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Stem Cell

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Mortality and Stem Cell Research Literatures

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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; technology; 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.

Abudayyeh, A. and R. Wanchoo (2022). "Kidney Disease Following Hematopoietic Stem Cell Transplantation." Adv Chronic Kidney Dis **29**(2): 103-115 e101.

Hematopoietic stem cell transplantation (SCT) provides a curative option for the treatment of several malignancies. Its growing use is associated with an increased burden of kidney disease. Acute kidney injury is usually seen within the first 100 days of transplantation and has an incidence ranging between 12 and 73%, with the highest rate in myeloablative allogeneic SCT. A large subset of patients after SCT develop chronic kidney disease. They can be broadly classified into thrombotic microangiopathy, nephrotic syndrome, and calcineurin toxicity. Dialysis requirement after SCT is associated with mortality exceeding 80%. Given the higher morbidity and mortality related to development kidney disease, nephrologists need to be aware of the various causes and best treatment options.

Afjeh-Dana, E., et al. (2022). "Stem Cell Differentiation into Cardiomyocytes: Current Methods and Emerging Approaches." Stem Cell Rev Rep.

Cardiovascular diseases (CVDs) are globally known to be important causes of mortality and disabilities. Common treatment strategies for CVDs, such as pharmacological therapeutics impose serious challenges due to the failure of treatments for myocardial necrosis. By contrast, stem cells (SCs) based therapies are seen to be promising approaches to CVDs treatment. In such approaches, cardiomyocytes are differentiated from SCs. To fulfill SCs complete potential, the method should be appointed to generate cardiomyocytes with more mature structure and well-functioning operations. For heart repairing applications, a greatly scalable and medical-grade cardiomyocyte generation must be used. Nonetheless, there are some challenges such as immune rejection, arrhythmogenesis, tumorigenesis, and graft cell death potential. Herein, we discuss the types of potential SCs, and commonly used methods including embryoid bodies related techniques, co-culture, mechanical stimulation, and electrical stimulation and their applications, advantages and limitations in this field. An estimated 17.9 million people died from CVDs in 2019, representing 32 % of all global deaths. Of these deaths, 85 % were due to heart attack and stroke.

Akinci, B., et al. (2022). "Therapeutic Plasma Exchange in Pediatric Patients With Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease After Hematopoietic Stem Cell Transplantation: A Single-Center Experience." Exp Clin Transplant.

OBJECTIVES: Sinusoidal obstruction syndrome/venoocclusive disease is a significant complication of hematopoietic stem cell transplantation. Due to high mortality rates, new treatment strategies have been investigated. Here, we have presented outcomes of therapeutic plasma exchange performed on patients with sinusoidal obstruction syndrome/veno-occlusive disease. MATERIAL AND METHODS: Our study included 70 pediatric patients diagnosed with sinusoidal obstruction syndrome/veno-occlusive disease. Therapeutic plasma exchange procedures in patients were evaluated retrospectively. RESULTS: There were 9 mild (12.9%), 9 moderate (12.9%), 21 severe (30%), and 31 very severe (44.2%) cases of sinusoidal obstruction syndrome/venoocclusive disease. Therapeutic plasma exchange was performed in 31 of the 70 study patients (59.6%). Moreover, 10/21 patients with severe (47.6%) and 21/31 patients with very severe (67.7%) disease underwent plasma exchange. Mean time from diagnosis of sinusoidal obstruction syndrome/venoocclusive disease to therapeutic plasma exchange initiation was 2.3 days. The 31 patients who received therapeutic plasma exchange had a total of 146 sessions. Overall survival rates at 100 days were 87.1% and 92.3% for patients who did and did not undergo therapeutic plasma exchange, respectively. When patients with mild and moderate disease who were not expected to undergo plasma exchange were excluded (n = 52), 100-day overall survival rates were 87.1% and 90.5% for those who did and did not undergo plasma exchange, respectively. When we compared severe versus very severe groups, no significant difference was found. CONCLUSIONS: Plasmapheresis had no positive effect on survival. However, overall survival in all groups was higher than that in the literature, despite the high number of patients with severe and very severe disease. Interpretation of the results is limited by the retrospective nature of the study. Thus, prospective, randomized controlled trials with larger numbers of patients are necessary to investigate the role of therapeutic plasma exchange in patients with sinusoidal obstruction syndrome/veno-occlusive disease.

Alatrash, G., et al. (2022). "Vorinostat Combined with Busulfan, Fludarabine, and Clofarabine Conditioning Regimen for Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Acute Leukemia: Long-Term Study Outcomes." Transplant Cell Ther.

Conditioning regimens play a major role in determining disease outcomes following allogeneic hematopoietic stem cell transplantation (allo-HSCT). The use of i.v. busulfan (Bu) as part of conditioning chemotherapy has been shown to be effective in controlling disease relapse; however, disease relapse remains a major cause of death following allo-HSCT. This study was conducted to determine the long-term outcomes of vorinostat with i.v. Bu plus dual nucleoside analogs clofarabine (Clo) and fludarabine (Flu) in the conditioning regimen for patients undergoing allo-HSCT. This was a rapid dose escalation phase I/II study designed to determine whether the addition of vorinostat would improve the efficacy of standard i.v. Bu/Flu/Clo conditioning regimen. This report presents the long-term disease outcomes of this combination in 68 patients with high-risk leukemia, including 31 (46%) with acute lymphoblastic leukemia (ALL) and 37 (54%) with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). Fifty-eight patients (85%) were in morphologic complete remission at time of transplantation, and 38 (56%) received a matched unrelated donor graft. Over the median follow-up of 37.6 months, 29 of the 68 patients died (43%), and the nonrelapse mortality (NRM) rate was 22% (n = 15). The median overall survival and median NRM were not reached. Nineteen patients (28%) experienced disease progression. The median progression-free survival was 36.8 months. Thirty-seven patients (57%) developed grade II-IV acute graft-versus-host disease (GVHD), and 20 patients (31%) developed chronic GVHD. Our results suggest a lack of benefit from adding a short course of vorinostat to i.v. Bu/Flu/Clo conditioning regimens for leukemia patients undergoing allo- HSCT.

Andersson, B. S., et al. (2022). "A randomized phase III study of pretransplant conditioning for AML/MDS with fludarabine and once daily IV busulfan +/- clofarabine in allogeneic stem cell transplantation." Bone Marrow Transplant.

Pretransplant conditioning with Fludarabine (Flu)-Busulfan (Bu) is safe, but clofarabine (Clo) has improved antileukemic activity. Hypothesis: Flu+Clo-Bu (FCB) yields superior progression-free survival (PFS) after allogeneic transplantation. We randomized 250 AML/MDS patients aged 3-70, Karnofsky Score >/=80, with matched donors, to FCB (n = 120) or Flu-Bu (n = 130), stratifying complete remission (CR) vs. No CR, (NCR). HCT-CI scores varied, from 0 to 10. All evaluable patients engrafted. Median follow-up was 66 months (interquartile range: 58-80). Three-year relapse incidence (RI), 25% with FCB, vs. 39% with Flu-Bu (p = 0.018), offset by higher non-relapse mortality, 22.6% (95%CI: 16-30.2%) vs. 12.3% (95%CI: 6.5-19%). Three-year PFS was 52% (95%CI: 44-62%) (FCB), vs. 48% (95%CI: 41-58%) (Flu-Bu).

FCB benefited CR patients less, NCR patients age </= 60 had 3-year 34% RI (95%CI: 19-49%) (FCB) vs. 56% (95%CI: 38-70%) after Flu-Bu (p = 0.037). NCR patients >60 years had 3-year RI 10.0% (FCB), vs. 56.0%, after Flu-Bu (p = 0.003). Bayesian regression analysis including treatment-covariate interactions showed FCB superiority in NCR patients with low HCT-CI (0-2). Serious adverse event profiles were similar for the regimens. Conditioning with FCB did not improve PFS overall, but improved disease control in NCR patients, mandating confirmatory trials. Remission status and HCT-CI should be considered when using FCB.

Azem, A., et al. (2022). "Graft-Versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplant: SARS-CoV-2 Vaccine as a Potential Trigger." Cureus **14**(6): e25738.

Allogeneic hematopoietic stem cell transplant (AHSCT) recipients are at a risk of developing immune-mediated tissue damage from activation of the donor's immunocompetent T cells by the recipient's normally expressed antigens, a phenomenon called graft-versus-host disease (GVHD). With the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), new vaccines have been developed to prevent morbidity and mortality, including the highly vulnerable hematologic malignancy patients after undergoing AHSCT. The early pathophysiologic events in GVHD include priming the donor T cells with molecules that are endogenous or pathogenic. In this case series, we present two cases of AHSCT recipients in which the SARS-CoV-2 vaccination series proceeded the development of GVHD manifesting with oral mucosal symptoms and derangement in the liver function tests. Our experience raises the question if any of the vaccine components serve as a molecular trigger for GVHD, making the current SARS-CoV-2 vaccines a risk factor for activating the immune system and developing GVHD.

Barzin, A., et al. (2022). "[Acute and chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation]." Rev Med Liege **77**(5-6): 345-353.

Acute and/or chronic graft-versus-host disease (GVHD) is a serious complication after allogeneic hematopoietic stem cell transplantation (alloHSCT). It is a multisystemic inflammatory and/or fibrotic disease that occurs when the immune cells derived from the graft (and therefore originating from the donor) recognize recipient's healthy tissues as foreign and react against them. Acute GVHD is one of the main causes of non-relapse mortality after alloHSCT. Chronic GVHD can be very disabling in its severe form and can also be responsible for late mortality, mainly due to long-term immune deficiency and opportunistic infections. In contrast, GVHD can be associated with certain beneficial effects in patients transplanted for hematological malignancies, through simultaneous <<graft versus tumour>> positive effects. Therefore, one of the challenges of alloHSCT is the prevention and treatment of severe forms of GVHD without losing the beneficial anti-tumour effects of the graft.

Bello, J. A. G., et al. (2022). "A retrospective review of infections and outcomes within 100 days of hematopoietic stem cell transplantation: insights from a new transplant program in the Philippines." IJID Reg **3**: 101-105.

Background: Few hematopoietic stem cell transplantations (HSCT) are performed in lower-middle income countries. Only four institutions in the Philippines are able to perform transplants. This study describes the experience of a newly established program. Methods: The charts of all adult patients who underwent HSCT at The Medical City from May 1, 2016 to December 31, 2019 were reviewed retrospectively. Results: A total of 33 patients were included in the cohort, of whom 31 (93.9%) underwent autologous HSCT and only two (6.1%) underwent allogeneic HSCT. Most were female (21/33, 63%), and median age was 51 years (range 21-67 years). The primary indication for transplantation was multiple myeloma (n = 21), followed by diffuse B-cell lymphoma (n = 6). Fifteen of the 33 patients had a history of treated tuberculosis (TB) disease (n = 4) or latent TB infection (n = 11). The median time for neutrophil recovery was 7.4 days (range 4-13 days). Transplant complications included neutropenic fever (n = 33, 100%) and mucositis (n = 14, 42.4%). Bacterial infection was documented in 12 (36.4%) patients, with nine (24.2%) developing a bacterial blood stream infection of which seven were related to a central line. The overall mortality rate was at 6.1% (2/33) in the first 30 days post-transplant, with no additional mortality in the succeeding days until day 100. Conclusions: This cohort with mostly autologous HSCT had favorable outcomes in the first 100 days. Rates of bacterial infection were high in the early post-transplant period. Latent TB infection was common, but no reactivation was observed. Longer-term follow-up of patients is needed to determine late post-transplant complications and outcomes.

Belmoufid, N., et al. (2022). "Neutropenic Enterocolitis as a Complication of Autologous Stem Cell Transplant in Patients With Multiple Myeloma: A Case Series." Cureus **14**(4): e24475.

Neutropenic enterocolitis (NE) is a rare but severe complication occurring in neutropenic patients

undergoing intensive chemotherapy. Mortality is high, so early diagnosis is required to start urgent medical or surgical treatment. Data analysis of the development of NE after hematopoietic stem cell transplantation remains scarce. The aim of this case series is to discuss five out of 100 patients receiving autologous stem cell transplants (ASCTs) for multiple myeloma complicated with NE between 2016 and 2020 in the hematology department of the Cheikh Khalifa International University Hospital, Casablanca, Morocco. The patients were diagnosed with IgA and IgG multiple myeloma and aged between 58 to 64 years. They received induction therapy with four cycles of a triplet regimen including a proteasome inhibitor, an immunomodulatory drug, and corticosteroids, allowing a complete remission. Intensification was based on ASCT with melphalan at 200 mg/m2. The period of aplasia was marked by the sudden appearance of NE, diagnosed based on clinical, biological, and imaging criteria. Treatment included antibiotherapy and supportive care. We report no complications in our cases, nor the need for surgical care. Therefore, we consider that early diagnosis and treatment allowed a good evolution in our case series. The management of NE must be multidisciplinary associating hematologists, gastroenterologists, radiologists, and biologists. More studies and trials are needed to establish specific diagnostic criteria and better treatment options.

Belyaev, A. M., et al. (2022). "The association of socioeconomic deprivation with access and survival after hematopoietic stem cell transplantation in New Zealand." Asia Pac J Clin Oncol.

BACKGROUND: Socioeconomic deprivation (SED) is a risk factor for reduced survival of hematopoietic stem cell transplant (HSCT) recipients. This study aimed to evaluate access and long-term survival of HSCT recipients. METHODS: This was a hospital HSCT Registry-based retrospective cohort study. Patients who underwent HSCT from January 2010 to June 2020 were identified. HSCT recipients younger than 16 years of age, patients who reported their residential address as a post office box or the Department of Corrections, and those who left the country after HSCT were excluded from the study. HSCT recipients with the 2018 New Zealand deprivation index (NZDep2018) deciles 8, 9, and 10 were assigned to the higher SED group and those with NZDep2018 deciles from 1 to 7 were allocated to the lower SED group. The total number of New Zealanders in the higher and lower SED strata was obtained from the 2018 Census. RESULTS: Eight hundred fifty-one HSCT recipients met the eligibility criteria. HSCT recipients from the higher and lower SED strata of the New Zealand population had similar access to HSCT (odds ratio = .9; 95% confidence interval (CI): .77-1.04; p = .155). Mortality in the higher and lower SED groups of HSCT recipients was 9.6/100 person-years (95% CI: 7.7-12/100 person-years) and 8.1/100 person-years (95% CI: 6.9-9.4/100 person-years), respectively. The mortality ratio was 1.2 (95% CI: .9-1.6), p = .098. Both groups had similar survival. CONCLUSION: New Zealand residents from the higher and lower SED strata have similar access to HSCT. SED is not associated with reduced survival in adult HSCT recipients.

Berical, A., et al. (2022). "Generation of Airway Epithelial Cell Air-Liquid Interface Cultures from Human Pluripotent Stem Cells." J Vis Exp(184).

Diseases of the conducting airway such as asthma, cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and viral respiratory infections are major causes of morbidity and mortality worldwide. In vitro platforms using human bronchial epithelial cells (HBECs) have been instrumental to our understanding of the airway epithelium in health and disease. Access to HBECs from individuals with rare genetic diseases or rare mutations is a bottleneck in lung research. Induced pluripotent stem cells (iPSCs) are readily generated by "reprogramming" somatic cells and retain the unique genetic background of the individual donor. Recent advances allow for the directed differentiation of iPSCs to lung epithelial progenitor cells, alveolar type 2 cells, as well as the cells of the conducting airway epithelium via basal cells, the major airway stem cells. Here we outline a protocol for the maintenance and expansion of iPSC-derived airway basal cells (hereafter iBCs) as well as their trilineage differentiation in air-liquid interface (ALI) cultures. iBCs are maintained and expanded as epithelial spheres suspended in droplets of extracellular matrix cultured in a primary basal cell medium supplemented with inhibitors of TGF-ss and BMP signaling pathways. iBCs within these epithelial spheres express key basal markers TP63 and NGFR, can be purified by fluorescence activated cell sorting (FACS), and when plated on porous membranes in standard ALI culture conditions, differentiate into a functional airway epithelium. ALI cultures derived from healthy donors are composed of basal, secretory and multiciliated cells and demonstrate epithelial barrier integrity, motile cilia, and mucus secretion. Cultures derived from individuals with CF or PCD recapitulate the dysfunctional CFTR-mediated chloride transport or immotile cilia, the respective disease-causing epithelial defects. Here, we present a protocol for the generation of human cells that can be applied for modeling and understanding airway diseases.

Beynarovich, A., et al. (2022). "Favorable outcomes of allogeneic hematopoietic stem cell transplantation with

fludarabine-bendamustine conditioning and posttransplantation cyclophosphamide in classical Hodgkin lymphoma." Int J Hematol.

INTRODUCTION: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for patients with relapsed and refractory classic Hodgkin lymphoma (rrHL). However, the optimal conditioning regimen and GVHD prophylaxis for rrHL remain undetermined. The aim of this study was to investigate outcomes of allo-HSCT with a fludarabine plus bendamustine (FluBe) conditioning regimen and GVHD prophylaxis with posttransplantation cyclophosphamide (PTCY) in patients with rrHL. METHODS: Allo-HSCT results in 58 adult patients with rrHL were analyzed retrospectively. RESULTS: Three-year overall survival and event-free survival were 81% (95% CI 65-91) and 55% (95% CI 38-72), respectively. The cumulative incidence of relapse (CIR) at 3 years was 33% (95% CI 13-51). The cumulative incidence of aGVHD grade II-IV and severe aGVHD grade III-IV was 36% (95% CI 22-48) and 22% (95% CI 9-33), respectively. The cumulative incidence of cGVHD was 32% (95% CI 17-45), including moderate or severe cGVHD in 17% (95% CI 4-28). Patients who developed aGVHD after allo-HSCT had significantly lower CIR (24% vs 49%, p = 0.004). The use of PBSC as a graft source also significantly reduced CIR (4% vs 61%, p = 0.002). CONCLUSIONS: FluBe-PTCY allo-HSCT facilitates favorable outcomes, low toxicity, and mortality in rrHL.

Bhatt, N. S., et al. (2022). "Clinical Characteristics and Outcomes of COVID-19 in Pediatric and Early Adolescent and Young Adult Haematopoietic Stem Cell Transplant Recipients: A Cohort Study." Transplant Cell Ther.

BACKGROUND: Adult hematopoietic stem cell transplantation (HSCT) recipients are at a high risk of adverse outcomes after COVID-19. While children have had better outcomes after COVID-19 compared to adults, data on risk factors and outcomes of COVID-19 among pediatric HSCT recipients are lacking. OBJECTIVES: To describe the risk-factors and outcomes of COVID-19 among pediatric and early adolescent and young adult HSCT recipients STUDY DESIGN: : We describe outcomes of HSCT recipients who were </=21 years of age at COVID-19 diagnosis and were reported to the Center for International Blood and Marrow Transplant Research between March 27, 2020, and May 7, 2021. The primary outcome was overall survival after COVID-19 diagnosis. We determined risk factors of COVID-19 as a secondary outcome, in a subset of allogeneic HSCT recipients. RESULTS: A total of 167 pediatric HSCT recipients (135 allogeneic; 32 autologous HSCT recipients) were included. Median time from HSCT to COVID-19 was 15 months (IQR 7-45) for allogeneic HSCT recipients and 16 months (6-59) for autologous HSCT recipients. Median follow-up from COVID-19 diagnosis was 53 days (range 1-270) and 37 days (1-179) for allogeneic and autologous HSCT recipients, respectively. While COVID-19 was mild in 87% (n=146/167), 10% (n=16/167) of patients required supplemental oxygen or mechanical ventilation. The 45-day overall survival was 95% (95% CI 90-99) and 90% (74-99) for allogeneic and autologous HSCT recipients, respectively. Cox regression analysis showed that patients with hematopoietic cell transplant comorbidity index (HCT-CI) score of 1-2 were more likely to be diagnosed with COVID-19 (HR 1.95; 95% CI 1.03-3.69, p=0.042) compared to those with HCT-CI of 0. CONCLUSIONS: Pediatric and early adolescent and young adult HSCT recipients with pre-HSCT comorbidities were more likely to be diagnosed with COVID-19. Overall mortality, albeit higher than the reported general population estimates, was lower when compared with previously published data focusing on adult HSCT recipients.

Bostankolu Degirmenci, B., et al. (2022). "Eltrombopag may induce bone marrow fibrosis in allogeneic hematopoietic stem cell transplant recipients with prolonged thrombocytopenia." Leuk Res **118**: 106870.

