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Stem Cell

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Stem Cell Therapy Benefits 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; therapy; benefits; 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.

Antonov, S. A. and E. V. Novosadova (2021). "Current State-of-the-Art and Unresolved Problems in Using Human Induced Pluripotent Stem Cell-Derived Dopamine Neurons for Parkinson's Disease Drug Development." Int J Mol Sci **22**(7).

Human induced pluripotent stem (iPS) cells have the potential to give rise to a new era in Parkinson's disease (PD) research. As a unique source of midbrain dopaminergic (DA) neurons, iPS cells provide unparalleled capabilities for investigating the pathogenesis of PD, the development of novel anti-parkinsonian drugs, and personalized therapy design. Significant progress in developmental biology of midbrain DA neurons laid the foundation for their efficient derivation from iPS cells. The introduction of 3D culture methods to mimic the brain microenvironment further expanded the vast opportunities of iPS cell-based research of the neurodegenerative diseases. However, while the benefits for basic and applied studies provided by iPS cells receive widespread coverage in the current literature, the drawbacks of this model in its current state, and in particular, the aspects of differentiation protocols requiring further refinement are commonly overlooked. This review summarizes the recent data on general and subtype-specific features of midbrain DA neurons and their development. Here, we review the current protocols for derivation of DA neurons from human iPS cells and outline their general weak spots. The associated gaps in the contemporary knowledge are considered and the possible directions for future research that may assist in improving the differentiation conditions and increase the efficiency of using iPS cell-derived neurons for PD drug development are discussed.

Armijo, E., et al. (2021). "Induced Pluripotent Stem Cell-Derived Neural Precursors Improve Memory, Synaptic and Pathological Abnormalities in a Mouse Model of Alzheimer's Disease." Cells **10**(7).

Alzheimer's disease (AD) is the most common type of dementia in the elderly population. The disease is characterized by progressive memory loss, cerebral atrophy, extensive neuronal loss, synaptic alterations, brain inflammation, extracellular accumulation of amyloid-beta (Abeta) plaques, and intracellular accumulation of hyper-phosphorylated tau (p-tau) protein. Many recent clinical trials have failed to show therapeutic benefit, likely because at the time in which patients exhibit clinical symptoms the brain is irreversibly damaged. In recent years, induced pluripotent stem cells (iPSCs) have been suggested as a promising cell therapy to recover brain functionality in

neurodegenerative diseases such as AD. To evaluate the potential benefits of iPSCs on AD progression, we stereotaxically injected mouse iPSC-derived neural precursors (iPSC-NPCs) into the hippocampus of aged triple transgenic (3xTg-AD) mice harboring extensive pathological abnormalities typical of AD. Interestingly, iPSC-NPCs transplanted mice showed improved memory, synaptic plasticity, and reduced AD brain pathology, including a reduction of amyloid and tangles deposits. Our findings suggest that iPSC-NPCs might be a useful therapy that could produce benefit at the advanced clinical and pathological stages of AD.

Asgari Taei, A., et al. (2021). "Enhancement of angiogenesis and neurogenesis by intracerebroventricular injection of secretome from human embryonic stem cell-derived mesenchymal stem cells in ischemic stroke model." Biomed Pharmacother **140**: 111709.

It is well accepted that the success of mesenchymal stem cells (MSCs) therapy against experimental stroke is mainly due to cellular paracrine manners rather than to replace lost tissue per se. Given such "bystander" effects, cell-free therapeutics manifest as a promising approach in regenerative medicine. Here we aimed at evaluating the effect of conditioned medium (CM) derived from human embryonic MSCs (hESC-MSC) on the neurological deficit, neurogenesis, and angiogenesis in experimental stroke. Adult male Wistar rats subjected to middle cerebral artery occlusion (MCAO), were treated with intracerebroventricular CM either one time (1 h post MCAO) or three times (1, 24, and 48 h post MCAO). Motor performance was assessed by the cylinder test on days 3 and 7. Cerebral samples were obtained for infarct size and molecular analysis on day 7 post-injury. Neurogenesis was evaluated by probing Nestin, Ki67, DCX, and Reelin transcripts and protein levels in the striatum, cortex, subventricular zone, and corpus callosum. The mRNA and protein expression of CD31 were also assessed in the striatum and cortical region to estimate angiogenesis post MCAO. Our findings demonstrate that CM treatment could significantly ameliorate neurological deficits and infarct volume in MCAO rats. Furthermore, ischemic stroke was associated with higher levels of neurogenesis and angiogenesis markers. Following treatment with CM, these markers were further potentiated in the brain regions. This study suggests that the therapeutic benefits of CM obtained from hESC-MSCs at least partly are mediated through improved neurogenesis and angiogenesis to accelerate the recovery of cerebral ischemia insult.

Barbuti, P. A., et al. (2021). "Recent Advances in the Development of Stem-Cell-Derived Dopaminergic Neuronal Transplant Therapies for Parkinson's Disease." Mov Disord **36**(8): 1772-1780.

The last decade has seen exciting advances in the development of potential stem cell-based therapies for Parkinson's disease (PD), which have used different types of stem cells as starting material. These cells have been developed primarily to replace dopamine-producing neurons in the substantia nigra that are progressively lost in the disease process. The aim is to largely restore lost motor functions, whilst not ever being curative. We discuss cell-based strategies that will have to fulfill important criteria to become effective and competitive therapies for PD. These criteria include reproducibly producing sufficient numbers of cells with an authentic substantia nigra dopamine neuron A9 phenotype, which can integrate into the host brain after transplantation and form synapses (considered crucial for long-term functional benefits). Furthermore, it is essential that transplanted cells exhibit no, or only very low levels of, proliferation without tumor formation at the site of grafting. Cumulative research has shown that stem cell-based approaches continue to have great potential in PD, but key questions remain to be answered. Here, we review the most recent progress in research on stem cell-based dopamine neuron replacement therapy for PD and briefly discuss what the immediate future might hold. (c) 2021 International Parkinson and Movement Disorder Society.

Barrera, J. A., et al. (2021). "Adipose-Derived Stromal Cells Seeded in Pullulan-Collagen Hydrogels Improve Healing in Murine Burns." Tissue Eng Part A **27**(11-12): 844-856.

Burn scars and scar contractures cause significant morbidity for patients. Recently, cell-based therapies have been proposed as an option for improving healing and reducing scarring after burn injury, through their known proangiogenic and immunomodulatory paracrine effects. Our laboratory has developed a pullulan-collagen hydrogel that, when seeded with mesenchymal stem cells (MSCs), improves cell viability and augments their proangiogenic capacity in vivo. Concurrently, recent research suggests that prospective isolation of cell subpopulations with desirable transcriptional profiles can be used to further improve cell-based therapies. In this study, we examined whether adipose-derived stem cell (ASC)-seeded hydrogels could improve wound healing following thermal injury using a murine contact burn model. Partial thickness contact burns were created on the dorsum of mice. On days 5 and 10 following injury, burns were debrided and received either ASC hydrogel, ASC injection alone, hydrogel alone, or no treatment. On days 10 and 25, burns were harvested for histologic and molecular analysis. This experiment was repeated using CD26(+)/CD55(+) FACS-enriched ASCs to further evaluate the regenerative potential of ASCs in wound healing. ASC

hydrogel-treated burns demonstrated accelerated time to reepithelialization, greater vascularity, and increased expression of the proangiogenic genes MCP-1, VEGF, and SDF-1 at both the mRNA and protein level. Expression of the profibrotic gene Timp1 and proinflammatory gene Tnfa was downregulated in ASC hydrogel-treated burns. ASC hydrogel-treated burns exhibited reduced scar area compared to hydrogel-treated and control wounds, with equivalent scar density. CD26(+)/CD55(+) ASC hydrogel treatment resulted in accelerated healing, increased dermal appendage count, and improved scar quality with a more reticular collagen pattern. Here we find that ASC hydrogel therapy is effective for treating burns, with demonstrated proangiogenic, fibromodulatory, and immunomodulatory effects. Enrichment for CD26(+)/CD55(+) ASCs has additive benefits for tissue architecture and collagen remodeling postburn injury. Research is ongoing to further facilitate clinical translation of this promising therapeutic approach. Impact statement Burns remain a significant public health burden. Stem cell therapy has gained attention as a promising approach for treating burns. We have developed a pullulan-collagen biomimetic hydrogel scaffold that can be seeded with adipose-derived stem cells (ASCs). We assessed the delivery and activity of our scaffold in a murine contact burn model. Our results suggest that localized delivery of ASC hydrogel treatment is a promising approach for the treatment of burn wounds, with the potential for rapid clinical translation. We believe our work will have broad implications for both hydrogel therapeutics and regenerative medicine and will be of interest to the general scientific community.

Blume, G. G., et al. (2021). "Tissue-engineered amniotic membrane in the treatment of myocardial infarction: a systematic review of experimental studies." Am J Cardiovasc Dis **11**(1): 1-11.

OBJECTIVE: myocardial infarction (MI) remains the leading cause of death worldwide. Cell-based therapies have become potential therapeutic approaches, attempting to recover the contractility of necrotic cardiomyocytes. In the present study, we aimed to systematically evaluate experimental studies on the use of tissue-engineered amniotic membrane (hAMC) in MI treatment. METHODS: a systematic review of literature published in PubMed, Embase and CENTRAL databases was conducted, until March 31, 2020, for experimental studies reporting on hAMC cell-therapy performed on LV function, MI size, paracrine effects, angiogenesis, and cell differentiation. Two reviewers selected the articles that met the inclusion criteria and disagreements were solved through a consensus. RESULTS: a total of 11 studies were included for data extraction. For the acute scenario, therapeutic use of hAMC after MI was capable of improving LV function in rats, mainly due to its paracrine effects (anti-apoptotic and anti-inflammatory) and associated with cardiomyocyte differentiation, MI size reduction and neo-angiogenesis. CONCLUSION: tissue engineered hAMC following MI provided clinically relevant benefits on cardiac function and ventricular remodeling.

Bogensperger, C., et al. (2021). "Ex Vivo Mesenchymal Stem Cell Therapy to Regenerate Machine Perfused Organs." Int J Mol Sci **22**(10).

Transplantation represents the treatment of choice for many end-stage diseases but is limited by the shortage of healthy donor organs. Ex situ normothermic machine perfusion (NMP) has the potential to extend the donor pool by facilitating the use of marginal quality organs such as those from donors after cardiac death (DCD) and extended criteria donors (ECD). NMP provides a platform for organ quality assessment but also offers the opportunity to treat and eventually regenerate organs during the perfusion process prior to transplantation. Due to their anti-inflammatory, immunomodulatory and regenerative capacity, mesenchymal stem cells (MSCs) are considered as an interesting tool in this model system. Only a limited number of studies have reported on the use of MSCs during ex situ machine perfusion so far with a focus on feasibility and safety aspects. At this point, no clinical benefits have been conclusively demonstrated, and studies with controlled transplantation set-ups are urgently warranted to elucidate favorable effects of MSCs in order to improve organs during ex situ machine perfusion.

Bregere, C., et al. (2021). "Microglia and Stem-Cell Mediated Neuroprotection after Neonatal Hypoxia-Ischemia." Stem Cell Rev Rep.

Neonatal hypoxia-ischemia encephalopathy (HIE) refers to a brain injury in term infants that can lead to death or lifelong neurological deficits such as cerebral palsy (CP). The pathogenesis of this disease involves multiple cellular and molecular events, notably a neuroinflammatory response driven partly by microglia, the brain resident macrophages. Treatment options are currently very limited, but stem cell (SC) therapy holds promise, as beneficial outcomes are reported in animal studies and to a lesser degree in human trials. Among putative mechanisms of action, immunomodulation is considered a major contributor to SC associated benefits. The goal of this review is to examine whether microglia is a cellular target of SC-mediated immunomodulation and whether the recruitment of microglia is linked to brain repair. We will first provide an overview on microglial activation in the rodent model of neonatal HI, and highlight its sensitivity to developmental age. Two complementary questions are then addressed: (i) do immune-related

treatments impact microglia and provide neuroprotection, (ii) does stem cell treatment modulates microglia? Finally, the immune-related findings in patients enrolled in SC based clinical trials are discussed. Our review points to an impact of SCs on the microglial phenotype, but heterogeneity in experimental designs and methodological limitations hamper our understanding of a potential contribution of microglia to SC associated benefits. Thorough analyses of the microglial phenotype are warranted to better address the relevance of the neuroimmune crosstalk in brain repair and improve or advance the development of SC protocols in humans.

Brzozowska, M. and A. Lewinski (2021). "Hormonal replacement therapy in women with a history of internal genital organ malignancy." Prz Menopauzalny **20**(1): 34-39.

Sudden cessation of ovary activity as a result of bilateral oophorectomy or chemo- or radiotherapy in premenopausal women is linked with more serious consequences that bear no comparison to natural menopause - to name just a few: higher rate of mortality, higher rate of colorectal and lung cancer, circulatory system diseases, cognitive disorders, Parkinson's disease, psychological disorders, osteoporosis, and sexual disorders. The prolonged period of estrogens deficit in premenopausal age is connected with worsened quality of life. The progress in oncological care means that in many malignant diseases, also in the case of gynaecological malignancies, the percentage of survivors increases. This makes improving the quality of life more and more important. The purpose of this review is to establish, based on EBM data, the answer to whether replacement hormonal therapy, being the most effective treatment of menopause symptoms, can be recommended for women who have undergone bilateral oophorectomy because of gynaecological cancer. On the basis of collected data, derived from meta-analysis, and studies which have been published within the last 20 years, it seems that the use of the appropriate type of hormonal replacement therapy (HRT) in properly selected gynaecological cancer survivors (epithelial ovarian cancer - EOC, endometrial cancer, squamous cell carcinoma of the cervix) is safe and effective. It seems that benefits connected with better quality of life that stem from the use of appropriate HRT in gynaecological cancer survivors predominate the unfounded fear of disease recurrence in selected patients' groups.

Casey, M. and K. Nakamura (2021). "The Cancer-Immunity Cycle in Multiple Myeloma." Immunotargets Ther **10**: 247-260.

