Stem Cell Reports **11**(2): 514-521.

Due to its lack of both innate and acquired immune responses to human cells, the NODSCIDIl2rgamma(-/-) (NSG) mouse model has become an important tool for human stem cell research. When compared with the mouse, the rat is physiologically more similar to humans and offers advantages in preclinical efficacy studies on human stem cells, particularly in evaluating neural, hepatic, and cardiac functions. Therefore, we generated a human SIRPalpha(+)Prdkc(-/-)Il2rgamma(-/-) rat model, denoted NSG-like (NSGL) rat, which expresses human SIRPalpha and is abolished in the development of B, T, and natural killer cells. When compared with Prdkc(-/-)Il2rgamma(-/-) (SG) rats, NSGL rats allow more efficient engraftment of human cancer cells and human pluripotent stem cells. In addition, only NSGL rats, but not SG rats, can be engrafted with human hematopoietic stem cells to reconstitute the human immune system. Therefore, NSGL rats represent an improved xenotransplantation model for efficacy studies of human stem cells.

Ye, R., et al. (2019). "Immune Signatures Associated With Clonal Isotype Switch After Autologous Stem Cell Transplantation for Multiple Myeloma." Clin Lymphoma Myeloma Leuk **19**(5): e213-e220.

BACKGROUND: High-dose chemotherapy and autologous stem cell transplantation (ASCT) are integral components of the overall treatment for patients with multiple myeloma (MM) aged </= 65 years. The emergence of oligoclonal immunoglobulin bands (ie, immunoglobulins differing from those originally identified at diagnosis [termed clonal isotype switch (CIS)]) has been reported in patients with MM after high-dose chemotherapy followed by autologous stem cell transplantation. However, the clinical relevance and the correlation with immune reconstitution remains unclear. PATIENTS AND METHODS: Patients with MM who had undergone ASCT from 2007 to 2016 were included in the present study. The percentage of natural killer cells, B-cells, and T-cells was measured using flow cytometry in pre- and post-ASCT bone marrow samples. CIS was defined as the appearance of a new serum monoclonal spike on serum protein electrophoresis and immunofixation that differed from original heavy or light chain detected at diagnosis. RESULTS: A retrospective analysis of 177 patients with MM who had undergone ASCT detected CIS in 39 (22%). CIS after ASCT correlated with improved progression-free survival (52.2 vs. 36.6 months; P = .21) and overall survival (75.1 vs. 65.4 months; P = .021). Patients with a relapse had an isotype that differed from a CIS, confirming the benign nature of this phenomenon. CIS was also associated with lower CD8 T-cell percentages and a greater CD4/CD8 ratio (2.8 vs. 0.2; P = .001) compared with patients who did not demonstrate a CIS, suggestive of more profound T-cell immune reconstitution in this group. CONCLUSION: Taken together, our data have demonstrated that a CIS is a benign phenomenon and correlates with a reduced disease burden and enriched immune repertoire beyond the B-cell compartment.

Yin, J., et al. (2020). "Increased Galectin-9 expression, a prognostic biomarker of aGVHD, regulates the immune response through the Galectin-9 induced MDSC pathway after allogeneic hematopoietic stem cell transplantation." Int Immunopharmacol **88**: 106929.

Galectin-9 (Gal-9) is a beta-galactoside-binding soluble lectin family member that exerts its primary biological functions via specific glycoconjugate interactions. Gal-9 expression is closely related to tumor occurrence, development, metastasis and prognosis. In transplant immunology, a high level of Gal-9 expression has been shown to markedly reduce the severity of acute graft rejection and effectively prolong survival time in organ and bone marrow transplantation (BMT) models. The main mechanism of Gal-9-mediated immunoregulation involves the Tim-3/Gal-9 axis in T cells. However, myeloid-derived suppressor cell (MDSC) accumulation in transgenic mice with persistently high Gal-9 expression was observed in a model of lung inflammation, indicating that a potential immunosuppressive mechanism distinct from the Gal-9/Tim-3 axis might exist. In the present study, increased Gal-9 expression and MDSC frequencies before acute graft-versus-host disease (aGVHD) onset were observed in patients who developed aGVHD. Patients with higher Gal-9 expression (>/=14.8417 ng/ml) exhibited reduced overall survival and increased cumulative incidences of GVHD at +100 day. We considered the elevated Gal-9 expression before aGVHD onset a secondary inflammatory response. This increase might be part of a negative feedback pathway corresponding to aGVHD pathogenesis. Additionally, a high Gal-9 concentration induced MDSC proliferation in vivo and in vitro. Gal-9-induced MDSCs (G9-MDSCs) suppressed T cell proliferation and activation. An infusion of G9-MDSCs into a graft contributed to the successful control of severe aGVHD and long-term survival in an allogeneic (allo)-BMT mouse model. Thus, we speculated that increased Gal-9