Poor graft function (PGF) and secondary failure of platelet recovery (SFPR) are significant causes of transplant related morbidity and mortality. Although thrombopoietin receptor agonists (TPO-RA), particularly Eltrombopag (EPAG), have been reported to be efficacious in the treatment of prolonged thrombocytopenia, potential long term adverse effects remain to be elucidated. This retrospective study was performed to determine the efficacy and toxicity profile of TPO-RAs in allogeneic hematopoietic stem cell transplant (alloHCT) recipients. Medical records of 27 patients [median age: 55(21-73) years; male/female: 15/12] who received posttransplant EPAG for SFPR or PGF were analysed. Eltrombopag was started on day 110(33-670) after transplant. Median initial dose was 25(25-50) mg/day which was properly escalated to a maximum dose of 75(50-100) mg/day. Duration of the treatment was median 120(31-377) days. Overall response rate (ORR) was 59.3% in the study population. Time-to-treatment response was 42(3-170) days. Mild-to-moderate bone marrow fibrosis was detected in the posttreatment biopsies of 12/22 patients (54.5%), 9 of whom did not represent any grade of myelofibrosis in their inital biopsies. The grade of posttreatment fibrosis was significantly increased when time-to-treatment response was longer (p = 0.008). Long term use of TPO-RAs may be considered as a potential cause of myelofibrosis in alloHCT recipients.

Boukouaci, W., et al. (2022). "Non-Classical HLA Determinants of the Clinical Response after Autologous Stem Cell Transplantation for Systemic Sclerosis." Int J Mol Sci **23**(13).

Systemic Sclerosis (SSc) is a chronic autoimmune disease with high morbidity and mortality. Autologous Hematopoietic Stem Cell Transplantation (AHSCT) is the best therapeutic option for rapidly progressive SSc, allowing increased survival with regression of skin and lung fibrosis. The immune determinants of the clinical response after AHSCT have yet to be well characterized. In particular, the pivotal role of the Human Leukocyte Antigen (HLA) system is not well understood, including the role of non-classical immuno-modulatory HLA-E and HLA-G molecules in developing tolerance and the role of Natural Killer cells (NK) in the immunomodulation processes. We retrospectively tested whether the genetic and/or circulating expression of the non-classical HLA-E and HLA-G loci, as well as the imputed classical HLA determinants of HLA-E expression, influence the observed clinical response to AHSCT at 12- and 24-month follow-up. In a phenotypically well-defined sample of 46 SSc patients classified as clinical responders or non-responders, we performed HLA genotyping using next-generation sequencing and circulating levels of HLA-G and quantified HLA-E soluble isoforms by ELISA. The -21HLA-B leader peptide dimorphism and the differential expression level of HLA-A and HLA-C alleles were imputed. We observed a strong trend towards better clinical response in HLA-E*01:03 or HLA-G 14bp Del allele carriers, which are known to be associated with high expression of the corresponding molecules. At 12-month post-AHSCT follow-up, higher circulating levels of soluble HLA-E were associated with higher values of modified Rodnan Skin Score (mRSS) ($p = 0.0275$), a proxy of disease severity. In the non-responder group, the majority of patients carried a double dose of the HLA-B Threonine leader peptide, suggesting a non-efficient inhibitory effect of the HLA-E molecules. We did not find any correlation between the soluble HLA-G levels and the observed clinical response after AHSCT. High imputed expression levels of HLA-C alleles, reflecting more efficient NK cell inhibition, correlated with low values of the mRSS 3 months after AHSCT ($p = 0.0087$). This first pilot analysis of HLA-E and HLA-G immuno-modulatory molecules suggests that efficient inhibition of NK cells contributes to clinical response after AHSCT for SSc. Further studies are warranted in larger patient cohorts to confirm our results.

Bronte, G., et al. (2022). "The application of cancer stem cell model in malignant mesothelioma." Crit Rev Oncol Hematol **174**: 103698.

The high mortality rate of malignant pleural mesothelioma led to study the mechanisms for chemoresistance. The cancer stem cell (CSC) model has been proposed to explain chemoresistance. CSCs are characterized by self-renewal capacity, that is detected through tumor-initiating cell assays. As in other malignancies, many studies sought to identify surface markers to isolate CSCs from malignant mesothelioma. Other studies characterized malignant mesothelioma CSCs for the expression of specific genes involved in stemness and the expression of proteins involved in chemoresistance. However, the main methods to characterize isolated CSCs include sphere formation, invasiveness, tumor-initiating capacity and expression of specific surface markers. The better knowledge of malignant mesothelioma CSCs allowed exploring new potential targets to develop specific treatments.

Buder, K., et al. (2022). "Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in children and adolescents." Cochrane Database Syst Rev **6**: CD009898.

BACKGROUND: Chronic graft-versus-host disease (cGvHD) is a major cause of morbidity and mortality after haematopoietic stem cell transplantation, occurring in 6% to 65% of the paediatric recipients. Currently, the therapeutic mainstay for cGvHD is treatment with corticosteroids, frequently combined with other immunosuppressive agents in people with steroid-refractory manifestations. There is no established standard treatment for steroid-refractory cGvHD. The therapeutic options for these patients include extracorporeal photopheresis (ECP), an immunomodulatory treatment that involves ex vivo collection of mononuclear cells from peripheral blood, exposure to the photoactive agent 8-methoxypsoralen, ultraviolet radiation and re-infusion of the processed cell product. The mechanisms of action of ECP are not completely understood. This is the second update of a Cochrane Review first published in 2014 and first updated in 2015. OBJECTIVES: To evaluate the effectiveness and safety of ECP for the management of cGvHD in children and adolescents after haematopoietic stem cell transplantation. SEARCH METHODS: We searched the Cochrane Register of Controlled Trials (CENTRAL) (2021), MEDLINE (PubMed) and Embase databases from their inception to 25 January 2021. We searched the reference lists of potentially relevant studies without any language restrictions. We searched five conference proceedings and nine clinical trial registries on 9 November 2020

and 12 November 2020, respectively. SELECTION CRITERIA: We aimed to include randomised controlled trials (RCTs) comparing ECP with or without alternative treatment versus alternative treatment alone in children and adolescents with cGvHD after haematopoietic stem cell transplantation. DATA COLLECTION AND ANALYSIS: Two review authors independently performed the study selection. We resolved disagreements in the selection of trials by consultation with a third review author. MAIN RESULTS: We found no studies meeting the criteria for inclusion in this 2021 review update. AUTHORS' CONCLUSIONS: We could not evaluate the efficacy of ECP in the treatment of cGvHD in children and adolescents after haematopoietic stem cell transplantation since the second review update again found no RCTs. Current recommendations are based on retrospective or observational studies only. Thus, ideally, ECP should be applied in the context of controlled trials only. However, performing RCTs in this population will be challenging due to the limited number of eligible participants, variable disease presentation and the lack of well-defined response criteria. International collaboration, multicentre trials and appropriate funding for such trials will be needed. If treatment decisions based on clinical data are made in favour of ECP, recipients should be carefully monitored for beneficial and harmful effects. In addition, efforts should be made to share this information with other clinicians, for example by setting up registries for children and adolescents treated with ECP.

Busmail, A., et al. (2022). "A Systematic Review on Pulmonary Complications Secondary to Hematopoietic Stem Cell Transplantation." Cureus **14**(5): e24807.

The main purpose of this systematic review was to identify and synthesize evidence about pulmonary complications following stem cell transplantation to raise awareness among physicians since it is a lesser-known topic. Studies that included targeted pulmonary complications that occurred after stem cell transplantation; in humans; and were randomized controlled trials, cohort studies, and case studies between January 2011 and 2021. Fifteen intervention features were identified and analyzed in terms of their association with successful or unsuccessful interventions. Fifteen of 15 studies that met inclusion criteria had positive results. Features that appeared to have the most consistent positive effects included relevant information consisting of clinical presentations and management of complications. Hematopoietic stem cell transplantation is a therapeutic method that has been introduced for various hematological diseases. Its main objective is to restore the hematopoietic function that has been eradicated or affected. The stem cell transplantation requires a period of administration of chemotherapeutic agents that may lead to infectious and/or non-infectious pulmonary complications that require follow-up. Noninfectious pulmonary complications include bronchiolitis obliterans, alveolar hemorrhage, fibroelastosis, pulmonary hypertension, and infections. Bronchiolitis obliterans syndrome is an obstructive lung disease that affects the small airways, reducing lung function, and it's the most frequent late-onset complication. Furthermore, diffuse pulmonary hemorrhage is a fatal adverse effect and the most common noninfectious pulmonary complication of acute leukemia, observed within the first weeks after the procedure. Pulmonary hypertension has multiple etiologies, mainly related to the pulmonary veno-occlusive disease. It carries a poor prognosis, with a 55% mortality rate. The area of hematology is very wide and prone to new development of treatments and procedures that could be available for new emerging diseases and improving survival rates.

Cao, X. H., et al. (2022). "Donor CSF3R with the rs3917980A/G or G/G genotype is correlated with better leukemia-free survival after allogenic hematopoietic stem cell transplantation." Genes Immun.

Polymorphisms in the granulocyte colony-stimulating factor receptor gene (GCSFR, CSF3R) have been reported to be associated with peripheral blood stem cell enrichment and hematological diseases. The aim of our study was to investigate the effects of donor CSF3R allelic polymorphisms on the outcomes of allogeneic stem cell transplantation. A total of 273 patients who were diagnosed with hematological diseases and treated with allogeneic hematopoietic stem cell transplantation(allo-HSCT) were enrolled in this study. Single-nucleotide polymorphisms in CSF3R were genotyped by targeted next-generation sequencing. There were six types of CSF3R genotypes with percentages over 1%. LFS and OS analyses showed that recipients receiving grafts from healthy donors with a rs3917980 G/G or A/G genotype had higher LFS rates than those receiving grafts from donors carrying a rs22754272 T/C genotype and the double-negative group ($p = 0.036$). Univariate cox analysis showed that donor CSF3R with the rs2275472 T/C genotype was associated with higher transplantation-related mortality (TRM) rates (HR = 2.853, 95% CI: 1.405-5.792, $p = 0.00371$) and lower rates of leukemia-free survival (LFS) (HR = 1.846; 95% CI: 1.018-3.347, $p = 0.0435$). In addition, donor CSF3R with the rs3917980G/G or A/G genotype was associated with better overall survival (OS) rates (HR = 0.560, 95% CI: 0.3162-0.9916, $p = 0.047$) and lower TRM rates (HR = 0.497, 95% CI: 0.2628-0.9397, $p = 0.0315$). Furthermore, multivariate cox analysis found

that rs2275472 T/C genotype was an independent risk factors for TRM rates (HR = 3.210, 95% CI: 1.573-6.55, p = 0.001), while no statistical difference was found between rs3917980G/G or A/G genotype and clinical outcomes. Our findings demonstrate the important prognostic value of genetic variations in donor CSF3R to predict clinical outcomes in patients undergoing allo-HSCT.

Chapchap, E. C., et al. (2022). "Need for hemodialysis in patients undergoing hematopoietic stem cell transplantation: risk factors and survival in a retrospective cohort." Hematol Transfus Cell Ther.

INTRODUCTION: Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) patients are exposed to acute and chronic nephrotoxic events (drugs, hypotension, infections, and microangiopathy). The need for hemodialysis (HD) may be associated with high mortality rates. However, the risk factors and clinical impact of HD are poorly understood. AIM: To analyze survival and risk factors associated with HD in allo-HSCT Patients and methods: single-center cohort study 185 (34 HD cases versus 151 controls) consecutive adult allo-HSCT patients from 2007-2019. We performed univariate statistical analysis, then logistic regression and competing risk regression were used to multivariate analysis. Survival was analyzed by Kaplan-Meier and Cox proportional-hazards models. RESULTS: The one-year HD cumulative incidence was 17.6%. Univariate analysis revealed that HD was significantly associated with male gender, age (p 0.056), haploidentical donor, grade II-IV acute GVHD, polymyxin B, amikacin, cidofovir, microangiopathy, septic shock (norepinephrine use) and steroid exposure. The median days of glycopeptides exposure (teicoplanin/vancomycin) was 16 (HD) versus 10 (no HD) (p 0.088). In multivariate analysis, we found: norepinephrine (hazard ratio, HR:3.3; 95% confidence interval, 95%CI:1.2-8.9; p 0.024), cidofovir drug (HR:11.0; 95%CI:4.6- 26.0; p < 0.001), haploidentical HSCT (HR:1.94; 95%CI:0.81-4.65; p 0.14) and Age (HR:1.01; 95%CI: 0.99-1.03; p 0.18) . The HD group had higher mortality rate (HR:6.68; 95% CI: 4.1-10.9; p < 0.001). CONCLUSION: HD was associated with decreased survival in allo-HSCT. Carefully use of nephrotoxic drugs and improving immune reconstitution could reduce severe infections (shock) and patients requiring cidofovir, which taken together may result in lower rates of HD, therefore improving survival.

Chavda, V. and S. Patel (2022). "Hyperglycaemic Metabolic Complications of Ischemic Brain: Current therapeutics, anti-diabetics and stem cell therapy." CNS Neurol Disord Drug Targets.

Stroke is the leading cause of morbidity and mortality in diabetic patients. Diabetes alters endothelial function and disrupts brain pathways, resulting in a variety of systemic metabolic complications. Diabetics not only have impaired neurotransmission, but they also have progressive neurodegeneration, which leads to long-term neurological complications. Diabetes risk factors and physiology alter the frequency and severity of cardiovascular and cerebrovascular events, necessitating more hospitalizations. Stroke and diabetes have a mutually reinforcing relationship that worsens their outcomes. Diabetes has far-reaching systemic consequences for human physiology as a metabolic syndrome. As a result, diabetic stroke patients require dual-therapeutics with dual protection. Scientific researchers have made tremendous progress in diabetes-related stroke and its therapeutics over the last few decades. We have summarised diabetic brain and associated risk factors, co-morbidities, biomarkers and hyperglycemia associated neurovascular insult and cognitive demur. In addition to providing an overview of the effects of hyperglycaemia on brain physiology, this article aims to summarise the evidence from current glucose-lowering treatment, recent advances in stroke therapeutics as well as exploring stem cell therapy in the management of diabetes associated stroke.

Chen, L., et al. (2022). "MiR-199a-3p in mouse bone marrow mesenchymal stem cell exosomes increases epithelial sodium channel expression in lung injury." Fundam Clin Pharmacol.

Acute lung injury (ALI) causes significant morbidity and mortality in critically ill patients, which often presents with extensive accumulation of activated inflammatory cells and diffused alveolar damage accompanied by oxidative stress. Exosomes are nanovesicles, which have notable anti-inflammatory and repair properties, thus alleviating the symptoms of ALI. Epithelial sodium channel (ENaC) is essential for the transepithelial absorption of Na(+) and fluid from alveolar spaces. We studied the effects of bone marrow mesenchymal stem cell exosomes (BMSC-exo) on the apoptosis and protein expression of ENaC in primary mouse alveolar epithelial type 2 cells (AT 2 cells). Moreover, the change of miR-199a-3p in AT 2 cells was detected by qRT-PCR, and we studied the regulation of miR-199a-3p on ENaC protein expression. Our results demonstrated that BMSC-exo could not only improve viability and reduce apoptosis in AT 2 cells, but also enhance the expression of ENaC protein and miR-199a-3p. Meanwhile, the upregulation of miR-199a-3p resulted in increased expression of ENaC protein. In summary, the BMSC-exo could participate in the regulation of ENaC through miR-199a-3p

originated from BMSC-exo, thereby providing a new pharmacological tool for the treatment of ALI.

Chiesa, R. and M. E. Bernardo (2022). "Haematopoietic stem cell gene therapy in inborn errors of metabolism." Br J Haematol **198**(2): 227-243.

Over the last 30 years, allogeneic haematopoietic stem cell transplantation (allo-HSCT) has been adopted as a therapeutic strategy for many inborn errors of metabolism (IEM), due to the ability of donor-derived cells to provide life-long enzyme delivery to deficient tissues and organs. However, (a) the clinical benefit of allo-HSCT is limited to a small number of IEM, (b) patients are left with a substantial residual disease burden and (c) allo-HSCT is still associated with significant short- and long-term toxicities and transplant-related mortality. Haematopoietic stem/progenitor cell gene therapy (HSPC-GT) was established in the 1990s for the treatment of selected monogenic primary immunodeficiencies and over the past few years, its use has been extended to a number of IEM. HSPC-GT is particularly attractive in neurodegenerative IEM, as gene corrected haematopoietic progenitors can deliver supra-physiological enzyme levels to difficult-to-reach areas, such as the brain and the skeleton, with potential increased clinical benefit. Moreover, HSPC-GT is associated with reduced morbidity and mortality compared to allo-HSCT, although this needs to be balanced against the potential risk of insertional mutagenesis. The number of clinical trials in the IEM field is rapidly increasing and some HSPC-GT products recently received market approval. This review describes the development of ex vivo HSPC-GT in a number of IEM, with a focus on recent results from GT clinical trials and risks versus benefits considerations, when compared to established therapeutic strategies, such as allo-HSCT.

Cioce, M., et al. (2022). "Nutritional status and quality of life in adults undergoing allogeneic hematopoietic stem cell transplantation." Int J Hematol.

Although the effects of malnutrition on morbidity and mortality in adult patients undergoing allogeneic hematopoietic stem cell transplantation are clear, the relationship with quality of life (QOL) is less clear. The purpose of this study was to assess the relationship between malnutrition and QOL. A prospective observational study was conducted in 36 adult patients undergoing allogeneic hematopoietic stem cell transplantation. Adapted criteria of the Global Leadership Initiative on malnutrition have been used for the diagnosis of malnutrition in clinical settings. A cancer linear analog scale was used to assess QOL. Overall QOL at 14 days after allogeneic hematopoietic stem cell transplantation was 37.1 (95% CI 2.9-45.39) in patients without severe malnutrition, versus 16.0 (95% CI - 6.6 to 38.6) in patients with severe malnutrition ($p = 0.05$). At discharge, it was 48.0 (95% CI 38.4-57.6) versus 34.0 (95% CI 4.1-63.9) ($p = 0.27$). The results of our study suggest that patients with severe malnutrition at discharge tend to have worse QOL. A larger cohort of patients is required to confirm this hypothesis.

de Sousa Arantes Ferreira, G., et al. (2022). "Liver Transplantation After Hematopoietic Stem Cell Transplant for the Treatment of Sickle Cell Disease: A Case Report." Transplant Proc.

Sickle cell anemia is the most common of the hemoglobinopathies, in which the abnormal hemoglobin formed in deoxygenation states undergoes a polymerization process with consequent erythrocyte deformation and vaso-occlusive events. The need for multiple blood transfusions, prolonged ineffective erythropoiesis, hemolysis, and increased iron absorption can cause iron overload in the liver, leading to liver fibrosis. Hematopoietic stem cell transplantation (HSCT) is currently the only treatment with a curative potential for this disease and can establish normal complete or partial donor-derived erythropoiesis and stabilize or restore function in affected organs, preventing further deterioration of function. However, it does not reverse preexisting liver fibrosis and siderosis. One of the possible complications of patients who undergo HSCT is chronic liver disease, which has a multifactorial cause, with iron overload being an important factor. In the long term, the prevalence of chronic liver disease in HSCT patients, including cirrhosis and its complications, can be significant. Solid organ transplantation after allogeneic hematopoietic cell transplantation for end-organ failure remains a very rare event. It may offer a valuable treatment strategy in selected recipients, although it is associated with significant morbidity and mortality. We report the case of a patient with sickle cell anemia who underwent HSCT and developed severe liver dysfunction requiring liver transplantation 13 years after the procedure. We found no previous report in the literature of orthotopic liver transplant after HCT for the treatment of sickle cell disease.

Flor-Park, M. V., et al. (2022). "Is Severity Score Associated with Indication for Hematopoietic Stem Cell Transplantation in Individuals with Sickle Cell Anemia?" Transplant Cell Ther.

BACKGROUND: Manifestations of sickle cell disease (SCD) begin early in childhood and cause morbidity and decreased life expectancy. Hematopoietic stem cell transplantation (HSCT) is curative but associated with risk of mortality

attributable to the transplant. This risk should be counterbalanced with SCD morbidity and mortality. A severity score using a Bayesian network model was previously validated to predict the risk of death in adult individuals with SCD. OBJECTIVE(S): The objective of this study is to calculate the severity scores of participants in a multi-center cohort of Brazilians with SCD, using a previously published Bayesian network-derived score, associated with risk of death and then compare the severity scores between participants with and without an indication for hematopoietic stem cell transplantation (HSCT) as defined by the Brazilian Ministry of Health (MoH) criteria. STUDY DESIGN: This is an observational, retrospective study. We analyzed 2063 individuals with sickle cell anemia (SS, SBeta0) from the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) Brazil SCD cohort and applied a Bayesian network-derived score to compare candidates and non- candidates for HSCT according to the Brazilian MoH transplant criteria. Classical statistical methods were used to analyze data and make comparisons. RESULTS: We compared severity scores between cohort members with (n=431) and without (n=1632) HSCT indications according to Brazilian MoH. Scores were not different in adult participants with >/=1 HSCT indication when compared to those with no indication (mean= 0.342 vs. 0.292; median=0.194 vs. 0.183, p=0.354) and ROC curves did not demonstrate an obvious threshold to differentiate participants with or without HSCT indications. CONCLUSION(S): Severity score may predict risk of death but does not differentiate HSCT candidates. Current indications should be evaluated to ensure patients with more severe disease who might benefit from HSCT are appropriately identified.

