Stem Cell and AI 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; AI: technology; life; research; literature

Introduction

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

The following introduces recent reports as references in the related studies. The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

Abdelwhab el, S. M., et al. (2016). "A Unique Multibasic Proteolytic Cleavage Site and Three Mutations in the HA2 Domain Confer High Virulence of H7N1 Avian Influenza Virus in Chickens." J Virol **90**(1): 400-411.

In 1999, after circulation for a few months in poultry in Italy, low-pathogenic (LP) avian influenza (AI) H7N1 virus mutated into a highly pathogenic (HP) form by acquisition of a unique multibasic cleavage site (mCS), PEIPKGSRVRR*GLF (asterisk indicates the cleavage site), in the hemagglutinin (HA) and additional alterations with hitherto unknown biological function. To elucidate these virulence-determining alterations, recombinant H7N1 viruses carrying specific mutations in the HA of LPAI A/chicken/Italy/473/1999 virus (Lp) and HPAI A/chicken/Italy/445/1999 virus (Hp) were generated. Hp with a monobasic CS or carrying the HA of Lp induced only mild or no disease in chickens, thus resembling Lp. Conversely, Lp with the HA of Hp was as virulent and transmissible as Hp. While Lp with a multibasic cleavage site (Lp_CS445) was less virulent than Hp, full virulence was exhibited when HA2 was replaced by that of Hp. In HA2, three amino acid differences consistently detected between LP and HP H7N1 viruses were successively introduced into Lp_CS445. Q450L in the HA2 stem domain increased virulence and transmission but was detrimental to replication in cell culture, probably due to low-pH activation of HA. A436T and/or K536R restored viral replication in vitro and in vivo. Viruses possessing A436T and K536R were observed early in the HPAI outbreak but were later superseded by viruses carrying all three mutations. Together, besides the mCS, stepwise mutations in HA2 increased the fitness of the Italian H7N1 virus in vivo. The shift toward higher virulence in the field was most likely gradual with rapid optimization. IMPORTANCE: In 1999, after 9 months of circulation of low-pathogenic (LP) avian influenza virus (AIV), a devastating highly pathogenic (HP) H7N1 AIV emerged in poultry, marking the largest epidemic of AIV reported in a Western country. The HPAIV possessed a unique multibasic cleavage site (mCS) complying with the minimum motif for HPAIV. The main finding in this report is the identification of three mutations in the HA2 domain that are required for replication and stability, as well as for virulence, transmission, and tropism of H7N1 in chickens. In addition to the mCS, Q450L was

required for full virulence and transmissibility of the virus. Nonetheless, it was detrimental to virus replication and required A436T and/or K536R to restore replication, systemic spread, and stability. These results are important for better understanding of the evolution of highly pathogenic avian influenza viruses from low-pathogenic precursors.

Abolghasemi, R., et al. (2022). "Synergistic inhibitory effect of human umbilical cord matrix mesenchymal stem cells-conditioned medium and atorvastatin on MCF7 cancer cells viability and migration." Cell Tissue Bank **23**(4): 767-789.

Recent studies have demonstrated inhibitory effects of mesenchymal stem cells on breast tumors. Likewise, the emerging interest in statins as anticancer agents is based on their pleiotropic effects. In the present study, we investigated whether atorvastatin and umbilical cord matrix derived mesenchymal stem cells-conditioned medium affect the MCF7 cancer cells viability and interactions. We measured the viability of MCF7 cancer cells by MTT assay, flow cytometry, and quantitative real-time PCR. Two-dimensional culture and hanging drop aggregation assay illustrated the morphological changes. We traced the MCF7 migration via scratch-wound healing test and trans-well assay. The results showed the inhibition of cancer cell viability in all treated groups compared to the control group. The effect of atorvastatin and conditioned medium combination was significantly more than each substance separately. The morphological changes indicated apoptosis in treated cells. The annexin V/PI flow cytometry especially in the combination-treated group displayed decreasing in DNA synthesis and cell cycle arrest in G1 and G2/M phases. As well, the mRNA expressions of caspases 3, 8, 9, and Bcl-2 genes were along with extrinsic and intrinsic apoptosis pathways. Conditioned medium disrupted the connections between cancer cells, so the spheroids in three-dimensional configuration lost their order and dispersed. The migration of treated cells across the wound area and trans-well diminished, particularly by the conditioned medium and atorvastatin combination. There fore, the synergistic anti-proliferative and anti-motility effect of atorvastatin along with human umbilical cord mesenchymal stem cells-derived conditioned medium on MCF7 breast cancer cells have been proved. The results might lead the development of novel adjuvant anticancer therapeutics based on targeting or modifying the extracellular matrix to increase chemotherapy results or to prevent metastatic colonization. Schematic representation of "Synergistic Inhibitory Effect of Human Umbilical Cord Matrix Mesenchymal Stem Cells-Conditioned Medium and Atorvastatin on MCF7 Cancer Cells Viablity and Migration" by: Dr. Reyhaneh Abolghasemi, Dr. Somayeh Ebrahimi-barough, Proffesor. Jafar Ai.

Abou-Antoun, T. J., et al. (2018). "Molecular and functional analysis of anchorage independent, treatment-evasive neuroblastoma tumorspheres with enhanced malignant properties: A possible explanation for radio-therapy resistance." PLoS One **13**(1): e0189711.

Despite significant advances in cancer treatment and management, more than 60% of patients with neuroblastoma present with very poor prognosis in the form of metastatic and aggressive disease. Solid tumors including neuroblastoma are thought to be heterogeneous with a sub-population of stem-like cells that are treatment-evasive with highly malignant characteristics. We previously identified a phenomenon of reversible adaptive plasticity (RAP) between anchorage dependent (AD) cells and anchorage independent (AI) tumorspheres in neuroblastoma cell cultures. To expand our molecular characterization of the AI tumorspheres, we sought to define the comprehensive proteomic profile of murine AD and AI neuroblastoma cells. The proteomic profiles of the two phenotypic cell populations were compared to each other to determine the differential protein expression and molecular pathways of interest. We report exclusive or significant up-regulation of tumorigenic pathways expressed by the AI tumorspheres compared to the AD cancer cells. These pathways govern metastatic potential, enhanced malignancy and epithelial to mesenchymal transition. Furthermore, radio-therapy induced significant up-regulation of specific tumorigenic and proliferative proteins, namely survivin, CDC2 and the enzyme Poly [ADP-ribose] polymerase 1. Bio-functional characteristics of the AI tumorspheres were resistant to sutent inhibition of receptor tyrosine kinases (RTKs) as well as to 2.5 Gy radio-therapy as assessed by cell survival, proliferation, apoptosis and migration. Interestingly, PDGF-BB stimulation of the PDGFRbeta led to transactivation of EGFR and VEGFR in AI tumorspheres more potently than in AD cells. Sutent inhibition of PDGFRbeta abrogated this transactivation in both cell types. In addition, 48 h sutent treatment significantly down-regulated the protein expression of PDGFRbeta, MYCN, SOX2 and Survivin in the AI tumorspheres and inhibited tumorsphere self-renewal. Radio-sensitivity in AI tumorspheres was enhanced when sutent treatment was combined with survivin knock-down. We conclude that AI tumorspheres have a differential protein expression compared to AD cancer cells that

contribute to their malignant phenotype and radio-resistance. Specific targeting of both cellular phenotypes is needed to improve outcomes in neuroblastoma patients.

Agelopoulos, K., et al. (2008). "Allelic imbalances of the egfr gene as key events in breast cancer progression--the concept of committed progenitor cells." Curr Cancer Drug Targets **8**(5): 431-445.

The introduction of concepts proposing multiple cellular subgroups in the normal female breast leads to the hypothesis that distinct cellular phenotypes in the female breast give rise to different subtypes of breast carcinomas e.g. expressing ER, HER2 and EGFR differentially. Therefore, origin of breast carcinoma types may be based on the formation of a cancer prone field in which the committed progenitor cells pass mutations to their progenies, glandular as well as myoepithelial cells. The existence of such field within the human breast was inferred from the results on primary breast cancer obtained by PCR-based microsatellite analysis of allelic imbalance (AI) of the EGF receptor gene. Here, normal breast tissue shows egfr AI adjacent to breast cancer tissue also harboring egfr gene AI. The therapeutic implications of such a model are fundamental, as tumors may display different phenotypes which arise from transformation of different progenitor cells as well as from transformation of more differentiated progenies within a cancer prone field. Thereby they may show up with different clinical courses of the disease, higher rates of metastases and responses to therapy. In this review, we discuss this mechanism focusing on the EGF receptor as an example for regulators of progenitor cell growth in many tissues. Phylloides tumors serve as a putative model for embryonic differentiation stage ruled by EGFR signaling and give insights into the tumor-host-interaction. The inhibition of the EGF receptor by specific monoclonal antibodies (e.g. Erbitux) will give an answer in as far EGFR-signaling is decisive for the development of an invasive breast cancer. For this purpose new models have been inaugurated which vary in the EGF receptor gene dosage and protein expression. Moreover, we discuss the EGF receptor as a target for the treatment of pre-malignant lesions with a high risk for malignant growth, e.g. DCIS, which certainly will be detected more frequently by mammography screening programs soon.

Agut, H. (2011). "Deciphering the clinical impact of acute human herpesvirus 6 (HHV-6) infections." J Clin Virol **52**(3): 164-171.

Human herpesvirus 6 (HHV-6) is a ubiquitous virus inducing a life-long latent infection of its human host. Acute infections (AIs) have been recognized as the cause of severe diseases. These AIs correspond to primary infections (PIs), mainly occurring in young children, endogenous reactivations (ENRs), observed at any age, and putative exogenous reinfections (EXRs). The diagnosis of AIs is now essentially based on the quantification of viral load in bodily fluids and organs by means of real time PCR. However, this diagnosis is currently bothered by the lack of well established viral load thresholds for the different levels of virus replication, the concomitant infection with the two variants HHV-6A and HHV-6B, and the existence, albeit at low frequency, of chromosomal integration of viral DNA. An additional challenge is the difficulty to establish the causality relationship between AI and disease. Although many AIs are asymptomatic or poorly symptomatic with a spontaneous favourable outcome, some have been credited with serious clinical manifestations affecting central nervous system, liver, gastrointestinal tract, lungs, and bone marrow. The main favouring factor for such serious diseases is cellular immune deficiency. These severe diseases can be exemplified by encephalitis cases either associated with PI in young children or with ENR, especially in haematopoietic stem cell transplant recipients. The antiviral drugs ganciclovir, foscarnet and cidofovir have proven to be efficient against AIs and related diseases but the indications and conditions of their use are not yet formally approved. This emphasizes the need for controlled studies addressing both the clinical impact and therapy of HHV-6 AIs.

Aida, S., et al. (2020). "Deep Learning of Cancer Stem Cell Morphology Using Conditional Generative Adversarial Networks." Biomolecules **10**(6).

Deep-learning workflows of microscopic image analysis are sufficient for handling the contextual variations because they employ biological samples and have numerous tasks. The use of well-defined annotated images is important for the workflow. Cancer stem cells (CSCs) are identified by specific cell markers. These CSCs were extensively characterized by the stem cell (SC)-like gene expression and proliferation mechanisms for the development of tumors. In contrast, the morphological characterization remains elusive. This study aims to investigate the segmentation of CSCs in phase contrast imaging using conditional generative adversarial networks (CGAN). Artificial intelligence (AI) was trained using fluorescence images of the Nanog-Green fluorescence protein, the expression of which was maintained in CSCs, and the phase contrast images. The AI model segmented the CSC region in the phase contrast image of the CSC

cultures and tumor model. By selecting images for training, several values for measuring segmentation quality increased. Moreover, nucleus fluorescence overlaid-phase contrast was effective for increasing the values. We show the possibility of mapping CSC morphology to the condition of undifferentiation using deep-learning CGAN workflows.