Multiple myeloma is a plasma cell malignancy that primarily affects the elderly. The global burden of multiple myeloma is increasing in many countries due to an aging population. Despite recent advances in therapy, myeloma remains an incurable disease, highlighting the pressing need for new therapies. Accumulating evidence supports that triggering the host immune system is a critical therapeutic mechanism of action by various anti-myeloma therapies. These anti-myeloma therapies include proteasome inhibitors, immunomodulatory drugs, monoclonal antibody drugs, and autologous stem cell transplantation. More recently, T cell-based immunotherapeutics (including chimeric antigen receptor T-cell therapies and bispecific T-cell engagers) have shown dramatic clinical benefits in patients with relapsed or refractory multiple myeloma. While immune-based therapeutic approaches are recognized as key modalities for improved clinical outcomes in myeloma patients, understanding the immune system in multiple myeloma patients remains elusive. The cancer-immunity cycle is a conceptual framework illustrating how immune cells recognize and eliminate tumor cells. Based on this framework, this review will provide an overview of the immune system in multiple myeloma patients and discuss potential therapeutic approaches to stimulate anti-tumor immunity.

Choudhury, S., et al. (2021). "Recent advances in the induced pluripotent stem cell-based skin regeneration." Wound Repair Regen **29**(5): 697-710.

Skin regeneration has been a challenging clinical problem especially in cases of chronic wounds such as diabetic foot ulcers, and epidermolysis bullosa-related skin blisters. Prolonged non-healing wounds often lead to bacterial infections increasing the severity of wounds. Current treatment strategies for chronic wounds include debridement of wounds along with antibiotics, growth factors, and stem cell transplantation therapies. However, the compromised nature of autologous stem cells in patients with comorbidities such as diabetes limits the efficacy of the therapy. The discovery of induced pluripotent stem cell (iPSC) technology has immensely influenced the field of regenerative therapy. Enormous efforts have been made to develop integration-free iPSCs suitable for clinical therapies. This review focuses on recent advances in the methods and reprogramming factors for generating iPSCs along with the existing challenges such as genetic alterations, tumorigenicity, immune rejection, and regulatory hurdles for the clinical application of iPSCs. Furthermore, this review also highlights the benefits of using iPSCs for the generation of skin cells and skin disease modeling over the existing clinical therapies for skin regeneration in chronic wounds and skin diseases.

Diaz-Navarro, R., et al. (2021). "Stem cell therapy for dilated cardiomyopathy." Cochrane Database Syst Rev **7**: CD013433.

BACKGROUND: Stem cell therapy (SCT) has been proposed as an alternative treatment for dilated cardiomyopathy (DCM), nonetheless its effectiveness remains debatable. OBJECTIVES: To assess the effectiveness and safety of SCT in adults with non-ischaemic DCM. SEARCH METHODS: We searched CENTRAL in the Cochrane Library, MEDLINE, and Embase for relevant trials in November 2020. We also searched two clinical trials registers in May 2020. SELECTION CRITERIA: Eligible studies were randomized controlled trials (RCT) comparing stem/progenitor cells with no cells in adults with non-ischaemic DCM. We included co-interventions such as the administration of stem cell mobilizing agents. Studies were classified and analysed into three categories according to the comparison intervention, which consisted of no intervention/placebo, cell mobilization with cytokines, or a different mode of SCT. The first two comparisons (no cells in the control group) served to assess the efficacy of SCT while the third (different mode of SCT) served to complement the review with information about safety and other information of potential utility for a better understanding of the effects of SCT. DATA COLLECTION AND ANALYSIS: Two review authors independently screened all references for eligibility, assessed trial quality, and extracted data. We undertook a quantitative evaluation of data using random-effects meta-analyses. We evaluated heterogeneity using the I(2) statistic. We could not explore potential effect modifiers through subgroup analyses as they were deemed uninformative due to the scarce number of trials available. We assessed the certainty of the evidence using the GRADE approach. We created summary of findings tables using GRADEpro GDT. We focused our summary of findings on all-cause mortality, safety, health-related quality of life (HRQoL), performance status, and major adverse cardiovascular events. MAIN RESULTS: We included 13 RCTs involving 762 participants (452 cell therapy and 310 controls). Only one study was at low risk of bias in all domains. There were many shortcomings in the publications that did not allow a precise assessment of the risk of bias in many domains. Due to the nature of the intervention, the main source of potential bias was lack of blinding of participants (performance bias). Frequently, the format of the continuous data available was not ideal for use in the meta-analysis and forced us to seek strategies for transforming data in a usable format. We are uncertain whether SCT reduces all-cause mortality in people with DCM compared to no intervention/placebo (mean follow-up 12 months) (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.54 to 1.31; I(2) = 0%; studies = 7, participants = 361; very low-certainty evidence). We are uncertain whether SCT increases the risk of procedural complications associated with cells injection in people with DCM (data could not be pooled; studies = 7; participants = 361; very low-certainty evidence). We are uncertain whether SCT improves HRQoL (standardized mean difference (SMD) 0.62, 95% CI 0.01 to 1.23; I(2) = 72%; studies = 5, participants = 272; very low-certainty evidence) and functional capacity (6-minute walk test) (mean difference (MD) 70.12 m, 95% CI -5.28 to 145.51; I(2) = 87%; studies = 5, participants = 230; very low-certainty evidence). SCT may result in a slight functional class (New York Heart Association) improvement (data could not be pooled; studies = 6, participants = 398; low-certainty evidence). None of the included studies reported major adverse cardiovascular events as defined in our protocol. SCT may not increase the risk of ventricular arrhythmia (data could not be pooled; studies = 8, participants = 504; low-certainty evidence). When comparing SCT to cell mobilization with granulocyte-colony stimulating factor (G-CSF), we are uncertain whether SCT reduces all-cause mortality (RR 0.46, 95% CI 0.16 to 1.31; I(2) = 39%; studies = 3, participants = 195; very low-certainty evidence). We are uncertain whether SCT increases the risk of procedural complications associated with cells injection (studies = 1, participants = 60; very low-certainty evidence). SCT may not improve HRQoL (MD 4.61 points, 95% CI -5.62 to 14.83; studies = 1, participants = 22; low-certainty evidence). SCT may improve functional capacity (6-minute walk test) (MD 140.14 m, 95% CI 119.51 to 160.77; I(2) = 0%; studies = 2, participants = 155; low-certainty evidence). None of the included studies reported MACE as defined in our protocol or ventricular arrhythmia. The most commonly reported outcomes across studies were based on physiological measures of cardiac function where there were some beneficial effects suggesting potential benefits of SCT in people with non-ischaemic DCM. However, it is unclear if this intermediate effects translates into clinical benefits for these patients. With regard to specific aspects related to the modality of cell therapy and its delivery, uncertainties remain as subgroup analyses could not be performed as planned, making it necessary to wait for the publication of several studies that are currently in progress before any firm conclusion can be reached. AUTHORS' CONCLUSIONS: We are uncertain whether SCT in people with DCM reduces the risk of all-cause mortality and procedural complications, improves HRQoL, and performance status (exercise capacity). SCT may improve functional class (NYHA), compared to usual care (no cells). Similarly, when compared to G-CSF, we are also uncertain whether SCT in people with DCM reduces the risk of all-cause mortality although some studies within this comparison observed

a favourable effect that should be interpreted with caution. SCT may not improve HRQoL but may improve to some extent performance status (exercise capacity). Very low-quality evidence reflects uncertainty regarding procedural complications. These suggested beneficial effects of SCT, although uncertain due to the very low certainty of the evidence, are accompanied by favourable effects on some physiological measures of cardiac function. Presently, the most effective mode of administration of SCT and the population that could benefit the most is unclear. Therefore, it seems reasonable that use of SCT in people with DCM is limited to clinical research settings. Results of ongoing studies are likely to modify these conclusions.

Domine Gomez, M., et al. (2021). "Exploratory composite endpoint demonstrates benefit of trilaciclib across multiple clinically meaningful components of myeloprotection in patients with small cell lung cancer." Int J Cancer **149**(7): 1463-1472.

Chemotherapy-induced myelosuppression is an acute, dose-limiting toxicity of chemotherapy regimens used in the treatment of extensive-stage small cell lung cancer (ES-SCLC). Trilaciclib protects haematopoietic stem and progenitor cells from chemotherapy-induced damage (myeloprotection). To assess the totality of the myeloprotective benefits of trilaciclib, including analysis of several clinically relevant but low-frequency events, an exploratory composite endpoint comprising five major adverse haematological events (MAHE) was prospectively defined: all-cause hospitalisations, all-cause chemotherapy dose reductions, febrile neutropenia (FN), prolonged severe neutropenia (SN) and red blood cell (RBC) transfusions on/after Week 5. MAHE and its individual components were assessed in three randomised, double-blind, placebo-controlled Phase 2 trials in patients receiving a platinum/etoposide or topotecan-containing chemotherapy regimen for ES-SCLC and in data pooled from the three trials. A total of 242 patients were randomised across the three trials (trilaciclib, n = 123; placebo, n = 119). In the individual trials and the pooled analysis, administering trilaciclib prior to chemotherapy resulted in a statistically significant reduction in the cumulative incidence of MAHE compared to placebo. In the pooled analysis, the cumulative incidences of all-cause chemotherapy dose reductions, FN, prolonged SN and RBC transfusions on/after Week 5 were significantly reduced with trilaciclib vs placebo; however, no significant difference was observed in rates of all-cause hospitalisations. Additionally, compared to placebo, trilaciclib significantly extended the amount of time patients remained free of MAHE. These data support the myeloprotective benefits of trilaciclib and its ability to improve the overall safety profile of myelosuppressive chemotherapy regimens used to treat patients with ES-SCLC.

Dunn, C. M., et al. (2021). "Strategies to address mesenchymal stem/stromal cell heterogeneity in immunomodulatory profiles to improve cell-based therapies." Acta Biomater.

Mesenchymal stromal cells (MSCs) have gained immense attention over the past two decades due to their multipotent differentiation potential and pro-regenerative and immunomodulatory cytokine secretory profiles. Their ability to modulate the host immune system and promote tolerance has prompted several allogeneic and autologous hMSC-based clinical trials for the treatment of graft-versus-host disease and several other immune-induced disorders. However, clinical success beyond safety is still controversial and highly variable, with inconclusive therapeutic benefits and little mechanistic explanation. This clinical variability has been broadly attributed to inconsistent MSC sourcing, phenotypic characterization, variable potency, and non-standard isolation protocols, leading to functional heterogeneity among administered MSCs. Homogeneous MSC populations are proposed to yield more predictable, reliable biological responses and clinically meaningful properties relevant to cell-based therapies. Limited comparisons of heterogeneous MSCs with homogenous MSCs are reported. This review addresses this gap in the literature with a critical analysis of strategies aimed at decreasing MSC heterogeneity concerning their reported immunomodulatory profiles. STATEMENT OF SIGNIFICANCE: This review collates, summarizes, and critically analyzes published strategies that seek to improve homogeneity in immunomodulatory functioning MSC populations intended as cell therapies to treat immune-based disorders, such as graft-vs-host-disease. No such review for MSC therapies, immunomodulatory profiles and cell heterogeneity analysis is published. Since MSCs represent the most clinically studied experimental cell therapy platform globally for which there remains no US domestic marketing approval, insights into MSC challenges in therapeutic product development are imperative to providing solutions for immunomodulatory variabilities.

Forsberg, M. H., et al. (2021). "Exosomes from primed MSCs can educate monocytes as a cellular therapy for hematopoietic acute radiation syndrome." Stem Cell Res Ther **12**(1): 459.

BACKGROUND: Acute radiation syndrome (ARS) is caused by acute exposure to ionizing radiation that damages multiple organ systems but especially the bone marrow (BM). We have previously shown that human macrophages educated with exosomes from human BM-derived mesenchymal stromal cells (MSCs) primed with lipopolysaccharide (LPS)

prolonged survival in a xenogeneic lethal ARS model. The purpose of this study was to determine if exosomes from LPS-primed MSCs could directly educate human monocytes (LPS-EEMos) for the treatment of ARS. METHODS: Human monocytes were educated by exosomes from LPS-primed MSCs and compared to monocytes educated by unprimed MSCs (EEMos) and uneducated monocytes to assess survival and clinical improvement in a xenogeneic mouse model of ARS. Changes in surface molecule expression of exosomes and monocytes after education were determined by flow cytometry, while gene expression was determined by qPCR. Irradiated human CD34+ hematopoietic stem cells (HSCs) were co-cultured with LPS-EEMos, EEMos, or uneducated monocytes to assess effects on HSC survival and proliferation. RESULTS: LPS priming of MSCs led to the production of exosomes with increased expression of CD9, CD29, CD44, CD146, and MCSP. LPS-EEMos showed increases in gene expression of IL-6, IL-10, IL-15, IDO, and FGF-2 as compared to EEMos generated from unprimed MSCs. Generation of LPS-EEMos induced a lower percentage of CD14(+) monocyte subsets that were CD16(+), CD73(+), CD86(+), or CD206(+) but a higher percentage of PD-L1(+) cells. LPS-EEMos infused 4 h after lethal irradiation significantly prolonged survival, reducing clinical scores and weight loss as compared to controls. Complete blood counts from LPS-EEMo-treated mice showed enhanced hematopoietic recovery post-nadir. IL-6 receptor blockade completely abrogated the radioprotective survival benefit of LPS-EEMos in vivo in female NSG mice, but only loss of hematopoietic recovery was noted in male NSG mice. PD-1 blockade had no effect on survival. Furthermore, LPS-EEMos also showed benefits in vivo when administered 24 h, but not 48 h, after lethal irradiation. Co-culture of unprimed EEMos or LPS-EEMos with irradiated human CD34+ HSCs led to increased CD34+ proliferation and survival, suggesting hematopoietic recovery may be seen clinically. CONCLUSION: LPS-EEMos are a potential counter-measure for hematopoietic ARS, with a reduced biomanufacturing time that facilitates hematopoiesis.

Guan, Y., et al. (2021). "Retinal Organoid Induction System for Derivation of 3D Retinal Tissues from Human Pluripotent Stem Cells." J Vis Exp(170).

Retinal degenerative diseases are the main causes of irreversible blindness without effective treatment. Pluripotent stem cells that have the potential to differentiate into all types of retinal cells, even mini-retinal tissues, hold huge promises for patients with these diseases and many opportunities in disease modeling and drug screening. However, the induction process from hPSCs to retinal cells is complicated and time-consuming. Here, we describe an optimized retinal induction protocol to generate retinal tissues with high reproducibility and efficiency, suitable for various human pluripotent stem cells. This protocol is performed without the addition of retinoic acid, which benefits the enrichment of cone photoreceptors. The advantage of this protocol is the quantification of EB size and plating density to significantly enhance the efficiency and repeatability of retinal induction. With this method, all major retinal cells sequentially appear and recapitulate the main steps of retinal development. It will facilitate downstream applications, such as disease modeling and cell therapy.