Foster, B. M., et al. (2022). "Bone Marrow-Derived Stem Cell Factor Regulates Prostate Cancer-Induced Shifts in Pre-Metastatic Niche Composition." Front Oncol **12**: 855188.

Skeletal metastasis is the leading cause of morbidity and mortality in prostate cancer, with 80% of advanced prostate cancer patients developing bone metastases. Before metastasis, bone remodeling occurs, stimulating pre-metastatic niche formation and bone turnover, and platelets govern this process. Stem cell factor (SCF, Kit Ligand) is increased in advanced prostate cancer patient platelet releasates. Further, SCF and its receptor, CD117/c-kit, correlate with metastatic prostate cancer severity. We hypothesized that bone-derived SCF plays an important role in prostate cancer tumor communication with the bone inducing pre-metastatic niche formation. We generated two cell-specific SCF knockout mouse models deleting SCF in either mature osteoblasts or megakaryocytes and platelets. Using two syngeneic androgen-insensitive murine prostate cancer cell lines, RM1 (Ras and Myc co-activation) and mPC3 (Pten and Trp53 deletion), we examined the role of bone marrow-derived SCF in primary tumor growth and bone microenvironment alterations. Platelet-derived SCF was required for mPC3, but not RM1, tumor growth, while osteoblast-derived SCF played no role in tumor size in either cell line. While exogenous SCF induced proangiogenic protein secretion by RM1 and mPC3 prostate cancer cells, no significant changes in tumor angiogenesis were measured by immunohistochemistry. Like our previous studies, tumor-induced bone formation occurred in mice bearing RM1 or mPC3 neoplasms, demonstrated by bone histomorphometry. RM1 tumor-bearing osteoblast SCF knockout mice did not display tumor-induced bone formation. Bone stromal cell composition analysis by flow cytometry showed significant shifts in hematopoietic stem cell (HSC), mesenchymal stem cell (MSC), and osteoblast cell percentages in mice bearing RM1 or mPC3 tumors. There were no significant changes in the percentage of macrophages, osteoclasts, or osteocytes. Our study demonstrates that megakaryocyte/platelet-derived SCF regulates primary mPC3 tumor growth, while SCF originating from osteoblasts plays a role in bone marrow-derived progenitor cell composition and pre-metastatic niche formation. Further, we show that both the source of SCF and the genetic profile of prostate cancer determine the effects of SCF. Thus, targeting the SCF/CD117 signaling axis with tyrosine kinase inhibitors could affect primary prostate carcinomas or play a role in reducing bone metastasis dependent on the gene deletions or mutations driving the patients' prostate cancer.

Galan Gomez, V., et al. (2022). "Experience of the Spanish Group for Hematopoietic Transplantation (GETMON-GETH) in allogenic Hematopoietic stem cell Transplantation in Philadelphia acute lymphoblastic leukemia." An Pediatr (Engl Ed) **96**(4): 309-318.

INTRODUCTION: Outcomes in patients diagnosed of acute lymphoblastic leukemia with Philadelphia chromosome (Ph-ALL) remains unfavourable compared to other subtypes of acute lymphoblastic leukemia despite improvements in drug treatments as well as advances in hematopoietic stem cell transplantation (HSCT). PATIENTS AND METHODS: The role of allogeneic HSCT in Ph-ALL patients has been analysed through a multicentric study where data belonging to 70 patients diagnosed of this entity in different centers that received HSCT between years 1998 and 2014, were reported by the Grupo Espanol de Trasplante Hematopoyetico (GETH). RESULTS: The performance of HSCT from year 2004, in first complete remission (CR) status with

thymoglobulin (ATG) based conditioning had a favorable impact on overall survival (OS). HSTC performance from year 2004, in first CR with ATG-based conditioning in addition to acute graft versus host disease (aGvHD) development, increased event free survival (EFS). Treatment with imatinib as well as undetectable minimal residual disease (MRD) prior to HSCT, combined with aGvHD, reduced risk of relapse (RR). Patient age less than 10 years when HSCT, first CR and ATG-based conditioning were associated to a lower transplant related mortality (TRM). CONCLUSIONS: Patients that could achieve first CR that also received ATG-based conditioning had a better OS and EFS, so HSCT should be considered for this group of patients.

Gao, G., et al. (2022). "Circ_0006790 carried by bone marrow mesenchymal stem cell-derived exosomes regulates S100A11 DNA methylation through binding to CBX7 in pancreatic ductal adenocarcinoma." Am J Cancer Res **12**(5): 1934-1959.

Extracellular vesicles, particularly exosomes, play a vital role via their cargoes. Their potential in pancreatic ductal adenocarcinoma (PDAC), one of the leading causes of cancer-related mortality worldwide is attracting interests. However, the roles and underlying mechanisms of exosomal circular RNAs (circRNAs) in the development of PDAC remain unclear yet. We aimed to illuminate the mechanisms of exosomal hsa_circ_0006790 (thereafter termed circ_6790) released by exosomes (Exo) derived from bone marrow mesenchymal stem cell (BM-MSC) during immune escape in PDAC in this study. BM-MSC-derived Exo inhibited growth, metastasis, and immune escape in PDAC. Exo enhanced circ_6790 expression in PDAC cells. Knockdown of circ_6790 in Exo significantly attenuated the anti-tumor effect of Exo. Circ_6790 facilitated the nuclear translocation of chromobox 7 (CBX7). CBX7 increased the DNA methylation of S100A11 by recruiting DNA methyltransferases to its promoter region, thereby inhibiting the transcription of S100A11. Inhibition of CBX7 or overexpression of S100A11 annulled the inhibitory effects of Exo on PDAC growth, metastasis, and immune escape. In conclusion, our results suggest that MSC-derived exosomal circ_6790 could downregulate S100A11 in PDAC cells and hamper immune escape via CBX7-catalyzed DNA hypermethylation.

Ge, J., et al. (2022). "Relationship of Oropharyngeal Colonization Microorganisms to Clinical Outcomes within 100 Days after Allogeneic Hematopoietic Stem Cell Transplantation." Transplant Cell Ther.

Little is known about oropharyngeal colonization microorganisms in patients during allogeneic hematopoietic stem cell transplantation (allo-HSCT), and updated epidemiologic investigations are advisable. This study aimed to characterize oropharyngeal colonization microorganisms in patients during allo-HSCT and confirm whether they were related to clinical outcomes. This retrospective, matched case-control study included 1267 consecutive patients undergoing allo-HSCT between January 2018 and December 2020 at our institution. Patients with oropharyngeal colonization microorganisms were those with a positive throat swab before or on the day of transplantation without the occurrence of any symptoms of infection. Propensity score matching was used. Characteristics of oropharyngeal colonization microorganisms were evaluated among patients in the transplant medicine wards and compared with clinical outcomes within 100 days in positive and negative colonization groups. A total of 127 patients had oropharyngeal colonization microorganisms before or on the day of transplantation. Using propensity score matching, we matched the 127 patients in the positive colonization group with 508 patients in the negative colonization group at a 1:4 ratio (total of 635 cases). None of the differences in clinical traits between the 2 groups remained significant. Among the 127 patients with oropharyngeal colonization microorganisms, 90 patients suffered from the documented infection subsequently, and the others were asymptomatic. A total of 82 single gram-negative bacteria were identified in 127 isolates. There were no differences between the positive and negative colonization groups in the occurrence of oral mucositis, Epstein-Barr virus, or acute graft-versus-host disease and relapse within 100 days. However, the rate of neutrophil or platelet recovery was significantly lower in the positive colonization group compared with the negative colonization group (hazard ratio [HR], .71; 95% confidence interval [CI], .59 to .84; $P < .001$; HR .69; 95% CI, .58 to .83; $P = .003$; separately). The risk of bloodstream infection was higher in the positive colonization group compared with the negative colonization group (HR, 6.09; 95% CI, 3.16 to 11.75; $P < .001$). The continency rate between the bacteria isolated from the blood samples and oropharyngeal colonization microorganisms among the patients with positive results was 73.3%. Patients in the positive colonization group were more vulnerable to cytomegalovirus infection compared with the negative colonization group (HR, 1.41; 95% CI, 1.00 to 1.99; $P = .049$). The nonrelapse mortality at day +100 was higher in the positive colonization group (HR, 3.46; 95% CI, 1.69 to 7.08; $P < .001$). The survival probability within 100 days was significantly lower in the positive colonization group (HR, 3.38; 95% CI, 1.78 to 6.41; $P < .001$). Our data show that the presence of oropharyngeal colonization microorganisms is related to clinical outcomes, and that oropharyngeal

microorganism monitoring may be useful during allo-HSCT.

Ghimire, S., et al. (2022). "Low Intestinal IL22 Associates With Increased Transplant-Related Mortality After Allogeneic Stem Cell Transplantation." Front Immunol **13**: 857400.

The role of IL-22 in adult patients undergoing allogeneic stem cell transplantation (SCT) is of major interest since animal studies showed a protective and regenerative effect of IL-22 in graft versus host disease (GvHD). However, no clinical data exist on the tissue expression. Here we demonstrate that patients not suffering from transplant-related mortality (TRM) show significantly upregulated IL22 expression during histological and clinical GI-GvHD ($p = 0.048$ and $p = 0.022$, respectively). In contrast, in GvHD patients suffering from TRM, IL22 was significantly lower ($p = 0.007$). Accordingly, lower IL22 was associated with a higher probability of TRM in survival analysis ($p = 0.005$). In a multivariable competing risk Cox regression analysis, low IL22 was identified as an independent risk factor for TRM ($p = 0.007$, hazard ratio 2.72, 95% CI 1.32 to 5.61). The expression of IL22 seemed to be microbiota dependent as broad-spectrum antibiotics significantly diminished IL22 expression ($p = 0.019$). Furthermore, IL22 expression significantly correlated with G-protein coupled receptor (GPR)43 ($r = 0.263$, $p = 0.015$) and GPR41 expression ($r = 0.284$, $p = 0.009$). In conclusion, our findings reveal an essential role of IL-22 for the prognosis of patients undergoing allogeneic SCT.

Giglio, F., et al. (2022). "Defibrotide Prophylaxis of Sinusoidal Obstruction Syndrome in Adults Treated With Inotuzumab Ozogamicin Prior to Hematopoietic Stem Cell Transplantation." Front Oncol **12**: 933317.

Sinusoidal Obstruction Syndrome (SOS) is a life threatening HSCT complication and it can rapidly evolve in Multiple Organ Dysfunction Syndrome, with a mortality exceeding 80%. Early treatment with defibrotide is the leading factor for efficacy. Its prophylactic use is recommended in the pediatric setting, but its value isn't validated for adults, although factors for individual risk assessment are debated. We here present a real-world experience of Defibrotide prophylaxis in adults at very high risk of SOS. We treated with prophylactic Defibrotide and Ursodeoxycholic Acid seven patients receiving allogeneic HSCT for high risk B-ALL, previously treated with single agent Inotuzomab-Ozogamicin. They all had other high risk factors for SOS such as previous hepatotoxicity, previous allo-HSCT, double alkylating conditioning. All patients received Treosulfan-Fludarabine conditioning, Thiotepa was added in 4 patients and 4GyTBI in 2 patients. GvHD prophylaxis included post-transplant cyclophosphamide, rapamycin and mycophenolate. Donor source was PBSC. Five patients received family MMRD transplant, 1 patient a MRD transplant and 1 patient a MUD transplant. Non-severe gastrointestinal bleeding occurred in two patients requiring defibrotide temporarily discontinuation. SOS occurred in 3/7 cases within 21 days after HSCT and no late-onset SOS were diagnosed. SOS caused death in all cases. All three patients were characterized by a common pattern of very high risk factors by prior HSCT, they all received a myeloablative conditioning with Treosulfan-Thiotepa and a MMRD transplant. Defibrotide prophylaxis apparently failed to protect against the development of SOS in those patients treated with a double alkylator-based conditioning regimen, while a possible efficacy for the other high-risk patients is debatable.

Grain, A., et al. (2022). "Hematopoietic stem cell transplantation for acute lymphoblastic leukemia: why do adolescents and young adults outcomes differ from those of children? A retrospective study on behalf of the Francophone Society of Stem Cell Transplantation and Cellular Therapy (SFGM-TC)." J Cancer Res Clin Oncol.

PURPOSE: In the acute lymphoblastic leukemia (ALL) landscape, adolescents and young adults (AYA) often present high-risk diseases and increased chemotherapy-related toxicity. Studies analyzing the outcomes of AYA after hematopoietic stem cell transplantation (HSCT) are scarce. Our study aimed to compare the outcomes of children and AYA with ALL after HSCT and to determine the factors influencing potential differences. METHOD: 891 patients, from the SFGM-TC registry, aged between 1 and 25 years who received HSCT between 2005 and 2012 were included. The outcomes of AYA were compared to the ones of their younger counterparts. RESULTS: Five-year OS and GRFS were lower in AYA: 53.1% versus 64% and 36% versus 47% ($p = 0.0012$ and $p = 0.007$, respectively). WhileCIR was similar in both groups, 5 year-treatment related mortality was higher in AYA: 19% versus 13% ($p = 0.04$). The lower GRFS in AYA was mainly explained by a higher chronic graft versus host disease (cGvHD) incidence: 32% versus 19% ($p < 0.001$). Use of peripheral blood stem cells and use of anti-thymoglobulin appeared to be the main factors impacting cGvHD occurrence in AYA. CONCLUSION: AYA have worse outcomes than children after HSCT for ALL because of a greater risk of TRM due to cGvHD. HSCT practices should be questioned in this population.

Gustine, J. N., et al. (2022). "Predictors of hematologic response and survival with stem cell transplantation in

AL amyloidosis: A 25-year longitudinal study." Am J Hematol.

High-dose melphalan and stem cell transplantation (HDM/SCT) is an effective treatment for selected patients with AL amyloidosis. We report the long-term outcomes of 648 patients with AL amyloidosis treated with HDM/SCT over 25 years. Hematologic CR was achieved by 39% of patients. The median duration of hematologic CR was 12.3 years, and 45% of patients with a hematologic CR had no evidence of a recurrent plasma cell dyscrasia at 15 years after HDM/SCT. With a median follow-up interval of 8 years, the median event-free survival (EFS) and overall survival (OS) were 3.3 and 7.6 years, respectively. Patients with a hematologic CR had a median OS of 15 years, and 30% of these patients survived >20 years. On multivariable analysis, dFLC >180 mg/L and BM plasma cells >10% were independently associated with shorter EFS, whereas BNP >81 pg/mL, troponin I > 0.1 ng/mL, and serum creatinine >2.0 mg/dL were independently associated with shorter OS. We developed a prognostic score for EFS, which incorporated dFLC >180 mg/L and BMPC% >10% as adverse risk factors. Patients with low-risk (0 factors), intermediate-risk (1 factor), and high-risk (2 factors) disease had median EFS estimates of 5.3, 2.8, and 1.0 years, respectively ($p < .001$). The 100-day treatment-related mortality rate was 3% in the latest treatment period (2012-2021), and the 25-year risk of t-MDS/AML was 3%. We conclude that HDM/SCT induces durable hematologic responses and prolonged survival with improved safety in selected patients with AL amyloidosis.

Gutierrez, A., et al. (2022). "Allogeneic Stem Cell Transplantation in Mantle Cell Lymphoma; Insights into Its Potential Role in the Era of New Immunotherapeutic and Targeted Therapies: The GETH/GELTAMO Experience." Cancers (Basel) **14**(11).

Allo-SCT is a curative option for selected patients with relapsed/refractory (R/R) MCL, but with significant NRM. We present the long-term results of patients receiving allo-SCT in Spain from March 1995 to February 2020. The primary endpoints were EFS, OS, and cumulative incidence (CI) of NRM, relapse, and GVHD. We included 135 patients, most (85%) receiving RIC. After a median follow-up of 68 months, 5-year EFS and OS were 47 and 50%, respectively. Overall and CR rates were 86 and 80%. The CI of relapse at 1 and 3 years were 7 and 12%. NRM at day 100 and 1 year were 17 and 32%. Previous ASCT and Grade 3-4 aGVHD were associated with a higher NRM. Grade 3-4 aGVHD, donor type (mismatch non-related), and the time-period 2006-2020 were independently related to worse EFS. Patients from 1995-2005 were younger, most from HLA-identical sibling donors, and were pretreated less. Our data confirmed that allo-SCT may be a curative option in R/R MCL with low a CI of relapse, although NRM is still high, being mainly secondary to aGVHD. The arrival of new, highly effective and low toxic immunotherapeutic or targeted therapies inevitably will relegate allo-SCT to those fit patients who fail these therapies, far away from the optimal timing of treatment.

Hamada, R., et al. (2022). "Intramuscular adipose tissue content predicts patient outcomes after allogeneic hematopoietic stem cell transplantation." Transplant Cell Ther.

During clinical courses involving allogeneic hematopoietic stem cell transplantation (allo-HSCT), multidisciplinary assessments for patients including physical functions are indispensable, and quantitative skeletal muscle loss is a poor prognostic marker. In addition, deteriorating quality of muscle due to intra-muscle adipose tissue degeneration can be important as well, because many patients are cachexic or sarcopenic before allo-HSCT, although this approach has not been employed yet. Therefore, we conducted a retrospective cohort study to evaluate the quality, as well as quantity of skeletal muscle using computed tomography (CT). Psoas muscle mass index (PMI) and radiographic density (RD) calculated by cross-sectional area and averaged CT values of the psoas major muscle at the umbilical level were used to determine the quantity and quality of muscle, respectively. In total, 186 adult patients, aged 17-68 years (median, 49) were included in this study, and 46 (24.7%) and 49 (26.3%) patients were assigned to the lower PMI and RG groups. Low RD was identified as an independent risk factor for poor overall survival after allo-HSCT (adjusted hazard ratio 2.54, $p<0.01$), while PMI was not significant. Decreased RD along with reduced 6-min walking distance before transplantation was also significant factor for increased non-relapse mortality (hazard ratio, 2.69, $p=0.01$). This study is the first to suggest the use of a qualitative skeletal muscle index to serve as a prognostic indicator following allo-HSCT. RD should be included in pre-transplant screening parameters, and approaches that include rehabilitation focused on improving both muscle quality and quantity may improve the prognosis of allo-HSCT.

Harada, K., et al. (2022). "Overcoming minimal residual disease using intensified conditioning with medium-dose etoposide, cyclophosphamide and total body irradiation in allogeneic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia in adults." Cytotherapy.

BACKGROUND AIMS: An intensified conditioning regimen incorporating medium-dose

etoposide (VP16) is an option for patients with acute lymphoblastic leukemia (ALL). However, the prognostic impacts of the addition of VP16 to cyclophosphamide (CY) and total body irradiation (TBI) in patients with Philadelphia chromosome-positive (Ph+) ALL with regard to minimal residual disease (MRD) status have not been elucidated. METHODS: The authors retrospectively compared the outcomes of patients with Ph+ ALL who underwent allogeneic transplantation following VP16/CY/TBI (n = 101) and CY/TBI (n = 563). RESULTS: At 4 years, the VP16/CY/TBI group exhibited significantly better disease-free survival (DFS) (72.6% versus 61.7%, P = 0.027) and relapse rate (11.5% versus 21.1%, P = 0.020) and similar non-relapse mortality (16.0% versus 17.2%, P = 0.70). In subgroup analyses, the beneficial effects of the addition of VP16 on DFS were more evident in patients with positive MRD status (71.2% versus 48.4% at 4 years, P = 0.022) than those with negative MRD status (72.8% versus 66.7% at 4 years, P = 0.24). Although MRD positivity was significantly associated with worse DFS in patients who received CY/TBI (48.4% versus 66.7%, P < 0.001), this was not the case in those who received VP16/CY/TBI (71.2% versus 72.8%, P = 0.86). CONCLUSIONS: This study demonstrated the benefits of the addition of VP16 in Ph+ ALL patients, especially those with positive MRD status. VP16/CY/TBI could be a potential strategy to overcome the survival risk of MRD positivity.

Harada, K., et al. (2022). "Outcomes of salvage haploidentical transplantation using posttransplant cyclophosphamide for graft failure following allogeneic hematopoietic stem cell transplantation." Int J Hematol.

Haploidentical donors have emerged as an alternative donor source for salvage stem cell transplantation (SCT) after graft failure; however, data regarding salvage haploidentical SCT using posttransplant cyclophosphamide (PTCy) are limited. Using nationwide data (2011-2019), we retrospectively investigated transplant outcomes after salvage haploidentical SCT using PTCy for graft failure (n = 33, median age 34 years). The total dose of PTCy was 75-100 mg/kg (standard dose) in 26 patients (78.8%) and 40-50 mg/kg (lower dose) in 5 patients (15.2%). The neutrophil engraftment rate at 30 days was 81.8%. One-year overall survival (OS) and non-relapse mortality (NRM) rates were 47.4% and 46.0%, respectively. The standard-dose group exhibited better OS (61.1% vs. 0.0% at 1 year, P = 0.022) and NRM (35.1% vs. 80.0% at 1 year, P = 0.052) than the lower-dose group. Moreover, the standard-dose group was less prone to both grades II-IV (11.5% vs. 40.0%) and III-IV (0.0% vs. 40.0%) acute graft-versus-host disease (GVHD). Use of cyclophosphamide in previous SCT and conditioning did not affect OS or NRM. In conclusion, haploidentical salvage SCT using PTCy offers promising survival outcomes. Prospective studies are required to validate the efficacy of salvage haploidentical SCT using PTCy.