Al Jaf, A. I. A., et al. (2024). "Remyelinating Drugs at a Crossroad: How to Improve Clinical Efficacy and Drug Screenings." Cells **13**(16).

Axons wrapped around the myelin sheath enable fast transmission of neuronal signals in the Central Nervous System (CNS). Unfortunately, myelin can be damaged by injury, viral infection, and inflammatory and neurodegenerative diseases. Remyelination is a spontaneous process that can restore nerve conductivity and thus movement and cognition after a demyelination event. Cumulative evidence indicates that remyelination can be pharmacologically stimulated, either by targeting natural inhibitors of Oligodendrocyte Precursor Cells (OPCs) differentiation or by reactivating quiescent Neural Stem Cells (qNSCs) proliferation and differentiation in myelinating Oligodendrocytes (OLs). Although promising results were obtained in animal models for demyelination diseases, none of the compounds identified have passed all the clinical stages. The significant number of patients who could benefit from remyelination therapies reinforces the urgent need to reassess drug selection approaches and develop strategies that effectively promote remyelination. Integrating Artificial Intelligence (AI)-driven technologies with patient-derived cell-based assays and organoid models is expected to lead to novel strategies and drug screening pipelines to achieve this goal. In this review, we explore the current literature on these technologies and their potential to enhance the identification of more effective drugs for clinical use in CNS remyelination therapies.

Al-Herz, W., et al. (2018). "DNA recombination defects in Kuwait: Clinical, immunologic and genetic profile." Clin Immunol **187**: 68-75.

Defects in DNA Recombination due to mutations in RAG1/2 or DCLRE1C result in combined immunodeficiency (CID) with a range of disease severity. We present the clinical, immunologic and molecular characteristics of 21 patients with defects in RAG1, RAG2 or DCLRE1C, who accounted for 24% of combined immune deficiency cases in the Kuwait National Primary Immunodeficiency Disorders Registry. The distribution of the patients was as follow: 8 with RAG1 deficiency, 6 with RAG2 deficiency and 7 with DCLRE1C deficiency. Nine patients presented with SCID, 6 with OS, 2 with leaky SCID and 4 with CID and granuloma and/or autoimmunity (CID-G/AI). Eight patients [(7 SCID and 1 OS) (38%)] received hematopoietic stem cell transplant (HSCT). The median age of HSCT was 11.5months and the median time from diagnosis to HSCT was 6months. Fifty percent of the transplanted patients are alive while only 23% of the untransplanted ones are alive.

Alini, M., et al. (2023). "An update on animal models of intervertebral disc degeneration and low back pain: Exploring the potential of artificial intelligence to improve research analysis and development of prospective therapeutics." JOR Spine **6**(1): e1230.

Animal models have been invaluable in the identification of molecular events occurring in and contributing to intervertebral disc (IVD) degeneration and important therapeutic targets have been identified. Some outstanding animal models (murine, ovine, chondrodystrophoid canine) have been identified with their own strengths and weaknesses. The llama/alpaca, horse and kangaroo have emerged as new large species for IVD studies, and only time will tell if they will surpass the utility of existing models. The complexity of IVD degeneration poses difficulties in the selection of the most appropriate molecular target of many potential candidates, to focus on in the formulation of strategies to effect disc repair and regeneration. It may well be that many therapeutic objectives should be targeted simultaneously to effect a favorable outcome in human IVD degeneration. Use of animal models in isolation will not allow resolution of this complex issue and a paradigm shift and adoption of new methodologies is required to provide the next step forward in the determination of an effective repairative strategy for the IVD. AI has improved the accuracy and assessment of spinal imaging supporting clinical diagnostics and research efforts to better understand IVD degeneration and its treatment. Implementation of AI in the evaluation of histology data has improved the usefulness of a popular murine IVD model and could also be used in an ovine histopathological grading scheme that has been used to quantify degenerative IVD changes and stem cell mediated regeneration. These models are also attractive candidates for the evaluation of novel anti-oxidant compounds that counter inflammatory conditions in degenerate IVDs and promote IVD regeneration. Some of these compounds also have pain-relieving properties. AI has facilitated development of facial recognition pain assessment in animal IVD models offering the possibility of correlating the potential pain alleviating properties of some of these compounds with IVD regeneration.

AlOraibi, S., et al. (2024). "Advancements in Umbilical Cord Biobanking: A Comprehensive Review of Current Trends and Future Prospects." Stem Cells Cloning **17**: 41-58.

Biobanking has emerged as a transformative concept in advancing the medical field, particularly with the exponential growth of umbilical cord (UC) biobanking in recent decades. UC blood and tissue provide a rich source of primitive hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) for clinical transplantation, offering distinct advantages over alternative adult stem cell sources. However, to fully realize the therapeutic potential of UC-derived stem cells and establish a comprehensive global UC-biobanking network, it is imperative to optimize and standardize UC processing, cryopreservation methods, quality control protocols, and regulatory frameworks, alongside developing effective consent provisions. This review aims to comprehensively explore recent advancements in UC biobanking, focusing on the establishment of rigorous safety and quality control procedures, the standardization of biobanking operations, and the optimization and automation of UC processing and cryopreservation techniques. Additionally, the review examines the expanded clinical applications of UC stem cells, addresses the challenges associated with umbilical cord biobanking and UC-derived stem cell therapies, and discusses the promising role of artificial intelligence (AI) in enhancing various operational aspects of biobanking, streamlining data processing, and improving data analysis accuracy while ensuring compliance with safety and quality standards. By addressing these critical areas, this review seeks to provide insights into the future direction of UC biobanking and its potential to significantly impact regenerative medicine.

Alzoubi, I., et al. (2024). "PathoGraph: An Attention-Based Graph Neural Network Capable of Prognostication Based on CD276 Labelling of Malignant Glioma Cells." Cancers (Basel) **16**(4).

Computerized methods have been developed that allow quantitative morphological analyses of whole slide images (WSIs), e.g., of immunohistochemical stains. The latter are attractive because they can provide high-resolution data on the distribution of proteins in tissue. However, many immunohistochemical results are complex because the protein of interest occurs in multiple locations (in different cells and also extracellularly). We have recently established an artificial intelligence framework, PathoFusion which utilises a bifocal convolutional neural network (BCNN) model for detecting and counting arbitrarily definable morphological structures. We have now complemented this model by adding an attention-based graph neural network (abGCN) for the advanced analysis and automated interpretation of such data. Classical convolutional neural network (CNN) models suffer from limitations when handling global information. In contrast, our abGCN is capable of creating a graph representation of cellular detail from entire WSIs. This abGCN method combines attention learning with visualisation techniques that pinpoint the location of informative cells and highlight cell-cell interactions. We have analysed cellular labelling for CD276, a protein of great interest in cancer immunology and a potential marker of malignant glioma cells/putative glioma stem cells (GSCs). We are especially interested in the relationship between CD276 expression and prognosis. The graphs permit predicting individual patient survival on the basis of GSC community features. Our experiments lay a foundation for the use of the BCNN-abGCN tool chain in automated diagnostic prognostication using immunohistochemically labelled histological slides, but the method is essentially generic and potentially a widely usable tool in medical research and AI based healthcare applications.

Andryushkova, A. A., et al. (2007). "Formation of different abzymes in autoimmune-prone MRL-lpr/lpr mice is associated with changes in colony formation of haematopoietic progenitors." J Cell Mol Med **11**(3): 531-551.

It was shown that IgGs from the sera of 2-7-month-old control non-autoimmune (CBA x C57BL)F1 and BALB/c mice and 2-3-month-old autoimmune prone MRL-lpr/lpr mice (conditionally healthy mice) are catalytically inactive. During spontaneous development of deep systemic lupus erythematosus (SLE)-like pathology a specific reorganization of immune system of these mice leads to conditions associated with a production of IgGs hydrolyzing DNA, ATP and polysaccharides with low catalytic activities (conditionally pre-diseased mice).A significant increase in DNase, ATPase and amylase IgG relative activities associated with a transition from pre-diseased to deep diseased mice is correlated with additional changes in differentiation and proliferation of mice bone marrow haematopoietic stem cells (HSCs) and lymphocyte proliferation in different organs. The highest increase in all abzyme activities was found in mice immunized with DNA, which in comparison with pre-diseased and diseased mice are characterized by a different profile of HSC differentiation and by a suppression of cell apoptosis. Abzyme activities in the serum of pregnant females were comparable with

those for pre-diseased mice, but the profile of HSC differentiation and cell apoptosis levels in pregnant and pre-diseased mice were quite different. Right after the beginning of lactation (4 days after delivery) and in a late time of lactation (14 days after delivery) there was an observed increase in cell apoptosis and two different stages of significant change in the HSC differentiation profiles; the first stage was accompanied with a significant increase and the second with a remarkable decrease in abzyme activities.

Asadi Sarabi, P., et al. (2024). "AI-Based solutions for current challenges in regenerative medicine." Eur J Pharmacol **984**: 177067.

The emergence of Artificial Intelligence (AI) and its usage in regenerative medicine represents a significant opportunity that holds the promise of tackling critical challenges and improving therapeutic outcomes. This article examines the ways in which AI, including machine learning and data fusion techniques, can contribute to regenerative medicine, particularly in gene therapy, stem cell therapy, and tissue engineering. In gene therapy, AI tools can boost the accuracy and safety of treatments by analyzing extensive genomic datasets to target and modify genetic material in a precise manner. In cell therapy, AI improves the characterization and optimization of cell products like mesenchymal stem cells (MSCs) by predicting their function and potency. Additionally, AI enhances advanced microscopy techniques, enabling accurate, non-invasive and quantitative analyses of live cell cultures. AI enhances tissue engineering by optimizing biomaterial and scaffold designs, predicting interactions with tissues, and streamlining development. This leads to faster and more cost-effective innovations by decreasing trial and error. The convergence of AI and regenerative medicine holds great transformative potential, promising effective treatments and innovative therapeutic strategies. This review highlights the importance of interdisciplinary collaboration and the continued integration of AI-based technologies, such as data fusion methods, to overcome current challenges and advance regenerative medicine.

Asmar, A. J., et al. (2024). "High-volume, label-free imaging for quantifying single-cell dynamics in induced pluripotent stem cell colonies." PLoS One **19**(2): e0298446.

To facilitate the characterization of unlabeled induced pluripotent stem cells (iPSCs) during culture and expansion, we developed an AI pipeline for nuclear segmentation and mitosis detection from phase contrast images of individual cells within iPSC colonies. The analysis uses a 2D convolutional neural network (U-Net) plus a 3D U-Net applied on time lapse images to detect and segment nuclei, mitotic events, and daughter nuclei to enable tracking of large numbers of individual cells over long times in culture. The analysis uses fluorescence data to train models for segmenting nuclei in phase contrast images. The use of classical image processing routines to segment fluorescent nuclei precludes the need for manual annotation. We optimize and evaluate the accuracy of automated annotation to assure the reliability of the training. The model is generalizable in that it performs well on different datasets with an average F1 score of 0.94, on cells at different densities, and on cells from different pluripotent cell lines. The method allows us to assess, in a non-invasive manner, rates of mitosis and cell division which serve as indicators of cell state and cell health. We assess these parameters in up to hundreds of thousands of cells in culture for more than 36 hours, at different locations in the colonies, and as a function of excitation light exposure.

Atwell, S., et al. (2023). "Label-free imaging of 3D pluripotent stem cell differentiation dynamics on chip." Cell Rep Methods **3**(7): 100523.

Massive, parallelized 3D stem cell cultures for engineering in vitro human cell types require imaging methods with high time and spatial resolution to fully exploit technological advances in cell culture technologies. Here, we introduce a large-scale integrated microfluidic chip platform for automated 3D stem cell differentiation. To fully enable dynamic high-content imaging on the chip platform, we developed a label-free deep learning method called Bright2Nuc to predict in silico nuclear staining in 3D from confocal microscopy bright-field images. Bright2Nuc was trained and applied to hundreds of 3D human induced pluripotent stem cell cultures differentiating toward definitive endoderm on a microfluidic platform. Combined with existing image analysis tools, Bright2Nuc segmented individual nuclei from bright-field images, quantified their morphological properties, predicted stem cell differentiation state, and tracked the cells over time. Our methods are available in an open-source pipeline, enabling researchers to upscale image acquisition and phenotyping of 3D cell culture.