Gubert, F., et al. (2021). "Mesenchymal Stem Cells Therapies on Fibrotic Heart Diseases." Int J Mol Sci **22**(14).

Stem cell therapy is a promising alternative approach to heart diseases. The most prevalent source of multipotent stem cells, usually called somatic or adult stem cells (mesenchymal stromal/stem cells, MSCs) used in clinical trials is bone marrow (BM-MSCs), adipose tissue (AT-MSCs), umbilical cord (UC-MSCs) and placenta. Therapeutic use of MSCs in cardiovascular diseases is based on the benefits in reducing cardiac fibrosis and inflammation that compose the cardiac remodeling responsible for the maintenance of normal function, something which may end up causing progressive and irreversible dysfunction. Many factors lead to cardiac fibrosis and failure, and an effective therapy is lacking to reverse or attenuate this condition. Different approaches have been shown to be promising in surpassing the poor survival of transplanted cells in cardiac tissue to provide cardioprotection and prevent cardiac remodeling. This review includes the description of pre-clinical and clinical investigation of the therapeutic potential of MSCs in improving ventricular dysfunction consequent to diverse cardiac diseases.

Gurunathan, S., et al. (2021). "Diverse Effects of Exosomes on COVID-19: A Perspective of Progress From Transmission to Therapeutic Developments." Front Immunol **12**: 716407.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new strain of coronavirus and the causative agent of the current global pandemic of coronavirus disease 2019 (COVID-19). There are currently no FDA-approved antiviral drugs for COVID-19 and there is an urgent need to develop treatment strategies that can effectively suppress SARS-CoV-2 infection. Numerous approaches have been researched so far, with one of them being the emerging exosome-based therapies. Exosomes are nano-sized, lipid bilayer-enclosed structures, share structural similarities with viruses secreted from all types of cells, including those lining the respiratory tract. Importantly, the interplay between exosomes and viruses could be potentially exploited for

antiviral drug and vaccine development. Exosomes are produced by virus-infected cells and play crucial roles in mediating communication between infected and uninfected cells. SARS-CoV-2 modulates the production and composition of exosomes, and can exploit exosome formation, secretion, and release pathways to promote infection, transmission, and intercellular spread. Exosomes have been exploited for therapeutic benefits in patients afflicted with various diseases including COVID-19. Furthermore, the administration of exosomes loaded with immunomodulatory cargo in combination with antiviral drugs represents a novel intervention for the treatment of diseases such as COVID-19. In particular, exosomes derived from mesenchymal stem cells (MSCs) are used as cell-free therapeutic agents. Mesenchymal stem cell derived exosomes reduces the cytokine storm and reverse the inhibition of host anti-viral defenses associated with COVID-19 and also enhances mitochondrial function repair lung injuries. We discuss the role of exosomes in relation to transmission, infection, diagnosis, treatment, therapeutics, drug delivery, and vaccines, and present some future perspectives regarding their use for combating COVID-19.

Harris, K., et al. (2021). "Current Status of CAR T Cell Therapy for Leukemias." Curr Treat Options Oncol **22**(7): 62.

OPINION STATEMENT: Chimeric antigen receptor (CAR) T-cell therapy has become the standard of care for children and young adults with relapsed and refractory B-cell acute lymphoblastic leukemia (B-ALL), and it is a highly promising therapy under investigation for adults with relapsed disease. Despite having potentially life-threatening toxicities, such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, the benefits of CAR T-cell therapy far outweigh these risks, particularly as increased experience and improved supportive care measures are mitigating these toxicities. CAR T cells can result in complete remission for significant proportion of patients with relapsed and refractory B-ALL and permit them to proceed to potentially curative allogeneic hematopoietic stem cell transplantation (allo-HSCT). CAR T cells may also be curative by themselves. Herein lie the greatest challenges and questions for clinical investigators, specifically, how are CAR T cells best employed and how do we overcome mechanisms of resistance to them? The primary clinical question is the timing and even the necessity of allo-HSCT. Relative to resistance, we know that target antigen loss, specifically CD19, is a major contributor to resistance. However, current investigations of alternative targets, such CD22, and CAR T cells expressing dual targeting antigen receptors have demonstrated encouraging initial results and provide a high degree of optimism that the efficacy and the broader application of CAR T-cell therapy will gradually increase in B-ALL. That optimism is not as high and the challenges are increased for the application of CAR T cells in T-cell leukemias and acute myeloid leukemia due to the relative lack of suitable leukemia surface targets that are not also expressed on normal hematopoietic progenitors. Despite these significant challenges, considerable research is being conducted into the development of CAR T cells for these diseases utilizing unique technologies, which may be applicable to other diseases.

He, W., et al. (2021). "NUPR1 is a novel potential biomarker and confers resistance to sorafenib in clear cell renal cell carcinoma by increasing stemness and targeting the PTEN/AKT/mTOR pathway." Aging (Albany NY) **13**(10): 14015-14038.

BACKGROUND: Sorafenib can improve the survival of metastatic clear cell renal cell carcinoma (ccRCC) patients. However, its benefits are modest, as patients eventually become resistant, and the mechanisms remain elusive. NUPR1, a stress-induced protein, has been reported in malignancies and functions as an oncogene by modulating the stress response, facilitating survival in harsh environments and conferring drug resistance. However, its role in ccRCC has not been explored. METHODS: The expression and clinical significance of NUPR1 were analyzed in ccRCC patients in in-house patients and The Cancer Genome Atlas (TCGA) cohorts. The biological functions of NUPR1 were investigated. Xenografts were performed to confirm the effects of NUPR1 on tumorigenesis. The molecular mechanism of NUPR1 was investigated in vitro and in vivo. RESULTS: NUPR1 expression was upregulated in tumor tissue. Further analysis showed that NUPR1 overexpression was associated with an aggressive phenotype and predicted a poor prognosis. Depletion of NUPR1 suppressed tumorigenesis and sensitized cells to sorafenib treatment. Finally, mechanistic investigations indicated that NUPR1 promoted tumorigenesis in ccRCC by increasing stemness and activating the PTEN/AKT/mTOR signaling pathway. CONCLUSIONS: Collectively, our results suggest that NUPR1 may serve as a predictor of ccRCC. Notably, NUPR1 silencing reversed sorafenib resistance in ccRCC. These findings provide a novel potential therapeutic target in the clinical management of ccRCC.

Hervieu, C., et al. (2021). "The Role of Cancer Stem Cells in Colorectal Cancer: From the Basics to Novel Clinical Trials." Cancers (Basel) **13**(5).

The treatment options available for colorectal cancer (CRC) have increased over the years and have

significantly improved the overall survival of CRC patients. However, the response rate for CRC patients with metastatic disease remains low and decreases with subsequent lines of therapy. The clinical management of patients with metastatic CRC (mCRC) presents a unique challenge in balancing the benefits and harms while considering disease progression, treatment-related toxicities, drug resistance and the patient's overall quality of life. Despite the initial success of therapy, the development of drug resistance can lead to therapy failure and relapse in cancer patients, which can be attributed to the cancer stem cells (CSCs). Thus, colorectal CSCs (CCSCs) contribute to therapy resistance but also to tumor initiation and metastasis development, making them attractive potential targets for the treatment of CRC. This review presents the available CCSC isolation methods, the clinical relevance of these CCSCs, the mechanisms of drug resistance associated with CCSCs and the ongoing clinical trials targeting these CCSCs. Novel therapeutic strategies are needed to effectively eradicate both tumor growth and metastasis, while taking into account the tumor microenvironment (TME) which plays a key role in tumor cell plasticity.

Hickson, L. J., et al. (2021). "A systematic review and meta-analysis of cell-based interventions in experimental diabetic kidney disease." Stem Cells Transl Med **10**(9): 1304-1319.

Regenerative, cell-based therapy is a promising treatment option for diabetic kidney disease (DKD), which has no cure. To prepare for clinical translation, this systematic review and meta-analysis summarized the effect of cell-based interventions in DKD animal models and treatment-related factors modifying outcomes. Electronic databases were searched for original investigations applying cell-based therapy in diabetic animals with kidney endpoints (January 1998-May 2019). Weighted or standardized mean differences were estimated for kidney outcomes and pooled using random-effects models. Subgroup analyses tested treatment-related factor effects for outcomes (creatinine, urea, urine protein, fibrosis, and inflammation). In 40 studies (992 diabetic rodents), therapy included mesenchymal stem/stromal cells (MSC; 61%), umbilical cord/amniotic fluid cells (UC/AF; 15%), non-MSC (15%), and cell-derived products (13%). Tissue sources included bone marrow (BM; 65%), UC/AF (15%), adipose (9%), and others (11%). Cell-based therapy significantly improved kidney function while reducing injury markers (proteinuria, histology, fibrosis, inflammation, apoptosis, epithelial-mesenchymal-transition, oxidative stress). Preconditioning, xenotransplantation, and disease-source approaches were effective. MSC and UC/AF cells had greater effect on kidney function while cell products improved fibrosis. BM and UC/AF tissue sources more effectively improved kidney function and proteinuria vs adipose or other tissues. Cell dose, frequency, and administration route also imparted different benefits. In conclusion, cell-based interventions in diabetic animals improved kidney function and reduced injury with treatment-related factors modifying these effects. These findings may aid in development of optimal repair strategies through selective use of cells/products, tissue sources, and dose administrations to allow for successful adaptation of this novel therapeutic in human DKD.

Huang, H., et al. (2021). "Suppression of mitochondrial ROS by prohibitin drives glioblastoma progression and therapeutic resistance." Nat Commun **12**(1): 3720.

Low levels of reactive oxygen species (ROS) are crucial for maintaining cancer stem cells (CSCs) and their ability to resist therapy, but the ROS regulatory mechanisms in CSCs remains to be explored. Here, we discover that prohibitin (PHB) specifically regulates mitochondrial ROS production in glioma stem-like cells (GSCs) and facilitates GSC radiotherapeutic resistance. We find that PHB is upregulated in GSCs and is associated with malignant gliomas progression and poor prognosis. PHB binds to peroxiredoxin3 (PRDX3), a mitochondrion-specific peroxidase, and stabilizes PRDX3 protein through the ubiquitin-proteasome pathway. Knockout of PHB dramatically elevates ROS levels, thereby inhibiting GSC self-renewal. Importantly, deletion or pharmacological inhibition of PHB potently slows tumor growth and sensitizes tumors to radiotherapy, thus providing significant survival benefits in GSC-derived orthotopic tumors and glioblastoma patient-derived xenografts. These results reveal a selective role of PHB in mitochondrial ROS regulation in GSCs and suggest that targeting PHB improves radiotherapeutic efficacy in glioblastoma.

Iqbal, M., et al. (2021). "Systematic Review/Meta-Analysis on Efficacy of Allogeneic Hematopoietic Cell Transplantation in Sickle Cell Disease: An International Effort on Behalf of the Pediatric Diseases Working Party of European Society for Blood and Marrow Transplantation and the Sickle Cell Transplantation International Consortium." Transplant Cell Ther **27**(2): 167 e161-167 e112.

Sickle cell disease (SCD) affects more than 300,000 children annually worldwide. Despite improved supportive care, long-term prognosis remains poor. Allogeneic hematopoietic cell transplantation (allo-HCT) is the sole validated curative option, resulting in sustained resolution of the clinical phenotype. The medical literature on allo-HCT for SCD is largely limited to children. Recent studies have evaluated allo-HCT efficacy in adults. Here, we conducted a systematic review/meta-analysis to assess the totality of evidence on the efficacy, or lack thereof,

of allo-HCT in treating SCD. We performed a comprehensive literature search using PubMed/Medline, Embase, and Cochrane library databases on November 13, 2019. Four authors independently extracted data on clinical outcomes related to benefits (overall survival [OS] and disease-free survival [DFS]) and harms (acute graft-versus-host disease [aGVHD], chronic graft-versus-host disease [cGVHD], nonrelapse mortality [NRM], and graft failure [GF]). Our search identified a total of 1906 references. Only 33 studies (n= 2853 patients) met our inclusion criteria. We also performed a subset analysis by age. Analyses of all-age groups showed pooled rates of 96% for OS, 90% for DFS, 20% for aGVHD, 10% for cGVHD, 4% for NRM, and 5% for GF. In the pediatric population, pooled rates for OS, DFS, aGVHD, cGVHD, NRM, and GF were 97%, 91%, 26%, 11%, 5%, and 3%, respectively. In adults, pooled rates for OS, DFS, aGVHD, cGVHD, NRM, and GF were 98%, 90%, 7%, 1%, 0%, and 14%, respectively. Our data show that allo-HCT is safe and effective, yielding pooled OS rates exceeding 90%. The high GF rate of 14% in adults is concerning and emphasizes the need to evaluate new strategies.

Khater, A. R. and T. Abou-Antoun (2021). "Mesenchymal Epithelial Transition Factor Signaling in Pediatric Nervous System Tumors: Implications for Malignancy and Cancer Stem Cell Enrichment." Front Cell Dev Biol **9**: 654103.

Malignant nervous system cancers in children are the most devastating and worrisome diseases, specifically due to their aggressive nature and, in some cases, inoperable location in critical regions of the brain and spinal cord, and the impermeable blood-brain barrier that hinders delivery of pharmaco-therapeutic compounds into the tumor site. Moreover, the delicate developmental processes of the nervous system throughout the childhood years adds another limitation to the therapeutic modalities and doses used to treat these malignant cancers. Therefore, pediatric oncologists are charged with the daunting responsibility of attempting to deliver effective cures to these children, yet with limited doses of the currently available therapeutic options in order to mitigate the imminent neurotoxicity of radio- and chemotherapy on the developing nervous system. Various studies reported that c-Met/HGF signaling is affiliated with increased malignancy and stem cell enrichment in various cancers such as high-grade gliomas, high-risk medulloblastomas, and MYCN-amplified, high-risk neuroblastomas. Therapeutic interventions that are utilized to target c-Met signaling in these malignant nervous system cancers have shown benefits in basic translational studies and preclinical trials, but failed to yield significant clinical benefits in patients. While numerous pre-clinical data reported promising results with the use of combinatorial therapy that targets c-Met with other tumorigenic pathways, therapeutic resistance remains a problem, and long-term cures are rare. The possible mechanisms, including the overexpression and activation of compensatory tumorigenic mechanisms within the tumors or ineffective drug delivery methods that may contribute to therapeutic resistance observed in clinical trials are elaborated in this review.