Hatfield, K. J., et al. (2022). "Pretransplant Systemic Lipidomic Profiles in Allogeneic Stem Cell Transplant Recipients." Cancers (Basel) **14**(12).

Allogeneic stem cell transplantation is used in the treatment of high-risk hematological malignancies. However, this treatment is associated with severe treatment-related morbidity and mortality. The metabolic status of the recipient may be associated with the risk of development of transplant-associated complications such as graft-versus-host disease (GVHD). To better understand the impact of the lipidomic profile of transplant recipients on posttransplant complications, we evaluated the lipid signatures of patients with hematological disease using non-targeted lipidomics. In the present study, we studied pretransplant serum samples derived from 92 consecutive patients with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). A total of 960 lipid biochemicals were identified, and the pretransplant lipidomic profiles differed significantly when comparing patients with and without the risk factors: (i) pretransplant inflammation, (ii) early fluid overload, and (iii) patients with and without later steroid-requiring acute GVHD. All three factors, but especially patients with pretransplant inflammation, were associated with decreased levels of several lipid metabolites. Based on the overall concentrations of various lipid subclasses, we identified a patient subset characterized by low lipid levels, increased frequency of MDS patients, signs of inflammation, decreased body mass index, and an increased risk of early non-relapse mortality. Metabolic targeting has been proposed as a possible therapeutic strategy in allotransplant recipients, and our present results suggest that the clinical consequences of therapeutic intervention (e.g., nutritional support) will also differ between patients and depend on the metabolic context.

Ho, M., et al. (2022). "Risk factors for the development of orthostatic hypotension during autologous stem cell transplant in patients with multiple myeloma." Leuk Lymphoma: 1-10.

Orthostatic hypotension (OH) is a well-recognized phenomenon occurring in multiple myeloma (MM) patients undergoing autologous stem cell transplant (ASCT), and is associated with significant morbidity and mortality. A retrospective analysis of patients admitted for first ASCT between June 2012 and April 2014 found that 161/222 (73%) patients were diagnosed with OH during the course of

ASCT, including 51 patients who were found to have OH on the day of first orthostatic vitals check. Excluding these 51 patients, 110/171 (64%) patients developed OH during the peri-transplant period, at a median of 7 days post ASCT (95% CI: 6.5-8.5). OH did not significantly impact length of hospitalization, progression free and overall survival. Multivariable analysis revealed four risk factors (i.e. >/=0.5% weight loss/day, white race, gabapentin, antihypertensives) and two protective factors (i.e. antihistamine, proton pump inhibitor) associated with the development of peri-transplant OH.

Hu, G., et al. (2022). "Comparisons of Long-Term Survival and Safety of Haploidentical Hematopoietic Stem Cell Transplantation After CAR-T Cell Therapy or Chemotherapy in Pediatric Patients With First Relapse of B-Cell Acute Lymphoblastic Leukemia Based on MRD-Guided Treatment." Front Immunol **13**: 915590.

Measurable residual disease (MRD) positivity before haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is an independent prognostic factor in determining outcomes in patients with B-cell acute lymphoblastic leukemia (ALL). In this study, we conducted a parallel comparison of the efficacy and safety in patients with suboptimal MRD response after reinduction who underwent haplo-HSCT after chimeric antigen receptor T-cell (CAR-T) therapy or chemotherapy. Forty B-cell ALL patients who relapsed after first-line chemotherapy and with an MRD >/=0.1% after reinduction were analyzed. The median pre-HSCT MRD in the CAR-T group (n = 26) was significantly lower than that in the chemotherapy group (n = 14) (0.009% vs. 0.3%, p = 0.006). The CAR-T group exhibited a trend toward improved 3-year leukemia-free survival and a significantly improved 3-year overall survival compared to the chemotherapy group [71.8% (95% confidence interval (CI): 53.9-89.6) vs. 44.4% (95% CI: 15.4-73.4), p = 0.19 and 84.6% (95% CI: 70.6-98.5) vs. 40.0% (95% CI: 12.7-67.2), p = 0.008; respectively]. Furthermore, no increased risk of graft-versus-host disease, treatment-related mortality, or infection was observed in the CAR-T group. Our study suggests that CAR-T therapy effectively eliminates pre-HSCT MRD, resulting in better survival in the context of haplo-HSCT.

Ichimura, K., et al. (2022). "Living Donor Liver Transplantation for Hepatic Venoocclusive Disease/Sinusoidal Obstruction Syndrome Originating from Hematopoietic Stem Cell Transplantation." Case Rep Transplant **2022**: 8361769.

Background: Venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a life-threatening hematopoietic stem cell transplantation (HSCT) complication. Cases of mild and moderate VOD/SOS are self-limiting; however, the mortality for severe VOD/SOS has reached 80%. Recently, defibrotide became available and has been used for VOD/SOS; however, the outcome for patients with severe VOD/SOS is not satisfactory, and liver transplantation is attempted in these severe cases. Method: We describe a case of living donor liver transplantation (LDLT) for acute liver failure secondary to VOD/SOS that originates from HSCT. Result: Liver regeneration after LDLT was impaired, and several infections were developed before liver regeneration completion. Our patient suffered sepsis and finally died of multiorgan failure. Conclusion: Severe VOD/SOS originating from HSCT is associated with a very poor prognosis. The liver transplantation outcome for VOD/SOS has not been satisfied, but it may provide long-term survival if successful. We considered liver transplantation as a therapeutic option, especially in cases where sufficient graft volume is secured, considering impaired liver regeneration under bone marrow suppression after HSCT.

Ishii, K., et al. (2022). "[HLA-haploidentical peripheral blood stem cell transplantation with post-transplantation cyclophosphamide for adult T-cell leukemia]." Rinsho Ketsueki **63**(5): 333-340.

Recently, allogeneic peripheral blood stem cell transplantation from human leukocyte antigen (HLA)-haploidentical donors using post-transplantation cyclophosphamide (PTCY-haploPBSCT) has become available in clinical practice. However, the efficacy of PTCY in adult T-cell leukemia (ATL) is not fully established yet. In this study, we retrospectively examined data of seven patients who underwent PTCY-haploPBSCT. The overall survival rate at 100 days after transplantation was 85.7%, and the 1-year overall survival rate was 68.6%. The cumulative incidence of relapse at 1 year was 31.4%, whereas the 1-year nonrelapse mortality was 17.1%. The cumulative incidence of grade III-IV acute graft-versus-host disease (GVHD) on day 100 was 14.3%, and the incidence of chronic GVHD at 1 year was 33.3%. These results suggest that PTCY-haploPBSCT can be a viable option even in patients with ATL. Further accumulation of knowledge and improvement of transplantation outcomes are warranted in the future.

Ishtiah, A. A. and B. H. Yahaya (2022). "The Enrichment of Breast Cancer Stem Cells from MCF7 Breast Cancer Cell Line Using Spheroid Culture Technique." Methods Mol Biol **2429**: 475-484.

Breast cancer is the most common malignancy worldwide in females, representing 29% of all cancer new cases and 14% of cancer deaths in the world.

Amongst the reasons for the high mortality rate is resistance to chemotherapy resulting in therapeutic failure. Various studies have shown that the presence of cancer stem cells (CSCs) in breast tumors is responsible for chemotherapy resistance and tumor recurrence. This CSC population possesses the characteristics of normal stem cells, including their ability to self-renewal and give rise to other epithelial cells. One thing that unique to the CSC population is their ability to escape from chemotherapy drugs; this can make them resistant to therapy and able to repopulate the cancer. Isolation and enrichment of breast CSCs (BCSCs) is required in order to study their characteristics and the behavior that enables them to drive breast tumor development, in order to develop better therapies. This chapter describes a method for the isolation and enrichment of BCSCs from the MCF7 breast cancer cell line, which consists of a heterogeneous breast cancer cell population. This method depends on cancer stem cell behavior, specifically an ability to self-renew and form spheroids in harsh conditions that allow only cancer cells with stem cell characteristics to survive and form spheroids.

Jentzsch, M., et al. (2022). "Impact of the MRD status in AML patients undergoing allogeneic stem cell transplantation in first vs second remission." Blood Adv.

Allogeneic hematopoietic stem cell transplantation (HSCT) offers the best chance for relapse-free survival to most acute myeloid leukemia (AML) patients. It might be performed in complete remission or delayed until after first relapse due to relevant treatment-related morbidity and mortality. The measurable residual disease (MRD) status at HSCT adds refined prognostic information to the assigned European LeukemiaNet (ELN) 2017 genetic risk at diagnosis. We analyzed 580 AML patients receiving allogeneic HSCT in either first (79%) or second (21%) remission. Although - due to common treatment strategies - some adverse risk characteristics, such as monosomal or complex karyotypes were less frequent in patients transplanted in second remission, they had worse outcomes compared to patients transplanted in first remission. The MRD status at HSCT was an independent prognostic factor irrespective of the number of remission at HSCT. Noteworthy, MRDpos patients transplanted in first remission and MRDneg patients transplanted in second remission had similar outcomes. In the clinically highly relevant group of ELN2017 intermediate risk individuals, the MRD status provided the highest prognostic value with very dismal outcomes of patients transplanted in MRDpos second remission. The adverse outcomes of MRDpos patients and individuals transplanted in second remission should be considered when planning consolidation treatment, to avert an allogeneic HSCT in MRDpos second remission when possible.

Jiang, W., et al. (2022). "Third-party CMV- and EBV-specific T cells for first viral reactivation after allogeneic stem cell transplant." Blood Adv.

Virus-specific T-cells (VST) from third-party donors mediate short- and long-term antiviral effects in allogeneic stem cell transplant (HSCT) recipients with relapsed or refractory viral infections. We investigated early administration of third-party VST together with antiviral therapy in patients requiring treatment for their first CMV or EBV infection. Thirty HSCT patients were treated with 1-4 VST infusions (2x107cells/m2; CMV=27, EBV=3) at a median of 4 days after initiation of antiviral treatment. The overall viral response rate was 100% with a complete response rate of 94%. Of the 28 patients who achieved a CR, 23 remained virus PCR negative (n=9) or below quantitation limit (n=14) for the duration of follow up. 4 patients had brief episodes of quantifiable reactivation not requiring additional therapy and one patient required a second infusion following initial CR, and remained PCR negative thereafter. All 3 patients treated for EBV PTLD achieved sustained CR. Rates of acute and chronic GVHD post-infusion were 13% (4/30) and 23% (7/30) respectively. There were no serious adverse events related to infusion. VST infusion was associated with rapid recovery of CD8+CD45RA-CD62L- and a slower recovery of CD4+CD45RA-CD62L- effector memory T-cells; CMV-specific T-cells comprised up to 13% of CD8+ cells. At 1 year post-transplant, non relapse mortality was 10%, cumulative incidence of relapse was 7%, overall survival was 88% and 25/27 patients had ECOG 0 or 1. Early administration of third-party VST in conjunction with antiviral treatment appears safe and leads to excellent viral control and clinical outcomes. Study ID ACTRN12618000343202.

Kaiser, M., et al. (2022). "Role of Extracellular Vesicles in stem cell therapy." Curr Stem Cell Res Ther.

Burn wounds are a major source of morbidity and mortality in both the military and the civilian settings. Research about the pathophysiology of thermal injury has revealed possible interventions that can aid this process to reduce scarring and wound contracture. Bone marrow derived Mesenchymal stem cells (BM-MSCs) have been an exciting topic in research for many years. They have been shown to facilitate wound healing and tissue regeneration, two areas that are vital in the healing process especially in burn wounds. More recently the discovery of Extracellular Vesicles (EVs) has allowed us to further characterize the immunomodulatory roles and

understand the cellular pathways implicated in wound healing. The purpose of this review is to discuss the role of EVs in wound healing, and to propose that EVs are the main mechanism that deliver cellular materials to target cells to coordinate wound healing following tissue injury.

Kumar, S., et al. (2022). "Long-Term Outcomes and Safety Trends of Autologous Stem-Cell Transplantation in Non-Hodgkin Lymphoma: A Report From A Tertiary Care Center in India." JCO Glob Oncol **8**: e2100383.

PURPOSE: Published experience with autologous stem-cell transplantation (ASCT) in non-Hodgkin lymphoma (NHL) from the Indian subcontinent is extremely limited. Here, we describe the activity and outcomes of this treatment modality at a large tertiary care center in India. PATIENTS AND METHODS: We retrospectively analyzed adult patients with NHL who were eligible for ASCT and autografted between January 1, 2002, and December 15, 2020, at our transplant unit. Toxicities, complications, and long-term outcomes were compared between patients who underwent transplant during 2002-2012 (group A) and 2013-2020 (group B). RESULTS: Overall, 80 patients (group A, n = 37; group B, n = 43) underwent ASCT using peripheral blood stem cells. At a median follow-up of 57.6 months, the 5-year event-free survival (EFS) and overall survival (OS) were 43.5% and 47.6%, respectively, for all patients. More recently (group B), patients had reduced 100-day transplant-related mortality (2.3% v 21.6%, P < .01), improved 3-year EFS (52.9% v 37.3%, P = .04), and superior OS (at 3-year; 63.4% v 43.2%, P = .02). Patients in group B also tolerated the procedure better, with improved resource utilization. In multivariate analysis, an International Prognostic Index (IPI) >/= 3 at diagnosis adversely affected EFS (hazard ratio [HR] = 2.82, P = .009) and OS (HR = 2.84, P = .01) after ASCT. Low pretransplant serum albumin levels were associated with inferior EFS (HR = 2.68, P = .02) and transplant-related mortality (odds ratio = 10.80, P = .02) after ASCT. CONCLUSION: It is feasible to achieve comparable short- and long-term outcomes in patients with NHL undergoing ASCT in a resource-poor country with improved supportive care and expertise of the transplant team and center.

Kwan, A. C. F., et al. (2022). "Toward optimization of cyclosporine concentration target to prevent acute graft-versus-host disease following myeloablative allogeneic stem cell transplant." Clin Transplant: e14732.

INTRODUCTION: Despite the common use of cyclosporine (CsA) for acute graft-versus-host disease (aGVHD) prophylaxis following allogeneic stem cell transplant, the optimal CsA trough target remains unknown. MATERIALS AND METHODS: Here, we report on outcomes of adult patients following myeloablative conditioning to identify an optimal CsA trough target and characterize the most relevant timeframe post-transplant for CsA trough targeting to minimize aGVHD. We retrospectively reviewed 399 consecutive patients who underwent first peripheral blood allogeneic stem cell transplant for hematological malignancies between January 2009 and December 2018. RESULTS: In the unadjusted and adjusted analyses, the incidence of grades 2-4 aGVHD was significantly higher among patients with an average CsA trough concentration <250 mcg/L compared to patients with an average CsA trough concentration >/=250 mcg/L during days 15-28 post-transplant (31.5% versus 18.8%, P = 0.037), with an odds ratio (OR) of 1.97 (95% confidence interval 1.04-3.71). In contrast, no correlations between CsA trough concentration and relapse, non-relapse mortality and overall survival was found. CONCLUSION: In conclusion, early post-transplant CsA trough concentrations are an important factor in the prophylaxis against aGVHD. Our findings suggest that CsA trough concentrations should be maximized between days 15-28 post-myeloablative transplant.

Lazzari, L., et al. (2022). "Post-transplant cyclophosphamide and sirolimus based graft-versus-host disease prophylaxis after allogeneic stem cell transplantation for acute myeloid leukemia." Bone Marrow Transplant.

Post-transplant cyclophosphamide (PTCy) has emerged as a promising graft-versus-host disease (GvHD) prophylaxis in allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, no studies have reported the efficacy of a GvHD prophylaxis based on PTCy with sirolimus (Sir-PTCy) in patients with acute myeloid leukemia (AML). In this retrospective study, we analyze the use of sirolimus in combination with PTCy, with or without mycophenolate mofetil (MMF), on 242 consecutive adult patients with AML undergoing a myeloablative first allo-HSCT from different donor types, in three European centers between January 2017 and December 2020. Seventy-seven (32%) patients received allo-HSCT from HLA-matched sibling donor, 101 (42%) from HLA-matched and mismatched unrelated donor, and 64 (26%) from haploidentical donor. Except for neutrophil and platelet engraftment, which was slower in the haploidentical cohort, no significant differences were observed in major transplant outcomes according to donor type in univariate and multivariate analysis. GvHD prophylaxis with Sir-PTCy, with or without MMF, is safe and effective in patients with AML undergoing myeloablative allo-HSCT, resulting in low

rates of transplant-related mortality, relapse/progression, and acute and chronic GvHD in all donor settings.

Lei, M., et al. (2022). "Comparison of Haploidentical Hematopoietic Stem Cell Transplant With or Without Unrelated Cord Blood Infusion in Severe Aplastic Anemia: Outcomes of a Multicenter Study." Front Immunol **13**: 912917.

The purpose of this study in severe aplastic anemia (SAA) patients was to compare the feasibility and efficacy of haploidentical hematological stem cell transplantation combined with a single unrelated cord blood (UCB) infusion (Haplo-cord-HSCT) or haplo-identical HSCT (Haplo-HSCT) alone. The five-year graft-versus-host disease (GVHD)-free or failure-free survival (GFFS) was similar between the two groups (72.4 +/- 3.4% vs. 65.4 +/- 5.2%, P = 0.178); however, the five-year overall survival (OS) was more favorable in the Haplo-cord-HSCT group than that in the Haplo-HSCT group (84.0 +/- 2.8% vs. 72.6 +/- 4.9%, P = 0.022), as was transplantation-related mortality (16.4% vs. 27.4%, P = 0.039). Multivariate analysis showed that Haplo-cord HSCT was the only independent determinant of increased OS (P = 0.013). Explorative subgroup analysis showed that only an Human leukocyte antigen-A (HLA-A) allele match between UCB and the recipient was a beneficial factor for GFFS in the Haplo-cord-HSCT group (P = 0.011). In the haplo-cord with an HLA-A match (n = 139) or mismatch (n = 32) or Haplo-HSCT groups, a haplo-cord HLA-A allele match was associated with lower I-IV and III-IV acute GVHD. The haplo-cord with an HLA-A match subgroup also had higher five-year OS than the Haplo-HSCT group (85.4 +/- 3.0% vs. 72.6 +/- 4.9%, P = 0.013), and higher five-year GFFS than the Haplo-cord HLA-A allele mismatch subgroup (76.2 +/- 3.6% vs. 56.3 +/- 8.8%, P = 0.011). These findings suggest that the coinfusion of a single UCB potentially improves survival of Haplo-HSCT in SAA patients and that an HLA-A allele-matched UCB is the preferred option.

Lew, M. V., et al. (2022). "Geriatric Assessment Reveals Actionable Impairments in Hematopoietic Stem Cell Transplantation Candidates Age 18 to 80 Years." Transplant Cell Ther.

Allogeneic hematopoietic stem cell transplantation (HCT) is a potentially curative treatment for both malignant and nonmalignant hematologic diseases; however, reported rates of treatment-related mortality approach 30%. Outcomes are worse in patients who begin HCT with functional impairments. To detect such impairments, a geriatric assessment (GA) is recommended in adults age >/=65 years. Younger HCT candidates also may be impaired because of chemotherapy regimens pre-HCT. Therefore, we hypothesized that GA can be beneficial for adult patients of all ages and subsequently created a clinical pretransplantation optimization program to assess all HCT candidates using a modified GA. One-hundred fifty-seven patients were evaluated in 4 functional domains- physical, cognitive, nutritional, and psychological-at 2 time points prior to HCT-new patient evaluation (NPE) and sign-off (SO)-between October 2017 and January 2020. At NPE, 80.9% of the patients had at least 1 domain with a functional impairment, and physical (P = .006), cognitive (P = .04), and psychological (P = .04) impairments were associated with an increased likelihood of not proceeding to HCT. In addition, patients age 18 to 39 years were more likely than older patients to have a physical function impairment (P = .001). Between NPE and SO, 51.9% of the patients had resolution of 1 or more impairments, and nutritional impairment at SO was predictive of worse overall survival (P = .01). Our study shows that GA can identify functional impairments in patients of all ages. Early identification of impairments could facilitate referrals to supportive care and resolution of impairments prior to HCT, suggesting that GA could be recommended for HCT candidates of all ages.

Li, Y., et al. (2022). "Comparisons of Modified Post-Transplantation Cyclophosphamide and Granulocyte Colony-Stimulating Factor/Antithymocyte Globulin Regimens for Haploidentical Stem Cell Transplantation in Patients with Aplastic Anemia." Transplant Cell Ther **28**(7): 396 e391-396 e399.