Baggio, L., et al. (2017). "Natural killer cell adoptive immunotherapy: Coming of age." Clin Immunol **177**: 3-11.

Cell therapy is a promising alternative to harsh chemotherapy and radiation therapy for cancer. Natural killer (NK) cells in particular have great

potential for direct use in adoptive immunotherapy (AI) for cancer and to improve the graft-vs-leukemia (GVL) effect of hematopoietic stem cell transplants (HSCTs). NK cell number and function are associated with a strong GVL effect without inducing graft-versus-host disease in most settings. Clinical trials demonstrating the therapeutic role of NK cells in HSCT recipients or testing the safety and efficacy of AI with NK cells have been primarily directed at treating acute myeloid leukemia, although investigators have used NK cells for treatment of other hematological diseases, sarcomas, carcinomas, and brain tumors. Major challenges must be overcome in making NK cell-based therapy cost-effective, the most important being the need to collect or generate an adequate number of effector cells. In this review, we discuss protocols for isolation, expansion, and in vitro propagation of large quantities of functional NK cells that meet the criteria for clinical applications. Among the methods described are the use of bioreactors for scaling up production and expansion of NK cells in the presence of interleukins and feeder cells. We also discuss novel methodologies that optimize the generation of clinical grade NK-cell products for AI.

Bagherpour, R., et al. (2024). "Application of Artificial Intelligence in Tissue Engineering." Tissue Eng Part B Rev.

Tissue engineering, a crucial approach in medical research and clinical applications, aims to regenerate damaged organs. By combining stem cells, biochemical factors, and biomaterials, it encounters challenges in designing complex 3D structures. Artificial intelligence (AI) enhances tissue engineering through computational modeling, biomaterial design, cell culture optimization, and personalized medicine. This review explores AI applications in organ tissue engineering (bone, heart, nerve, skin, cartilage), employing various machine learning (ML) algorithms for data analysis, prediction, and optimization. Each section discusses common ML algorithms and specific applications, emphasizing the potential and challenges in advancing regenerative therapies.

Bahmad, H. F., et al. (2019). "The synthetic retinoid ST1926 attenuates prostate cancer growth and potentially targets prostate cancer stem-like cells." Mol Carcinog **58**(7): 1208-1220.

Retinoids are vitamin A derivatives that regulate crucial biological processes such as cellular proliferation, apoptosis, and differentiation. The use of natural retinoids in cancer therapy is limited due to their toxicity and the acquired resistance by cancer cells. Therefore, synthetic retinoids were developed, such as the atypical adamantyl retinoid ST1926 that provides enhanced bioavailability and reduced toxicity. We have assessed the in vitro and in vivo antitumor properties and mechanism of action of ST1926 in targeting cancer stem-like cells population of human prostate cancer (PCa) cell lines, DU145 and PC3, and mouse PCa cell lines, PLum-AD and PLum-AI. We demonstrated that ST1926 substantially reduced proliferation of PCa cells and induced cell cycle arrest, p53-independent apoptosis, and early DNA damage. It also decreased migration and invasion of PCa cells and significantly reduced prostate spheres formation ability in vitro denoting sufficient eradication of the self-renewal ability of the highly androgen-resistant cancer stem cells. Importantly, ST1926 potently inhibited PCa tumor growth and progression in vivo. Our results highlight the potential of ST1926 in PCa therapy and warrant its clinical development.

Becerril-Rico, J., et al. (2024). "Circulating Gastric Cancer Stem Cells as Blood Screening and Prognosis Factor in Gastric Cancer." Stem Cells Int **2024**: 9999155.

Gastric cancer (GC) is the fourth leading cause of cancer-related death, associated with late diagnosis and treatment resistance. Currently, screening tests for GC are not cost-effective or have low accuracy. Previously, we described an extended phenotype of gastric cancer stem cells (GCSCs; CD24(+)CD44(+)CD54(+)EpCAM(+)) that is associated with metastasis and tumor stage in GC patients. The goal of the current research is to evaluate the presence of these GCSCs in the peripheral blood of GC patients and healthy volunteers. A total of 73 blood samples were collected from 32 GC patients and 41 healthy volunteers. After peripheral blood mononuclear cell (PBMC) extraction, multiparametric flow cytometry was performed looking for GCSCs. Using clustering data through artificial intelligence (AI), we defined high/low levels of circulating GCSCs (cGCSCs) and proceeded to evaluate its association with clinical and prognostic variables. Finally, a diagnostic test analysis was performed evaluating patients and healthy volunteers. We found that cGCSCs are present in most GC patients with a mean concentration of 0.48%. The AI clustering showed two groups with different cGCSC levels and clinical characteristics. Through statistical analysis, we confirmed the association between cGCSC levels and lymph node metastasis, distant metastasis, and overall survival. The diagnostic test analysis showed sensibility, specificity, and area under the curve (AUC) of 83%, 95%, and 0.911, respectively. Our results suggest that the assessment of cGCSCs

CD24(+)CD44(+)CD54(+)EpCAM(+) could be a potential noninvasive test, with prognostic value, as well as highly sensitive and specific for screening or diagnosis of GC; however, a larger scale study will be necessary to confirm this.

Becker-Catania, S. G., et al. (2006). "Loss of arginase I results in increased proliferation of neural stem cells." J Neurosci Res **84**(4): 735-746.

Loss of arginase I (AI) results in a metabolic disorder characterized by growth retardation, increased mental impairment and spasticity, and potentially fatal hyperammonemia. This syndrome plus a growing body of evidence supports a role for arginase and arginine metabolites in normal neuronal development and function. Here we report our initial observations of the effects of AI loss on proliferation and differentiation of neural stem cells (NSCs) isolated from the germinal zones of embryonic and newborn AI knockout (KO) mice compared with heterozygous (HET) and wild-type (WT) control animals. By using both short and long-term proliferation assays (3 and 10 days, respectively), we found a 1.5-2-fold increase in the number of KO cells compared with WT. FACS analysis showed an increase in KO cells in the synthesis phase of the cell cycle vs. WT cells. After NSC differentiation, AI-deficient cells expressed beta-tubulin, SMI81 (SNAP25), glial fibrillary acidic protein, and CNPase, which are markers consistent with neurons, astrocytes, and oligodendrocytes. Many KO cells exhibited a more mature morphology and expressed mature neuronal markers that were decreased or not present in HET or WT cells. Limited, comparative expression array and quantitative RT-PCR analysis identified differences in the levels of several mRNAs encoding structural, signaling, and arginine metabolism proteins between KO and WT cells. The consequence of these changes may contribute to the differential phenotypes of KO vs. WT cells. It appears that AI may play an important and unanticipated role in growth and development of NSCs.

Bhowmik, P. K., et al. (2006). "Sucrose metabolism of perennial ryegrass in relation to cold acclimation." Z Naturforsch C J Biosci **61**(1-2): 99-104.

Sugar metabolism is one of the important factors involved in winter hardiness and since the discovery of sucrose biosynthesis, considerable advances have been made in understanding its regulation and crucial role. This investigation examined the changes in activities of sucrose metabolizing enzymes and sugar content during cold hardening of perennial ryegrass (Lolium perenne L.). Changes in acid invertase (AI), sucrose synthase (SS) and sucrose phosphate synthase (SPS) along with all the three soluble sugars glucose, fructose and sucrose were measured in leaves and stem base tissue during cold acclimation. Although fructans were the predominant carbohydrate the changes in glucose, fructose and sucrose were significant. All the three soluble sugars in both leaf and stem tissues started to decrease from the first day and continued up to day 7 and thereafter started to increase until day 28. AI in the soluble fraction showed a higher activity than that in the cell wall bound fraction. In both the leaf and stem bases soluble AI activity increased during the first week and after that it started to decrease gradually. On the other hand both the SS and SPS increased gradually throughout the acclimation period. Sucrose content was negatively correlated with AI and positively correlated with SS and SPS accounting well for the relation between the substrate and enzyme activity. These results suggest that AI, SS and SPS in ryegrass are regulated by cold acclimation and play an important role in sugar accumulation and acquisition of freezing tolerance.

Bi, L., et al. (2015). "Effects of autologous bone marrow-derived stem cell mobilization on acute tubular necrosis and cell apoptosis in rats." Exp Ther Med **10**(3): 851-856.

The aim of this study was to investigate the effects of stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) on bone marrow-derived stem cell (BMSC) mobilization in rat models of renal ischemia/reperfusion (I/R) injury. In addition, the effects of SCF and G-CSF on cellular apoptosis were explored in order to determine the protective mechanism of the two factors against renal I/R injury. A unilateral renal I/R injury model was established for the model and treatment groups. The treatment and treatment control groups were subcutaneously injected with SCF (200 microg/kg/day) and G-CSF (50 microg/kg/day) 24 h after the establishment of the model for five consecutive days. The total number of leukocytes in the peripheral blood and the cellular percentages of cluster of differentiation (CD)34(+), renal CD34(+) and apoptotic cells were detected. The total number of leukocytes in the peripheral blood and the percentages of CD34(+) cells in the treatment and treatment control groups reached maximum levels on the fifth postoperative day and were significantly higher than those in the normal control and model groups. The number of renal CD34(+) cells in the treatment group was significantly increased compared with that in the treatment control and model groups. The apoptotic indices (AIs) of the model and treatment groups were higher than those of the normal control and treatment control groups. The AI of the model group was significantly higher than that of the treatment group.

In conclusion, the combined application of SCF and G-CSF can mobilize sufficient numbers of BMSCs and cause cellular 'homing' to the injured site, thus inhibiting apoptosis and promoting the repair of renal tubular injury.

Bi, X., et al. (2017). "ATP-Binding Cassette Transporter A1 Deficiency in Human Induced Pluripotent Stem Cell-Derived Hepatocytes Abrogates HDL Biogenesis and Enhances Triglyceride Secretion." EBioMedicine **18**: 139-145.

Despite the recognized role of the ATP-binding Cassette Transporter A1 (ABCA1) in high-density lipoprotein (HDL) metabolism, our understanding of ABCA1 deficiency in human hepatocytes is limited. To define the functional effects of human hepatocyte ABCA1 deficiency, we generated induced pluripotent stem cell (iPSC)-derived hepatocyte-like cells (HLCs) from Tangier disease (TD) and matched control subjects. Control HLCs exhibited robust cholesterol efflux to apolipoprotein A-I (apoA-I) and formed nascent HDL particles. ABCA1-deficient HLCs failed to mediate lipid efflux or nascent HDL formation, but had elevated triglyceride (TG) secretion. Global transcriptome analysis revealed significantly increased ANGPTL3 expression in ABCA1-deficient HLCs. Angiopoietin-related protein 3 (ANGPTL3) was enriched in plasma of TD relative to control subjects. These results highlight the required role of ABCA1 in cholesterol efflux and nascent HDL formation by hepatocytes. Furthermore, our results suggest that hepatic ABCA1 deficiency results in increased hepatic TG and ANGPTL3 secretion, potentially underlying the elevated plasma TG levels in TD patients.

Binzagr, F. (2024). "Explainable AI-driven model for gastrointestinal cancer classification." Front Med (Lausanne) **11**: 1349373.