expression after allo-hematopoietic stem cell transplantation is a potential prognostic biomarker of aGVHD. The Gal-9-associated immunosuppressive effects on aGVHD development might occurr through G9-MDSCs and were independent of the Gal-9/Tim-3 axis.

Yoon, J. Y., et al. (2020). "Stem/progenitor cell marker expression in clear cell renal cell carcinoma: a potential relationship with the immune microenvironment to be explored." BMC Cancer **20**(1): 272.

BACKGROUND: Clear cell renal cell carcinoma (ccRCC) is a markedly heterogeneous disease in many aspects, including the tumour microenvironment. Our previous study showed the importance of the tumour microenvironment in ccRCC xeno-transplant success rates. In order to better understand the potential relationship between TICs and the immune microenvironment, we employed a multi-modal approach, examining RNA and protein expression (flow cytometry, immunohistochemistry). METHODS: We first examined the gene expression pattern of 18 stem/progenitor marker genes in the cancer genome atlas (TCGA) ccRCC cohort. Flow cytometry was next employed to examine lineage-specific expression levels of stem/progenitor markers and immune population makeup in six, disaggregated, primary ccRCC specimens. Immunohistochemistry was performed on a commercial ccRCC tissue microarray (TMA). RESULTS: The 18 genes differed with respect to their correlation patterns with one another and to their prognostic significance. By flow cytometry, correlating expression frequency of 12 stem/progenitor markers and CD10 resulted in two clusters-one with CD10 (marker of proximal tubular differentiation), and second cluster containing mostly mesenchymal stem cell (MSC) markers, including CD146. In turn, these clusters differed with respect to their correlation with different CD45(+) lineage markers and their expression of immune checkpoint pathway proteins. To confirm these findings, four stem/progenitor marker expression patterns were compared with CD4, CD8 and CD20 in a ccRCC TMA which showed a number of similar trends with respect to frequency of the different tumour-infiltrating leukocytes. CONCLUSION: Taken together, we observed heterogeneous but patterned expression levels of different stem/progenitor markers. Our results suggest a non-random relationship between their expression patterns with the immune microenvironment populations in ccRCC.

Yoshida, S., et al. (2020). "Syngeneic Mesenchymal Stem Cells Reduce Immune Rejection After Induced Pluripotent Stem Cell-Derived Allogeneic Cardiomyocyte Transplantation." Sci Rep **10**(1): 4593.

Avoiding immune rejection after allogeneic induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) transplantation is a concern. However, mesenchymal stem cells (MSCs) can suppress immune rejection. To determine whether MSC co-transplantation can reduce immune rejection after allogeneic iPSC-CM transplantation, the latter cell type, harbouring a luciferase transgene, was subcutaneously transplanted alone or together with syngeneic MSCs into BALB/c mice. Bioluminescence imaging revealed that MSC co-transplantation significantly improved graft survival (day 7: iPSC-CMs alone 34 +/- 5%; iPSC-CMs with MSCs, 61 +/- 7%; P = 0.008). MSC co-transplantation increased CD4 + CD25 + FOXP3 + regulatory T cell numbers, apoptotic CD8-positive T cells, and IL-10 and TGF-beta expression at the implantation site. Analysis using a regulatory T cell depletion model indicated that enhanced regulatory T cell populations in the iPSC-CM with MSC group partially contributed to the extended iPSC-CM survival. Further, MSCs affected activated lymphocytes directly through cell-cell contact, which reduced the CD8/CD4 ratio, the proportion of Th1-positive cells among CD4-positive cells, and the secretion of several inflammation-related cytokines. Syngeneic MSC co-transplantation might thus control allogeneic iPSC-CM rejection by mediating immune tolerance via regulatory T cells and cell-cell contact with activated lymphocytes; this approach has promise for cardiomyogenesis-based therapy using allogeneic iPSC-CMs for severe heart failure.