Khodayari, H., et al. (2021). "Stem cells-derived natural killer cells for cancer immunotherapy: current protocols, feasibility, and benefits of ex vivo generated natural killer cells in treatment of advanced solid tumors." Cancer Immunol Immunother.

Nowadays, natural killer (NK) cell-based immunotherapy provides a practical therapeutic strategy for patients with advanced solid tumors (STs). This approach is adaptively conducted by the autologous and identical NK cells after in vitro expansion and overnight activation. However, the NK cell-based cancer immunotherapy has been faced with some fundamental and technical limitations. Moreover, the desirable outcomes of the NK cell therapy may not be achieved due to the complex tumor microenvironment by inhibition of intra-tumoral polarization and cytotoxicity of implanted NK cells. Currently, stem cells (SCs) technology provides a powerful opportunity to generate more effective and universal sources of the NK cells. Till now, several strategies have been developed to differentiate types of the pluripotent and adult SCs into the mature NK cells, with both feeder layer-dependent and/or feeder laye-free strategies. Higher cytokine production and intra-tumoral polarization capabilities as well as stronger anti-tumor properties are the main features of these SCs-derived NK cells. The present review article focuses on the principal barriers through the conventional NK cell immunotherapies for patients with advanced STs. It also provides a comprehensive resource of protocols regarding the generation of SCs-derived NK cells in an ex vivo condition.

Knapik, D. M., et al. (2021). "Nonoperative and Operative Soft-Tissue and Cartilage Regeneration and Orthopaedic Biologics of the Knee: An Orthoregeneration Network (ON) Foundation Review." Arthroscopy **37**(8): 2704-2721.

Orthoregeneration is defined as a solution for orthopedic conditions that harnesses the benefits of biology to improve healing, reduce pain, improve function, and optimally, provide an environment for tissue regeneration. Options include: drugs, surgical intervention, scaffolds, biologics as a product of cells, and physical and electro-magnetic stimuli. The goal of regenerative medicine is to enhance the healing of tissue after musculoskeletal injuries as both isolated treatment and adjunct to surgical management, using novel therapies to improve recovery and outcomes.

Various orthopaedic biologics (orthobiologics) have been investigated for the treatment of pathology involving the knee, including symptomatic osteoarthritis and chondral injuries, as well as injuries to tendon, meniscus, and ligament, including the anterior cruciate ligament. Promising and established treatment modalities include hyaluronic acid (HA) in liquid or scaffold form; platelet-rich plasma (PRP); bone marrow aspirate (BMA) comprising mesenchymal stromal cells (MSCs), hematopoietic stem cells, endothelial progenitor cells, and growth factors; connective tissue progenitor cells (CTPs) including adipose-derived mesenchymal stem cells (AD-MSCs) and tendon-derived stem cells (TDSCs); matrix cell-based therapy including autologous chondrocytes or allograft; vitamin D; and fibrin clot. Future investigations should standardize solution preparations, because inconsistent results reported may be due to heterogeneity of HA, PRP, BMAC, or MSC preparations and regimens, which may inhibit meaningful comparison between studies to determine the true efficacy and safety for each treatment.

Kraj, P. (2021). "Bone Morphogenic Protein Signaling and Melanoma." Curr Treat Options Oncol **22**(6): 48.

OPINION STATEMENT: Malignant melanoma is a deadly form of skin cancer caused by neoplastic transformation of melanocytic cells. Despite recent progress in melanoma therapy, by inhibition of activated oncogenes or immunotherapy, survival rate for metastatic melanoma patients remains low. The remarkable phenotypic plasticity of melanoma cells allows for rapid development of invasive properties and metastatic tumors, the main cause of mortality in melanoma patients. Phenotypic and molecular analyses of developing tumors revealed that epithelial-mesenchymal transition (EMT), a cellular and molecular mechanism, controls transition from mature melanocyte to less differentiated melanocyte lineage progenitor cells forming melanoma tumors. This transition is facilitated by persistence of transcriptional regulatory circuit characteristic of embryonic stage in mature melanocytes. Switching of the developmental program of mature melanocyte to EMT is induced by accumulated mutations, especially targeting BRAF, N-RAS, or MEK1/2 signaling pathways, and further promoted by dynamic stimuli from local environment including hypoxia, interactions with extracellular matrix and growth factors or cytokines. Recent reports demonstrate that signaling mediated by transforming growth factor-beta (TGF-beta) and bone morphogenic proteins (BMPs) play critical roles in inducing EMT by controlling expression of critical transcription factors. BMPs are essential modulators of differentiation, proliferation, apoptosis, invasiveness, and metastases in developing melanoma tumors. They control transcription and epigenetic landscape of melanoma cells. Better understanding of the role of BMPs may lead to new strategies to control EMT processes in melanocyte cell lineage and to achieve clinical benefits for the patients.

Lafauy, P., et al. (2021). "Millettocalyxin B Inhibits Migratory Behavior of Lung Cancer Cells via Integrin alpha5 Suppression." Anticancer Res **41**(8): 3843-3849.

BACKGROUND/AIM: Integrin-targeting compounds have shown clinically significant benefits in many patients. Here, we examined the activity of millettocalyxin B, extracted from the stem bark of Millettia erythrocalyx, in lung cancer cells. MATERIALS AND METHODS: The viability of human lung cancer cells was investigated by the 3-(4,5-dimethylthiazol-2-yl)-2,5diphenyl tetrazoliumbromide (MTT) assay. Migration and invasion assays were performed. Phalloidin-rhodamine staining was used to determine the formation of filopodia. Western blot analysis and immunofluorescence staining were used to identify the signaling proteins involved in migration regulation. RESULTS: Non-toxic concentrations (0-25 muM) of millettocalyxin B reduced migration and invasion of lung cancer A549 cells. Filopodia were significantly reduced in millettocalyxin B-treated cells. The migration regulatory proteins including integrin alpha5, active FAK, active Akt, and Cdc42 were significantly decreased in Millettocalyxin B-treated cells. CONCLUSION: Our findings revealed a novel anti-migration and anti-invasion effects and the underlying mechanism of millettocalyxin B, which may be exploited for cancer treatment.

Lim, J. R., et al. (2021). "Cancer stem cell characteristics and their potential as therapeutic targets." Med Oncol **38**(7): 76.

Cancer stem cells (CSCs) are a tumour subpopulation whose capacity for self-renewal, differentiation and proliferation generates unfavourable patient outcomes, including therapeutic resistance and metastasis. Much research has focused on the generation, biomarkers and therapeutic resistance of CSCs, as well as the development of CSC-targeted therapies. Reviews to date have either addressed general CSC characteristics or focused on CSCs from a well-studied cancer. Increasingly, specific treatment plans based on identification of molecular features and biomarkers of a patient's cancer, rather than classification according to tissue origin or bulk tumour properties, are leading to better patient outcomes. Here, we compare CSC characteristics, specifically their biomarkers and molecular features, and identify those that are common to a number of cancers. Identification of CSC markers that suggest therapeutic strategies has led to several successful in vitro and animal tests, recommending clinical trials of treatments with

potentially enhanced therapeutic benefits, especially for recurring cancers.

Liu, S. C., et al. (2021). "Isoorientin inhibits epithelial-to-mesenchymal properties and cancer stem-cell-like features in oral squamous cell carcinoma by blocking Wnt/beta-catenin/STAT3 axis." Toxicol Appl Pharmacol **424**: 115581.

Oral squamous cell carcinoma (OSCC) is among the most prevalent cancers of the head and neck. This study revealed that isoorientin attenuates OSCC cell stemness and epithelial-mesenchymal transition potential through the inhibition of JAK/signal transducer and activator of transcription 3 (STAT3) and Wnt/beta-catenin signaling in cell lines. Our findings indicated that isoorientin is a potential inhibitor of beta-catenin/STAT3 in vitro and in vivo. We analyzed possible synergism between isoorientin and cisplatin in OSCC. A sulforhodamine B assay, colony formation assay, tumorsphere-formation assay, and Wnt reporter activity assay were used for determining cell invasion, cell migration, drug cytotoxicity, and cell viability with potential molecular mechanisms in vitro. Isoorientin reduced the expression of p-STAT3, beta-catenin, and p-GSK3 as well as downstream effectors TCF1/TCF7 and LEF1 and significantly reduced beta-catenin colocalization in the nucleus. Isoorientin markedly strengthened the cytotoxic effects of cisplatin against SAS and SCC-25. Therefore, combining isoorientin and cisplatin treatments can potentially improve the anticancer effect of cisplatin. Isoorientin inhibited the tumorigenicity and growth of OSCC through the abrogation of Wnt/beta-catenin/STAT3 signaling in vivo. Thus, isoorientin disrupted the beta-catenin signaling pathway through the inactivation of STAT3 signaling. In conclusion, targeting OSCC-SC-mediated stemness with isoorientin to eradicate OSCC-SCs may be an effective strategy for preventing relapse and metastasis of OSCC and providing long-term survival benefits.

Lwin, S. M., et al. (2021). "The promise and challenges of cell therapy for psoriasis." Br J Dermatol.

The management of moderate-to-severe psoriasis has been transformed by the introduction of biological therapies. These medicines, particularly those targeting interleukin (IL)-17 and IL-23p19, can offer clear or nearly clear skin for the majority of patients with psoriasis, with good long-term drug survival. However, as currently used, none of these therapies is curative and disconcertingly there is a small but increasing number of patients with severe psoriasis who have failed all currently available therapeutic modalities. A similar scenario has occurred in other immune-mediated inflammatory diseases (IMIDs) where treatment options are limited in severely affected patients. In these cases, cell therapy, including haematopoietic stem cell transplantation (HSCT) and mesenchymal stromal cells (MSC), has been utilized. This review discusses the various forms of cell therapy currently available, their utility in the management of IMIDs and emerging evidence for efficacy in severe psoriasis that is unresponsive to biological therapy. Balancing the risks and benefits of treatment vs. the underlying disease is key; cell therapy carries significant risks, costs, regulation and other complexities, which must be justified by outcomes. Although HSCT has anecdotally been reported to benefit severe psoriasis, sometimes with apparent cure, this has mainly been in the setting of other coincidental 'routine' indications. In psoriasis, cell therapies, such as MSC and regulatory T cells, with a lower risk of complications are likely to be more appropriate. Well-designed controlled trials coupled with mechanistic studies are warranted if advanced cell therapies are to be developed and delivered as a realistic option for severe psoriasis.

Martirosyan, N. L. (2021). "Pharmacologic and Cell-Based Therapies for Acute Spinal Cord Injury." Neurosurg Clin N Am **32**(3): 389-395.

This article provides a review of current pharmacologic and cell-based modalities used for the management of acute spinal cord injury (SCI). The literature search was focused on clinical trials performed in the United States and Canada. Despite the significant advance in research, there is no definitive treatment option for SCI. Instead, existing pharmacologic and cell-based modalities provide only minimal neurologic recovery benefits. This can be attributed to the complex pathophysiology of SCI and spinal cord regeneration. Further research is imperative to better understand these mechanisms and discover definitive treatment modalities.

Mateos, M. V., et al. (2021). "Effect of prior treatments on selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma." J Hematol Oncol **14**(1): 59.

Therapeutic regimens for previously treated multiple myeloma (MM) may not provide prolonged disease control and are often complicated by significant adverse events, including peripheral neuropathy. In patients with previously treated MM in the Phase 3 BOSTON study, once weekly selinexor, once weekly bortezomib, and 40 mg dexamethasone (XVd) demonstrated a significantly longer median progression-free survival (PFS), higher response rates, deeper responses, a trend to improved survival, and reduced incidence and severity of bortezomib-induced peripheral neuropathy when compared with standard twice weekly bortezomib and 80 mg dexamethasone (Vd). The pre-specified analyses described here evaluated the influence of the number of prior lines of therapy, prior treatment with lenalidomide, prior proteasome inhibitor (PI) therapy, prior

immunomodulatory drug therapy, and prior autologous stem cell transplant (ASCT) on the efficacy and safety of XVd compared with Vd. In this 1:1 randomized study, enrolled patients were assigned to receive once weekly oral selinexor (100 mg) with once weekly subcutaneous bortezomib (1.3 mg/m(2)) and 40 mg per week dexamethasone (XVd) versus standard twice weekly bortezomib and 80 mg per week dexamethasone (Vd). XVd significantly improved PFS, overall response rate, time-to-next-treatment, and showed reduced all grade and grade >/= 2 peripheral neuropathy compared with Vd regardless of prior treatments, but the benefits of XVd over Vd were more pronounced in patients treated earlier in their disease course who had either received only one prior therapy, had never been treated with a PI, or had prior ASCT. Treatment with XVd improved outcomes as compared to Vd regardless of prior therapies as well as manageable and generally reversible adverse events. XVd was associated with clinical benefit and reduced peripheral neuropathy compared to standard Vd in previously treated MM. These results suggest that the once weekly XVd regimen may be optimally administered to patients earlier in their course of disease, as their first bortezomib-containing regimen, and in those relapsing after ASCT.Trial registration: ClinicalTrials.gov (NCT03110562). Registered 12 April 2017. https://clinicaltrials.gov/ct2/show/NCT03110562 .

Mathur, S. and J. Stamford (2021). "Bringing Advanced Therapies for Parkinson's Disease to the Clinic: The Patient's Perspective." J Parkinsons Dis **11**(s2): S141-S145.

There is an urgent unmet need in the Parkinson's disease community-advanced therapies to modify the inevitable decline that occurs in those affected by this progressive neurodegenerative disease for which there is no cure. This will require collaboration from all stakeholders and central to those partnerships are patients themselves. But participation in clinical trials and clinical use of advanced therapies have their own risk profile above and beyond standard therapeutics as evidenced by past invasive procedures. Therefore, it is of utmost importance that clear, evidence-based information about these potential treatments be clearly communicated by those exploring their use to ensure safe and informed participation from the patient community. Likewise, patients must weigh the benefits of these treatments their limitations and risks in order to truly give informed consent to participate in bringing these treatments to the clinic. Here we explore these issues from the patient perspective.

Matta, A., et al. (2021). "A comparative study of mesenchymal stem cell transplantation and NTG-101 molecular therapy to treat degenerative disc disease." Sci Rep **11**(1): 14804.