Although the detection procedure has been shown to be highly effective, there are several obstacles to overcome in the usage of AI-assisted cancer cell detection in clinical settings. These issues stem mostly from the failure to identify the underlying processes. Because AI-assisted diagnosis does not offer a clear decision-making process, doctors are dubious about it. In this instance, the advent of Explainable Artificial Intelligence (XAI), which offers explanations for prediction models, solves the AI black box issue. The SHapley Additive exPlanations (SHAP) approach, which results in the interpretation of model predictions, is the main emphasis of this work. The intermediate layer in this study was a hybrid model made up of three Convolutional Neural Networks (CNNs) (InceptionV3, InceptionResNetV2, and VGG16) that combined their predictions. The KvasirV2 dataset, which comprises pathological symptoms associated to cancer, was used to train the model. Our combined model yielded an accuracy of 93.17% and an F1 score of 97%. After training the combined model, we use SHAP to analyze images from these three groups to provide an explanation of the decision that affects the model prediction.

Blana, V. A. and G. J. Nychas (2014). "Presence of quorum sensing signal molecules in minced beef stored under various temperature and packaging conditions." Int J Food Microbiol **173**: 1-8.

The presence of acylated homoserine lactones (AHLs) and autoinducer-2 (AI-2)-like activity was observed in meat stored under various temperatures (0, 5, 10 and 15 degrees C) and packaging (air, modified atmospheres and modified atmospheres with oregano essential oil) conditions, and correlated with the ephemeral spoilage organisms that comprise the microbial community generally associated with this product. Quorum sensing signal molecules were found to be affected by the packaging conditions e.g. temperature and atmosphere used for meat preservation as a consequence of the development of a distinct microbial community. AHL signal molecules were detected at all incubation temperatures in minced beef samples, both stored aerobically and under modified atmospheres, when both pseudomonads and Enterobacteriaceae populations ranged from 10(7) to 10(9)CFU/g, but no signal molecules were detected in minced beef stored under modified atmospheres in the presence of volatile compounds of oregano essential oil, where both these groups failed to grow in high numbers. Additionally, no significant AI-2 activity was observed in the tested cell-free meat extracts (CFME), regardless of the indigenous bacterial populations. The presence of N-(beta-ketocaproyl)-homoserine lactone was confirmed with TLC analysis of CFME.

Blervaque, L., et al. (2020). "COPD is deleterious for pericytes: implications during training-induced angiogenesis in skeletal muscle." Am J Physiol Heart Circ Physiol **319**(5): H1142-H1151.

Improvements in skeletal muscle endurance and oxygen uptake are blunted in patients with chronic obstructive pulmonary disease (COPD), possibly because of a limitation in the muscle capillary oxygen supply. Pericytes are critical for capillary blood flow adaptation during angiogenesis but may be impaired by COPD systemic effects, which are mediated by circulating factors. This study compared the pericyte coverage of muscle capillaries in response to 10 wk of exercise training in patients

with COPD and sedentary healthy subjects (SHS). Fourteen patients with COPD were compared with seven matched SHS. SHS trained at moderate intensity corresponding to an individualized moderate-intensity patient with COPD trained at the same relative (%V̇o(2): COPD-RI) or absolute (mL.min(-1).kg(-1): COPD-AI) intensity as SHS. Capillary-to-fiber ratio (C/F) and NG2(+) pericyte coverage were assessed from vastus lateralis muscle biopsies, before and after 5 and 10 wk of training. We also tested in vitro the effect of COPD and SHS serum on pericyte morphology and mesenchymal stem cell (MSC) differentiation into pericytes. SHS showed greater improvement in aerobic capacity (V̇o(2VT)) than both patients with COPD-RI and patients with COPD-AI (Group x Time: P = 0.004). Despite a preserved increase in the C/F ratio, NG2(+) pericyte coverage did not increase in patients with COPD in response to training, contrary to SHS (Group x Time: P = 0.011). Conversely to SHS serum, COPD serum altered pericyte morphology (P < 0.001) and drastically reduced MSC differentiation into pericytes (P < 0.001). Both functional capacities and pericyte coverage responses to exercise training are blunted in patients with COPD. We also provide direct evidence of the deleterious effect of COPD circulating factors on pericyte morphology and differentiation.NEW & NOTEWORTHY This work confirms the previously reported impairment in the functional response to exercise training of patients with COPD compared with SHS. Moreover, it shows for the first time that pericyte coverage of the skeletal capillaries is drastically reduced in patients with COPD compared with SHS during training-induced angiogenesis. Finally, it provides experimental evidence that circulating factors are involved in the impaired pericyte coverage of patients with COPD.

Bogdanovic, A. D., et al. (1997). "Incidence and role of apoptosis in myelodysplastic syndrome: morphological and ultrastructural assessment." Leukemia **11**(5): 656-659.

By application of morphological and ultrastructural methods for identification of apoptosis, we analyzed the incidence of morphologically evident apoptosis in the bone marrow of 30 patients with myelodysplastic syndrome (MDS), and in the bone marrow of 12 healthy individuals. According to FAB classification, out of 30 patients, eight (26.6%) had refractory anemia, three (10%) had refractory anemia with ringed sideroblasts, 14 (46.6%) had refractory anemia with excess of blasts and two (6.8%) had refractory anemia with excess of blasts in transformation. Three patients (10%) had chronic myelomonocytic leukemia. Cells in apoptosis were examined on semithin slides and expressed as the apoptotic index (AI) (percent counted on at least 1000 cells). An overall increase in apoptosis in patients with MDS was found (median AI in patients vs controls, 3.13% vs 1.05%, P < 0.01 by Mann-Whitney U test). Also, negative correlation between AI and white blood cell count was found (linear r= -0.53, or Spearman rank R= -0.52, both P < 0.01). In patients with evident karyotype changes AI was not higher than in patients with normal karyotype. This suggests that discrete alterations in apoptosis are present even in karyotypically 'normal' clones. Our results strongly support the hypothesis that apoptosis has a role in ineffective hematopoiesis and may be a mechanism responsible for the paradox of hypercellular bone marrow and peripheral blood pancytopenia in MDS.

Bonios, M., et al. (2011). "Myocardial substrate and route of administration determine acute cardiac retention and lung bio-distribution of cardiosphere-derived cells." J Nucl Cardiol **18**(3): 443-450.

BACKGROUND: Quantification of acute myocardial retention and lung bio-distribution of cardiosphere-derived cells (CDCs) following transplantation is important to improve engraftment. METHODS AND RESULTS: We studied acute(1 hour) cardiac/lung retention in 4 groups (n = 25) of rats (normal--NL, acute ischemia-reperfusion--AI-RM, acute permanent ligation-PL, and chronic infarct by ischemia-reperfusion--CI-R) using intra-myocardial delivery, 1 group using intracoronary delivery (acute ischemia-reperfusion, AI-RC, n = 5) and 1 group using intravenous delivery (acute ischemia-reperfusion, AI-RV, n = 5) of CDCs by PET. Cardiac retention was similar in the NL, AI-RM, CI-R, and A-IRC groups (13.6% +/- 2.3% vs. 12.0% +/- 3.9% vs. 9.9 +/- 2.8 vs. 15.4% +/- 5.5%; P = NS), but higher in PL animals (22.9% +/- 5.2%; P < .05). Low cardiac retention was associated with significantly higher lung activity in NL and AI-RM groups (43.3% +/- 5.6% and 39.9% +/- 9.3%), compared to PL (28.5% +/- 5.9%), CI-R (20.2% +/- 9.3%), and A-IRC (19.9% +/- 5.6%) animals (P < .05 vs. AI-RM and NL). Lung activity was highest following intravenous CDC delivery (55.1% +/- 9.3%, P < .001) and was associated with very low cardiac retention (0.8% +/- 1.06%). Two-photon microscopy indicated that CDCs escaped to the lungs via the coronary veins following intra-myocardial injection. CONCLUSIONS: Acute cardiac retention and lung bio-distribution vary with the myocardial substrate and injection route. Intra-myocardially injected CDCs escape into the lungs via coronary veins, an effect that is more pronounced in perfused myocardium.

Borges, L. R., et al. (2020). "Diagnosis of acute graft-

versus-host disease in the gastrointestinal tract of patients undergoing allogeneic hematopoietic stem cell transplantation. A descriptive and critical study of diagnostic tests." Hematol Transfus Cell Ther **42**(3): 245-251.

INTRODUCTION: Acute graft-versus-host disease (GVHD) is one of the major causes of morbidity and mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (AHSCT) and has become the subject of several studies to understand and treat it. OBJECTIVE: This study does a descriptive analysis of the apoptotic index (AI) evaluation and intestinal permeability (IP) alterations in association with the clinical, endoscopic and histopathological data on patients undergoing AHSCT, with emphasis on acute intestinal graft-versus-host disease (GVHD) diagnosis. METHODS: Thirty-one patients were divided into two groups-one of patients with a clinical GVHD diagnosis and one of those without GVHD diagnosis. RESULTS: Thirteen deaths (41.9%) occurred during the study period, thereby reaffirming the severity of the alterations found in the patients. Fifteen patients subjected to 21 esophagogastroduodenoscopy procedures prior to D + 90 post-transplant had visible endoscopic alterations and 19 biopsies revealed histological alterations to the stomach and duodenum. Higher apoptotic indices, not reaching statistical significance, were observed in patients who died of graft versus host disease (GVHD), in the more acute forms of GVHD and where clinical GVHD was present. The intestinal permeability evaluation was performed on nine patients able to undergo it in the three proposed study periods, which showed alterations, some of which were pronounced even during pre-transplant and, therefore, the pre-conditioning phase. CONCLUSION: Clinical judgment remains a fundamental tool in the diagnosis of GVHD. This study points to the known limitations of traditional diagnostic aids (endoscopy and histology) and points to new methods not usually employed in clinical practice.

Bruggenthies, J. B., et al. (2024). "Insights into the Identification of iPSC- and Monocyte-Derived Macrophage-Polarizing Compounds by AI-Fueled Cell Painting Analysis Tools." Int J Mol Sci **25**(22).

Macrophage polarization critically contributes to a multitude of human pathologies. Hence, modulating macrophage polarization is a promising approach with enormous therapeutic potential. Macrophages are characterized by a remarkable functional and phenotypic plasticity, with pro-inflammatory (M1) and anti-inflammatory (M2) states at the extremes of a multidimensional polarization spectrum. Cell morphology is a major indicator for macrophage activation, describing M1(-like) (rounded) and M2(-like) (elongated) states by different cell shapes. Here, we introduced cell painting of macrophages to better reflect their multifaceted plasticity and associated phenotypes beyond the rigid dichotomous M1/M2 classification. Using high-content imaging, we established deep learning- and feature-based cell painting image analysis tools to elucidate cellular fingerprints that inform about subtle phenotypes of human blood monocyte-derived and iPSC-derived macrophages that are characterized as screening surrogate. Moreover, we show that cell painting feature profiling is suitable for identifying inter-donor variance to describe the relevance of the morphology feature 'cell roundness' and dissect distinct macrophage polarization signatures after stimulation with known biological or small-molecule modulators of macrophage (re-)polarization. Our novel established AI-fueled cell painting analysis tools provide a resource for high-content-based drug screening and candidate profiling, which set the stage for identifying novel modulators for macrophage (re-)polarization in health and disease.

Budinger, E., et al. (2006). "Multisensory processing via early cortical stages: Connections of the primary auditory cortical field with other sensory systems." Neuroscience **143**(4): 1065-1083.