Zaghi, E., et al. (2019). "Innate Immune Responses in the Outcome of Haploidentical Hematopoietic Stem Cell Transplantation to Cure Hematologic Malignancies." Front Immunol **10**: 2794.

In the context of allogeneic transplant platforms, human leukocyte antigen (HLA)-haploidentical hematopoietic stem cell transplantation (haplo-HSCT) represents one of the latest and most promising curative strategies for patients affected by high-risk hematologic malignancies. Indeed, this platform ensures a suitable stem cell source immediately available for virtually any patents in need. Moreover, the establishment in recipients of a state of immunologic tolerance toward grafted hematopoietic stem cells (HSCs) remarkably improves the clinical outcome of this transplant procedure in terms of overall and disease free survival. However, the HLA-mismatch between donors and recipients has not been yet fully exploited in order to optimize the Graft vs. Leukemia effect. Furthermore, the efficacy of haplo-HSCT is currently hampered by several life-threatening side effects including the onset of Graft vs. Host Disease (GvHD) and the occurrence of opportunistic viral infections. In this context, the quality and the kinetic of the immune cell reconstitution (IR) certainly play a major role and several experimental efforts have been greatly endorsed to better understand and accelerate the post-transplant recovery of a fully competent immune

system in haplo-HSCT. In particular, the IR of innate immune system is receiving a growing interest, as it recovers much earlier than T and B cells and it is able to rapidly exert protective effects against both tumor relapses, GvHD and the onset of life-threatening opportunistic infections. Herein, we review our current knowledge in regard to the kinetic and clinical impact of Natural Killer (NK), gammadelta and Innate lymphoid cells (ILCs) IRs in both allogeneic and haplo-HSCT. The present paper also provides an overview of those new therapeutic strategies currently being implemented to boost the alloreactivity of the above-mentioned innate immune effectors in order to ameliorate the prognosis of patients affected by hematologic malignancies and undergone transplant procedures.

Zdziarski, P. (2019). "CMV-Specific Immune Response-New Patients, New Insight: Central Role of Specific IgG during Infancy and Long-Lasting Immune Deficiency after Allogenic Stem Cell Transplantation." Int J Mol Sci **20**(2).

Although the existing paradigm states that cytomegalovirus (CMV) reactivation is under the control of the cellular immune response, the role of humoral and innate counterparts are underestimated. The study analyzed the host(-)virus interaction i.e., CMV-immune response evolution during infection in three different clinical situations: (1) immunodeficient CMV-positive human leukocyte antigen (HLA)-matched bone marrow recipients after immunoablative conditioning as well as immunocompetent, (2) adult, and (3) infant with primary immune response. In the first situation, a fast and significant decrease of specific immunity was observed but reconstitution of marrow-derived B and natural killer (NK) cells was observed prior to thymic origin of T cells. The lowest CMV-IgG (93.2 RU/mL) was found just before CMV viremia. It is noteworthy that the sole and exclusive factor of CMV-specific immune response is a residual recipient antibody class IgG. The CMV-quantiferon increase was detected later, but in the first phase, phytohemagglutinin (PHA)-induced IFN-gamma release was significantly lower than that of CMV-induced ("indeterminate" results). It corresponds with the increase of NK cells at the top of lymphocyte reconstitution and undetected CMV-specific CD8 cells using a pentamer technique. In immunocompetent adult (CMV-negative donor), the cellular and humoral immune response increased in a parallel manner, but symptoms of CMV mononucleosis persisted until the increase of specific IgG. During infancy, the decrease of the maternal CMV-IgG level to 89.08 RU/mL followed by clinical sequel, i.e., CMV replication, were described. My observations shed light on a unique host-CMV interaction and CMV-IgG role: they indicate that its significant decrease predicts CMV replication. Before primary cellular immune response development, the high level of residual CMV-IgG (about >100 R/mL) from mother or recipient prevents virus reactivation. The innate immune response and NK-dependent IFN-secretion should be further investigated.

Zhai, Y., et al. (2020). "Single-Cell RNA-Sequencing Shift in the Interaction Pattern Between Glioma Stem Cells and Immune Cells During Tumorigenesis." Front Immunol **11**: 581209.