Haploidentical stem cell transplantation (HSCT) has become an alternative treatment option for patients with aplastic anemia (AA) without matched sibling donors or matched unrelated donors. Recently, post-transplantation cyclophosphamide (PTCy) and granulocyte colony-stimulating factor (G-CSF)/antithymocyte globulin (ATG) regimens have become the most common protocols used worldwide. In this retrospective study, we retrospectively reviewed and analyzed the clinical data of 130 AA patients who underwent haploidentical HSCT and received the modified PTCy (mPTCy) regimen (n = 55) or G-CSF/ATG regimen (n = 75) between January 2013 and June 2021 across 7 transplantation centers. Neutrophil engraftment was successful in all patients within 30 days in the G-CSF/ATG group. The cumulative neutrophil engraftment rate in the mPTCy group was 96.36% (95% confidence interval [CI], 94.57 to 97.57; P = .010). The median time to neutrophil engraftment in the G-CSF/ATG group was 10 days (range, 7 to 28 days), which was more rapid than that observed in the mPTCy group (P < .001). There was no significant difference in the incidence of graft-versus-host disease

(GVHD) between the 2 groups. The cumulative incidence of grade II-IV acute GVHD was 18.40% (95% CI, 4.27% to 40.31%) in the mPTCy group and 19.32% (95% CI, 5.86% to 38.58%) in the G-CSF/ATG group, whereas the cumulative incidence of grade III-IV acute GVHD was 7.31% (95% CI, .09% to 37.48%) in the mPTCy group and 7.57% (95% CI, .20 to 34.19) in the G-CSF/ATG group. Similarly, there were no significant between-group differences in overall survival (OS), failure-free survival (FFS), and GVHD-free relapse-free survival (GRFS). The 2-year OS, FFS, and GRFS rates were 95.91% (95% CI, 84.59% to 98.96%), 92.25% (95% CI, 80.59% to 97.03%), and 86.68% (95% CI, 73.98% to 93.44%), respectively, in the mPTCy group and 86.67% (95% CI, 76.64% to 92.59%), 81.28% (95% CI, 70.45% to 88.46%), and 77.20% (95% CI, 65.89% to 85.16%), respectively, in the G-CSF/ATG group. Transplantation-related mortality (TRM) was significantly higher in the G-CSG/ATG group than in the mPTCy group (13.33% versus 1.96%; P = .022). In multivariate analysis, the use of a female donor, a higher Hematopoietic Cell Transplantation Comorbidity Index, and grade III-IV acute GVHD were associated with worse survival outcomes. The mPTCy and G-CSF/ATG regimens led to similar outcomes in AA patients, but quicker engraftment was observed with the ATG/G-CSF regimen, and a lower incidence of TRM was observed with the mPTCy regimen.

Lin, F., et al. (2022). "The impact of pretransplant serum ferritin on haploidentical hematopoietic stem cell transplant for acquired severe aplastic anemia in children and adolescents." Pediatr Blood Cancer: e29845.

Haploidentical hematopoietic stem cell transplant (haplo-HSCT) provides an important alternative for children and adolescents with acquired severe aplastic anemia (SAA) lacking matched donors. To test whether pretransplant serum ferritin (SF) represents a candidate predictor for survival and a potential biomarker for graft-versus-host disease (GvHD) in pediatric haplo-HSCT, we retrospectively evaluated 147 eligible patients with SAA who underwent haplo-HSCT. The patients were divided into the low-SF group (< 1000 ng/mL) and the high-SF group (>/= 1000 ng/mL). We found that SF >/=1000 ng/mL independently increased the risk of grade II-IV aGvHD (HR = 2.596; 95% CI, 1.304-5.167, P = 0.007) and grade III-IV aGvHD (HR = 3.350; 95% CI, 1.162-9.658, P = 0.025). Similar probabilities of transplant-related mortality at 100 days were observed in the two groups (6.19 +/- 2.45% vs 8.00 +/- 3.84%, P = 0.168). The two-year overall survival (85.29 +/- 3.89% vs 92.00% +/- 3.84%, P = 0.746) and failure-free survival (83.23% +/- 4.08% vs 83.37% +/- 6.27%, P = 0.915) were comparable. GvHD-/failure-free survival were 60.06 +/- 5.10% and 75.56 +/- 6.87%, respectively (P = 0.056). In conclusion, elevated pretransplant SF level is associated with higher incidences of grade II-IV aGvHD and grade III-IV aGvHD. However, it is not associated with worse survival after haplo-HSCT for children and adolescent patients with SAA.

Liu, L. W., et al. (2022). "Letermovir Discontinuation at Day 100 After Allogeneic Stem Cell Transplant Is Associated With Increased CMV-Related Mortality." Transplant Cell Ther.

Letermovir is approved by the Food and Drug Administration for cytomegalovirus (CMV) prophylaxis in CMV seropositive recipients of allogeneic stem cell transplantation (alloSCT) up to day 100. Letermovir use up to day 100 after alloSCT has demonstrated a significantly lower incidence of clinically significant CMV infection (csCMVi) at 24 weeks and an overall mortality benefit as far as 48 weeks after transplantation. We report data on csCMVi incidence beyond 24 weeks and overall survival (OS) beyond 48 weeks and outcomes for patients who had a prior alloSCT, are CMV seronegative with seropositive donor (D+/R-), or are high risk (defined as those receiving haploidentical transplants, mismatched transplants, T-cell-depleted grafts, umbilical cord blood transplants, prednisone >/=1 mg/kg or equivalent steroid use, or the use of 2 or more immunosuppressants). Additionally, risk factors for CMV-related mortality and possible extended duration of letermovir are reported. This is a single-center, retrospective cohort study of 333 alloSCTs with CMV seropositive donors or recipients performed at Siteman Cancer Center and Barnes-Jewish Hospital from January 2016 to June 2019. The primary endpoint of csCMVi at day 180 was 19.46% with letermovir and 39.13% without letermovir (P < .0001). The secondary endpoints are as follows: day 100 csCMVi was 8.1% with letermovir and 34.8% without (P < .0001), day 365 csCMVi was 24.8% with letermovir and 41.3% without (P = .001). Our multivariate analyses demonstrated that exposure to letermovir was associated with improved OS (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.25-0.77), nonrelapse mortality (HR 0.50; 95% CI 0.27-0.94) and CMV-related mortality (HR 0.40; 95% CI 0.16-0.95) during day 0 to day 99 but worse CMV-related mortality during day 180 to day 364 (HR 3.19; 95% CI 1.29-7.92). Patients with serum IgG levels <400 mg/dL at day 100, high-risk transplants (P = .004), post-transplantation cyclophosphamide (PTCy; P = .001), and mismatched-unrelated donors (MMUD; P = .02) experienced increased CMV reactivation. The CMV D+/R- cohort demonstrated no difference in CMV reactivation overall (P = .19), but the subset receiving

PTCy showed decreased reactivation with letermovir (P = .03). Discontinuation of letermovir at day 100 leads to increased incidence of late CMV reactivation and CMV-related mortality. Letermovir use in CMV recipient seropositive alloSCT may need to be extended. Serum IgG levels <400 mg/dL at day 100 was associated with increased CMV reactivation. Patients with subclinical CMV viremia before transplantation, high-risk transplants, PTCy, or MMUD had decreased CMV reactivation with letermovir. Although there was no difference in CMV reactivation in the CMV D+/R- cohort, the subset treated with PTCy for acute graft-versus-host disease prophylaxis had decreased CMV reactivation with letermovir.

Lueck, C., et al. (2022). "Increased late non-cardiac non-relapse mortality in patients with atrial fibrillation diagnosed during hospital stay for allogeneic stem cell transplantation." Transplant Cell Ther.

BACKGROUND: Atrial fibrillation (AF) is the most common arrhythmia in adults but its impact on allogeneic stem cell transplantation (SCT) is not well characterized. OBJECTIVES: We studied AF manifestation during hospital stay for allogeneic stem cell transplantation (referred to as AFiH) and analyzed incidence, risk factors for and clinical impact of AFiH on ICU- / hospital- / and overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM) and GvHD-relapse-free survival (GRFS). STUDY DESIGN: We conducted a retrospective matched cohort study in 553 consecutive SCT patients at Hannover Medical School between 01/2013 and 10/2019. Patients with AFiH were compared to a non-AFiH control cohort matched for HCTCI, The European Group for Blood and Marrow Transplantation (EBMT) risk score, disease, conditioning regimen and availability of molecular genetic data for patients with myeloid diseases. RESULTS: AFiH occurred in 46 patients (8%) at a median 2 (IQR 0-8) days after SCT. Patients' history of AF, elevated NT-proBNP and hs-TnT but not conventional echocardiographic parameters were predictive for AFiH. AFiH occurred more often in patients with mutations in DMT3A, TET2 and ASXL1 genes related to clonal hematopoiesis as compared to patients with wildtype alleles with the highest impact of DMT3A mutations. Intensive care unit (ICU) admission was significantly higher in the AFiH cohort (46% vs. 7%) without significant differences in ICU or post-ICU hospital survival (62% vs. 40% and 52% vs. 40%, respectively). The main cause of death was sepsis. In terms of long-term outcome, incidence of relapse and grade II-IV degrees graft versus host disease (GvHD) were not different between the AFiH and the non-AFiH cohort. However, overall survival was significantly shorter in the AFiH cohort (1-year: 39% vs. 65%) due to late non-cardiac, non-relapse mortality (1-year: 49% and 27%). CONCLUSION: Although the underlying cellular and molecular mechanisms remain to be characterized in further detail, these data clearly demonstrate the impact of in-patient AF manifestation/AFiH on long-term outcome of SCT patients.

Ma, X., et al. (2022). "Comparable clinical outcomes of haploidentical hematopoietic stem cell transplantation in patients with hepatitis-associated aplastic anemia and non-hepatitis-associated aplastic anemia." Ann Hematol **101**(8): 1815-1823.

Hepatitis-associated aplastic anemia (HAAA), a rare subtype of aplastic anemia (AA), is defined as bone marrow failure occurring after acute hepatitis. Severe HAAA requires immunosuppressive therapy (IST) or hematopoietic stem cell transplantation (HSCT) as lifesaving treatment. The outcomes of HAAA patients who underwent haploidentical hematopoietic stem cell transplantation (haplo-HSCT) have not been systematically evaluated. We retrospectively compared the characteristics of 15 patients with HAAA and 60 non-hepatitis-associated aplastic anemia (non-HAAA) patients, all 75 of whom underwent haplo-HSCT in our hospital between January 2006 and October 2021. The median ages of the patients were 18 years old (range, 3-36) for HAAA patients and 13 years (range, 2-45) for non-HAAA patients (p = 0.693). The median time for neutrophil engraftment was 14 days (range, 11-22) in the HAAA group and 12 days (range, 10-21) in the non-HAAA group (p = 0.363). At the time of analysis, 15 HAAA patients and 58 non-HAAA patients were alive, and their median follow-up times were 37 (range, 3-87) months and 31 (range, 2-110) months (p = 0.347), respectively. There were no significant differences in the three-year overall survival (OS) rates (100% vs. 96.7 +/- 0.33%, P = 0.638) or liver event-free survival (LEFS) (80.0 +/- 0.17% vs. 76.7 +/- 0.19%, P = 0.747) between the two groups. Despite the small number of HAAA patients due to the rarity of the disease, these results, such as the similar incidence rates of 3-year OS and fewer liver events than expected, suggest that haplo-HSCT is a feasible treatment for HAAA a when there are no human leukocyte antigen (HLA)-matched donors available and has a low risk of transplant-related mortality and complications.

Malagola, M., et al. (2022). "Results of an Innovative Program for Surveillance, Prophylaxis, and Treatment of Infectious Complications Following Allogeneic Stem Cell Transplantation in Hematological Malignancies (BATMO Protocol)." Front Oncol **12**: 874117.

Background: Infectious complications are a significant cause of morbidity and mortality in patients

undergoing allogeneic haematopoietic stem cell transplantation (Allo-SCT). The BATMO (Best-Antimicrobial-Therapy-TMO) is an innovative program for infection prevention and management and has been used in our centre since 2019. The specific features of the BATMO protocol regard both prophylaxis during neutropenia (abandonment of fluoroquinolone, posaconazole use in high-risk patients, aerosolized liposomal amphotericin B use until engraftment or a need for antifungal treatment, and letermovir use in CMV-positive recipients from day 0 to day +100) and therapy (empirical antibiotics based on patient clinical history and colonization, new antibiotics used in second-line according to antibiogram with the exception of carbapenemase-producing K pneumoniae for which the use in first-line therapy is chosen). Methods: Data on the infectious complications of 116 transplant patients before BATMO protocol (Cohort A; 2016 - 2018) were compared to those of 84 transplant patients following the introduction of the BATMO protocol (Cohort B; 2019 - 2021). The clinical and transplant characteristics of the 2 Cohorts were comparable, even though patients in Cohort B were at a higher risk of developing bacterial, fungal, and CMV infections, due to a significantly higher proportion of myeloablative regimens and haploidentical donors. Results: No change in the incidence of infections with organ localization was observed between the two Cohorts. A significant reduction in Clostridioides difficile infections by day +100 was observed in Cohort B (47% vs. 15%; p=0.04). At day +30, a higher incidence of Gram-negative bloodstream infections (BSIs) was observed in Cohort B (12% vs. 23%; p=0.05). By day +100 and between days +100 and +180, the incidence of BSIs and of the various etiological agents, the mortality from Gram-negative bacteria, and the incidence of invasive fungal infections were not different in the two Cohorts. The incidence of CMV reactivations by day +100 dropped drastically in patients of Cohort B, following letermovir registration (51% vs. 15%; p=0.00001). Discussion: The results of this study suggest that the BATMO program is safe. In particular, the choice to avoid prophylaxis with fluoroquinolone was associated with an increase in Gram-negative BSIs by day +30, but this did not translate into higher levels of mortality. Moreover, this strategy was associated with a significant reduction of Clostridiodes difficile infections. The efficacy of anti-CMV prophylaxis with letermovir was confirmed by a significant reduction in CMV reactivations. Even though patients in Cohort B were at higher risk of developing fungal infections (more haploidentical transplants with more myeloablative regimens), the extensive use of posaconazole for prophylaxis balanced this risk, and no increase in the incidence of fungal-associated complications was observed.

Montazersaheb, S., et al. (2022). "An Overview of Autophagy in Hematopoietic Stem Cell Transplantation." Front Bioeng Biotechnol **10**: 849768.

Autophagy is a fundamental homeostatic process crucial for cellular adaptation in response to metabolic stress. Autophagy exerts its effect through degrading intracellular components and recycling them to produce macromolecular precursors and energy. This physiological process contributes to cellular development, maintenance of cellular/tissue homeostasis, immune system regulation, and human disease. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only preferred therapy for most bone marrow-derived cancers. Unfortunately, HSCT can result in several serious and sometimes untreatable conditions due to graft-versus-host disease (GVHD), graft failure, and infection. These are the major cause of morbidity and mortality in patients receiving the transplant. During the last decade, autophagy has gained a considerable understanding of its role in various diseases and cellular processes. In light of recent research, it has been confirmed that autophagy plays a crucial role in the survival and function of hematopoietic stem cells (HSCs), T-cell differentiation, antigen presentation, and responsiveness to cytokine stimulation. Despite the importance of these events to HSCT, the role of autophagy in HSCT as a whole remains relatively ambiguous. As a result of the growing use of autophagy-modulating agents in the clinic, it is imperative to understand how autophagy functions in allogeneic HSCT. The purpose of this literature review is to elucidate the established and implicated roles of autophagy in HSCT, identifying this pathway as a potential therapeutic target for improving transplant outcomes.

Nagler, A., et al. (2022). "Outcome of human umbilical cord blood stem cell transplantation (CBT) for acute myeloid leukemia in patients achieving first complete remission after one versus two induction courses: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)." Bone Marrow Transplant.

We compared transplantation outcomes of adult patients with AML that underwent cord blood transplantation (CBT) in CR1 following 1 versus 2 induction courses. Study included 325 patients, 243 (75%) with 1 and 82 (25%) with 2 induction courses. Engraftment was lower for patients achieving CR1 after 1 vs. 2 induction courses: 91% vs. 99% (p = 0.02). Incidence of acute GVHD was similar, 38% and 36% (p = 0.81), as was 2-year chronic GVHD at 23.4% and

27.5%, respectively (p = 0.65). Two-year non-relapse mortality (NRM), relapse incidence (RI), leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) were not statistically different between patients achieving CR1 with 1 vs. 2 induction courses with 23% vs. 24% (p = 0.87), 25% vs. 30% (p = 0.4), 52% vs. 46% (p = 0.3), 59% vs. 50% (p = 0.2), and 44% vs. 41% (p = 0.66), respectively. Results were confirmed by multivariable analysis, NRM (hazard ratio (HR) = 1.1; 95% CI, 0.6-1.8, p = 0.7), RI (HR = 1.4; 95% CI, 0.9-2.3, p = 0.1), LFS (HR = 1.3; 95% CI, 0.9-1.8, p = 0.2), OS (HR = 1.3; 95% CI, 0.9-1.9, p = 0.1), and GRFS (HR = 1.1; 95% CI, 0.8-1.5, p = 0.5). Overall, outcomes of AML patients undergoing CBT in CR1 achieved after 1 or 2 induction courses are similar.

Nagler, A., et al. (2022). "Longitudinal outcome over two decades of unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: an ALWP/EBMT analysis." Clin Cancer Res.

INTRODUCTION: We evaluated outcome of unrelated transplantation for primary refractory/relapsed (ref/rel) acute myeloid leukemia (AML) comparing two cohorts according to the year of transplant, 2000-2009 and 2010-2019. METHODS: Multivariable analyses were performed using the Cox proportional-hazards regression model. RESULTS: 3430 patients were included, 876 underwent a transplant between 2000-2009 and 2554 in 2010-2019. Median follow up was 8.7 (95% CI: 7.8-9.4) and 3.4 (95% CI: 3.1-3.6) years (p<0.001). Median age was 52 (18-77) and 56 (18-79) years (p<0.0001). 45.5% and 55.5% had refractory AML while 54.5% and 44.5 % had relapsed AML. Conditioning was myeloablative in 60% and 52%, respectively. Neutrophil recovery, day 100 incidence of acute and 2-year incidence of chronic graft-versus-host disease (GVHD) were similar between the two periods. Two-year relapse incidence was higher for patients transplanted in the 2000-2009 period vs. those transplanted in 2010-2019; 50.2% vs. 45.1%; (hazard ratio (HR)=0.85 (95% CI: 0.74-0.97), p=0. 002). Leukemia-free survival, overall survival and GVHD-free, relapse-free survival were lower for the 2000-2009 period, 26% vs. 32.1% (HR=0.87 (95% CI: 0.78-0.97), p=0.01), 32.1% vs. 38.1% (HR=0.86 (95% CI: 0.77-0.96), p=0.01) and 21.5% vs. 25.3% (HR=0.89 (95% CI: 0.81-0.99), p=0.03, respectively. Two-year non-relapse mortality was not significantly different, 23.8% vs. 23.7% (HR=0.91 (95% CI: 0.76-1.11), p=0.34. CONCLUSION: Outcome of unrelated transplantation for patients with ref/rel AML has improved in the last two decades, rescuing about one third of the patients.

Nassar, A. P., Jr., et al. (2022). "Characteristics and outcomes of autologous hematopoietic stem cell transplant recipients admitted to intensive care units: A multicenter study." J Crit Care **71**: 154077.

PURPOSE: Studies of critically ill hematopoietic stem cell transplantation (HSCT) recipients have mainly been single-center and focused on allogenic HSCT recipients. We aimed to describe a cohort of autologous HSCT with an unplanned intensive care unit (ICU) admission. METHODS: This study is a retrospective cohort study of autologous HSCT performed as a treatment for a hematological malignancy, during their first unplanned ICU admission in 50 hospitals in Brazil. We assessed the hospital mortality and the association between mechanical ventilation, vasopressors, and renal replacement therapy and hospital mortality in autologous HSCT recipients, adjusted for potential confounders. RESULTS: We included 301 patients. Multiple myeloma was the most common malignancy driving to HSCT. ICU and hospital mortality were 22.9% and 37.5%, respectively. After adjustment for potential confounders, mechanical ventilation (OR = 9.10; CI 95%, 4.82-17.15) was associated with hospital mortality, but vasopressors (OR = 1.43; CI 95%, 0.77-2.64) and renal replacement therapy (OR = 1.30; CI 95%, 0.63-2.66) were not. CONCLUSIONS: In this large cohort of critically ill autologous HSCT recipients, mechanical ventilation was the only organ support-therapy associated with increased mortality in autologous HSCT recipients.

Oh, S. J., et al. (2022). "Anti-Viral Activities of Umbilical Cord Mesenchymal Stem Cell-Derived Small Extracellular Vesicles Against Human Respiratory Viruses." Front Cell Infect Microbiol **12**: 850744.