It is still a popular view that primary sensory cortices are unimodal, but recent physiological studies have shown that under certain behavioral conditions primary sensory cortices can also be activated by multiple other modalities. Here, we investigate the anatomical substrate, which may underlie multisensory processes at the level of the primary auditory cortex (field AI), and which may, in turn, enable AI to influence other sensory systems. We approached this issue by means of the axonal transport of the sensitive bidirectional neuronal tracer fluorescein-labeled dextran which was injected into AI of Mongolian gerbils (Meriones unguiculatus). Of the total number of retrogradely labeled cell bodies (i.e. cells of origin of direct projections to AI) found in non-auditory sensory and multisensory brain areas, approximately 40% were in cortical areas and 60% in subcortical structures. Of the cell bodies in the cortical areas about 82% were located in multisensory cortex, viz., the dorsoposterior and ventroposterior, posterior parietal cortex, the claustrum, and the endopiriform nucleus, 10% were located in the primary somatosensory cortex (hindlimb and trunk region), and 8% in secondary visual cortex. The cortical regions with retrogradely labeled cells also contained anterogradely labeled axons and their terminations, i.e. they are also target

areas of direct projections from AI. In addition, the primary olfactory cortex was identified as a target area of projections from AI. The laminar pattern of corticocortical connections suggests that AI receives primarily cortical feedback-type inputs and projects in a feedforward manner to its target areas. Of the labeled cell bodies in the subcortical structures, approximately 90% were located in multisensory thalamic, 4% in visual thalamic, and 6% in multisensory lower brainstem structures. At subcortical levels, we observed a similar correspondence of retrogradely labeled cells and anterogradely labeled axons and terminals in visual (posterior limitans thalamic nucleus) and multisensory thalamic nuclei (dorsal and medial division of the medial geniculate body, suprageniculate nucleus, posterior thalamic cell group, zona incerta), and in the multisensory nucleus of the brachium of the inferior colliculus. Retrograde, but not anterograde, labeling was found in the multisensory pontine reticular formation, particularly in the reticulotegmental nucleus of the pons. Conversely, anterograde, but no retrograde, labeling was found in the visual laterodorsal and lateroposterior thalamic nuclei, in the multisensory peripeduncular, posterior intralaminar, and reticular thalamic nuclei, as well as in the multisensory superior and pericentral inferior colliculi (including cuneiform and sagulum nucleus), pontine nuclei, and periaqueductal gray. Our study supports the notion that AI is not merely involved in the analysis of auditory stimulus properties but also in processing of other sensory and multisensory information. Since AI is directly connected to other primary sensory cortices (viz. the somatosensory and olfactory ones) multisensory information is probably also processed in these cortices. This suggests more generally, that primary sensory cortices may not be unimodal.

Camus, V., et al. (2023). "Complete hematologic response after belinostat treatment and allogeneic stem cell transplantation for multiple relapsed/refractory angioimmunoblastic T-cell lymphoma: A case report." Clin Case Rep **11**(6): e7623.

KEY CLINICAL MESSAGE: This case report highlights the potential of belinostat for the treatment of relapsed/refractory peripheral T-cell lymphomas, for which effective therapies are still scarce. ABSTRACT: Peripheral T-cell lymphomas have an aggressive disease course associated with poor outcomes. We report a young patient with highly pretreated relapsed/refractory nodal follicular helper T-cell lymphoma (angioimmunoblastic-type [nTFHL-AI]), who successfully received an allogeneic stem cell transplantation following belinostat therapy. The complete hematologic response achieved has lasted more than 2 years.

Carnevali, D., et al. (2024). "A deep learning method that identifies cellular heterogeneity using nanoscale nuclear features." Nat Mach Intell **6**(9): 1021-1033.

Cellular phenotypic heterogeneity is an important hallmark of many biological processes and understanding its origins remains a substantial challenge. This heterogeneity often reflects variations in the chromatin structure, influenced by factors such as viral infections and cancer, which dramatically reshape the cellular landscape. To address the challenge of identifying distinct cell states, we developed artificial intelligence of the nucleus (AINU), a deep learning method that can identify specific nuclear signatures at the nanoscale resolution. AINU can distinguish different cell states based on the spatial arrangement of core histone H3, RNA polymerase II or DNA from super-resolution microscopy images. With only a small number of images as the training data, AINU correctly identifies human somatic cells, human-induced pluripotent stem cells, very early stage infected cells transduced with DNA herpes simplex virus type 1 and even cancer cells after appropriate retraining. Finally, using AI interpretability methods, we find that the RNA polymerase II localizations in the nucleoli aid in distinguishing human-induced pluripotent stem cells from their somatic cells. Overall, AINU coupled with super-resolution microscopy of nuclear structures provides a robust tool for the precise detection of cellular heterogeneity, with considerable potential for advancing diagnostics and therapies in regenerative medicine, virology and cancer biology.

Castiello, M. C., et al. (2023). "Partial correction of immunodeficiency by lentiviral vector gene therapy in mouse models carrying Rag1 hypomorphic mutations." Front Immunol **14**: 1268620.

INTRODUCTION: Recombination activating genes (RAG) 1 and 2 defects are the most frequent form of severe combined immunodeficiency (SCID). Patients with residual RAG activity have a spectrum of clinical manifestations ranging from Omenn syndrome to delayed-onset combined immunodeficiency, often associated with granulomas and/or autoimmunity (CID-G/AI). Lentiviral vector (LV) gene therapy (GT) has been proposed as an alternative treatment to the standard hematopoietic stem cell transplant and a clinical trial for RAG1 SCID patients recently started. However, GT in patients with hypomorphic RAG mutations poses additional risks, because of the residual endogenous RAG1 expression and the general state of immune dysregulation and associated inflammation.

METHODS: In this study, we assessed the efficacy of GT in 2 hypomorphic Rag1 murine models (Rag1(F971L/F971L) and Rag1(R972Q/R972Q)), exploiting the same LV used in the clinical trial encoding RAG1 under control of the MND promoter. RESULTS AND DISCUSSION: Starting 6 weeks after transplant, GT-treated mice showed a decrease in proportion of myeloid cells and a concomitant increase of B, T and total white blood cells. However, counts remained lower than in mice transplanted with WT Lin- cells. At euthanasia, we observed a general redistribution of immune subsets in tissues, with the appearance of mature recirculating B cells in the bone marrow. In the thymus, we demonstrated correction of the block at double negative stage, with a modest improvement in the cortical/medullary ratio. Analysis of antigenspecific IgM and IgG serum levels after in vivo challenge showed an amelioration of antibody responses, suggesting that the partial immune correction could confer a clinical benefit. Notably, no overt signs of autoimmunity were detected, with B-cell activating factor decreasing to normal levels and autoantibodies remaining stable after GT. On the other hand, thymic enlargement was frequently observed, although not due to vector integration and insertional mutagenesis. In conclusion, our work shows that GT could partially alleviate the combined immunodeficiency of hypomorphic RAG1 patients and that extensive efficacy and safety studies with alternative models are required before commencing RAG gene therapy in thesehighly complex patients.

Chai, S. Y., et al. (2022). "Integrating artificial intelligence into haematology training and practice: Opportunities, threats and proposed solutions." Br J Haematol **198**(5): 807-811.

There remains a limited emphasis on the use beyond the research domain of artificial intelligence (AI) in haematology and it does not feature significantly in postgraduate medical education and training. This perspective article considers recent developments in the field of AI research in haematology and anticipates the potential benefits and risks associated with its deeper integration into the specialty. Anxiety towards the greater use of AI in healthcare stems from legitimate concerns surrounding data protection, lack of transparency in clinical decision-making, and erosion of the doctor-patient relationship. The specialty of haematology has successfully embraced multiple disruptive innovations. We are at the cusp of a new era of closer integration of AI into routine haematology practice that will ultimately benefit patient care but to harness its benefits the next generation of haematologists will need access to bespoke learning opportunities with input from data scientists.

Chakrabarti, L., et al. (2012). "Reversible adaptive plasticity: a mechanism for neuroblastoma cell heterogeneity and chemo-resistance." Front Oncol **2**: 82.

We describe a novel form of tumor cell plasticity characterized by reversible adaptive plasticity in murine and human neuroblastoma. Two cellular phenotypes were defined by their ability to exhibit adhered, anchorage dependent (AD) or sphere forming, anchorage independent (AI) growth. The tumor cells could transition back and forth between the two phenotypes and the transition was dependent on the culture conditions. Both cell phenotypes exhibited stem-like features such as expression of nestin, self-renewal capacity, and mesenchymal differentiation potential. The AI tumorspheres were found to be more resistant to chemotherapy and proliferated slower in vitro compared to the AD cells. Identification of specific molecular markers like MAP2, beta-catenin, and PDGFRbeta enabled us to characterize and observe both phenotypes in established mouse tumors. Irrespective of the phenotype originally implanted in mice, tumors grown in vivo show phenotypic heterogeneity in molecular marker signatures and are indistinguishable in growth or histologic appearance. Similar molecular marker heterogeneity was demonstrated in primary human tumor specimens. Chemotherapy or growth factor receptor inhibition slowed tumor growth in mice and promoted initial loss of AD or AI heterogeneity, respectively. Simultaneous targeting of both phenotypes led to further tumor growth delay with emergence of new unique phenotypes. Our results demonstrate that neuroblastoma cells are plastic, dynamic, and may optimize their ability to survive by changing their phenotype. Phenotypic switching appears to be an adaptive mechanism to unfavorable selection pressure and could explain the phenotypic and functional heterogeneity of neuroblastoma.

Chang, L. B., et al. (2018). "Therapeutic potential of amniotic fluid stem cells to treat bilateral ovarian dystrophy in dairy cows in a subtropical region." Reprod Domest Anim **53**(2): 433-441.

Amniotic fluid is a rich source of multipotent mesenchymal stem cells (MSCs). Amniotic fluid stem cells (AFSCs) have become a new source of stem cells; they have low immunogenicity and are easily harvested. For this reason, they may be useful in clinical tissue engineering. Moreover, AFSCs have anti-inflammatory properties and can repair tissues. This study evaluated the utility of AFSC injection to treat

bilateral ovarian dystrophy in Holstein-Friesian cows. Bovine AFSCs (BAFSCs) were collected at slaughter from Holstein-Friesian cows during the third or fourth month of pregnancy and cultured in vitro. The BAFSCs began to show a fibroblast-like morphology. They were positive for beta-integrin, CD44, CD73, CD106 and Oct4 and negative for CD34 and CD45. After induction, the cells differentiated into mesodermal lineages. Bilateral ovarian dystrophy was confirmed by ultrasonography in 16 lactating cows. The subsequent experiment lasted 15 weeks. Serum was collected weekly to analyse progesterone concentrations, and weekly ultrasonography recorded ovarian changes. Each cow was equipped with an automatic heat detection system to facilitate oestrus observation and breeding records. The progesterone concentration of two cows in the treatment group (25%) significantly increased during weeks 10-15. On ultrasonography, the treatment group demonstrated mature follicles after BAFSCs injection, and foetuses were visualized approximately 40 days after artificial insemination (AI). Oestrus rates in the control and treatment groups were 0% (0/8) and 50% (4/8), respectively; pregnancy rates were 0% (0/8) and 25% (2/8), respectively. Calves were successfully delivered in both cases of pregnancy. These results show that BAFSCs can alleviate bovine ovarian dystrophy and restore fertility.

Chang, Y. M., et al. (2021). "Adipose derived mesenchymal stem cells along with Alpinia oxyphylla extract alleviate mitochondria-mediated cardiac apoptosis in aging models and cardiac function in aging rats." J Ethnopharmacol **264**: 113297.