Glioblastoma is one of the most common neoplasms in the central nervous system characterized by limited immune response and unlimited expansion capability. Cancer stem cells (GSCs), a small fraction of the tumor cells, possess a pivotal regulation capability in the tumor microenvironment with a superior proliferation ability. We aimed to reveal the interaction between glioma stem cells (GSCs) and immune cells during tumorigenesis. Single-cell sequencing data from seven surgical specimens of glioblastoma patients and patient-derived GSCs cocultured with peripheral leukocytes were used for the analysis. Cell grouping and trajectory analysis were performed using Seurat and Monocle 3 packages in R software. The gene set of Cancer Genome Anatomy Project was used to define different cell types. Cells with the ability of proliferation and differentiation in glioblastoma tissue were defined as GSCs, which had a similar expression pattern to that in the GSCs in vitro. Astrocytes in glioblastoma were mainly derived from differentiated GSCs, while oligodendrocytes were most likely to be derived from different precursor cells. No remarkable evolutionary trajectory was observed among the subgroups of T cells in glioblastoma. The immune checkpoint interaction between GSCs and immune cells was changed from stimulatory to inhibitory during tumorigenesis. The patient-derived GSCs system is an ideal model for GSC research. The above research revealed that the interaction pattern between GSC glioma stem cells and immune cells during tumorigenesis provides a theoretical basis for GSC glioma stem cell-targeted immunotherapy.

Zhang, P. and G. R. Hill (2019). "Interleukin-10 mediated immune regulation after stem cell transplantation: Mechanisms and implications for therapeutic intervention." Semin Immunol **44**: 101322.

Interleukin-10 (IL-10) is a multi-faceted anti-inflammatory cytokine which plays an essential role in immune tolerance. Indeed, deficiency of IL-10 or its receptor results in aberrant immune responses that lead to immunopathology. Graft-versus-host disease (GVHD) is the limiting complication of allogeneic stem cell transplantation (SCT) and results from an imbalance in pathological versus regulatory immune networks. A number of immune cells exert their immunomodulatory role through secretion of IL-10 or

induction of IL-10-secreting cells after SCT. Type-1 regulatory T cells (Tr1 cells) and FoxP3(+) regulatory T cells (Tregs) are predominant sources of IL-10 after SCT and the critical role of this cytokine in preventing GVHD is now established. Recently, intriguing interactions among IL-10, immune cells, commensal microbes and host tissues in the gastrointestinal (GI) tract and other barrier surfaces have been uncovered. We now understand that IL-10 secretion is dynamically modulated by the availability of antigen, co-stimulatory signals, cytokines, commensal microbes and their metabolites in the microenvironment. In this review, we provide an overview of the control of IL-10 secretion and signaling after SCT and the therapeutic interventions, with a focus on Tr1 cells.

Zhang, Y., et al. (2020). "Knockout of beta-2 microglobulin reduces stem cell-induced immune rejection and enhances ischaemic hindlimb repair via exosome/miR-24/Bim pathway." J Cell Mol Med **24**(1): 695-710.

Generating universal human umbilical mesenchymal stem cells (UMSCs) without immune rejection is desirable for clinical application. Here we developed an innovative strategy using CRISPR/Cas9 to generate B2M(-) UMSCs in which human leucocyte antigen (HLA) light chain beta2-microglobulin (B2M) was deleted. The therapeutic potential of B2M(-) UMSCs was examined in a mouse ischaemic hindlimb model. We show that B2M(-) UMSCs facilitated perfusion recovery and enhanced running capability, without inducing immune rejection. The beneficial effect was mediated by exosomes. Mechanistically, microRNA (miR) sequencing identified miR-24 as a major component of the exosomes originating from B2M(-) UMSCs. We identified Bim as a potential target of miR-24 through bioinformatics analysis, which was further confirmed by loss-of-function and gain-of-function approaches. Taken together, our data revealed that knockout of B2M is a convenient and efficient strategy to prevent UMSCs-induced immune rejection, and it provides a universal clinical-scale cell source for tissue repair and regeneration without the need for HLA matching in the future.

Zhou, L. and D. P. Lu (2019). "Immune reconstitution of HLA-A*0201/BMLF1- and HLA-A*1101/LMP2-specific Epstein Barr virus cytotoxic T lymphocytes within 90 days after haploidentical hematopoietic stem cell transplantation." Virol J **16**(1): 19.