The endemic and pandemic caused by respiratory virus infection are a major cause of mortality and morbidity globally. Thus, broadly effective antiviral drugs are needed to treat respiratory viral diseases. Small extracellular vesicles derived from human umbilical cord mesenchymal stem cells (U-exo) have recently gained attention as a cell-free therapeutic strategy due to their potential for safety and efficacy. Anti-viral activities of U-exo to countermeasure respiratory virus-associated diseases are currently unknown. Here, we tested the antiviral activities of U-exo following influenza A/B virus (IFV) and human seasonal coronavirus (HCoV) infections in vitro. Cells were subject to IFV or HCoV infection followed by U-exo treatment. U-exo treatment significantly reduced IFV or HCoV replication and combined treatment with recombinant human interferon-alpha protein (IFN-alpha) exerted synergistically enhanced antiviral effects against IFV or HCoV. Interestingly, microRNA (miR)-

125b, which is one of the most abundantly expressed small RNAs in U-exo, was found to suppress IFV replication possibly via the induction of IFN-stimulated genes (ISGs). Furthermore, U-exo markedly enhanced RNA virus-triggered IFN signaling and ISGs production. Similarly, human nasal epithelial cells cultured at the air-liquid interface (ALI) studies broadly effective anti-viral and anti-inflammatory activities of U-exo against IFV and HCoV, suggesting the potential role of U-exo as a promising intervention for respiratory virus-associated diseases.

Otegbeye, F., et al. (2022). "Natural Killer Cell Alloreactivity Predicted By Killer Cell Immunoglobulin-Like Receptor Ligand Mismatch Does Not Impact Engraftment in Umbilical Cord Blood and Haploidentical Stem Cell Transplantation." Transplant Cell Ther.

Natural killer cell alloreactivity is determined by killer cell immunoglobulin-like receptor (KIR) ligands in donor and recipient pairs. A small, single institution study suggested that the risk of primary graft failure after cord blood hematopoietic cell transplantation (CBT) can be predicted by host-versus-graft (HvG)-directed natural killer cell alloreactivity. In the haploidentical transplantation (Haplo HCT) cohort, graft failures were observed only in graft-versus-host (GvH) KIR ligand mismatched pairs. A subsequent study was designed to explore the association between HvG and GvH KIR ligand mismatching and engraftment in both CBT and Haplo HCT using the large, multicenter transplant population of the Center for International Blood and Transplant Research database. Nine hundred single CBT (sCBT), 954 double CBT (dCBT), and 671 Haplo HCT performed between 2008 and 2017 for acute leukemias and myelodysplastic syndrome were examined. Several models of KIR-L interactions were analyzed by multiple regression analyses for their association with engraftment, overall survival (OS), and transplant-related mortality (TRM). In sCBT, although HvG or bidirectional KIR ligand mismatch (KIR-L-MM) was initially associated with higher TRM in the first 6 months after transplantation, this effect was nullified after 6 months such that long-term survival was not different compared to GvH KIR-L-MM or KIR-L matched (KIR-L-M) pairs. There was no significant difference in neutrophil and platelet engraftment. In dCBT, no significant differences were seen in engraftment, OS and TRM. In the Haplo cohort there was faster platelet recovery in the GvH KIR-L-MM/KIR-L-M pairs versus HvG KIR-L-MM or bidirectional mismatch (HR 1.23, P= .0116). There was no significant association with OS, TRM, or neutrophil engraftment. In this large registry study, KIR-L mismatching did not significantly impact engraftment, TRM, or survival in CBT and Haplo HCT, although an association with platelet engraftment in Haplo HCT was demonstrated.

Pan, T., et al. (2022). "Efficacy of azacitidine in preventing relapse after hematopoietic stem cell transplantation for advanced myeloid malignancies: a systematic review and meta-analysis." Expert Rev Hematol **15**(5): 457-464.

BACKGROUND: Relapse is the leading cause of death from myeloid malignancies after allogeneic hematopoietic stem cell transplantation (HSCT). Azacitidine has gained attention in recent years in the prophylaxis of relapsed refractory hematologic malignancies. This study evaluated the efficacy of AZA in preventing relapse after HSCT in patients with myeloid malignancies. METHODS: A systematic review and meta-analysis of all available cohort studies were performed regarding the application of AZA for prophylaxis of relapse after HSCT for advanced MDS and AML. Databases were searched for relevant studies. Endpoints included 2-year relapse rate, survival, relapse-related mortality, as well as the incidence of graft-versus-host disease (GVHD). RESULTS: A total of 444 patients from 13 studies were included in this analysis. The pooled estimate of the cumulative incidence of relapse after two years in enrolled patients was 25% (95% confidence interval [CI], 18%-33%). The pooled estimates of 2-year survival probabilities were 65% (95% CI, 50%-79%). The pooled cumulative incidence of relapse-related mortality was 28% (95% CI, 22%-34%). The pooled estimated incidence of acute and chronic GVHD, respectively, were 28% (95% CI, 22%-34%) and 38% (95% CI, 27%-49%). CONCLUSION: AZA administration is efficacious for relapse prevention after HSCT in myeloid malignancies.

Prem, S., et al. (2022). "Relationship between certain HLA alleles and the risk of cytomegalovirus reactivation following allogeneic hematopoietic stem cell transplantation." Transpl Infect Dis: e13879.

INTRODUCTION: Evidence is emerging to support an association between certain human leukocyte antigen (HLA) alleles and the risk of cytomegalovirus (CMV) reactivation following allogeneic hematopoietic stem cell transplant (allo-HSCT). The primary aim of this study was to identify HLA alleles associated with resistance or susceptibility to CMV reactivation. METHODS: We studied 586 adults who underwent allo-HSCT for high-risk hematological malignancies. High-resolution HLA typing data were available for recipients and donors. HLA class I and II alleles observed at a frequency of >5% in our population were included in the analysis. A CMV viremia level of more than 200 IU/ml on

weekly monitoring was considered to be indicative of CMV reactivation. RESULTS: The median follow-up time in surviving patients was 21 months (range 4-74 months). The cumulative incidence of CMV reactivation at 6 months in the entire cohort was 55% (95% confidence interval [CI] 50.8%-59.2%). Mismatched donors, increasing recipient age, occurrence of acute graft versus host disease and recipient CMV seropositivity were associated with an increased risk of CMV reactivation. HLA B*07:02 (hazard ratio 0.59, 95% CI 0.40-0.83) was associated with a decreased risk of CMV reactivation. Patients who developed CMV reactivation had a lower incidence of relapse, higher transplant-related mortality (TRM) and lower overall survival (OS) than those without CMV reactivation. There was an adverse correlation of OS and TRM with increasing numbers of CMV reactivations. CONCLUSION: We observed that HLA B*07:02 was associated with a decreased risk of CMV reactivation. CMV reactivation was associated with lower relapse post-transplant, but this did not translate into a survival benefit due to higher TRM.

Puerta-Alcalde, P., et al. (2022). "Cytokine response as a biomarker for early diagnosis and outcome prediction of stem cell transplant recipients and acute leukemia patients with invasive aspergillosis." Med Mycol.

We aimed to determine the role of serum cytokine expression in invasive aspergillosis (IA) diagnosis and outcome prediction in hematologic patients. In this multicenter study, serum cytokines (IL6, IL10, INF-gamma, IL12, IL4, TNF-alpha, IL17 and IL23) were prospectively recruited from all consecutive patients with hematologic malignances at IA diagnosis and compared to control patients matched by center, age, baseline disease and therapeutic regimen. We included 36 patients with IA and 36 controls. Serum levels of IL6 and IL10 cytokines on day 0 were significantly increased in patients with IA when compared to controls ($p = 0.001$ and $p = 0.025$, respectively), even in those who were neutropenic. No differences were observed for the other cytokines. IL6 and IL10 predicted IA with an area under the ROC curve of 0.74 (95% CI 0.62-0.86) and 0.64 (95% CI 0.51-0.77), respectively. The best cut-off point in predicting IA was 20.85 pg/mL for IL6 (sensitivity 72.2%; specificity 77.8%; PPV 76.5% and NPV 73.7%), and 0.045 pg/mL for IL10 (sensitivity 62.9%; specificity 63.9%; PPV 62.9% and NPV 63.9%). IL6 levels were associated with increased mortality, with the best cut-off value being 65.59 pg/mL in mortality prediction. In conclusion, in addition to current tests in place, IL6 and IL10 levels-as measured in plasma-may help clinicians diagnose IA. High levels of IL6 at IA diagnosis are related with worse outcomes.

We evaluated the role of serum cytokine expression in invasive aspergillosis (IA) diagnosis and outcome. Serum levels of IL6 and IL10 are increased in patients with IA compared to controls, and IL6 levels are associated with mortality.
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Puyade, M., et al. (2022). "Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis, the Ottawa Protocol." Curr Protoc **2**(5): e437.

Autologous hematopoietic stem cell transplantation (aHSCT) is increasingly used to treat patients with highly active multiple sclerosis (MS) refractory to disease-modifying therapy. Briefly, cyclophosphamide and filgrastim are used to mobilize autologous hematopoietic stem cells (HSC) into the circulation. HSC are harvested by leukapheresis, purified using a CD34 immunomagnetic selection process, and cryopreserved. Busulphan, cyclophosphamide, and rabbit anti-thymocyte globulin are used to destroy the patient's autoreactive immune system, followed by infusion of the previously collected HSC, which reconstitute a naive and self-tolerant immune system. Many MS patients experience durable remissions with no evidence of new disease activity following aHSCT. Treatment-related toxicity is rare, but potentially life-threatening complications necessitate appropriate patient selection by MS neurologists and HSCT physicians. AHSCT must be performed with a highly trained multidisciplinary team expert to minimize morbidity and mortality. We present the current aHSCT procedure for an MS indication at The Ottawa Hospital, developed from our program's 20-year experience. (c) 2022 Wiley Periodicals LLC. Basic Protocol 1: Candidate selection Basic Protocol 2: Autologous hematopoietic stem cell mobilization, collection, purification, and cryopreservation Basic Protocol 3: Autologous hematopoietic stem cell transplantation Basic Protocol 4: Supportive care following recovery from aHSCT (Beyond 100 days) Basic Protocol 5: Ongoing evaluation of multiple sclerosis.

Raj, R., et al. (2022). "Donor Characteristics Predict the Success of Allogeneic Hematopoietic Stem Cell Transplantation in Thalassemia Major: A Single-Center Analysis of 250 Patients." Indian J Hematol Blood Transfus **38**(2): 411-415.

Introduction We present data on the impact of donor characteristics in a uniform cohort of children who underwent hematopoietic stem cell transplantation (HSCT) for thalassemia major. Patients and methods We performed a retrospective study in children undergoing matched related (MRD) or unrelated (MUD) HSCT from January 2009 to December 2019. Results We analyzed data on 250 patients (age seven months-

19 years), MRD n = 187, MUD n = 63. We documented sex mismatch in 44% of HSCTs. The graft rejection rate was 3.7%; all had a sex mismatched HSCT (P value = 0.001). Graft versus host disease (GVHD) was higher when donors were above two years as compared to less than two years (23%vs.6.5%, P value = 0.006), with higher rates of mixed chimerism when donors were < two years at 33.3%vs.8.3% in > two years (P value = 0.0001). Mortality and GVHD were higher in the MUD group as compared to the MRD group (15%vs.5%, P value = 0.009; 42.9%vs. 23.4%, P value = 0.0001 respectively). Overall survival was 92.8% with a median follow up of 5.4 years, and was superior in MRD versus MUD group (9.4 years versus 4.8 years P = 0.008). Conclusion The risk of graft rejection was higher with donor-recipient sex mismatch; while initial mortality and chronic GVHD was higher with MUD HSCT.

Ruggeri, A., et al. (2022). "Comparison of outcomes after unrelated double-unit cord blood and haploidentical peripheral blood stem cell transplantation in adults with acute myeloid leukemia, a study on behalf of Eurocord and ALWP-EBMT." Transplant Cell Ther.

BACKGROUND: Unmanipulated haploidentical stem cell transplantation with post-transplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis (Haplo-PTCY) and unrelated double-unit umbilical cord blood transplant (dUCBT) are feasible options to treat patients with high risk acute myeloid leukemia (AML). OBJECTIVES: The aim of our study was to compare outcomes after dUCBT and Haplo-HCT using PBSC in adult patients with AML in complete remission (CR) transplanted in European Society for Blood and Marrow Transplantation (EBMT) affiliated centers. STUDY DESIGN: In a population of adults with de novo AML in first or second CR, we compared outcomes after dUCBT (n=165) and after Haplo-PTCY PBSC (n=544) performed between January 2013 and December 2018. Patients receiving in-vivo antithymocyte globuline (ATG), Campath, or ex-vivo T-cell depletion were excluded. RESULTS: Median follow-up was 33 months for Haplo-PTCY and 52 months for dUCBT. No statically significant differences were observed between the two approaches in grade-II-IV acute-GVHD (hazard ratio [HR]=1.31, p=0.18), and grade-III-IV (HR=1.17, p=0.56) or in chronic-GVHD (HR=0.86, p=0.48) or relapse (HR=1.07, p=0.77), non-relapse mortality (NRM; HR=0.94, p=0.77), leukemia-free survival (LFS; HR=0.99, p=0.95) and overall survival (OS; HR=0.99, p=0.97) when comparing dUCBT with Haplo-PTCY. Favourable cytogenetic risk was the only factor predictive of lower relapse incidence. Younger age at transplant was associated with lower NRM and higher LFS and OS. CONCLUSION: Both dUCBT and Haplo-PTCY with PBSC can be considered as valid approaches for adult AML patients in complete remission. New strategies should be investigated in both settings to define the most appropriate conditioning regimen and potentially, to decrease relapse incidence and NRM through better immune reconstitution and optimal supportive care.

Schober, S. J., et al. (2022). "No Improvement of Survival for Alveolar Rhabdomyosarcoma Patients After HLA-Matched Versus -Mismatched Allogeneic Hematopoietic Stem Cell Transplantation Compared to Standard-of-Care Therapy." Front Oncol **12**: 878367.

Background: Patients with stage IV alveolar rhabdomyosarcoma (RMA) have a 5-year-survival rate not exceeding 30%. Here, we assess the role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for these patients in comparison to standard-of-care regimens. We also compare the use of HLA-mismatched vs. HLA-matched grafts after reduced vs. myeloablative conditioning regimens, respectively. Patients and Methods: In this retrospective analysis, we compare event-free survival (EFS), overall survival (OS), and toxicity of HLA-mismatched vs. -matched transplanted patients in uni- and multivariate analyses (total: n = 50, HLA-matched: n = 15, HLA-mismatched: n = 35). Here, the factors age at diagnosis, age at allo-HSCT, sex, Oberlin score, disease status at allo-HSCT, and HLA graft type are assessed. For 29 primarily transplanted patients, three matched non-transplanted patients per one transplanted patient were identified from the CWS registry. Outcomes were respectively compared for OS and EFS. Matching criteria included sex, age at diagnosis, favorable/unfavorable primary tumor site, and metastatic sites. Results: Median EFS and OS did not differ significantly between HLA-mismatched and -matched patients. In the mismatched group, incidence of acute GvHD was 0.87 (grade III-IV: 0.14) vs. 0.80 in HLA-matched patients (grade III-IV: 0.20). Transplant-related mortality (TRM) of all patients was 0.20 and did not differ significantly between HLA-mismatched and -matched groups. A proportion of 0.58 relapsed or progressed and died of disease (HLA-mismatched: 0.66, HLA-matched: 0.53) whereas 0.18 were alive in complete remission (CR) at data collection. Multivariate and competing risk analyses confirmed CR and very good partial response (VGPR) status prior to allo-HSCT as the only decisive predictor for OS ($p < 0.001$). Matched-pair survival analyses of primarily transplanted patients vs. matched non-transplanted patients also identified disease status prior to allo-HSCT (CR, VGPR) as the only significant predictor for EFS. Here, OS was not affected, however. Conclusion: In this retrospective analysis, only a

subgroup of patients with good response at allo-HSCT survived. There was no survival benefit of allo-transplanted patients compared to matched controls, suggesting the absence of a clinically relevant graft-versus-RMA effect in the current setting. The results of this analysis do not support further implementation of allo-HSCT in RMA stage IV patients.

Shan, M., et al. (2022). "The Clinical Value of Procalcitonin in the Neutropenic Period After Allogeneic Hematopoietic Stem Cell Transplantation." Front Immunol **13**: 843067.

The diagnostic value of procalcitonin and the prognostic role of PCT clearance remain unclear in neutropenic period after allogeneic hematopoietic stem cell transplantation introduction. This study evaluated 219 febrile neutropenic patients (116, retrospectively; 103, prospectively) who underwent allo-HSCT from April 2014 to March 2016. The area under the receiver operator characteristic curve (AUC) of PCT for detecting documented infection (DI) was 0.637, and that of bloodstream infection (BSI) was 0.811. In multivariate analysis, the inability to decrease PCT by more than 80% within 5-7 days after the onset of fever independently predicted poor 100-day survival following allo-HSCT (P = 0.036). Furthermore, the prognostic nomogram combining PCTc and clinical parameters showed a stable predictive performance, supported by the C-index of 0.808 and AUC of 0.813 in the primary cohort, and C-index of 0.691 and AUC of 0.697 in the validation cohort. This study demonstrated the diagnostic role of PCT in documented and bloodstream infection during the neutropenic period after allo-HSCT. PCTc might serve as a predictive indicator of post-HSCT 100-day mortality. A nomogram based on PCTc and several clinical factors effectively predicted the 100-day survival of febrile patients and may help physicians identify high-risk patients in the post-HSCT neutropenic period.

Shen, M. Z., et al. (2022). "A comprehensive model to predict severe acute graft-versus-host disease in acute leukemia patients after haploidentical hematopoietic stem cell transplantation." Exp Hematol Oncol **11**(1): 25.

BACKGROUND: Acute graft-versus-host disease (aGVHD) remains the major cause of early mortality after haploidentical related donor (HID) hematopoietic stem cell transplantation (HSCT). We aimed to establish a comprehensive model which could predict severe aGVHD after HID HSCT. METHODS: Consecutive 470 acute leukemia patients receiving HID HSCT according to the protocol registered at https://clinicaltrials.gov (NCT03756675) were enrolled, 70% of them (n = 335) were randomly selected as training cohort and the remains 30% (n = 135) were used as validation cohort. RESULTS: The equation was as follows: Probability (grade III-IV aGVHD) = [Formula: see text], where Y = -0.0288 x (age) + 0.7965 x (gender) + 0.8371 x (CD3 + /CD14 + cells ratio in graft) + 0.5829 x (donor/recipient relation) - 0.0089 x (CD8 + cell counts in graft) - 2.9046. The threshold of probability was 0.057392 which helped separate patients into high- and low-risk groups. The 100-day cumulative incidence of grade III-IV aGVHD in the low- and high-risk groups was 4.1% (95% CI 1.9-6.3%) versus 12.8% (95% CI 7.4-18.2%) (P = 0.001), 3.2% (95% CI 1.2-5.1%) versus 10.6% (95% CI 4.7-16.5%) (P = 0.006), and 6.1% (95% CI 1.3-10.9%) versus 19.4% (95% CI 6.3-32.5%) (P = 0.017), respectively, in total, training, and validation cohort. The rates of grade III-IV skin and gut aGVHD in high-risk group were both significantly higher than those of low-risk group. This model could also predict grade II-IV and grade I-IV aGVHD. CONCLUSIONS: We established a model which could predict the development of severe aGVHD in HID HSCT recipients.

Sheshadri, A., et al. (2022). "Lung Function Monitoring After Lung Transplantation and Allogeneic Hematopoietic Stem Cell Transplantation." Clin Ther **44**(5): 755-765 e756.

PURPOSE: Bronchiolitis obliterans syndrome (BOS) is a major cause of morbidity and mortality in lung transplantation and allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. Clinical guidelines recommend lung function monitoring to aid early identification of BOS, but real-world rates of pulmonary function testing (PFT) have not been studied. The purpose of this study was to quantify PFT rates in lung transplantation and allo-HSCT recipients. METHODS: This longitudinal retrospective study used US data from the IQVIA PharMetrics Plus commercial claims database (January 1, 2006-September 30, 2018) and the Medicare Limited Data Set (January 1, 2010-December 31, 2018). Study recipients had no evidence of transplantation 12 months before transplantation, which was identified by using diagnosis and procedure codes. PFTs were identified by using procedure codes. Outcomes were percentage of recipients who received >/=1 PFT in each follow-up year, including spirometry, lung diffusion capacity, lung function volume test, and plethysmography, including the average number of total and specific tests per recipient. FINDINGS: The study identified 367 commercially insured and 1776 Medicare recipients who underwent lung transplantation; 92% and 86% received >/=1 lung function test in the first year after transplantation, respectively. Among recipients observable 3 years after transplant, 85% and 83% received >/=1 PFT. Among

2187 commercially insured and 1864 Medicare recipients who underwent allo-HSCT, 44% and 36% received >/=1 lung function test in the first posttransplant year. In the third year after transplant, only 31% and 26% of observable allo-HSCT recipients underwent any PFT. IMPLICATIONS: Morbidity and mortality from BOS remain high in lung transplant and allo-HSCT recipients, but lung function testing in the first posttransplant year is not universal, with substantially lower rates among allo-HSCT recipients. Furthermore, testing rates in all cohorts declined over time. Increased and sustained monitoring could lead to earlier detection of BOS and earlier intervention and treatment.