ETHNOPHARMACOLOGICAL RELEVANCE: The Fructus (Alpinia oxyphylla MIQ) known as Yi Zhi Ren in Chinese medicine has been used as a food and herbal medicinal substance in China for centuries; in the year 2015 Chinese Pharmacopoeia Commission reported water extracts of Alpinia oxyphyllae Fructus (AoF) as a popular medication for aging-related diseases in the form of tonic, aphrodisiac, and health-care food in south China. AIM OF THE STUDY: Adipose mesenchymal stem cells are physiologically and therapeutically associated with healthy vascular function and cardiac health. However aging conditions hinder stem cell function and increases the vulnerability to cardiovascular diseases. In this study, the effect of the anti-aging herbal medicine AoF to enhance the cardiac restorative function of adipose-derived mesenchymal stem cells (ADMSCs) in aging condition was investigated. MATERIALS AND METHODS: Low dose (0.1 muM) Doxorubicin and D-galactose (150 mg/kg/day for 8 weeks) were used to respectively induce aging in vitro and in vivo. For In vivo studies, 20 week old WKY rats were divided into Control, Aging induced (AI), AI + AoF, AI + ADMSC, AI + AoF Oral + ADMSC, and AI + AoF treated ADMSC groups. AoF (100 mg/kg/day) was administered orally and ADMSCs (1 x 10(6) cells) were injected (IV). RESULTS: AoF preconditioned ADMSC showed reduction in low dose Dox induced mitochondrial apoptosis and improved DNA replication in H9c2 cardiomyoblasts. In vivo experiments confirmed that both a combined treatment with AoF-ADMSCs and with AoF preconditioned ADMSCs reduced aging associated cardiac damages which was correlated with reduction in apoptosis and expression of senescence markers (P21 and beta-gal). Survival and longevity markers were upregulated up on combined administration of AoF and ADMSCs. The cardiac performance of the aging-induced rats was improved significantly in the treatment groups. AoF along with ADMSCs might activate paracrine factors to restore the performance of an aging heart. CONCLUSION: Hence, we propose that ADMSCs combined with AoF have promising therapeutic properties in the treatment of healthy aging heart.

Charruyer, A., et al. (2016). "Phycosaccharide AI, a mixture of alginate polysaccharides, increases stem cell proliferation in aged keratinocytes." Exp Dermatol **25**(9): 738-740.

Chen, J., et al. (2023). "Deep learning models for cancer stem cell detection: a brief review." Front Immunol **14**: 1214425.

Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), are a subset of tumor cells that persist within tumors as a distinct population. They drive tumor initiation, relapse, and metastasis through self-renewal and differentiation into multiple cell types, similar to typical stem cell processes. Despite their importance, the morphological features of CSCs have been poorly understood. Recent advances in artificial intelligence (AI) technology have provided automated recognition of biological images of various stem cells, including CSCs, leading to a surge in deep learning research in this field. This mini-review explores the emerging trend of deep learning research in the field of CSCs. It introduces diverse convolutional neural network (CNN)-based deep learning models for stem cell research and discusses the application of deep learning for CSC research. Finally, it provides perspectives and limitations in the field of deep learning-based stem cell research.

Chen, J. Y., et al. (2014). "Therapeutic effects of

mesenchymal stem cell-derived microvesicles on pulmonary arterial hypertension in rats." Acta Pharmacol Sin **35**(9): 1121-1128.

AIM: Microvesicles (MVs) are nanoscale membrane fragments released from virtually all cell types upon activation or apoptosis, and may contribute to the beneficial effects of stem cell therapy. In this study, we investigated the therapeutic effects of mesenchymal stem cell (MSC) derived MVs (MSC-MVs) on pulmonary artery hypertension (PAH) in rats. METHODS: MSC-MVs were isolated from rat bone marrow MSCs that were cultured in a serum-free conditioned medium. Transmission electron microscopy (TEM), flow cytometry and nanoparticle tracking analysis (NTA) were used to characterize the MVs. Adult SD rats were injected with monocrotaline (50 mg/kg, sc) to induce PAH. Three weeks later, the rats were intravenously injected with MSCs, MSC-MVs or saline for 2 weeks. At the end of treatments, the hemodynamic parameters and pathological right ventricular and pulmonary arterial remodeling were analyzed in each group. RESULTS: The MSC-MVs showed general morphologic characteristics of MVs and expressed annexin V and CD29 markers under TEM, and their size ranged from 40 to 300 nm. Intravenous injection of MSC-MVs or MSCs significantly ameliorated the mean pulmonary artery pressure (mPAP) and mean right ventricle pressure (mRVP) in PAH rats. Furthermore, intravenous injection of MSC-MVs or MSCs significantly decreased the right ventricle (RV) hypertrophy and pulmonary arteriole area index (AI) and thickness index (TI) in PAH rats. CONCLUSION: Intravenous injection of MSC-MVs or MSCs produces similar beneficial effects for treating PAH, and our results provide a basis for cell-free approach in stem cell therapy.

Cheng, L. and M. H. Kuehn (2023). "Human Retinal Organoids in Therapeutic Discovery: A Review of Applications." Handb Exp Pharmacol **281**: 157-187.

Human embryonic stem cells (hESCs)- and induced pluripotent stem cells (hiPSCs)-derived retinal organoids (ROs) are three-dimensional laminar structures that recapitulate the developmental trajectory of the human retina. The ROs provide a fascinating tool for basic science research, eye disease modeling, treatment development, and biobanking for tissue/cell replacement. Here we review the previous studies that paved the way for RO technology, the two most widely accepted, standardized protocols to generate ROs, and the utilization of ROs in medical discovery. This review is conducted from the perspective of basic science research, transplantation for regenerative medicine, disease modeling, and therapeutic development for drug screening and gene therapy. ROs have opened avenues for new technologies such as assembloids, coculture with other organoids, vasculature or immune cells, microfluidic devices (organ-on-chip), extracellular vesicles for drug delivery, biomaterial engineering, advanced imaging techniques, and artificial intelligence (AI). Nevertheless, some shortcomings of ROs currently limit their translation for medical applications and pose a challenge for future research. Despite these limitations, ROs are a powerful tool for functional studies and therapeutic strategies for retinal diseases.

Chowdhury, M. A., et al. (2023). "Stem cell therapy for heart failure in the clinics: new perspectives in the era of precision medicine and artificial intelligence." Front Physiol **14**: 1344885.

Stem/progenitor cells have been widely evaluated as a promising therapeutic option for heart failure (HF). Numerous clinical trials with stem/progenitor cell-based therapy (SCT) for HF have demonstrated encouraging results, but not without limitations or discrepancies. Recent technological advancements in multiomics, bioinformatics, precision medicine, artificial intelligence (AI), and machine learning (ML) provide new approaches and insights for stem cell research and therapeutic development. Integration of these new technologies into stem/progenitor cell therapy for HF may help address: 1) the technical challenges to obtain reliable and high-quality therapeutic precursor cells, 2) the discrepancies between preclinical and clinical studies, and 3) the personalized selection of optimal therapeutic cell types/populations for individual patients in the context of precision medicine. This review summarizes the current status of SCT for HF in clinics and provides new perspectives on the development of computation-aided SCT in the era of precision medicine and AI/ML.

Chu, C. Y., et al. (2009). "Protective effects of leaf extract of Zanthoxylum ailanthoides on oxidation of low-density lipoprotein and accumulation of lipid in differentiated THP-1 cells." Food Chem Toxicol **47**(6): 1265-1271.

It has been reported that extracts of stem and leaf of Zanthoxylum ailanthoides (ZLE) possess antioxidative properties. However, the biological importance of the ZLE is not well known. In our preliminary study, it showed that ZLE prepared from 75% alcohol highly contains flavonoids (5.8%). By HPLC analysis, it shows that the ZLE consists of flavonoid glycosides including rutin and hyperoside. We investigate the effects of ZLE on the oxidation of low-density lipoprotein (LDL; d=1.019-1.063 g/mL)

and the uptake of lipid in macrophage. Firstly, we explored the effect of ZLE on the oxidation of LDL by employing copper (II) sulfate (CuSO4) as an oxidative inducer. Oxidation was monitored by the formation of conjugated diene and thiobarbituric acid relative substances (TBARS), relative electrophoretic mobility (REM), and fragmentation of apolipoprotein B-100 (Apo B). Our data showed that ZLE reduced the oxidation properties of LDL induced by CuSO4. In addition, ZLE inhibited lipid accumulation in differentiated THP-1 cells treated with ox-LDL involving decreasing the expression of scavenger receptors such as scavenger receptor class AI (SR-AI) and CD36, which belongs to the class B scavenger receptor (SR-B). These results demonstrate the protective effect of ZLE on LDL oxidation and lipid accumulation in macrophage.

Consiglieri, G., et al. (2024). "Early skeletal outcomes after hematopoietic stem and progenitor cell gene therapy for Hurler syndrome." Sci Transl Med **16**(745): eadi8214.

Mucopolysaccharidosis type I Hurler (MPSIH) is characterized by severe and progressive skeletal dysplasia that is not fully addressed by allogeneic hematopoietic stem cell transplantation (HSCT). Autologous hematopoietic stem progenitor cell-gene therapy (HSPC-GT) provides superior metabolic correction in patients with MPSIH compared with HSCT; however, its ability to affect skeletal manifestations is unknown. Eight patients with MPSIH (mean age at treatment: 1.9 years) received lentiviral-based HSPC-GT in a phase 1/2 clinical trial (NCT03488394). Clinical (growth, measures of kyphosis and genu velgum), functional (motor function, joint range of motion), and radiological [acetabular index (AI), migration percentage (MP) in hip x-rays and MRIs and spine MRI score] parameters of skeletal dysplasia were evaluated at baseline and multiple time points up to 4 years after treatment. Specific skeletal measures were retrospectively compared with an external cohort of HSCT-treated patients. At a median follow-up of 3.78 years after HSPC-GT, all patients treated with HSPC-GT exhibited longitudinal growth within WHO reference ranges and a median height gain greater than that observed in patients treated with HSCT after 3-year follow-up. Patients receiving HSPC-GT experienced complete and earlier normalization of joint mobility compared with patients treated with HSCT. Mean AI and MP showed progressive decreases after HSPC-GT, suggesting a reduction in acetabular dysplasia. Typical spine alterations measured through a spine MRI score stabilized after HSPC-GT. Clinical, functional, and radiological measures suggested an early beneficial effect of HSPC-GT on MPSIH-typical skeletal features. Longer follow-up is needed to draw definitive conclusions on HSPC-GT's impact on MPSIH skeletal dysplasia.

Cui, C., et al. (2024). "Hospital healthcare resource utilization and costs for chimeric antigen T-cell therapy and autologous hematopoietic cell transplant in patients with large B-cell lymphoma in the United States." Leuk Lymphoma **65**(7): 922-931.

The efficacy of chimeric antigen receptor (CAR) T-cell therapy for large B-cell lymphoma (LBCL) is well-established. This study, using the Premier PINC AI Healthcare Database, assessed hospital costs and healthcare resource utilization (HRU) between CAR T-cell therapy and autologous hematopoietic cell transplant (AHCT) for 733 LBCL patients from 01/01/2017-04/30/2021 (166 CAR T and 567 AHCT from 37 US hospital systems. CAR T-cell therapy had higher index costs but lower non-pharmacy costs, shorter hospital stays, lower ICU utilization than AHCT. The CAR T-cell cohort also presented fewer preparatory costs and HRU. At a 180-day follow-up, AHCT had lower hospitalization rates and costs. Overall, despite higher index costs, CAR T-cell therapy has lower non-pharmacy costs and HRU during the index procedure and requires less preparation time with lower preparation HRUs and costs than AHCT. This has important implications for resource management and informed decision-making for stakeholders.

Cui, G., et al. (2007). "Gossypol with methyltestosterone and ethinylestradiol male does not affect rat spermatogonial stem cell differentiation." Arch Androl **53**(2): 91-98.

The purpose of this study was to investigate whether administration of the regimen of gossypol at 12 mg/kg/day combined with methyltestosterone at 20 mg/kg/day and ethinylestradiol at 100 microg/kg/day for a long term of twenty-four weeks could affect the existence and differentiation of rat spermatogonial stem cell. This was assessed by conducting TdT-mediated dUTP nick end-labeling detection, spermatogonial stem cell transplantation and fertility recovery evaluation. Our results showed that spontaneous apoptosis was observed in normal rats' testes from the control group with an apoptotic index (AI) average of 10.24+/-1.52. In the regimen-treated group, the predominant apoptotic cells were spermatocytes and spermatids in the seminiferous tubules. Spermatogonia were not apoptotic (AI averaged 113.42+/-13.24). Two to three months after transplantation of spermatogonial stem cells isolated from regimen-treated rats into recipient nude mice, elongated rat spermatids were identified in the

seminiferous tubules of recipient nude mice. Six weeks after withdrawal of the administration, fertility of the regimen-treated rats was recovered compared with that of the control group. The number of litters produced by females mated with regimen-treated males averaged 9.88+/-0.166 matched 10.30+/-0.171 of control group and the litters of the first generation appeared to be normal. These results indicated that the administration of this regimen did not affect the existence and differentiation potential of spermatogonial stem cells of the regimen-treated rats.