Cellular replacement therapy using mesenchymal stem cells (MSCs) and/or the delivery of growth factors are at the forefront of minimally invasive biological treatment options for Degenerative Disc Disease (DDD). In this study, we compared the therapeutic potential of a novel drug candidate, NTG-101 to MSCs, including rat cartilage derived stem cells (rCDSCs), bone marrow stem cells (rBMSCs) and human Umbilical Cord Derived Mesenchymal Stem Cells (hUCMSCs) for the treatment of DDD. We induced DDD using a validated image-guided needle puncture injury in rat-tail IVDs. Ten weeks post-injury, animals were randomized and injected with MSCs, NTG-101 or vehicle. At the end of the study, histological analysis of the IVD-Nucleus Pulposus (NPs) injected with NTG-101 or rCDSCs showed a healthy or mild degenerative phenotype in comparison to vehicle controls. Immunohistochemical analysis revealed strong expression of aggrecan, collagen 2, brachyury and Oct4 in IVD-NPs injected with NTG-101. Our results also demonstrated suppression of inflammation induced p38 and NFkappaB resulting in inhibition of catabolic genes, but activation of Smad-2/3, Erk-1/2 and Akt-dependent signaling inducing anabolic genes in IVD-NP on treatment with NTG-101. In conclusion, a single injection of NTG-101 into the degenerative disc demonstrated superior benefits compared to stem cell transplantation.

Metselaar, D. S., et al. (2021). "Radiosensitization in Pediatric High-Grade Glioma: Targets, Resistance and Developments." Front Oncol **11**: 662209.

Pediatric high-grade gliomas (pHGG) are the leading cause of cancer-related death in children. These epigenetically dysregulated tumors often harbor mutations in genes encoding histone 3, which contributes to a stem cell-like, therapy-resistant phenotype. Furthermore, pHGG are characterized by a diffuse growth pattern, which, together with their delicate location, makes complete surgical resection often impossible. Radiation therapy (RT) is part of the standard therapy against pHGG and generally the only modality, apart from surgery, to provide symptom relief and a delay in tumor progression. However, as a single treatment modality, RT still offers no chance for a cure. As with most therapeutic approaches, irradiated cancer cells often acquire resistance mechanisms that permit survival or stimulate regrowth after treatment, thereby limiting the efficacy of RT. Various preclinical studies have investigated radiosensitizers in pHGG models, without leading to an improved clinical outcome for these patients. However, our recently improved molecular understanding of pHGG generates new opportunities to (re-)evaluate radiosensitizers in these malignancies. Furthermore, the use of radio-

enhancing agents has several benefits in pHGG compared to other cancers, which will be discussed here. This review provides an overview and a critical evaluation of the radiosensitization strategies that have been studied to date in pHGG, thereby providing a framework for improving radiosensitivity of these rapidly fatal brain tumors.

Mohty, R., et al. (2021). "Nutritional Supplements and Complementary/Alternative Medications in Patients With Hematologic Diseases and Hematopoietic Stem Cell Transplantation." Transplant Cell Ther **27**(6): 467-473.

This perspective article discusses the various practices classified as complementary and alternative medicine (CAM) and reviews the benefits and uncertainties with respect to nutritional supplements in patients with hematological disease. It considers the high prevalence of CAM use especially among cancer survivors, particularly patients with hematologic malignancies and allogeneic stem cell transplant survivors, many of whom believe (because of extensive advertising) that supplements are anticancer/antitoxic agents, despite the paucity of evidence to support any benefit and the enormous cost to the individual. CAM constitutes various practices and nutritional behaviors including prayers, relaxation, spiritual healing, nutritional supplements, meditation, religious counseling, massage, and support groups. We highlighted the current literature regarding CAM practices and focused our discussion on the omnipresent nutritional supplements in particular to further expound on their benefits and adverse effects. As the number of survivors after HSCT increases over the next several years along with prevalence of CAM use, it becomes imperative to ascertain any beneficial potential, as well as toxicities associated with CAM use in this population.

Mupfudze, T. G., et al. (2021). "A Qualitative Analysis of State Medicaid Coverage Benefits for Allogeneic Hematopoietic Cell Transplantation (alloHCT) for Patients with Sickle Cell Disease (SCD)." Transplant Cell Ther **27**(4): 345-351.

Sickle cell disease (SCD) is the most common inherited hemoglobin disorder, affecting approximately 100,000 people in the United States. Allogeneic hematopoietic cell transplantation (alloHCT), also known as bone marrow transplant (BMT), is currently the only established curative option for SCD. However, alloHCT is an optional benefit under Medicaid. This study of alloHCT coverage for patients with SCD aims to understand the scope of state Medicaid coverage benefits and BMT financial coordinators' experience working with their state Medicaid programs. States estimated to have more than 50 newborns diagnosed with SCD in 2016 and at least one active BMT Clinical Trials Network (1503 [STRIDE 2], NCT02766465) transplant center (TC) were eligible to participate in this study. Qualitative, semi-structured interviews 30 to 60 minutes in length were conducted with BMT financial coordinators via telephone between May and October 2019. A total of 10 BMT financial coordinators from 10 TCs representing eight states (Florida, Georgia, Illinois, Michigan, New York, Pennsylvania, Texas, and Virginia) participated in the semi-structured interviews. Coordinators in all of the included states reported that alloHCT in children with SCD with a human leukocyte antigen-matched sibling donor was covered by their state Medicaid programs. However, only two states (Florida and Texas) had legislative policies mandating coverage of routine medical costs for patients in clinical trials. TCs in two states (Illinois and Pennsylvania) reported accepting out-of-state Medicaid insurance, but only one state (Michigan) covered both travel and lodging for the patient and one caregiver. Four themes emerged when coordinators were asked about their perspectives and experiences working with their corresponding state Medicaid programs: (1) state Medicaid eligibility criteria based on disability were perceived as being restrictive, and Medicaid reimbursement rates were reported to be low; (2) Medicaid fee-for-service plans were perceived as being more comprehensive and easier to navigate compared to comprehensive managed care (CMC) plans; (3) there is a need to address caregiver and financial assistance beyond the health care costs; and (4) completing the insurance authorization process leading up to alloHCT is critical, including peer-to-peer reviews. There is limited legislative policy to help ensure access to clinical trials and provide out-of-state benefits and travel and lodging for Medicaid enrollees with SCD. These data provide insight into potential areas that could influence changes in policy to enhance access to curative therapy for SCD.

Nair, D. R. and B. Thomas (2021). "Stem Cell Based Treatment Strategies for Degenerative Diseases of the Retina." Curr Stem Cell Res Ther.

BACKGROUND: The main cause of progressive vision impairment in retinal degenerative diseases is the dysfunction of photoreceptors and the underlying retinal pigment epithelial cells. The inadequate regenerative capacity of the neural retina and lack of established therapeutic options demand the development of clinical grade protocols to halt degenerative process in the eye or to replace the damaged cells by using stem cell derived products. Recently, stem cell-based regenerative therapies are at the forefront of clinical investigations for retinal dystrophies. <P> Objective: This article will review different stem cell-based therapies currently employed for retinal degenerative diseases, recent clinical trials, and major challenges in the translation of these

therapies from bench to bedside. <P> Methodology: A systematic literature review was carried out to identify potentially relevant articles published in MEDLINE/PubMed, Embase, ClinicalTrials.gov, Drugs@FDA, European Medicines Agency, World Health Organization International Clinical Trials Registry Platform and CENTRAL <P> Result: Transplantation of healthy cells to replace the damaged cells in the outer retina is a clinically relevant concept because the inner retina that communicates with the visual areas of the brain remains functional even after the photoreceptors are completely lost. Different methods have been established for the differentiation of pluripotent stem cells into different retinal cell types that can be used for therapies. Factors released from transplanted somatic stem cells showed trophic support and photoreceptor rescue during early stages of the disease. Several preclinical and phase I/II clinical studies using terminally differentiated photoreceptor/ retinal pigment epithelial cells derived from pluripotent stem cells have shown proof of concept for visual restoration in Age-related macular degeneration (AMD), Stargardt disease and Retinitis pigmentosa (RP). <P> Conclusion: Cell replacement therapy has great potential for vision restoration. The results obtained from the initial clinical trials are encouraging and indicates its therapeutic benefits. The current status of the therapies suggests that there is a long way to go before these results can be applied to routine clinical practice. Input from the ongoing multicentre clinical trials will give a more refined idea for the future design of clinical- grade protocols to transplant GMP level HLA matched cells.

Nehra, M., et al. (2021). "Nanobiotechnology-assisted therapies to manage brain cancer in personalized manner." J Control Release **338**: 224-243.

There are numerous investigated factors that limit brain cancer treatment efficacy such as ability of prescribed therapy to cross the blood-brain barrier (BBB), tumor specific delivery of a therapeutics, transport within brain interstitium, and resistance of tumor cells against therapies. Recent breakthroughs in the field of nano-biotechnology associated with developing multifunctional nano-theranostic emerged as an effective way to manage brain cancer in terms of higher efficacy and least possible adverse effects. Keeping challenges and state-of-art accomplishments into consideration, this review proposes a comprehensive, careful, and critical discussion focused on efficient nano-enabled platforms including nanocarriers for drug delivery across the BBB and nano-assisted therapies (e.g., nano-immunotherapy, nano-stem cell therapy, and nano-gene therapy) investigated for brain cancer treatment. Besides therapeutic efficacy point-of-view, efforts are being made to explore ways projected to tune such developed nano-therapeutic for treating patients in personalized manner via controlling size, drug loading, delivery, and retention. Personalized brain tumor management based on advanced nano-therapies can potentially lead to excellent therapeutic benefits based on unique genetic signatures in patients and their individual disease profile. Moreover, applicability of nano-systems as stimulants to manage the brain cancer growth factors has also been discussed in photodynamic therapy and radiotherapy. Overall, this review offers a comprehensive information on emerging opportunities in nanotechnology for advancing the brain cancer treatment.

Nguyen Thanh, L., et al. (2021). "Can Autologous Adipose-Derived Mesenchymal Stem Cell Transplantation Improve Sexual Function in People with Sexual Functional Deficiency?" Stem Cell Rev Rep.

BACKGROUND: Sexual functional deficiency occurs at some point in life and becomes a problematic issue in middle-aged adulthood. Regenerative medicine, especially mesenchymal stem cell (MSC) transplantation, has developed extensively, with preclinical and clinical trials emphasizing the benefits of stem cell therapy for restoration of sexual deficiency. This study was designed to develop a new therapeutic stem cell treatment for people with sexual functional deficiency. METHODS: Thirty-one patients, including 15 males and 16 females with a medical history of reduced sexual activity, met the inclusion criteria and were enrolled in the study, phase I/IIa clinical trial with a 12-month follow-up. Adipose tissue-derived mesenchymal stem/stromal cells (ADSC) were isolated by type I collagenase digestion and cultured at the Stem Cell Core Facility under ISO 14644-1. Each participant received 1 million cells/kg of body weight via the intravenous route. Safety was evaluated by assessing the occurrence of adverse events or severe adverse events. Efficacy was assessed in males by monitoring testosterone levels and administering the International Index of Erectile Function (IIEF) questionnaire and in females by monitoring anti-Mullerian hormone (AMH), estradiol (E2), and follicle-stimulating hormone (FSH) levels and administering the Female Sexual Functioning Index (FSFI) questionnaire at baseline and 3-, 6-, and 12-months post-transplantation. RESULTS: There was no occurrence of severe adverse events after ADSC administration in our study. Post-transplantation sexual satisfaction was observed in all patients enrolled in this study. Testosterone levels in males increased soon after transplantation and were maintained at high levels for up to 6 months before decreasing again at the 12-month follow-up. No significant changes in AMH, FSH or E2 levels were recorded in female patients.

Nooka, A. K., et al. (2021). ""I took the road less traveled, and that has made all the difference": Making a case for high-dose therapy and autologous stem cell transplantation in elderly patients with newly diagnosed multiple myeloma." Cancer.

LAY SUMMARY: Elderly patients with myeloma derive benefits from transplantation similar to those for younger patients. Age should not be the sole criterion for determining transplant eligibility. Performance status assessment and other tools for assessing comorbidities such as the Charlson comorbidity score may potentially help in determining transplant eligibility and will allow us to move away from our heavy reliance on numerical age.

Ozaki, S., et al. (2021). "Propensity-score matched analysis of the efficacy of maintenance/continuous therapy in newly diagnosed patients with multiple myeloma: a multicenter retrospective collaborative study of the Japanese Society of Myeloma." J Cancer Res Clin Oncol.

BACKGROUND: Maintenance +/- consolidation or continuous therapy is considered a standard of care for both transplant-eligible and -ineligible patients with multiple myeloma (MM). However, long-term benefits of such therapy have not yet been clarified in the context of clinical practice. PURPOSE: To clarify the efficacy of maintenance/continuous approach, we retrospectively analyzed the cohort data of newly diagnosed MM patients by propensity-score matching based on age, gender, revised International Staging System (R-ISS) stage, and implementation of transplantation to reduce the bias due to confounding variables. FINDINGS: Among 720 patients, 161 were identified for each of the maintenance and no maintenance groups. Maintenance/continuous therapy employed immunomodulatory drugs (n = 83), proteasome inhibitors (n = 48), combination of both (n = 29), or dexamethasone alone (n = 1). Progression-free survival (PFS) was significantly prolonged in the maintenance group compared with the no maintenance group (median 37.7 and 21.9 months, p = 0.0002, respectively). Prolongation of PFS was observed in both transplanted and non-transplanted patients (p = 0.017 and p = 0.0008, respectively), with standard risk (p < 0.00001), R-ISS stage I (p = 0.037) and stage II (p = 0.00094), and those without obtaining complete response (p = 0.0018). There was no significant benefit in overall survival (OS), but it tended to be better in the maintenance group in non-transplanted patients. Regarding the treatment pattern, the substitution or addition of drugs different from the induction therapy and the combination with immunomodulatory drugs and proteasome inhibitors appeared to be more beneficial for PFS but not OS. CONCLUSION: These results support the benefit of current maintenance/continuous approach in routine clinical practice in the management of MM.

Pastor, D., et al. (2021). "Shock wave and mesenchymal stem cells as treatment in the acute phase of spinal cord injury: A pilot study." Rehabilitacion (Madr).