Shiraiwa, S., et al. (2022). "Risk factors for lower respiratory tract disease and outcomes in allogeneic hematopoietic stem cell transplantation recipients with influenza virus infection." J Infect Chemother **28**(9): 1279-1285.

INTRODUCTION: Influenza virus infection (IVI) is frequent in allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients, and reports from several countries indicate high morbidity and mortality from progression to lower respiratory tract disease (LRTD). However, there have been no reports on IVI clinical characteristics, treatment outcomes, and risk factor for progression to LRTD among allo-HSCT recipients in Japan. METHODS: We retrospectively reviewed the medical charts of allo-HSCT recipients who developed IVI between 2012 and 2019. RESULTS: Forty-eight cases of IVI following allo-HSCT were identified at our institution. The median age was 42 years, and median time from allo-HSCT to IVI was 25 months. Thirty-seven patients (77.1%) were administered neuraminidase inhibitors (NAIs) as antiviral therapy within 48 h of symptom onset (early therapy), whereas 11 (22.9%) received NAI over 48 h after onset (delayed therapy). Subsequently, 12 patients (25.0%) developed LRTD after IVI. Multivariate analysis identified older age (hazard ratio [HR], 7.65; 95% confidence interval [CI], 2.22-26.3) and bronchiolitis obliterans (HR, 5.74; 95% CI, 1.57-21.0) as independent risk factors for progression to LRTD. Moreover, land-mark analysis showed that early therapy prevented progression to LRTD (11.8% vs. 45.5%, P = 0.013). The IVI-related mortality rate was 2.1%. CONCLUSIONS: Early NAI treatment is recommended for reducing the risk of LRTD progression due to IVI in allo-HSTC recipients, particularly for older patients and those with bronchiolitis obliterans.

Siamakpour-Reihani, S., et al. (2022). "Evaluating immune response and metabolic related biomarkers pre-allogenic hematopoietic stem cell transplant in acute myeloid leukemia." PLoS One **17**(6): e0268963.

Although hematopoietic stem cell transplantation (HCT) is the only curative treatment for acute myeloid leukemia (AML), it is associated with significant treatment related morbidity and mortality. There is great need for predictive biomarkers associated with overall survival (OS) and clinical outcomes. We hypothesized that circulating metabolic, inflammatory, and immune molecules have potential as predictive biomarkers for AML patients who receive HCT treatment. This retrospective study was designed with an exploratory approach to comprehensively characterize immune, inflammatory, and metabolomic biomarkers. We identified patients with AML who underwent HCT and had existing baseline plasma samples. Using those samples (n = 34), we studied 65 blood based metabolomic and 61 immune/inflammatory related biomarkers, comparing patients with either long-term OS (>/= 3 years) or short-term OS (OS </= 1 years). We also compared the immune/inflammatory response and metabolomic biomarkers in younger vs. older AML patients (</=30 years vs. >/= 55 years old). In addition, the biomarker profiles were analyzed for their association with clinical outcomes, namely OS, chronic graft versus host disease (cGVHD), acute graft versus host disease (aGVHD), infection and relapse. Several baseline biomarkers were elevated in older versus younger patients, and baseline levels were lower for three markers (IL13, SAA, CRP) in patients with OS >/= 3 years. We also identified immune/inflammatory response markers associated with aGVHD (IL-9, Eotaxin-3), cGVHD (Flt-1), infection (D-dimer), or relapse (IL-17D, bFGF, Eotaxin-3). Evaluation of metabolic markers demonstrated higher baseline levels of medium- and long-chain acylcarnitines (AC) in older patients, association with aGVHD (lactate, long-chain AC), and cGVHD (medium-chain AC). These differentially expressed profiles merit further evaluation as predictive biomarkers.

Stanojevic, M., et al. (2022). "Viral infection in hematopoietic stem cell transplantation: an International Society for Cell & Gene Therapy Stem Cell Engineering Committee review on the role of cellular therapy in prevention and treatment." Cytotherapy.

Despite recent advances in the field of HSCT, viral infections remain a frequent causeof morbidity and mortality among HSCT recipients. Adoptive transfer of viral specific T cells has been successfully used both as prophylaxis and treatment of viral infections in immunocompromised HSCT recipients. Increasingly, precise risk stratification of HSCT recipients with infectious complications should

incorporate not only pretransplant clinical criteria, but milestones of immune reconstitution as well. These factors can better identify those at highest risk of morbidity and mortality and identify a population of HSCT recipients in whom adoptive therapy with viral specific T cells should be considered for either prophylaxis or second line treatment early after inadequate response to first line antiviral therapy. Broadening these approaches to improve outcomes for transplant recipients in countries with limited resources is a major challenge. While the principles of risk stratification can be applied, early detection of viral reactivation as well as treatment is challenging in regions where commercial PCR assays and antiviral agents are not readily available.

Suwannaying, K., et al. (2022). "Treatment outcomes of high-dose chemotherapy plus stem cell rescue in high-risk neuroblastoma patients in Thailand." Clin Exp Pediatr.

Background: In 2013, the Thai Pediatric Oncology Group (ThaiPOG) introduced a national protocol in which high-dose chemotherapy plus stem cell rescue is performed without immunotherapy. Methods: This study aimed to elucidate the outcomes of high-risk neuroblastoma (HR-NB) patients treated with the ThaiPOG protocol. This retrospective cohort review included 48 patients (30 male, 18 female) with a median age of 3 years (range, 8 months to 18 years) who were treated at five ThaiPOG treatment centers in Thailand in 2000-2018. Results: Eight of the 48 patients showed MYCN amplification. Twenty-three patients (48%) received 131I-meta-iodobenzylguanidine prior to high-dose chemotherapy and stem cell rescue. The majority of patients achieved a complete or very good response prior to consolidation treatment. The 5-year overall survival (OS) and event-free survival (EFS) rates were 45.1% and 40.4%, respectively. Patients aged > 2 years had a non-significantly higher mortality risk (hazard ratio [HR], 2.66; 95% confidence interval [CI], 0.92-7.68; P = 0.07). The MYCN amplification group had lower OS and EFS rates than the MYCN non-amplification group, but the difference was not statistically significant (45% OS and 37.5% EFS versus 33.3% OS and 16.6% EFS; P = 0.67 and 0.67, respectively). Cis-retinoic acid treatment for 12 months was a strong prognostic factor that could reduce mortality rates among HR-NB patients (HR, 0.27; 95% CI, 0.09-0.785; P = 0.01). Conclusion: High-dose chemotherapy plus stem cell rescue followed by cis-retinoic acid for 12 months was well tolerated and could improve the survival rates of patients with HR-NB.

Telang, N. (2022). "Stem Cell Models for Cancer Therapy." Int J Mol Sci **23**(13).

Metastatic progression of female breast and colon cancer represents a major cause of mortality in women. Spontaneous/acquired resistance to conventional and targeted chemo-endocrine therapy is associated with the emergence of drug-resistant tumor-initiating cancer stem cell populations. The cancer-initiating premalignant stem cells exhibit activation of select cancer cell signaling pathways and undergo epithelial-mesenchymal transition, leading to the evolution of a metastatic phenotype. The development of reliable cancer stem cell models provides valuable experimental approaches to identify novel testable therapeutic alternatives for therapy-resistant cancer. Drug-resistant stem cell models for molecular subtypes of clinical breast cancer and for genetically predisposed colon cancer are developed by selecting epithelial cells that survive in the presence of cytostatic concentrations of relevant therapeutic agents. These putative stem cells are characterized by the expression status of select cellular and molecular stem cell markers. The stem cell models are utilized as experimental approaches to examine the stem-cell-targeted growth inhibitory efficacy of naturally occurring dietary phytochemicals. The present review provides a systematic discussion on (i) conceptual and experimental aspects relevant to the chemo-endocrine therapy of breast and colon cancer, (ii) molecular/cellular aspects of cancer stem cells and (iii) potential stem-cell-targeting lead compounds as testable alternatives against the progression of therapy-resistant breast and colon cancer.

Teschner, D., et al. (2022). "Cytomegalovirus infection and rehospitalization rates after allogeneic hematopoietic stem cell and solid organ transplantation: a retrospective cohort study using German claims data." Infection.

PURPOSE: This study aimed to describe the cytomegalovirus (CMV) infection rate, rehospitalizations, and comorbidities following allogeneic hematopoietic stem cell transplantation (allo-HSCT) and solid organ transplantation (SOT). METHODS: Patients who received allo-HSCT or SOT in 01/07/2015-30/06/2018 were identified using anonymized German claims data. The transplantation-related hospital admission date was defined as the index date, and patients were followed for up to 12 months (or death, first event relevant). The frequency of CMV infections (confirmed outpatient/inpatient diagnoses, ICD-10-GM codes: B25.-/B27.1) and the rate, number, and duration of all-cause rehospitalizations in the follow-up period were evaluated. RESULTS: A total of 226 allo-HSCT and 250 SOT patients were identified (mean age 52.8 years, 38.9% female). During the 12 months after transplantation, 29.2% of allo-HSCT patients and 16.8% of SOT patients received a CMV diagnosis. The

majority of these diagnoses were given during the initial hospitalization or within the following 3 months. Across transplantation types, CMV patients had more hospital readmission days per patient-year (allo-HSCT 93.3 vs. 49.4, p = 0.001; SOT 42.0 vs. 20.7, p = 0.005), with a longer mean duration of readmissions (allo-HSCT 22.4 vs. 15.4 days, p < 0.001; SOT 11.6 vs. 7.5 days, p = 0.003). Comorbidity burden in transplantation patients was substantial, with several diagnoses being significantly more common among patients with CMV vs. non-CMV. One-year mortality did not differ significantly between patients with/without CMV. CONCLUSION: Burden of transplant recipients with CMV in terms of rehospitalizations and comorbidities is substantial, highlighting the need for improved CMV prevention and treatment.

Thurlapati, A., et al. (2022). "Successfully treated acute adult T-cell leukemia with haploidentical stem cell transplantation." Proc (Bayl Univ Med Cent) **35**(4): 557-559.

Adult T-cell leukemia-lymphoma caused by human T-lymphotropic virus type 1 is a rare and aggressive tumor with high morbidity and mortality. Historically it has been treated with chemotherapy, but more recent studies suggest improvement in survival with the combination of chemotherapy and stem cell transplantation. Our case study reports a middle-aged African American woman with no other risk factors diagnosed with the acute form of adult T-cell leukemia-lymphoma and in remission after completing chemotherapy and a haploidentical stem cell transplantation.

Tiong, T. Y., et al. (2022). "Targeting the SREBP-1/Hsa-Mir-497/SCAP/FASN Oncometabolic Axis Inhibits the Cancer Stem-like and Chemoresistant Phenotype of Non-Small Cell Lung Carcinoma Cells." Int J Mol Sci **23**(13).

BACKGROUND: Lung cancer remains a leading cause of cancer-related death, with an annual global mortality rate of 18.4%. Despite advances in diagnostic and therapeutic technologies, non-small cell lung carcinoma (NSCLC) continues to be characterized by a poor prognosis. This may be associated with the enrichment of cancer stem cells (CSCs) and the development of chemoresistance-a double-edged challenge that continues to impede the improvement of long-term outcomes. Metabolic reprogramming is a new hallmark of cancer. Sterol regulatory element-binding proteins (SREBPs) play crucial regulatory roles in the synthesis and uptake of cholesterol, fatty acids, and phospholipids. Recent evidence has demonstrated that SREBP-1 is upregulated in several cancer types. However, its role in lung cancer remains unclear. OBJECTIVE: This study investigated the role of SREBP-1 in NSCLC biology, progression, and therapeutic response and explored the therapeutic exploitability of SREBP-1 and SREBP-1-dependent oncometabolic signaling and miRNA epigenetic regulation. METHODS: We analyzed SREBP-1 levels and biological functions in clinical samples and the human NSCLC cell lines H441 and A549 through shRNA-based knock down of SREBP function, cisplatin-resistant clone generation, immunohistochemical staining of clinical samples, and cell viability, sphere-formation, Western blot, and quantitative PCR assays. We conducted in-silico analysis of miRNA expression in NSCLC samples by using the Gene Expression Omnibus (GSE102286) database. RESULTS: We demonstrated that SREBP-1 and SCAP are highly expressed in NSCLC and are positively correlated with the aggressive phenotypes of NSCLC cells. In addition, downregulation of the expression of tumor-suppressing hsa-miR-497-5p, which predictively targets SREBP-1, was observed. We also demonstrated that SREBP-1/SCAP/FASN lipogenic signaling plays a key role in CSCs-like and chemoresistant NSCLC phenotypes, especially because the fatostatin or shRNA targeting of SREBP-1 significantly suppressed the viability, cisplatin resistance, and cancer stemness of NSCLC cells and because treatment induced the expression of hsa-miR-497. CONCLUSION: Targeting the SREBP-1/hsa-miR-497 signaling axis is a potentially effective anticancer therapeutic strategy for NSCLC.

Tsamadou, C., et al. (2022). "Donor genetic determinant of thymopoiesis rs2204985 impacts clinical outcome after single HLA mismatched hematopoietic stem cell transplantation." Bone Marrow Transplant.

A common genetic variant within the T cell receptor alpha (TCRA)-T cell receptor delta (TCRD) locus (rs2204985) has been recently found to associate with thymic function. Aim of this study was to investigate the potential impact of donor rs2204985 genotype on patient's outcome after unrelated hematopoietic stem cell transplantation (uHSCT). 2016 adult patients were retrospectively analyzed. rs2204985 genotyping was performed by next generation sequencing, p < 0.05 was considered significant and donor rs2204985 GG/AG genotypes were set as reference vs. the AA genotype. Multivariate analysis of the combined cohort regarding the impact of donor's rs2204985 genotype indicated different risk estimates in 10/10 and 9/10 HLA matched transplantations. A subanalysis on account of HLA incompatibility revealed that donor AA genotype in single HLA mismatched cases (n = 624) associated with significantly inferior overall- (HR: 1.48, p = 0.003) and

disease-free survival (HR: 1.50, p = 0.001). This effect was driven by a combined higher risk of relapse incidence (HR: 1.40, p = 0.026) and non-relapse mortality (HR: 1.38, p = 0.042). This is the first study to explore the role of rs2204985 in a clinical uHSCT setting. Our data suggest that donor rs2204985 AA genotype in combination with single HLA mismatches may adversely impact post-HSCT outcome and should thus be avoided.

Tun, A. M., et al. (2022). "Progression-Free Survival at 24 Months as A Landmark After Autologous Stem Cell Transplant in Relapsed or Refractory Diffuse Large B-cell Lymphoma." Transplant Cell Ther.

BACKGROUND: Patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) who achieve progression-free survival (PFS) at 24 months (PFS24) following immunochemotherapy (IC) have excellent overall survival (OS) comparable to that of the age- and sex-matched general population. However, a similar landmark has not been established for patients with relapsed or refractory (RR) DLBCL following frontline IC who are subsequently treated with salvage therapy followed by autologous stem cell transplant (ASCT). OBJECTIVE: To evaluate the role of PFS24 as a landmark after ASCT in patients with RR DLBCL. STUDY DESIGN: Patients with RR DLBCL after frontline R-CHOP or R-CHOP-like IC who underwent salvage therapy and ASCT at Mayo Clinic between July 2000 and December 2017 and University of Iowa between April 2003 and April 2020 were identified from institutional lymphoma and transplant databases. Clinical characteristics, treatment information, and outcome data were abstracted. PFS, OS, and post-ASCT relapse survival (PRS) were analyzed using Kaplan-Meier method, and cumulative incidences of relapse vs non-relapse mortality and different causes of death were compared accounting for competing events. RESULTS: A total of 437 patients were identified. Median age at ASCT was 61 years (range 19-78), and 280 (64%) were male. After a median post-ASCT follow up of 8.0 years (95% CI 7.2-8.7), 215 patients had a relapse (or disease progression), 180 within 2 years and 35 after 2 years. For the entire cohort, post-ASCT relapse rate was much higher than non-relapse mortality rate (48.1 vs 9.1% at 5-years). Median PFS and OS after ASCT was 2.7 and 5.4 years, respectively. Lymphoma was the primary cause of death after ASCT. In contrast, for patients who had achieved PFS24 (n=220), rates of post-PFS24 relapse and non-relapse mortality were similar (14.8% and 12.3% at 5-years). Median PFS and OS after achieving PFS24 was 10.0 and 11.5 years, respectively. Lymphoma related and unrelated death rates were similar after achieving PFS24. For all patients who had a post-ASCT relapse, median PRS was 0.7 (95% CI 0.5-0.9) years, and late relapse (>2 vs </=2 years after ASCT) was associated with better PRS (median 2.3 [1.7-4.8] vs 0.5 [0.3-0.7] years, p<0.001). CONCLUSION: PFS24 is an important landmark associated with post-ASCT outcomes in patients with RR DLBCL following frontline IC.

Vaitkute, G., et al. (2022). "Linking gastrointestinal microbiota and metabolome dynamics to clinical outcomes in paediatric haematopoietic stem cell transplantation." Microbiome **10**(1): 89.

BACKGROUND: Haematopoietic stem cell transplantation is a curative procedure for a variety of conditions. Despite major advances, a plethora of adverse clinical outcomes can develop post-transplantation including graft-versus-host disease and infections, which remain the major causes of morbidity and mortality. There is increasing evidence that the gastrointestinal microbiota is associated with clinical outcomes post-haematopoietic stem cell transplantation. Herein, we investigated the longitudinal dynamics of the gut microbiota and metabolome and potential associations to clinical outcomes in paediatric haematopoietic stem cell transplantation at a single centre. RESULTS: On admission (baseline), the majority of patients presented with a different gut microbial composition in comparison with healthy control children with a significantly lower alpha diversity. A further, marked decrease in alpha diversity was observed immediately post-transplantation and in most microbial diversity, and composition did not return to baseline status whilst hospitalised. Longitudinal trajectories identified continuous fluctuations in microbial composition, with the dominance of a single taxon in a significant proportion of patients. Using pam clustering, three clusters were observed in the dataset. Cluster 1 was common pre-transplantation, characterised by a higher abundance of Clostridium XIVa, Bacteroides and Lachnospiraceae; cluster 2 and cluster 3 were more common post-transplantation with a higher abundance of Streptococcus and Staphylococcus in the former whilst Enterococcus, Enterobacteriaceae and Escherichia predominated in the latter. Cluster 3 was also associated with a higher risk of viraemia. Likewise, further multivariate analysis reveals Enterobacteriaceae, viraemia, use of total parenteral nutrition and various antimicrobials contributing towards cluster 3, Streptococcaceae, Staphylococcaceae, Neisseriaceae, vancomycin and metronidazole contributing towards cluster 2. Lachnospiraceae, Ruminococcaceae, Bifidobacteriaceae and not being on total parenteral nutrition contributed to cluster 1. Untargeted metabolomic analyses revealed changes that paralleled fluctuations in microbiota composition; importantly, low faecal butyrate was associated with a higher risk of

viraemia. CONCLUSIONS: These findings highlight the frequent shifts and dominations in the gut microbiota of paediatric patients undergoing haematopoietic stem cell transplantation. The study reveals associations between the faecal microbiota, metabolome and viraemia. To identify and explore the potential of microbial biomarkers that may predict the risk of complications post-HSCT, larger multi-centre studies investigating the longitudinal microbial profiling in paediatric haematopoietic stem cell transplantation are warranted. Video abstract.

Vogel, M., et al. (2022). "A Limited Role for AMD3100 Induced Stem Cell Mobilization for Modulation of Thoracic Trauma Outcome." Shock **57**(6): 260-267.

ABSTRACT: Thoracic trauma is a major cause of mortality due to the associated inflammatory acute respiratory distress syndrome and morbidity due to impaired tissue regeneration. Trauma-induced lung inflammation is characterized by the early recruitment of cells with pro- or anti-inflammatory activity to the lung. Therapeutic interventions reducing the level of tissue inflammation may result in decreased tissue damage and improved healing and recovery. Stem cells might be able to improve trauma outcome via immunomodulation or by enhancing tissue regeneration.Here, we describe the migratory dynamics of murine mesenchymal, hematopoietic and endothelial stem and progenitor cells (SPCs) as well as mature inflammatory cells (monocytes, neutrophils, lymphocytes) to peripheral blood (PB) and lung tissue between 0.2 and 48 h post-blunt chest trauma (TXT). We demonstrate that the kinetics of immune cell and SPC distribution upon trauma are both cell-type and tissue-dependent. We identified a transient, early increase in the number of inflammatory cells in PB and lung at 2 h post-TXT and a second wave of infiltrating SPCs in lungs by 48 h after TXT induction, suggesting a role for SPCs in tissue remodeling after the initial inflammatory phase. Cxcl12/Cxcr4 blockade by AMD3100 within the first 6 h after TXT, while inducing a strong and coordinated mobilization of SPCs and leukocytes to PB and lung tissue, did not significantly affect TXT associated inflammation or tissue damage as determined by inflammatory cytokine levels, plasma markers for organ function, lung cell proliferation and survival, and myofibroblast/fibroblast ratio in the lung. Further understanding the dynamics of the distribution of endogenous SPCs and inflammatory cells will therefore be indispensable for stem cell-based or immunomodulation therapies in trauma.