Dallinger, G., et al. (1999). "Transcriptional elongation of the rat apolipoprotein A-I gene: identification and mapping of two arrest sites and their signals." J Lipid Res **40**(7): 1229-1239.

Previous studies have shown that the elongation phase of apoA-I gene transcription is regulated and contributes to hormone-induced changes in the expression of this gene in rat liver. We have now identified, by in vitro transcription studies with HeLa nuclear extracts, two transcriptional arrest sites within exon 3 and intron 3, respectively. Two truncated transcripts of 510 and approximately 1100 nucleotides in length, termed attenuator 1 RNA and attenuator 2 RNA, respectively, were observed when a rat apoA-I genomic fragment extending from -309 to +1842 relative to the transcription start site was transcribed in vitro in the presence of KCl or Sarkosyl. The attenuation events were promoter-independent as transcription of the apoA-I gene driven by the cytomegalovirus promoter resulted in transcriptional arrest at both sites. Transcription studies using deletion constructs as templates identified nucleotides +976 to +1158 as a region that contained the signal for transcriptional arrest at attenuator site 2. Computational analysis predicted a stem;-loop structure in the nascent RNA immediately upstream of the arrest site. Deletion of attenuator 2 signal or deletion of sequences +147 to +216 located far upstream of the actual elongation block site 1 abrogated arrest at site 1. Thus, complex long-range interactions may be involved in the transcriptional arrest at site 1. These elongation blocks identified in vitro are consistent with earlier in vivo data based on nuclear run-on assays and represent, to our knowledge, the first example describing transcriptional attenuation as a mechanism controlling the expression of a member of the apolipoprotein gene family.

Daoud, G., et al. (2016). "Primary versus castration-resistant prostate cancer: modeling through novel murine prostate cancer cell lines." Oncotarget **7**(20): 28961-28975.

Cell lines representing the progression of prostate cancer (PC) from an androgen-dependent to an androgen-independent state are scarce. In this study, we used previously characterized prostate luminal epithelial cell line (Plum), under androgen influence, to establish cellular models of PC progression. Cells derived from orthotopic tumors have been isolated to develop an androgen-dependent (PLum-AD) versus an androgen-independent (PLum-AI) model. Upon immunofluorescent, qRT-PCR and Western blot analyses, PLum-AD cells mostly expressed prostate epithelial markers while PLum-AI cells expressed mesenchymal cell markers. Interestingly, both cell lines maintained a population of stem/progenitor cells. Furthermore, our data suggest that both cell lines are tumorigenic; PLum-AD resulted in an adenocarcinoma whereas PLum-AI resulted in a sarcomatoid carcinoma when transplanted subcutaneously in NOD-SCID mice. Finally, gene expression profiles showed enrichment in functions involved in cell migration, apoptosis, as well as neoplasm invasiveness and metastasis in PLum-AI cells. In conclusion, these data suggest that the newly isolated cell lines represent a new in vitro model of androgen-dependent and -independent PC.

Daouk, R., et al. (2020). "Genome-wide gene expression analysis of a murine model of prostate cancer progression: Deciphering the roles of IL-6 and p38 MAPK as potential therapeutic targets." PLoS One **15**(8): e0237442.

BACKGROUND: Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among adult males globally. The poor prognosis of PCa is largely due to late diagnosis of the disease when it has already progressed to an advanced stage marked by androgen-independence, thus necessitating new strategies for early detection and treatment. We construe that these direly needed advances are limited by our poor understanding of early events in the progression of PCa and that would thus represent ideal targets for early intervention. To begin to fill this void, we interrogated molecular "oncophenotypes" that embody the transition of PCa from an androgen-dependent (AD) to-independent (AI) state. METHODS: To accomplish this aim, we used our previously established AD and AI murine PCa cell lines, PLum-AD and PLum-AI, respectively, which recapitulate primary and progressive PCa morphologically and molecularly. We statistically surveyed global gene expressions in these cell lines by microarray analysis. Differential profiles were functionally interrogated by pathways, gene set enrichment and topological gene network analyses. RESULTS: Gene expression analysis of PLum-AD and PLum-AI transcriptomes (n = 3 each), revealed

723 differentially expressed genes (392 upregulated and 331 downregulated) in PLum-AI compared to PLum-AD cells. Gene set analysis demonstrated enrichment of biological functions and pathways in PLum-AI cells that are central to tumor aggressiveness including cell migration and invasion facilitated by epithelial-to-mesenchymal transition (EMT). Further analysis demonstrated that the p38 mitogen-activated protein kinase (MAPK) was predicted to be significantly activated in the PLum-AI cells, whereas gene sets previously associated with favorable response to the p38 inhibitor SB203580 were attenuated (i.e., inversely enriched) in the PLum-AI cells, suggesting that these aggressive cells may be therapeutically vulnerable to p38 inhibition. Gene set and gene-network analysis also alluded to activation of other signaling networks particularly those associated with enhanced EMT, inflammation and immune function/response including, but not limited to Tnf, IL-6, Mmp 2, Ctgf, and Ptges. Accordingly, we chose SB203580 and IL-6 to validate their effect on PLum-AD and PLum-AI. Some of the common genes identified in the gene-network analysis were validated at the molecular and functional level. Additionally, the vulnerability to SB203580 and the effect of IL-6 were also validated on the stem/progenitor cell population using the sphere formation assay. CONCLUSIONS: In summary, our study highlights pathways associated with an augmented malignant phenotype in AI cells and presents new high-potential targets to constrain the aggressive malignancy seen in the castration-resistant PCa.

Davidsson, J. and M. Risling (2011). "A new model to produce sagittal plane rotational induced diffuse axonal injuries." Front Neurol **2**: 41.

A new in vivo animal model that produces diffuse brain injuries in sagittal plane rearward rotational acceleration has been developed. In this model, the skull of an anesthetized adult rat is tightly secured to a rotating bar. During trauma, the bar is impacted by a striker that causes the bar and the animal head to rotate rearward; the acceleration phase last 0.4 ms and is followed by a rotation at constant speed and a gentle deceleration when the bar makes contact with a padded stop. The total head angle change is less than 30 degrees . By adjusting the air pressure in the rifle used to accelerate the striker, resulting rotational acceleration between 0.3 and 2.1 Mrad/s(2) can be produced. Numerous combinations of trauma levels, post-trauma survival times, brain and serum retrieval, and tissue preparation techniques were adopted to characterize this new model. The trauma caused subdural bleedings in animals exposed to severe trauma. Staining brain tissue with beta-Amyloid Precursor Protein antibodies and FD Neurosilver that detect degenerating axons revealed wide spread axonal injuries (AI) in the corpus callosum, the border between the corpus callosum and cortex and in tracts in the brain stem. The observed AIs were apparent only when the rotational acceleration level was moderate and above. On the contrary, only limited signs of contusion injuries were observed following trauma. Macrophage invasions, glial fibrillary acidic protein redistribution or hypertrophy, and blood brain barrier (BBB) changes were unusual. S100 serum analyses indicate that blood vessel and glia cell injuries occur following moderate levels of trauma despite the absence of obvious BBB injuries. We conclude that this rotational trauma model is capable of producing graded axonal injury, is repeatable and produces limited other types of traumatic brain injuries and as such is useful in the study of injury biomechanics, diagnostics, and treatment strategies following diffuse axonal injury.

Dawson, C. A., et al. (2024). "Hormone-responsive progenitors have a unique identity and exhibit high motility during mammary morphogenesis." Cell Rep **43**(12): 115073.

Hormone-receptor-positive (HR(+)) luminal cells largely mediate the response to estrogen and progesterone during mammary gland morphogenesis. However, there remains a lack of consensus on the precise nature of the precursor cells that maintain this essential HR(+) lineage. Here we refine the identification of HR(+) progenitors and demonstrate their unique regenerative capacity compared to mature HR(+) cells. HR(+) progenitors proliferate but do not expand, suggesting rapid differentiation. Subcellular resolution, 3D intravital microscopy was performed on terminal end buds (TEBs) during puberty to dissect the contribution of each luminal lineage. Surprisingly, HR(+) TEB progenitors were highly elongated and motile compared to columnar HR(-) progenitors and static, conoid HR(+) cells within ducts. This dynamic behavior was also observed in response to hormones. Development of an AI model for motility dynamics analysis highlighted stark behavioral changes in HR(+) progenitors as they transitioned to mature cells. This work provides valuable insights into how progenitor behavior contributes to mammary morphogenesis.

De Filippis, R., et al. (2022). "Use of High-Plex Data Reveals Novel Insights into the Tumour Microenvironment of Clear Cell Renal Cell Carcinoma." Cancers (Basel) **14**(21).

Although immune checkpoint inhibitors (ICIs) have significantly improved the oncological

outcomes, about one-third of patients affected by clear cell renal cell carcinoma (ccRCC) still experience recurrence. Current prognostic algorithms, such as the Leibovich score (LS), rely on morphological features manually assessed by pathologists and are therefore subject to bias. Moreover, these tools do not consider the heterogeneous molecular milieu present in the Tumour Microenvironment (TME), which may have prognostic value. We systematically developed a semi-automated method to investigate 62 markers and their combinations in 150 primary ccRCCs using Multiplex Immunofluorescence (mIF), NanoString GeoMx((R)) Digital Spatial Profiling (DSP) and Artificial Intelligence (AI)-assisted image analysis in order to find novel prognostic signatures and investigate their spatial relationship. We found that coexpression of cancer stem cell (CSC) and epithelial-to-mesenchymal transition (EMT) markers such as OCT4 and ZEB1 are indicative of poor outcome. OCT4 and the immune markers CD8, CD34, and CD163 significantly stratified patients at intermediate LS. Furthermore, augmenting the LS with OCT4 and CD34 improved patient stratification by outcome. Our results support the hypothesis that combining molecular markers has prognostic value and can be integrated with morphological features to improve risk stratification and personalised therapy. To conclude, GeoMx((R)) DSP and AI image analysis are complementary tools providing high multiplexing capability required to investigate the TME of ccRCC, while reducing observer bias.

De Wilde, S. and C. Graux (2024). "Complete hematologic response in a patient with multiple pretreated angioimmunoblastic T-cell lymphoma after belinostat therapy followed by allogeneic stem cell transplantation: A case report." Clin Case Rep **12**(7): e9159.

KEY CLINICAL MESSAGE: Belinostat therapy followed by hematopoietic stem cell transplantation is a promising salvage strategy for heavily pretreated patients with peripheral T-cell lymphoma. ABSTRACT: Effective treatments for peripheral T-cell lymphoma in the relapsed and refractory (r/r) setting are limited. However, with the development and approval of innovative therapies, effective therapeutic options are becoming available for this patient population. This case report describes the treatment course of a patient with multiple r/r nodal follicular T-helper cell lymphoma of angioimmunoblastic type. Treatment with the histone deacetylase inhibitor belinostat as bridging, enabled allogeneic stem cell transplantation and resulted in a durable complete hematologic response for at least 21 months post-transplantation.

Degany, O., et al. (2024). "[Lorenzo's Oil and Adrenoleukodystrophy Examining an Artificial Intelligence Tool Intended for Conducting Literature Searches and Analyses]." Harefuah **163**(11): 684-686.