BACKGROUND: Haploidentical hematopoietic stem cell transplant (haplo-HSCT) recipients are at high risk for Epstein Barr virus (EBV)-related diseases. EBV-specific CD8(+) cytotoxic T cells can control EBV-infected B cell expansion; however, no studies have investigated EBV-specific immune reconstitution after HSCT, particularly haplo-HSCT. Therefore, in this study, we aimed to characterize EBV-specific immune cell reconstitution after haplo-HSCT. METHODS: HLA-A*1101 and HLA-A*0201 pentamers folded with immunodominant EBV peptides were used to detect EBV-specific CD8(+) T cells by flow cytometry in peripheral blood mononuclear cells from 19 haplo-HSCT recipients and the results were compared with those in controls. We also compared the EBV-specific pentamer-binding cell frequencies in patients with or without EBV-related diseases by flow cytometry. RESULTS: Pentamer-binding EBV-specific CD8(+) T cells were detected at + 30, + 60 and + 90 days after haplo-HSCT in EBV-seropositive patients subjected to haplo-HSCT from an EBV-seropositive donor. The frequencies of the HLA-A*0201/BMLF1-GLC pentamer in haplo-HSCT patients at + 30 days were significantly lower than those in HLA-A*0201-positive healthy controls ($p = 0.019$) and patients at + 60 days ($p = 0.003$). The frequencies of the HLA-A*1101/LMP2-SSC pentamer at + 30, + 60, and + 90 days were significantly decreased compared with those in healthy controls ($p = 0.009$, 0.019, and 0.039, respectively); however, the frequencies of the HLA-A*1101/LMP2-SSC pentamer did not differ significantly among patients at + 30, + 60, and + 90 days ($p = 0.886$). There was a significant difference in the frequency of the HLA-A*0201/BMLF1-GLC pentamer at + 60 days between patients with and without EBV-related diseases ($p = 0.024$). Patients with EBV-related diseases showed lower percentages of HLA-A*0201/BMLF1-GLC specific CD8(+) T cells. CONCLUSIONS: Haplo-HSCT recipients could generate EBV-specific CD8(+) T cells within + 30 days after transplantation. The HLA-A*0201/BMLF1-GLC pentamer cell frequency at + 60 days may be a useful indicator for monitoring EBV-related diseases in patients after haplo-HSCT. Transfusion with EBV-CTLs within 60 days after haplo-HSCT may have prophylactic effects against EBV-related diseases.

Zhou, Z., et al. (2020). "The clinical characteristics of patients with acute leukemia or stem cell transplantation exhibiting immune based platelet refractoriness." Transfus Apher Sci **59**(3): 102725.

BACKGROUND: To investigate the related factors influencing immune platelet transfusion refractoriness (PTR) in acute leukemia (AL) from induction to consolidation and compare management for immune PTR, so as to improve the Platelet increment in AL. METHODS: The primary analysis included 890 patients with AL, 225 of whom were the immune PTR (25 %).They are patients in our center from induction to consolidation or transplantation in the past 10 years. Flow cytometry, karyotype characteristics and other basic information were compared between the immune PTR vs control (no-PTR) groups. We analyzed the treatment outcomes of

immune PTR including matched platelets, intravenous immunoglobulin (IVIG), increasing apheresis platelet does. RESULTS: Immune PTR is more likely to occur in patients with poor prognosis in acute lymphoblastic leukemia (ALL) (P = 0.01).There is a relation between NPM1 mutation and occurrence of immune PTR (P = 0.029).The incidence of PTR at 35-59Y was higher than that at <35Y(OR = 0.68, 95 % CI = 0.48-0.96) and >/=60Y(OR = 0.49,95 % CI = 0.28-0.83), and the difference was statistically significant(P = 0.03, P = 0.01).The Platelet increment with 1 unit (u) was 47.12 %, 2 u increased to 71.14 %, and the matched 2 u (75.11 %) had the best effect. IVIG improved the Platelet increment, but there was no difference between 0.4 g/kg IVIG and 1 g/kg IVIG. Immune PTR is more likely to occur in the ages of 35-60 years. CONCLUSION: There are specific AL patient characteristics which predispose to the phenomenon of immune based PTR. Meanwhile, increasing the IVIG dose could not improve Platelet increment obviously.

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