INTRODUCTION: Spinal cord injury (SCI) is a complex pathology with thousands of patients worldwide. During the acute early phase, neural tissue shows some regenerative properties that disappear at the chronic phase. Shock Waves and Stem Cells have been proposed as a possible therapy. METHODS: Here, we analyse Shock Waves' immediate effect over spinal cord genetic response in the injured and healthy spinal cord and the effect of Shock Waves and combined Shock Waves plus Stem Cells distally grafted to treat the first month after spinal cord injury. RESULTS: The immediate application of shock waves increases VEGF (Vascular Endothelial Growth Factor) but reduces the BDNF (Brain-Derived Growth Factor) RNA (Ribonucleic acid) response. Shock wave therapy increases GFAP (Glial fibrillary acidic protein) positive cells and vascularity during the treatment's acute phase. CONCLUSION: Shock wave treatment seems to be enough to produce benefits in the acute phase of spinal cord injury, with no accumulative positive effects when mesenchymal stem cell graft is applied together.

Pastore, I., et al. (2021). "Hematopoietic Stem Cells in Type 1 Diabetes." Front Immunol **12**: 694118.

Despite the increasing knowledge of pathophysiological mechanisms underlying the onset of type 1 diabetes (T1D), the quest for therapeutic options capable of delaying/reverting the diseases is still ongoing. Among all strategies currently tested in T1D, the use of hematopoietic stem cell (HSC)-based approaches and of teplizumab, showed the most encouraging results. Few clinical trials have already demonstrated the beneficial effects of HSCs in T1D, while the durability of the effect is yet to be established. Investigators are also trying to understand whether the use of selected and better-characterized HSCs subsets may provide more benefits with less risks. Interestingly, ex vivo manipulated HSCs showed promising results in murine models and the recent introduction of the humanized mouse models accelerated the translational potentials of such studies and their final road to clinic. Indeed, immunomodulatory as well as trafficking abilities can be enhanced in genetically modulated HSCs and genetically engineered HSCs may be viewed as a novel "biologic" therapy, to be further tested and explored in T1D and in other autoimmune/immune-related disorders.

Patwardhan, A. G. and S. Belemkar (2021). "An update on Alzheimer's disease: Immunotherapeutic agents,

stem cell therapy and gene editing." Life Sci **282**: 119790.

Alzheimer's disease is a chronic lifestyle ailment whose occurrence has come to light with the increasing life expectancy due to better healthcare. The patient burden for AD is set to double by the year 2060 and advancement in research is of utmost importance to combat this problem. AD is characterized by the pathological hallmarks of amyloid plaques and neurofibrillary tangles. The disease has been implicated to have a genetic predisposition. The current treatment strategies are at best ameliorative in nature and offer no substantive cure. Immunotherapeutic approaches employed have shown few therapeutic benefits but the accelerated approval of aducanumab by the US-FDA shows clinical benefit merit. In addition, newer therapeutic approaches are the need of the hour. This review aims to highlight the pathology of the disease, followed by an insight into newer approaches like stem cell therapy and gene editing, focusing on possible CRISPR mediated targets.

Paz-Artigas, L., et al. (2021). "Benefits of cryopreservation as long-term storage method of encapsulated cardiosphere-derived cells for cardiac therapy: A biomechanical analysis." Int J Pharm **607**: 121014.

Cardiosphere-derived cells (CDCs) encapsulated within alginate-poly-L-lysine-alginate (APA) microcapsules present a promising treatment alternative for myocardial infarction. However, clinical translatability of encapsulated CDCs requires robust long-term preservation of microcapsule and cell stability, since cell culture at 37 degrees C for long periods prior to patient implantation involve high resource, space and manpower costs, sometimes unaffordable for clinical facilities. Cryopreservation in liquid nitrogen is a well-established procedure to easily store cells with good recovery rate, but its effects on encapsulated cells are understudied. In this work, we assess both the biological response of CDCs and the mechanical stability of microcapsules after long-term (i.e., 60 days) cryopreservation and compare them to encapsulated CDCs cultured at 37 degrees C. We investigate for the first time the effects of cryopreservation on stiffness and topographical features of microcapsules for cell therapy. Our results show that functionality of encapsulated CDCs is optimum during 7 days at 37 degrees C, while cryopreservation seems to better guarantee the stability of both CDCs and APA microcapsules properties during longer storage than 15 days. These results point out cryopreservation as a suitable technique for long-term storage of encapsulated cells to be translated from the bench to the clinic.

Planat-Benard, V., et al. (2021). "MSCs and Inflammatory Cells Crosstalk in Regenerative Medicine: Concerted Actions for Optimized Resolution Driven by Energy Metabolism." Front Immunol **12**: 626755.

Mesenchymal stromal cells (MSCs) are currently widely used in cell based therapy regarding to their remarkable efficacy in controlling the inflammatory status in patients. Despite recent progress and encouraging results, inconstant therapeutic benefits are reported suggesting that significant breakthroughs in the understanding of MSCs immunomodulatory mechanisms of action remains to be investigated and certainly apprehended from original point of view. This review will focus on the recent findings regarding MSCs close relationship with the innate immune compartment, i.e. granulocytes and myeloid cells. The review will also consider the intercellular mechanism of communication involved, such as factor secretion, cell-cell contact, extracellular vesicles, mitochondria transfer and efferocytosis. Immune-like-properties of MSCs supporting part of their therapeutic effect in the clinical setting will be discussed, as well as their potentials (immunomodulatory, anti-bacterial, anti-inflammatory, anti-oxidant defenses and metabolic adaptation...) and effects mediated, such as cell polarization, differentiation, death and survival on various immune and tissue cell targets determinant in triggering tissue regeneration.

Popescu, S., et al. (2021). "Dual Stem Cell Therapy Improves the Myocardial Recovery Post-Infarction through Reciprocal Modulation of Cell Functions." Int J Mol Sci **22**(11).

Mesenchymal stromal cells (MSC) are promising candidates for regenerative therapy of the infarcted heart. However, poor cell retention within the transplantation site limits their potential. We hypothesized that MSC benefits could be enhanced through a dual-cell approach using jointly endothelial colony forming cells (ECFC) and MSC. To assess this, we comparatively evaluated the effects of the therapy with MSC and ECFC versus MSC-only in a mouse model of myocardial infarction. Heart function was assessed by echocardiography, and the molecular crosstalk between MSC and ECFC was evaluated in vitro through direct or indirect co-culture systems. We found that dual-cell therapy improved cardiac function in terms of ejection fraction and stroke volume. In vitro experiments showed that ECFC augmented MSC effector properties by increasing Connexin 43 and Integrin alpha-5 and the secretion of healing-associated molecules. Moreover, MSC prompted the organization of ECFC into vascular networks. This indicated a reciprocal modulation in the functionality of MSC and ECFC. In conclusion, the crosstalk between MSC and ECFC augments the therapeutic properties of MSC and enhances the angiogenic properties of ECFC. Our data consolidate the dual-cell therapy as a step forward for

the development of effective treatments for patients affected by myocardial infarction.

Ramalho, B. D. S., et al. (2021). "Cell therapy and delivery strategies for spinal cord injury." Histol Histopathol: 18350.

Spinal cord injury (SCI) is a complex neuropathological condition that represents a major challenge for clinicians and scientists due to patient's functional dysfunction and paralysis. Several treatments have been proposed including biological factors, drugs and cells administered in various ways. Stem cells arise as good candidates to treat SCI since they are known to secrete neurotrophic factors, improving neuroregeneration, but also due to their role in modulating the inflammatory process, favoring a pro-regenerative status. There are several types of cells that have been tested to treat SCI in experimental and clinical studies, but we still face many unanswered questions; one of them is the type of cells that can offer the best benefits and, also the ideal dose and administration routes. This review aimed to summarize recent research on cell treatment, focusing on current delivery strategies for SCI therapy and their effects in tissue repair and regeneration.

Rastegari, E., et al. (2021). "An Update on Mesoporous Silica Nanoparticle Applications in Nanomedicine." Pharmaceutics **13**(7).

The efficient and safe delivery of therapeutic drugs, proteins, and nucleic acids are essential for meaningful therapeutic benefits. The field of nanomedicine shows promising implications in the development of therapeutics by delivering diagnostic and therapeutic compounds. Nanomedicine development has led to significant advances in the design and engineering of nanocarrier systems with supra-molecular structures. Smart mesoporous silica nanoparticles (MSNs), with excellent biocompatibility, tunable physicochemical properties, and site-specific functionalization, offer efficient and high loading capacity as well as robust and targeted delivery of a variety of payloads in a controlled fashion. Such unique nanocarriers should have great potential for challenging biomedical applications, such as tissue engineering, bioimaging techniques, stem cell research, and cancer therapies. However, in vivo applications of these nanocarriers should be further validated before clinical translation. To this end, this review begins with a brief introduction of MSNs properties, targeted drug delivery, and controlled release with a particular emphasis on their most recent diagnostic and therapeutic applications.

Razeghian-Jahromi, I., et al. (2021). "Surfing the clinical trials of mesenchymal stem cell therapy in ischemic cardiomyopathy." Stem Cell Res Ther **12**(1): 361.

While existing remedies failed to fully address the consequences of heart failure, stem cell therapy has been introduced as a promising approach. The present review is a comprehensive appraisal of the impacts of using mesenchymal stem cells (MSCs) in clinical trials mainly conducted on ischemic cardiomyopathy. The benefits of MSC therapy for dysfunctional myocardium are likely attributed to numerous secreted paracrine factors and immunomodulatory effects. The positive outcomes associated with MSC therapy are scar size reduction, reverse remodeling, and angiogenesis. Also, a decreasing in the level of chronic inflammatory markers of heart failure progression like TNF-alpha is observed. The intense inflammatory reaction in the injured myocardial micro-environment predicts a poor response of scar tissue to MSC therapy. Subsequently, the interval delay between myocardial injury and MSC therapy is not yet determined. The optimal requested dose of cells ranges between 100 to 150 million cells. Allogenic MSCs have different advantages compared to autogenic cells and intra-myocardial injection is the preferred delivery route. The safety and efficacy of MSCs-based therapy have been confirmed in numerous studies, however several undefined parameters like route of administration, optimal timing, source of stem cells, and necessary dose are limiting the routine use of MSCs therapeutic approach in clinical practice. Lastly, pre-conditioning of MSCs and using of exosomes mediated MSCs or genetically modified MSCs may improve the overall therapeutic effect. Future prospective studies establishing a constant procedure for MSCs transplantation are required in order to apply MSC therapy in our daily clinical practice and subsequently improving the overall prognosis of ischemic heart failure patients.

Sagoo, P. and H. B. Gaspar (2021). "The transformative potential of HSC gene therapy as a genetic medicine." Gene Ther.

Hematopoietic stem cells (HSCs) are precursor cells that give rise to blood, immune and tissue-resident progeny in humans. Their position at the starting point of hematopoiesis offers a unique therapeutic opportunity to treat certain hematologic diseases by implementing corrective changes that are subsequently directed through to multiple cell lineages. Attempts to exploit HSCs clinically have evolved over recent decades, from initial approaches that focused on transplantation of healthy donor allogeneic HSCs to treat rare inherited monogenic hematologic disorders, to more contemporary genetic modification of autologous HSCs offering the promise of benefits to a wider range of diseases. We are on the cusp of an exciting new era as the transformative potential of HSC gene therapy to offer durable delivery of gene-corrected cells to a range of tissues and organs, including the central nervous system, is beginning to be

realized. This article reviews the rationale for targeting HSCs, the approaches that have been used to date for delivering therapeutic genes to these cells, and the latest technological breakthroughs in manufacturing and vector design. The challenges faced by the biotechnology cell and gene therapy sector in the commercialization of HSC gene therapy are also discussed.

Shoushrah, S. H., et al. (2021). "Sinking Our Teeth in Getting Dental Stem Cells to Clinics for Bone Regeneration." Int J Mol Sci **22**(12).

Dental stem cells have been isolated from the medical waste of various dental tissues. They have been characterized by numerous markers, which are evaluated herein and differentiated into multiple cell types. They can also be used to generate cell lines and iPSCs for long-term in vitro research. Methods for utilizing these stem cells including cellular systems such as organoids or cell sheets, cell-free systems such as exosomes, and scaffold-based approaches with and without drug release concepts are reported in this review and presented with new pictures for clarification. These in vitro applications can be deployed in disease modeling and subsequent pharmaceutical research and also pave the way for tissue regeneration. The main focus herein is on the potential of dental stem cells for hard tissue regeneration, especially bone, by evaluating their potential for osteogenesis and angiogenesis, and the regulation of these two processes by growth factors and environmental stimulators. Current in vitro and in vivo publications show numerous benefits of using dental stem cells for research purposes and hard tissue regeneration. However, only a few clinical trials currently exist. The goal of this review is to pinpoint this imbalance and encourage scientists to pick up this research and proceed one step further to translation.

Sivaraj, D., et al. (2021). "Hydrogel Scaffolds to Deliver Cell Therapies for Wound Healing." Front Bioeng Biotechnol **9**: 660145.

Cutaneous wounds are a growing global health burden as a result of an aging population coupled with increasing incidence of diabetes, obesity, and cancer. Cell-based approaches have been used to treat wounds due to their secretory, immunomodulatory, and regenerative effects, and recent studies have highlighted that delivery of stem cells may provide the most benefits. Delivering these cells to wounds with direct injection has been associated with low viability, transient retention, and overall poor efficacy. The use of bioactive scaffolds provides a promising method to improve cell therapy delivery. Specifically, hydrogels provide a physiologic microenvironment for transplanted cells, including mechanical support and protection from native immune cells, and cell-hydrogel interactions may be tailored based on specific tissue properties. In this review, we describe the current and future directions of various cell therapies and usage of hydrogels to deliver these cells for wound healing applications.

Smith, J. A., et al. (2021). "Stem Cell Therapies for Progressive Multiple Sclerosis." Front Cell Dev Biol **9**: 696434.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and axonal degeneration. MS patients typically present with a relapsing-remitting (RR) disease course, manifesting as sporadic attacks of neurological symptoms including ataxia, fatigue, and sensory impairment. While there are several effective disease-modifying therapies able to address the inflammatory relapses associated with RRMS, most patients will inevitably advance to a progressive disease course marked by a gradual and irreversible accrual of disabilities. Therapeutic intervention in progressive MS (PMS) suffers from a lack of well-characterized biological targets and, hence, a dearth of successful drugs. The few medications approved for the treatment of PMS are typically limited in their efficacy to active forms of the disease, have little impact on slowing degeneration, and fail to promote repair. In looking to address these unmet needs, the multifactorial therapeutic benefits of stem cell therapies are particularly compelling. Ostensibly providing neurotrophic support, immunomodulation and cell replacement, stem cell transplantation holds substantial promise in combatting the complex pathology of chronic neuroinflammation. Herein, we explore the current state of preclinical and clinical evidence supporting the use of stem cells in treating PMS and we discuss prospective hurdles impeding their translation into revolutionary regenerative medicines.