Wells, J. R., et al. (2022). "Delayed platelet recovery and mortality after allogeneic stem cell transplantation in children." Bone Marrow Transplant.

Wen, B., et al. (2022). "Oral eltrombopag versus subcutaneous recombinant human thrombopoietin for promoting platelet engraftment after allogeneic stem cell transplantation: A prospective, non-inferiority, randomized controlled trial." Hematol Oncol.

Delayed platelet engraftment (DPE) is associated with poor survival and increased transplantation-related mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Therefore, treatments are needed to improve platelet engraftment and prevent DPE. We performed a phase three, non-inferior, randomized controlled study of eltrombopag or recombinant human thrombopoietin (rhTPO) to promot platelet engraftment after allo-HSCT. Candidates for allo-HSCT were randomly assigned to receive oral eltrombopag (50 mg daily) or subcutaneous rhTPO (15000U daily) from the first-day post-transplantation. The primary endpoint was the cumulative numbers of platelet engraftment (platelet recovery >/=20 x 10(9) /L, without transfusion, for seven consecutive days) on day 60 after transplantation. We performed intention-to-treat analyses with a non-inferior margin of -15%. A total of 92 participants underwent randomization. 44 and 48 patients were randomized to the eltrombopag and rhTPO groups, respectively. The median duration of follow-up was 360 days (range: 12-960 days). The cumulative incidence of platelet engraftment on day 60 after transplantation in eltrombopag group was 86.4% (38/44) compared with 85.4% (41/48) in the rhTPO group (absolute risk difference [ARD] 1%, one-sided lower limit of 95% confidence interval [CI] -13.28%, Pnon-inferirioty = 0.014). The rate of DPE in the eltrombopag group was 6.8% (3/44) compared with 12.5% (6/48) in the rhTPO group (ARD -5.7%, one-sided higher limit of 95% CI 6.28%, Pnon-inferirioty = 0.063). Approximately, three-fourths of non-hematologic adverse events were not observed in the eltrombopag group but three patients (3/48, 6%) experienecd them in the rhTPO group. In addition, platelet transfusions unite from day 0 to day 21, or from day 22 to day 60, progression-free survival, overall survival were not significantly different between both groups. Eltrombopag was non-inferior to rhTPO in promoting platelet engraftment post allo-HSCT for patients with hematological malignancy. Oral eltrombopag was more convenient for patients than subcutaneous rhTPO (NCT03515096).

Wieczorek, M., et al. (2022). "Neurological complications in adult allogeneic hematopoietic stem cell transplant patients: Incidence, characteristics and

long-term follow-up in a multicenter series." Bone Marrow Transplant **57**(7): 1133-1141.

Neurological complications (NCs) represent a diagnostic and clinical challenge in allogeneic hematopoietic stem cell transplant (alloHSCT) patients. We retrospectively analyzed NC incidence, etiology, timing, characteristics, outcome, and long-term effects in 2384 adult patients transplanted in seven Italian institutions between January 2007 and December 2019. Ninety-three (3.9%) patients were affected by 96 NCs that were infectious (29.2%), immune/inflammatory (26%), drug-related (12.5%), cerebrovascular (5.2%), metabolic (3.1%), related to central nervous system disease relapse (11.5%) and malignancy (3.1%), or undefined (9.4%). Six patients (6.4%) had neurological manifestations of chronic graft-versus-host disease (GVHD). NCs occurred on average at day +128 (from -5 to +4063). Early (< day +120) and late NCs had similar frequencies (46.9% vs 53.1%, p = 0.39). Thirty-one patients (33.3%) were affected by acute or chronic GVHD at the NC onset. With a median follow-up of 25.4 (0.4-163) months, the overall mortality due to NCs was 22.6%. The median time between NC onset and death was 36 (1-269) days. Infectious NCs were the main cause (61.9%) of NC-related mortality. A persistent neurological impairment occurred in 20.4% patients, 57.9% of whom being affected by immune/inflammatory NCs. This study highlights the rare, yet severe impact of alloHSCT-associated NCs on patient survival and long-term functional ability.

Wuputra, K., et al. (2022). "Stem Cell Biomarkers and Tumorigenesis in Gastric Cancer." J Pers Med **12**(6).

Stomach cancer has a high mortality, which is partially caused by an absence of suitable biomarkers to allow detection of the initiation stages of cancer progression. Thus, identification of critical biomarkers associated with gastric cancer (GC) is required to advance its clinical diagnoses and treatment. Recent studies using tracing models for lineage analysis of GC stem cells indicate that the cell fate decision of the gastric stem cells might be an important issue for stem cell plasticity. They include leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5(+)), Cholecystokinin receptor 2 (Cckr2(+)), and axis inhibition protein 2 (Axin2(+)) as the stem cell markers in the antrum, Trefoil Factor 2 (TFF2(+)), Mist1(+) stem cells, and Troy+ chief cells in the corpus. By contrast, Estrogen receptor 1 (eR1), Leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1), SRY (sex determining region Y)-box 2 (Sox2), and B lymphoma Mo-MLV insertion region 1 homolog (Bmi1) are rich in both the antrum and corpus regions. These markers might help to identify the cell-lineage identity and analyze the plasticity of each stem cell population. Thus, identification of marker genes for the development of GC and its environment is critical for the clinical application of cancer stem cells in the prevention of stomach cancers.

Yan, F., et al. (2022). "Mesenchymal Stem Cell-Derived Exosome-Loaded microRNA-129-5p Inhibits TRAF3 Expression to Alleviate Apoptosis and Oxidative Stress in Heart Failure." Cardiovasc Toxicol **22**(7): 631-645.

Heart failure (HF) represents a main global healthy and economic burden with unacceptably high morbidity and mortality rates. In the current study, we evaluated the potential effect of mesenchymal stem cell (MSC)-derived exosomes (MSC-Exos) on oxygen-glucose deprivation (OGD)-induced damages to HL-1 cells and HF mice and searched for the possible mechanism. MSC-Exos ameliorated oxidative stress and reduced apoptosis in OGD-treated HL-1 cells. By microarray analysis, we found that MSC-Exos treatment significantly increased the microRNA (miR)-129-5p expression in HL-1 cells. miR-129-5p inhibitor attenuated the protective effect of MSC-Exos on OGD-treated HL-1 cells. miR-129-5p targeted tumor necrosis factor receptor-associated factor 3 (TRAF3), and TRAF3 loss reversed the effect of miR-129-5p inhibitor by blunting the NF-kappaB signaling. MSC-Exos injection alleviated ventricular dysfunction and suppressed oxidative stress, apoptosis, inflammation, and fibrosis in cardiomyocytes in mice with HF by inhibiting NF-kappaB signaling pathway through miR-129-5p/TRAF3. Our findings suggest that exosomal miR-129-5p from MSCs protects the heart from failure by targeting TRAF3 and the following NF-kappaB signaling. This regulatory axis may be a possible therapeutic target for HF.

Yang, G., et al. (2022). "Mesenchymal Stem Cell Application and Its Therapeutic Mechanisms in Intracerebral Hemorrhage." Front Cell Neurosci **16**: 898497.

Intracerebral hemorrhage (ICH), a common lethal subtype of stroke accounting for nearly 10-15% of the total stroke disease and affecting two million people worldwide, has a high mortality and disability rate and, thus, a major socioeconomic burden. However, there is no effective treatment available currently. The role of mesenchymal stem cells (MSCs) in regenerative medicine is well known owing to the simplicity of acquisition from various sources, low immunogenicity, adaptation to the autogenic and allogeneic systems, immunomodulation, self-recovery by secreting extracellular vesicles (EVs), regenerative repair, and antioxidative stress. MSC therapy provides an increasingly attractive therapeutic approach for ICH. Recently, the functions of MSCs such as neuroprotection, anti-inflammation, and improvement

in synaptic plasticity have been widely researched in human and rodent models of ICH. MSC transplantation has been proven to improve ICH-induced injury, including the damage of nerve cells and oligodendrocytes, the activation of microglia and astrocytes, and the destruction of blood vessels. The improvement and recovery of neurological functions in rodent ICH models were demonstrated via the mechanisms such as neurogenesis, angiogenesis, anti-inflammation, anti-apoptosis, and synaptic plasticity. Here, we discuss the pathological mechanisms following ICH and the therapeutic mechanisms of MSC-based therapy to unravel new cues for future therapeutic strategies. Furthermore, some potential strategies for enhancing the therapeutic function of MSC transplantation have also been suggested.

Yoshimura, H., et al. (2022). "Real-world efficacy of letermovir prophylaxis for cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation: A single-center retrospective analysis." J Infect Chemother **28**(9): 1317-1323.

INTRODUCTION: Cytomegalovirus (CMV) infection is a common complication following allogeneic hematopoietic stem cell transplantation (aHSCT) and is associated with increased mortality. Letermovir (LET) is a novel antiviral drug used to prevent CMV infection. METHODS: We analyzed 111 consecutive patients who underwent aHSCT, retrospectively, to evaluate the efficacy of LET prophylaxis for clinically significant CMV infection (csCMVi) in real-world situations. In addition, we analyzed the influence of LET on transplant outcomes. Thirty-eight patients who were administered LET prophylactically were compared with 73 patients without LET prophylaxis after aHSCT. RESULTS: On day 180, the cumulative incidence of csCMVi in patients who received LET prophylaxis was significantly lower than that in patients without LET prophylaxis (29.7% vs. 56.2%, $P < 0.001$). Among the patients who developed csCMVi, the interval from aHSCT to the initiation of preemptive therapy was significantly longer in patients who received LET prophylaxis than in those who did not (129.5 days vs. 42 days, $P < 0.001$). The six-month overall survival was 86.1% in patients who received LET prophylaxis and 66.8% in the non-LET group ($P = 0.035$). CONCLUSION: LET prophylaxis was highly effective in preventing csCMVi and could potentially improve transplant outcomes, particularly when initiated early after transplantations.

Yui, S., et al. (2022). "Safety and efficacy of high-dose cytarabine MEAM therapy and other treatments for auto-peripheral blood stem cell transplantation: A retrospective comparative study." Asia Pac J Clin Oncol.

AIM: The MEAM regimen consisting of ranimustine (MCNU), etoposide (ETP), cytarabine (Ara-C), and melphalan (MEL) is widely used before auto-peripheral blood stem cell transplantation (auto-PBSCT) for malignant lymphoma in Japan. The MEAM regimen generally consists of 200-400 mg/m(2) for 4 days, but we decided to increase the dosage of Ara-C from the standard to 2 g/m(2) for 2 days with the aim of increasing drug transferability to the central nervous system. We evaluate the safety and therapeutic efficacy of high-dose Ara-C MEAM therapy. METHODS: The high-dose Ara-C MEAM protocol consisted of MCNU 300 mg/m(2) on day -7, ETP 200 mg/m(2) on days -6, -5, -4, -3 and Ara-C 2 g/m(2) on day -4 -3, and MEL 140 mg/m(2) on day -2. We retrospectively analyzed 37 cases of malignant lymphoma at our institution between May 2014 and July 2020. RESULTS: All patients got engraftment and there were no cases of treatment-related mortality. In all cases, the 3-year overall survival (OS) and progression-free survival (PFS) after transplantation were 80.6% and 65.7%, respectively. Twenty-one cases of diffuse large B-cell lymphoma recurrence, for which there is proven usefulness of auto-PBSCT, showed good results after transplantation, with the 3-year OS and PFS after transplantation being 100% and 74.3%, respectively. CONCLUSION: The safety and efficacy of high-dose Ara-C MEAM therapy were demonstrated, but the expected therapeutic effect on central nervous system lesions could not be fully evaluated owing to the small number of cases.

Zama, D., et al. (2022). "Pediatric cancer and hematopoietic stem cell transplantation patients requiring renal replacement therapy: results of the retrospective nationwide AIEOP study." Leuk Lymphoma: 1-8.

In children affected by malignancies and/or who received hematopoietic stem cell transplantation (HSCT), acute kidney injury (AKI) may occur causing a high mortality rate, despite the implementation of renal replacement therapy (RRT). We performed a nationwide, multicenter, retrospective, observational cohort study including consecutive patients between January 2010 and December 2019. One hundred and fourteen episodes of AKI requiring RRT coming from nine different Italian centers were included. The overall mortality rate was 61.4%. At the 3-month follow-up, the mortality rate was 47.4%. The mortality rate was higher in transplanted patients than those receiving chemotherapy. In particular, HSCT ($p = 0.048$) and invasive mechanical ventilation ($p = 0.040$) were significantly associated with death at three months after the end of dialysis in the multivariate analysis.

Pediatric patients affected by malignancies complicated by AKI requiring RRT have a high mortality. The main factors associated to death are respiratory failure and having received HSCT.

Zeng, Q., et al. (2022). "Autologous hematopoietic stem cell transplantation followed by interleukin-2 for adult acute myeloid leukemia patients with favorable or intermediate risk after complete remission." Ann Hematol **101**(8): 1711-1718.

High-dose chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) is generally the optimal option for patients with acute myeloid leukemia (AML). However, for favorable- and intermediate-risk patients, the regimen remains less understood due to graft versus host disease (GVHD) and increased non-relapsed mortality (NRM) caused by allo-HSCT. Additionally, the benefit of maintenance therapy has not yet been conclusively proven. Here, we conducted a retrospective study on the long-term outcome of AML patients with favorable or intermediate risk who underwent autologous hematopoietic stem cell transplantation (auto-HSCT) followed by interleukin-2 (IL-2) subcutaneous injection as maintenance therapy. A total of 49 patients from 2007 to 2019 were included in our study. They all received a daunorubicin + cytarabine regimen as induction chemotherapy followed by four to six cycles of consolidation therapy with medium- or high-dose cytarabine. Once patients achieved complete remission (CR1), they started receiving auto-HSCT followed by IL-2 injections. The results showed that no patients stopped receiving IL-2 injections on account of adverse side effects, and the 5-year overall survival (OS) and leukemia-free survival (LFS) rates were 85.6 +/- 5.0% and 78.5 +/- 6.1%, respectively. The multivariate analysis also suggested that age, gender, initial white blood cell (WBC) count, AML subtype, cytogenetic risk, and conditioning regimen did not affect the prognosis. In conclusion, auto-HSCT followed by IL-2 injection is an effective treatment that can improve the prognosis of AML for patients with favorable or intermediate risk.

Zhang, M., et al. (2022). "Safety and efficiency of stem cell therapy for COVID-19: a systematic review and meta-analysis." Glob Health Res Policy **7**(1): 19.

BACKGROUND: With the COVID-19 pandemic continuing, various treatments have become widely practiced. Stem cells have a wide range of applications in the treatment of lung diseases and have therefore been experimentally used to treat patients with COVID-19, but whether the expanded use of stem cells is safe and reliable still lacks enough evidence. To address this issue, we systematically reviewed the safety and efficiency of stem cell therapy in COVID-19 cases. METHODS: We searched PubMed, Embase, Web of Science, The Cochrane Library, CNKI, WanFang, VIP and SinoMed up to January 18, 2022. The included studies were assessed using the Risk-of-bias tool 1.0 and MINORS instrument. The adverse events, mortality, length of hospital day and laboratory parameters were analyzed by meta-analysis. We adhered to PRISMA reporting guideline. RESULTS: We have included 17 studies meeting the inclusion data. There were no significant differences in AEs (OR = 0.39, 95% CI = 0.12 to 1.33, P = 0.13, I(2) = 58%) and SAEs (OR = 0.21, 95% CI = 0.04 to 1.03, P = 0.05, I(2) = 0%) between stem cell therapy group and control group. The analysis showed that stem cell treatment could significantly reduce the mortality rate(OR = 0.24, 95% CI = 0.13 to 0.45, P < 0.01, I(2) = 0%), but was not able to cause changes in length of hospital stay or most laboratory parameters. CONCLUSIONS: The present study shows that stem cell therapy for COVID-19 has a remarkable effect on efficiency without increasing risks of adverse events and length of hospital stay. It is potentially necessary to establish the criteria for COVID-19 for stem cell therapy.

Zhang, Y., et al. (2022). "Significance of Placental Mesenchymal Stem Cell in Placenta Development and Implications for Preeclampsia." Front Pharmacol **13**: 896531.

The well-developed placentation is fundamental for the reproductive pregnancy while the defective placental development is the pathogenetic basis of preeclampsia (PE), a dangerous complication of pregnancy comprising the leading causes of maternal and perinatal morbidity and mortality. Placenta-derived mesenchymal stem cells (PMSCs) are a group of multipotent stem cells that own a potent capacity of differentiating into constitutive cells of vessel walls. Additionally, with the paracrine secretion of various factors, PMSCs inextricably link and interact with other component cells in the placenta, collectively improving the placental vasculature, uterine spiral artery remolding, and uteroplacental interface immunoregulation. Recent studies have further indicated that preeclamptic PMSCs, closely implicated in the abnormal crosstalk between other ambient cells, disturb the homeostasis and development in the placenta. Nevertheless, PMSCs transplantation or PMSCs exosome therapies tend to improve the placental vascular network and trophoblastic functions in the PE model, suggesting PMSCs may be a novel and putative therapeutic strategy for PE. Herein, we provide an overview of the multifaceted contributions of PMSCs in early placental development. Thereinto, the intensive interactions between PMSCs and other component cells in the placenta were particularly

highlighted and further extended to the implications in the pathogenesis and therapeutic strategies of PE.

Zhao, F., et al. (2022). "Higher Dose of CD34(+) cells Promotes Early Reconstitution of Natural Killer Cells and Is Associated with Better Outcomes After Unmanipulated Hematopoietic Stem Cell Transplantation for Myeloid Malignancies." Transplant Cell Ther.

Natural killer (NK) cells are the first lymphocyte population to recover after allogenic hematopoietic stem cell transplantation (allo-HSCT) and mediate potent graft versus leukemia effect, particularly in the settings of T-cell depletion. However, the significance of NK cells after unmanipulated transplantation is less clear, and factors affecting early NK reconstitution remain elusive. We retrospectively analyze 180 patients with acute myeloid leukemia or myelodysplastic syndrome who received unmanipulated allografts. We focus on the early NK reconstitution and its association with disease relapse, overall survival, and cytomegalovirus (CMV) reactivation. We also analyze factors that affect NK recovery, such as dose of CD34(+) cells in the graft and T-cell recovery after transplantation. Penalized splines and receiver operator characteristic curves demonstrate a strong association between blood NK counts at 30 days after allo-HSCT (NK30) and all-cause mortality, with the cutoff value being close to the median value that divides patients dichotomously. Subsequent analysis shows that rapid NK recovery (higher NK30 or higher NK60) is associated with reduced disease relapse and better survival. Robust NK recovery (NK30 and NK60) also correlates with lower incidence of CMV reactivation. We find that NK30 is associated with the numbers of CD34(+) cells ($r=0.739$, $P < .001$) but not mature NK cells contained in the graft. In a small subset (N=12) of the cohort, patients in continuous complete remission (N=6) demonstrate higher frequencies of CD34(+)CD7(+) progenitor cells and CD56(bright) NK cells in the day 30 bone marrow as compared to patients with disease relapse within 1 year (N=6). Furthermore, neither T-cell recovery after transplantation nor application of anti-thymocyte globulins (ATG) in the conditioning regimen demonstrate suppressive effect on NK recovery. Rapid NK cell recovery is associated with improved prognosis of unmanipulated transplantation for myeloid malignancies. Manipulation of NK cell recovery represents a feasible approach to improve transplant outcomes for example by optimizing CD34(+) cells in the graft.

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References

[1]. Baidu. http://www.baidu.com. 2022.
[2]. Cancer Biology. http://www.cancerbio.net. 2022.
[3]. Google. http://www.google.com. 2022.
[4]. Journal of American Science. http://www.jofamericanscience.org. 2022.
[5]. Life Science Journal. http://www.lifesciencesite.com. 2022.
[6]. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92. doi:10.7537/marsjas010205.14. http://www.jofamericanscience.org/journals/am-sci/0102/14-mahongbao.pdf.
[7]. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96. doi:10.7537/marsnsj050107.10. http://www.sciencepub.net/nature/0501/10-0247-mahongbao-eternal-ns.pdf.
[8]. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15. doi:10.7537/marslsj020105.03. http://www.lifesciencesite.com/lsj/life0201/life-0201-03.pdf.
[9]. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. doi:10.7537/marsnsj080210.03. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
[10]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. doi:10.7537/marsnsj010103.01. http://www.sciencepub.net/nature/0101/01-ma.pdf.
[11]. Marsland Press. http://www.sciencepub.net. 2022.
[12]. Marsland Press. http://www.sciencepub.org. 2022.
[13]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2022.
[14]. Nature and Science. http://www.sciencepub.net/nature. 2022.
[15]. Stem Cell. http://www.sciencepub.net/stem. 2022.
[16]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2022.

6/25/2022