Sonoda, S., et al. (2021). "Targeting of Deciduous Tooth Pulp Stem Cell-Derived Extracellular Vesicles on Telomerase-Mediated Stem Cell Niche and Immune Regulation in Systemic Lupus Erythematosus." J Immunol.

Systemic transplantation of stem cells from human exfoliated deciduous teeth (SHED) is used to treat systemic lupus erythematosus (SLE)-like disorders in MRL/lpr mice. However, the mechanisms underlying the SHED-based therapy remain unclear. In this study, we hypothesized that trophic factors within SHED-releasing extracellular vesicles (SHED-EVs) ameliorate the SLE-like phenotypes in MRL/lpr mice. SHED-EVs were isolated from the culture supernatant of SHED. SHED-EVs were treated with or without RNase and systemically administered to MRL/lpr mice. Subsequently, recipient bone marrow mesenchymal stem cells (BMMSCs) isolated from SHED-EV-

administered MRL/lpr mice were examined for the in vitro and in vivo activity of hematopoietic niche formation and immunoregulation. Furthermore, the recipient BMMSCs were secondarily transplanted into MRL/lpr mice. The systemic SHED-EV infusion ameliorated the SLE-like phenotypes in MRL/lpr mice and improved the functions of recipient BMMSCs by rescuing Tert mRNA-associated telomerase activity, hematopoietic niche formation, and immunoregulation. The secondary transplantation of recipient BMMSCs recovered the immune condition and renal functions of MRL/lpr mice. The RNase treatment depleted RNAs, such as microRNAs, within SHED-EVs, and the RNA-depleted SHED-EVs attenuated the benefits of SHED-EVs in MRL/lpr mice.

Sun, Y., et al. (2021). "Clinical risk score for predicting invasive fungal disease after allogeneic hematopoietic stem cell transplantation: Analysis of the China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study." Transpl Infect Dis **23**(4): e13611.

BACKGROUND AND OBJECTIVE: Invasive fungal disease (IFD) is associated with a high mortality for patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study aimed not only to develop a proven/probable IFD risk-scoring model but to identify high-risk populations that would benefit from anti-fungal prophylaxis. METHODS: Data from the China Assessment of Antifungal Therapy in Hematological Diseases (CAESAR) study were retrieved, and all patients (n = 1053) undergoing allo-HSCT were randomly divided into the training set (n = 685) for model development and the validation set (n = 368) for model verification. A weighted risk score for proven or probable IFD was established through multivariate logistic regression analysis. RESULTS: The study population had a mean age of 28.95 years and the majority underwent myeloablative transplantation in complete remission 1 (53.4%). Five risk factors of IFD were identified, namely neutropenia lasting longer than 14 days, corticosteroid use, diabetes, haploidentical donor, and unrelated donor. Based on the risk score for IFD, the patients were categorized into three groups: low risk (score 0-4, 1.5%-4.0%), intermediate risk (score 5-8, 9.8%), and high risk (score>8, 24.7%-14.0%). Anti-fungal prophylaxis may provide benefits for patients with intermediate (8.5% vs. 18.5%, P = .0085) or high risk (19.4% vs. 30.8%, P = .4651) but not low risk (2.1% vs. 3.8%, P = .6136) of IFD. CONCLUSION: A practical weighted risk score for IFD in patients receiving allo-HSCT was established, which can aid decision-making regarding the administration of anti-fungal prophylaxis.

Szuber, N. and A. Tefferi (2021). "Current Management of Chronic Neutrophilic Leukemia." Curr Treat Options Oncol **22**(7): 59.

OPINION STATEMENT: Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm (MPN) characterized by oncogenic driver mutations in colony-stimulating factor 3 receptor (CSF3R). Due in large part to the rarity of the disease and dearth of clinical trials, there is currently no standard of care for CNL. Available therapies range from conventional oral chemotherapy to targeted JAK inhibitors to hematopoietic stem cell transplant (HSCT), the latter representing the only potentially curative modality. For this reason, coupled with CNL's typically aggressive clinical course, allogeneic HSCT remains the primary recommended therapy for eligible patients. For ineligible patients, a number of nontransplant therapies have been evaluated in limited trials. These agents may additionally be considered "bridging" therapies pre-transplant in order to control myeloproliferation and alleviate symptoms. Historically, the most commonly utilized first-line agent has been hydroxyurea, though most patients ultimately require second (or subsequent)-line therapy; still hydroxyurea remains the conventional frontline option. Dasatinib has demonstrated efficacy in vitro in cases of CSF3R terminal membrane truncation mutations and may cautiously be considered upfront in such instances, though no substantive studies have validated its efficacy in vivo. Numerous other chemotherapy agents, practically re-appropriated from the pharmaceutical arsenal of MPN, have been utilized in CNL and are typically reserved for second/subsequent-line settings; these include interferon-alpha (IFN-a), hypomethylating agents, thalidomide, cladribine, and imatinib, among others. Most recently, ruxolitinib, a JAK1/2 inhibitor targeting JAK-STAT signaling downstream from CSF3R, has emerged as a potentially promising new candidate for the treatment of CNL. Increasingly robust data support the clinical efficacy, with associated variable reductions in allele burden, and tolerability of ruxolitinib in patients with CNL, particularly those carrying the CSF3RT618I mutation. Similar to conventional nontransplant strategies, however, no disease-modifying or survival benefits have been demonstrated. While responses to JAK-STAT inhibition in CNL have not been uniform, data are sufficient to recommend consideration of ruxolitinib in the therapeutic repertory of CNL. There remains a major unmet need for prospective trials with investigational therapies in CNL.

Tan, Y., et al. (2021). "Low-intensity pulsed ultrasound stimulates proliferation of stem/progenitor cells: what we need to know to translate basic science research into clinical applications." Asian J Androl.

Low-intensity pulsed ultrasound (LIPUS) is a promising therapy that has been increasingly explored in basic research and clinical applications. LIPUS is an appealing therapeutic option as it is a noninvasive treatment that has many advantages, including no risk of infection or tissue damage and no known adverse reactions. LIPUS has been shown to have many benefits including promotion of tissue healing, angiogenesis, and tissue regeneration; inhibition of inflammation and pain relief; and stimulation of cell proliferation and differentiation. The biophysical mechanisms of LIPUS remain unclear and the studies are ongoing. In recent years, more and more research has focused on the relationship between LIPUS and stem/progenitor cells. A comprehensive search of the PubMed and Embase databases to July 2020 was performed. LIPUS has many effects on stem cells. Studies show that LIPUS can stimulate stem cells in vitro; promote stem cell proliferation, differentiation, and migration; maintain stem cell activity; alleviate the problems of insufficient seed cell source, differentiation, and maturation; and circumvent the low efficiency of stem cell transplantation. The mechanisms involved in the effects of LIPUS are not fully understood, but the effects demonstrated in studies thus far have been favorable. Much additional research is needed before LIPUS can progress from basic science research to large-scale clinical dissemination and application.

Ueda, N., et al. (2021). "Prognostic Impact of the Fractionation of Total Body Irradiation for Patients with Acute Myeloid Leukemia Undergoing Myeloablative Allogeneic Hematopoietic Cell Transplantation." Transplant Cell Ther **27**(2): 185 e181-185 e186.

Fractionated total body irradiation (TBI) at a total dose of 12 Gy is widely used for patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplantation (HCT); however, there is limited information regarding the optimal number of fractions. To address this issue, Japanese nationwide transplantation registry data were analyzed. Because it was found that TBI was delivered almost exclusively in 4 (n = 1215, 30%) or 6 fractions (n = 2697, 67%), we focused on comparing 4- versus 6-fraction TBI. Compared to 6-fraction TBI, the 4-fraction version was associated with reduced risk of overall mortality (P = .002) and relapse (P = .018), while there was no difference in the risk of nonrelapse mortality (P = .422). The 4-fraction version did not aggravate acute graft-versus-host disease (GVHD), interstitial pneumonia, or sinusoidal obstruction syndrome of the liver. Chronic GVHD developed more frequently with the use of 4-fraction TBI, although the incidence of extensive chronic GVHD was similar. Subgroup analyses revealed that the 4-fraction version provided benefits for patients in non-complete remission (non-CR) but not for those in CR at transplantation. These findings suggest the advantage of 4-fraction over 6-fraction TBI for patients with AML undergoing allogeneic HCT in non-CR.

Vado, Y., et al. (2021). "Design and Validation of a Process Based on Cationic Niosomes for Gene Delivery into Novel Urine-Derived Mesenchymal Stem Cells." Pharmaceutics **13**(5).

BACKGROUND: Mesenchymal stem cells (MSCs) are stem cells present in adult tissues. They can be cultured, have great growth capacity, and can differentiate into several cell types. The isolation of urine-derived mesenchymal stem cells (hUSCs) was recently described. hUSCs present additional benefits in the fact that they can be easily obtained noninvasively. Regarding gene delivery, nonviral vectors based on cationic niosomes have been used and are more stable and have lower immunogenicity than viral vectors. However, their transfection efficiency is low and in need of improvement. METHODS: We isolated hUSCs from urine, and the cell culture was tested and characterized. Different cationic niosomes were elaborated using reverse-phase evaporation, and they were physicochemically characterized. Then, they were screened into hUSCs for transfection efficiency, and their internalization was evaluated. RESULTS: GPxT-CQ at a lipid/DNA ratio of 5:1 (w/w) had the best transfection efficiency. Intracellular localization studies confirmed that nioplexes entered mainly via caveolae-mediated endocytosis. CONCLUSIONS: In conclusion, we established a protocol for hUSC isolation and their transfection with cationic niosomes, which could have relevant clinical applications such as in gene therapy. This methodology could also be used for creating cellular models for studying and validating pathogenic genetic variants, and even for performing functional studies. Our study increases knowledge about the internalization of tested cationic niosomes in these previously unexplored cells.

Vanmeerbeek, I., et al. (2021). "Early memory differentiation and cell death resistance in T cells predicts melanoma response to sequential anti-CTLA4 and anti-PD1 immunotherapy." Genes Immun **22**(2): 108-119.

Immune checkpoint blockers (ICBs)-based immunotherapy has revolutionised oncology. However, the benefits of ICBs are limited to only a subset of patients. Herein, the biomarkers-driven application of ICBs promises to increase their efficacy. Such biomarkers include lymphocytic IFNgamma-signalling and/or cytolytic activity (granzymes and perforin-1) footprints, whose levels in pre-treatment tumours can predict favourable patient survival following ICB-treatment. However, it is not clear whether such biomarkers have the same value in predicting survival

of patients receiving first-line anti-CTLA4 ICB-therapy, and subsequently anti-PD1 ICB-therapy (i.e., sequential ICB-immunotherapy regimen). To address this, we applied highly integrated systems/computational immunology approaches to existing melanoma bulk-tumour transcriptomic and single-cell (sc)RNAseq data originating from immuno-oncology clinical studies applying ICB-treatment. Interestingly, we observed that CD8(+)/CD4(+)T cell-associated IFNgamma-signalling or cytolytic activity signatures fail to predict tumour response in patients treated with anti-CTLA4 ICB-therapy as a first-line and anti-PD1 ICB-therapy in the second-line setting. On the contrary, signatures associated with early memory CD8(+)/CD4(+)T cells (integrating TCF1-driven stem-like transcriptional programme), capable of resisting cell death/apoptosis, better predicted objective response rates to ICB-immunotherapy, and favourable survival in the setting of sequential ICB-immunotherapy. These observations suggest that sequencing of ICB-therapy might have a specific impact on the T cell-repertoire and may influence the predictive value of tumoural immune biomarkers.

Wang, P., et al. (2021). "Efficacy and Safety of Anti-PD-1 Plus Anlotinib in Patients With Advanced Non-Small-Cell Lung Cancer After Previous Systemic Treatment Failure-A Retrospective Study." Front Oncol **11**: 628124.

Background: Pre-clinical and clinical evidences support that simultaneous blockade of programmed death-1 (PD-1) and vascular endothelial growth factor receptor (VEGFR) can enhance antigen-specific T-cell migration, and show tolerable toxicity with favorable antitumor activity in patients. In this study, we aimed to assess the safety and efficacy of anlotinib, a novel multitarget tyrosine kinase inhibitor for VEGFR, platelet-derived growth receptor (PDGFR), and the stem cell-factor receptor (c-Kit), combined with anti-PD-1 treatment in patients with advanced NSCLC. Methods: Sixty-seven patients with previously treated advanced NSCLC receiving anti-PD-1 agents concomitant with anlotinib were retrospectively enrolled in an IRB approved study. Anti-PD-1 agents including pembrolizumab, nivolumab, camrelizumab, toripalimab, sintilimab, and tislelizumab were administered every two or three weeks until disease progression or unacceptable toxicity was reached. Anlotinib was administered orally once daily on days 1-14 of a 21-day cycle. The safety and tolerability of the combination treatment were assessed by the incidence of adverse events. The efficacy of the treatment was assessed by the tumor response and survival. Results: With a median follow-up period of 8.7 months, treatment-related adverse events occurred in 85% (57/67) of patients and grade 3-4 adverse events were observed in 27 patients (40%). No unexpected adverse events or significantly increased toxicities were observed. Complete response was not observed, 19 patients had partial response (28.4%), 39 had stable disease (58.2%) and 9 had progressive disease (13.4%). The overall response (ORR) and disease control rates (DCR) were 28.4% and 86.6%, respectively. The median progression-free survival (PFS) was 6.9 months (95% CI, 5.5-8.3 months) and overall survival (OS) was 14.5 months (95% CI, 10.9-18.1 months). The benefit of anti-PD-1 plus anlotinib was also observed in patients with EGFR mutation positive, liver metastases and brain metastases. Conclusion: Anti-PD-1 treatment concomitant with anlotinib has tolerable toxicity and favorable antitumor activity in patients with previously treated advanced NSCLC. Our results add to the growing evidence that supports the benefits of combining immunotherapy with antiangiogenic drugs. This combination could be further evaluated with or without chemotherapy, since no additional toxicity was observed in the combination treatment.

Wei, S. T., et al. (2021). "Gain of CXCR7 function with mesenchymal stem cell therapy ameliorates experimental arthritis via enhancing tissue regeneration and immunomodulation." Stem Cell Res Ther **12**(1): 314.

BACKGROUND: The major barriers to mesenchymal stem cell (MSC) therapy in rheumatoid arthritis (RA) are a low extent of tissue regeneration and insufficient immunomodulation after cell transplantation. In addition, the role of C-X-C chemokine receptor type 7 (CXCR7) and its mechanism of action in MSC-mediated osteogenic or chondrogenic differentiation and immunomodulation are unclear. METHODS: Gain of CXCR7 function on human MSCs was carried out by lentiviral vector-mediated CXCR7 overexpression or CXCR7 agonist, TC14012. These cells were determined the role and potential mechanisms for CXCR7-regulated MSC differentiation and immunomodulation using cellular and molecular assays. The therapeutic benefits in RA were investigated in rats with collagen-induced arthritis (CIA). RESULTS: CXCR7 was upregulated in MSCs during the induction of osteogenic or chondrogenic differentiation. Blockage of CXCR7 function inhibited osteogenic or chondrogenic differentiation of MSCs whereas gain of CXCR7 function had the opposite effects. Besides, MSCs with CXCR7 gain-of-function facilitated macrophage apoptosis and regulatory T cell differentiation in a co-culture system. Gain of CXCR7 function also promoted the production of anti-inflammatory soluble factors. A gene expression profiling assay and signaling reporter assays revealed that CXCR7 could regulate several candidate genes related to the PPAR, WNT, Hedgehog or Notch pathways, and their signaling activities, which are

known to control cell differentiation and immunomodulation.

Woods, W., et al. (2021). "Stem cell sprays for neurological injuries: a perspective." Emerg Top Life Sci.

Injuries to the brain and spinal cord have major clinical consequences with high costs for healthcare systems. Neural cell transplantation therapies have significant translational potential to promote regeneration post-injury with clinical trials commencing for various pathologies. However, there are challenges associated with current clinical approaches used for systemic or direct delivery of transplant cells to neural tissue in regenerative applications. These include risks associated with surgical microinjection into neural tissue (e.g. haemorrhage, cell clumping) and high cell loss due to systemic clearance or with cell passage through fine gauge needles into densely packed neural tissue. This article presents lines of evidence supporting the concept that cell spray delivery technology can offer significant translational benefits for neural transplantation therapy, versus current cell delivery methods. Potential benefits include rapid/homogenous cell delivery, release over large surface areas, minimal invasiveness, compatibility with neurosurgical procedures in acute injury, no predictable clinical complications and the capacity to combine cell therapies with drug/biomolecule delivery. Accordingly, we consider that the development of cell spray delivery technology represents a key goal to develop advanced cell therapies for regenerative neurology.

Wu, Y., et al. (2021). "Mesenchymal Stem Cells: An Overview of Their Potential in Cell-Based Therapy for Diabetic Nephropathy." Stem Cells Int **2021**: 6620811.

Diabetic nephropathy (DN) is a devastating complication associated with diabetes mellitus, and it is the leading cause of end-stage renal diseases (ESRD). Over the last few decades, numerous studies have reported the beneficial effects of stem cell administration, specifically mesenchymal stem or stromal cells (MSCs), on tissue repair and regeneration. MSC therapy has been considered a promising strategy for ameliorating the progression of DN largely based on results obtained from several preclinical studies and recent Phase I/II clinical trials. This paper will review the recent literature on MSC treatment in DN. In addition, the roles and potential mechanisms involved in MSC treatment of DN will be summarized, which may present much needed new drug targets for this disease. Moreover, the potential benefits and related risks associated with the therapeutic action of MSCs are elucidated and may help in achieving a better understanding of MSCs.

Xu, Q., et al. (2021). "Clinical Benefits and Safety of FMS-Like Tyrosine Kinase 3 Inhibitors in Various Treatment Stages of Acute Myeloid Leukemia: A Systematic Review, Meta-Analysis, and Network Meta-Analysis." Front Oncol **11**: 686013.

Background: Given the controversial roles of FMS-like tyrosine kinase 3 inhibitors (FLT3i) in various treatment stages of acute myeloid leukemia (AML), this study was designed to assess this problem and further explored which FLT3i worked more effectively. Methods: A systematic review, meta-analysis and network meta-analysis (NMA) were conducted by filtering PubMed, Embase, Cochrane library, and Chinese databases. We included studies comparing therapeutic effects between FLT3i and non-FLT3i group in AML, particularly FLT3(+) patients, or demonstrating the efficiency of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in FLT3(+) AML. Relative risk (RR) with 95% confidence intervals (CI) was used for estimating complete remission (CR), early death and toxicity. Hazard ratio (HR) was used to assess overall survival (OS), event-free survival (EFS), relapse-free survival (RFS) and cumulative incidence of relapse (CIR). Results: After addressing all criteria, 39 studies were eventually analyzed. Better CR was accomplished by FLT3i in untreated AML (RR 0.88, $p = 0.04$) and refractory and relapsed FLT3(+) AML (rrAML) (RR 0.61, $p < 0.01$) compared to non-FLT3i arm, followed by improved survival (untreated AML: OS, HR 0.76; EFS, HR 0.67; RFS, HR 0.72; all $p < 0.01$; FLT3(+) rrAML: OS, HR 0.60, $p < 0.01$; RFS, HR 0.40, $p = 0.01$). In addition, allo-HSCT improved survival in FLT3(+) AML (OS, HR 0.53; EFS, HR 0.50; RFS, HR 0.57; CIR, HR 0.26; all $p < 0.01$), which was further prolonged by FLT3i administrated after allo-HSCT (OS, HR 0.45; RFS, HR 0.34; CIR, HR 0.32; all $p < 0.01$). Additionally, FLT3i consistently improved OS ($p < 0.05$) regardless of FLT3-ITD ratio, when compared to non-FLT3i group. Besides, FLT3i showed significantly increased risk of thrombocytopenia, neutropenia, anemia, skin- and cardiac-related adverse effects, increased alanine aminotransferase, and increased risk of cough and dyspnea ($p < 0.05$). In NMA, gilteritinib showed the highest probability for improved prognosis. Conclusions: FLT3i safely improved prognosis in induction/reinduction stage of FLT3(+) AML and further boosted survival benefits from allo-HSCT as maintenance therapy, suggesting better prognosis if FLT3i is combined before and after allo-HSCT. In NMA, gilteritinib potentially achieved the best prognosis, which should be identified in direct trials.

Zeraatpisheh, Z., et al. (2021). "Local delivery of fingolimod through PLGA nanoparticles and PuraMatrix-embedded neural precursor cells promote

motor function recovery and tissue repair in spinal cord injury." Eur J Neurosci **54**(4): 5620-5637.

Spinal cord injury (SCI) is a devastating clinical problem that can lead to permanent motor dysfunction. Fingolimod (FTY720) is a sphingosine structural analogue, and recently, its therapeutic benefits in SCI have been reported. The present study aimed to evaluate the therapeutic efficacy of fingolimod-incorporated poly lactic-co-glycolic acid (PLGA) nanoparticles (nanofingolimod) delivered locally together with neural stem/progenitor cells (NS/PCs) transplantation in a mouse model of contusive acute SCI. Fingolimod was encapsulated in PLGA nanoparticles by the emulsion-evaporation method. Mouse NS/PCs were harvested and cultured from embryonic Day 14 (E14) ganglionic eminences. Induction of SCI was followed by the intrathecal delivery of nanofingolimod with and without intralesional transplantation of PuraMatrix-encapsulated NS/PCs. Functional recovery, injury size and the fate of the transplanted cells were evaluated after 28 days. The nanofingolimod particles represented spherical morphology. The entrapment efficiency determined by UV-visible spectroscopy was approximately 90%, and the drug content of fingolimod loaded nanoparticles was 13%. About 68% of encapsulated fingolimod was slowly released within 10 days. Local delivery of nanofingolimod in combination with NS/PCs transplantation led to a stronger improvement in neurological functions and minimized tissue damage. Furthermore, co-administration of nanofingolimod and NS/PCs not only increased the survival of transplanted cells but also promoted their fate towards more oligodendrocytic phenotype. Our data suggest that local release of nanofingolimod in combination with three-dimensional (3D) transplantation of NS/PCs in the acute phase of SCI could be a promising approach to restore the damaged tissues and improve neurological functions.

Zerjav Tansek, M., et al. (2021). "Therapy-type related long-term outcomes in mucopolysaccaridosis type II (Hunter syndrome) - Case series." Mol Genet Metab Rep **28**: 100779.

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a rare, X-linked recessive multisystem lysosomal storage disease due to iduronate-2-sulfatase enzyme deficiency. We presented three unrelated Slovenian patients with the severe form of MPS II that received three different management approaches: natural course of the disease without received specific treatment, enzyme replacement therapy (ERT), and hematopoietic stem cell transplantation (HSCT). The decision on the management depended on disease severity, degree of cognitive impairment, and parent's informed decision. The current benefits of MPS II treatments are limited. The lifelong costly intravenous ERT brings significant benefits but the patients with severe phenotypes and neurological involvement progress to cognitive decline and disability regardless of ERT, as demonstrated in published reviews and our case series. The patient after HSCT was the only one of the three cases reported to show a slowly progressing cognitive development. The type of information from the case series is insufficient for generalized conclusions, but with advanced myeloablative conditioning, HSCT may be a preferred treatment option in early diagnosed MPS II patients with the severe form of the disease and low disease burden at the time of presentation.

Zhang, X. and Z. B. Jin (2021). "Directed Induction of Retinal Organoids from Human Pluripotent Stem Cells." J Vis Exp(170).

Retinal cell transplantation is a promising therapeutic approach, which could restore the retinal architecture and stabilize or even improve the visual capabilities to the degenerated retina. Nevertheless, progress in cell replacement therapy presently faces the challenges of requiring an off-the-shelf source of high quality and standardized human retinas. Therefore, an easy and stable protocol is needed for the experiments. Here, we develop an optimized protocol, based on a self-organizing method with the use of exogenous molecules and reagent A as well as manual excision to generate the three-dimensional human retina organoids (RO). The human Pluripotent Stem Cells (PSCs)-derived RO expresses specific markers for photoreceptors. With the addition of COCO, a multifunctional antagonist, the differentiation efficiency of photoreceptor precursors and cones is significantly increased. The efficient use of this system, which has the benefits of cell lines and primary cells, and without the sourcing issues associated with the latter, could produce confluent retinal cells, especially photoreceptors. Thus, the differentiation of PSCs to RO provides an optimal and biorelevant platform for disease modelling, drug screening and cell transplantation.

Zhou, L., et al. (2021). "Rapamycin treated tol-dendritic cells derived from BM-MSCs reversed graft rejection in a rat liver transplantation model by inducing CD8(+)CD45RC(-)Treg." Mol Immunol **137**: 11-19.

OBJECTIVE: To investigate the influence of tolerance dendritic cells (tolDCs), generated from Bone marrow mesenchymal stem cells (BM-MSCs) treated with rapamycin (Rapa) on liver allograft survival in a rat acute liver transplantation model. METHODS: Different GM-CSF induction project was used to obtain immature DCs (imDCs), mature DCs (matDCs) or tolDCs from BM-MSCs. First, MLR was performed to analyze the activity of tolDCs on polyclonaly stimulated total T cells. Then, co-cultured imDCs,

matDCs and tolDCs with CD8(+)T cells isolated by magnetic activated cell sorting to analyze the influence on its regulatory characteristic. Last, the established rat acute liver transplantation model were adoptive transfused with imDCs, matDCs or tolDCs isolated by anti-CD11c immunomagnetic beads. The phenotype of DC cells and level of CD8(+)Treg in the culture system and in vivo, the expression of CD8 and CD45RC in the tissues were analyzed by flow cytometry and immunohistochemistry, respectively. RESULTS: The loGM-CSF plus IL-4 decreased the costimulatory molecules of CD80/86 and MHC class II of DCs comparison with hiGM-CSF from BM-MSCs no matter whether stimulation by LPS ($P<0.05$). Rapa treated not only reduced the expression of CD80/86 and MHC class II but also down-regulated the expression of CD11c after LPS stimulation which was more obviously in tolDCs by loGM-CSF project ($P<0.05$). Moreover, tolDCs displayed a rather higher level of IL-10 and low level of IL-12p70 than others ($P<0.01$), which shown a rather lower stimulative effect on the proliferation of T cells comparison with matDCs and imDCs. Co-cultured with CD8(+)Treg showed an improvement on induction of CD8(+)TCR(+)CD45RC(-)T cells (CD8(+)Treg) in ex vivo. The rats transfused with tolDCs has a delayed survival benefits with high level of CD8(+)Tregs ($P<0.01$) and high expression of CD45RC in liver tissue ($P<0.01$) and spleen when comparison with other groups. The infused tolDCs improved a mean survival time (MST) of 32 days comparison with a MTS of 9.5 days and 15.75 days displayed by rat that per-infused with matDCs and imDCs, respectively. CONCLUSION: Rapa modified tolDCs derived from BM-MSCs reversed graft rejection by improve tolerance characteristics of CD8(+)CD45RC(-)Treg in acute liver rat transplantation.

Zubkova, E. S., et al. (2021). "Transduction of rat and human adipose-tissue derived mesenchymal stromal cells by adeno-associated viral vector serotype DJ." Biol Open.

Ex vivo, gene therapy is a powerful approach holding great promises for the treatment of both genetic and acquired diseases. Adeno-associated virus (AAV) vectors are safe and efficient delivery system for modification of mesenchymal stem cells (MSC) that could maximize their therapeutic benefits. Assessment to MSC viability and functional activity after infection with new AAV serotypes is necessary, due to AAV tropism to specific cell types. We infected human and rat adipose-tissue MSC with hybrid AAV-DJ serotype vectors carrying GFP and SCF genes. GFP expression from AAV-DJ was about 1.5-fold superior to that observed with AAV-2 and lasted for at least 21 days as was evaluated by flow cytometry and fluorescence microscopy. AAV-DJ proves to be suitable for the infection of rat and human MSC with a similar efficiency. Infected MSC were still viable however showing 25-30%. growth rate slowdown. Moreover, we found increase of SERPINB2 mRNA expression in human MSC whereas expression of other oxidative stress markers and extracellular matrix proteins was not affected. These results suggest that there is a differential cellular response in MSC infected with AAV viral vectors, which should be taken into account as it can affect the expected outcome for the therapeutic application.

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