Adrenoleukodystrophy is a genetic metabolic disorder characterized by a heterogeneous phenotype. Its severe form, known as cerebral adrenoleukodystrophy, involves unpredictable cerebral damage and progressive central nervous system deterioration. This rare condition became famous because of a Hollywood movie in which the Italian parents of a child with the condition supposedly discovered a medication for treating the condition. But real life does not emulate movies and hematopoietic stem cell transplantation remains the standard of care for patients diagnosed at an early disease stage. This article describes a patient with cerebral adrenoleukodystrophy diagnosed at an advanced disease stage. The literature search aimed to identify therapies to prevent further deterioration suggested autologous hematopoietic stem cell-based gene therapy and metabolic therapies. Consensus is a Chat GPT-based AI tool trained on millions of scientific publications, intended for conducting evidence-based literature searches and analyses. The case presented was used to conduct a parallel literature review using Consensus. While the generated output contained no hallucinations (a problem often seen with other large language models), the quality of the selected articles and their interpretation in the context of the specific case fell short of that achieved by experienced researchers or physicians.

Deshpande, S., et al. (2013). "Reconciling the effects of inflammatory cytokines on mesenchymal cell osteogenic differentiation." J Surg Res **185**(1): 278-285.

Therapies using mesenchymal stem cells are a popular current avenue for development and utilization, especially in the fields of de novo tissue engineering (Sanchez-Ramos J, Song S, Cardozo-Pelaez F, et al. Adult bone marrow stromal cells differentiate into neural cells in vitro. Exp Neurol 2000;164:247.) or tissue regeneration after physical injury (Kitoh H, Kitakoji T, Tsuchiya H, et al. Transplantation of marrow-derived mesenchymal stem cells and platelet-rich plasma during distraction osteogenesis-a preliminary result of three cases. Bone 2004;35:892; Shumakov VI, Onishchenko NA, Rasulov MF, Krasheninnikov ME, Zaidenov VA. Mesenchymal bone marrow stem cells more effectively stimulate regeneration of deep burn wounds than embryonic fibroblasts. Bull Exp Biol Med 2003;136:192; Bruder SP, Fink DJ, Caplan AI.

Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. J Cell Biochem 1994;56:283.). The osteogenic potential of these cells is of particular interest, given their recent usage for the closure of critical-sized bone defects and other nonhealing bone scenarios such as a nonunion. Recent literature suggests that inflammatory cytokines can significantly impact the osteogenic potential of these cells. A review of relevant, recent literature is presented regarding the impact of the inflammatory cascade on the osteogenic differentiation of these cells and how this varies across species. Finally, we identify areas of conflicting or absent evidence regarding the behavior of mesenchymal stem cells in response to inflammatory cytokines.

Dilek, I., et al. (1998). "Acquired ichthyosis associated with chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation in a patient with chronic myelogenous leukemia." Bone Marrow Transplant **21**(11): 1159-1161.

Acquired ichthyosis (AI) has rarely been described following bone marrow transplantation (BMT). We report a 29-year-old male, who underwent allogeneic peripheral blood stem cell transplantation (alloPBSCT) for chronic myelogenous leukemia, and who developed AI associated with chronic graft-versus-host disease (cGVHD). Both of these disorders were treated successfully with cyclosporin A. We conclude that AI may be related to an autoimmune process on the basis of cGVHD, and dermathopathologic evaluation must be performed in patients with skin changes suggesting AI following allogeneic bone marrow transplantation.

Dimitrakopoulou-Strauss, A., et al. (2010). "Prediction of chemotherapy outcome in patients with metastatic soft tissue sarcomas based on dynamic FDG PET (dPET) and a multiparameter analysis." Eur J Nucl Med Mol Imaging **37**(8): 1481-1489.

PURPOSE: Dynamic PET studies with (18)F-FDG were performed in patients with metastatic soft tissue sarcomas who received conventional chemotherapy with doxorubicin hydrochloride (Adriamycin) and ifosfamide (AI-G). The goal of the study was to evaluate the impact of full kinetic analysis and assess its value with regard to the therapy outcome based on survival data. METHODS: The evaluation included 17 patients with 29 metastatic lesions of soft tissue sarcomas, who were treated with chemotherapy consisting of an AI-G regimen prior to high-dose chemotherapy and peripheral blood stem cell transplantation where applicable. Patients were examined prior to onset of therapy and after completion of the first cycle of AI-G. Restaging data (n = 17) based on Response Evaluation Criteria in Solid Tumors were available. Survival data (n = 14) served for reference. The following parameters were retrieved from the dynamic PET studies: standardized uptake value (SUV), fractal dimension, two-compartment model with computation of k1, k2, k3, k4 (unit: 1/min), the fractional blood volume and the FDG influx calculated according to Patlak. RESULTS: The mean SUV was 6.9 prior to therapy and 4.7 after one cycle. The mean influx was 0.066 prior to therapy in comparison to 0.058 after one cycle. We dichotomized the patients according to the median survival time of 320 days into response (n = 6) and non-response (n = 8). The mean SUV was 7.6 in the group of responders and 5.4 in the group of non-responders prior to therapy. Responders revealed a mean SUV of 3.8 after therapy as compared to 5.0 SUV for non-responders. We used discriminant analysis to classify the patients into the two response groups. The classification of the non-responders was generally higher (negative predictive value > 61%) than for the responders. Finally, the combined use of the four predictor variables, namely mean SUV and k1 of both studies led to the highest accuracy of 90% for both groups. CONCLUSION: The data demonstrate that only a multiparameter analysis based on a combination of the absolute values of mean SUV and k1 of a baseline study and a follow-up study after completion of one cycle was the best combination for a group-based analysis, into response or non-response. The quantitative assessment of the FDG kinetics in tumours should be used to quantify the "inhibitory effect" of chemotherapy and to individualize treatment. The main effect of the AI-G therapy may be on angiogenesis (k1 effect) rather than on proliferation.

Ding, Z., et al. (2024). "Understanding molecular characteristics of extracellular vesicles derived from different types of mesenchymal stem cells for therapeutic translation." Extracell Vesicle **3**.

Mesenchymal stem cells (MSCs) have been studied for decades as candidates for cellular therapy, and their secretome, including secreted extracellular vesicles (EVs), has been identified to contribute significantly to regenerative and reparative functions. Emerging evidence has suggested that MSC-EVs alone, could be used as therapeutics that emulate the biological function of MSCs. However, just as with MSCs, MSC-EVs have been shown to vary in composition, depending on the tissue source of the MSCs as well as the protocols employed in culturing

the MSCs and obtaining the EVs. Therefore, the importance of careful choice of cell sources and culture environments is receiving increasing attention. Many factors contribute to the therapeutic potential of MSC-EVs, including the source tissue, isolation technique, and culturing conditions. This review illustrates the molecular landscape of EVs derived from different types of MSC cells along with culture strategies. A thorough analysis of publicly available omic datasets was performed to advance the precision understanding of MSC-EVs with unique tissue source-dependent molecular characteristics. The tissue-specific protein and miRNA-driven Reactome ontology analysis was used to reveal distinct patterns of top Reactome ontology pathways across adipose, bone marrow, and umbilical MSC-EVs. Moreover, a meta-analysis assisted by an AI technique was used to analyze the published literature, providing insights into the therapeutic translation of MSC-EVs based on their source tissues.

Diniz, B. S., et al. (2015). "Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression." Mol Psychiatry **20**(5): 594-601.

Cognitive impairment is highly prevalent among individuals with late-life depression (LLD) and tends to persist even after successful treatment. The biological mechanisms underlying cognitive impairment in LLD are complex and likely involve abnormalities in multiple pathways, or 'cascades,' reflected in specific biomarkers. Our aim was to evaluate peripheral (blood-based) evidence for biological pathways associated with cognitive impairment in older adults with LLD. To this end, we used a data-driven comprehensive proteomic analysis (multiplex immunoassay including 242 proteins), along with measures of structural brain abnormalities (gray matter atrophy and white matter hyperintensity volume via magnetic resonance imaging), and brain amyloid-beta (Abeta) deposition (PiB-positron emission tomography). We analyzed data from 80 older adults with remitted major depression (36 with mild cognitive impairment (LLD+MCI) and 44 with normal cognitive (LLD+NC)) function. LLD+MCI was associated with differential expression of 24 proteins ($P<0.05$ and q-value <0.30) related mainly to the regulation of immune-inflammatory activity, intracellular signaling, cell survival and protein and lipid homeostasis. Individuals with LLD+MCI also showed greater white matter hyperintensity burden compared with LLD+NC ($P=0.015$). We observed no differences in gray matter volume or brain Abeta deposition between groups. Machine learning analysis showed that a group of three proteins (Apo AI, IL-12 and stem cell factor) yielded accuracy of 81.3%, sensitivity of 75% and specificity of 86.4% in discriminating participants with MCI from those with NC function (with an averaged cross-validation accuracy of 76.3%, sensitivity of 69.4% and specificity of 81.8% with nested cross-validation considering the model selection bias). Cognitive impairment in LLD seems to be related to greater cerebrovascular disease along with abnormalities in immune-inflammatory control, cell survival, intracellular signaling, protein and lipid homeostasis, and clotting processes. These results suggest that individuals with LLD and cognitive impairment may be more vulnerable to accelerated brain aging and shed light on possible mediators of their elevated risk for progression to dementia.

Domingo-Gonzalez, R., et al. (2013). "Prostaglandin E2-induced changes in alveolar macrophage scavenger receptor profiles differentially alter phagocytosis of Pseudomonas aeruginosa and Staphylococcus aureus post-bone marrow transplant." J Immunol **190**(11): 5809-5817.

The effectiveness of hematopoietic stem cell transplantation as a therapy for malignant and nonmalignant conditions is complicated by pulmonary infections. Using our syngeneic bone marrow transplant (BMT) mouse model, BMT mice with a reconstituted hematopoietic system displayed increased susceptibility to Pseudomonas aeruginosa and Staphylococcus aureus. BMT alveolar macrophages (AMs) exhibited a defect in P. aeruginosa phagocytosis, whereas S. aureus uptake was surprisingly enhanced. We hypothesized that the difference in phagocytosis was due to an altered scavenger receptor (SR) profile. Interestingly, MARCO expression was decreased, whereas SR-AI/II was increased. To understand how these dysregulated SR profiles might affect macrophage function, CHO cells were transfected with SR-AI/II, and phagocytosis assays revealed that SR-AI/II was important for S. aureus uptake but not for P. aeruginosa. Conversely, AMs treated in vitro with soluble MARCO exhibited similar defects in P. aeruginosa internalization as did BMT AMs. The 3'-untranslated region of SR-AI contains a putative target region for microRNA-155 (miR-155), and miR-155 expression is decreased post-BMT. Anti-miR-155-transfected AMs exhibited an increase in SR-AI/II expression and S. aureus phagocytosis. Elevated PGE2 has been implicated in driving an impaired innate immune response post-BMT. In vitro treatment of AMs with PGE2 increased SR-AI/II and decreased MARCO and miR-155. Despite a difference in phagocytic ability, BMT AMs harbor a killing defect to both P. aeruginosa and S. aureus. Thus, our data suggest that PGE2-driven alterations

in SR and miR-155 expression account for the differential phagocytosis of P. aeruginosa and S. aureus, but impaired killing ultimately confers increased susceptibility to pulmonary infection.

Dumont, S., et al. (2010). "Two new lipoaminoacids with complementary modes of action: new prospects to fight out against skin aging." Int J Cosmet Sci **32**(1): 9-27.

The mode of action of two cosmetic active ingredients (AIs), palmitoyl glycine (PG) and cocoyl alanine (CA) was studied with cDNA array experiments and quantitative PCR confirmations, which were performed on experimentally aged human fibroblasts. These preliminary studies revealed complementary profiles. Thus, specific supplementary investigations were then carried out for each AI. Protocols used were based either on in vitro models: (i) biochemical assays, (ii) monolayer cell culture (primary human fibroblasts and keratinocytes) and (iii) the model of capillary-like tube formation by human endothelial cells or on ex vivo models, i.e. topically treated skin explants and both immunohistochemical and Chromameter(TM) investigations. New prospects are proposed to fight out against skin aging. Indeed, PG and CA showed complementary properties and thus enabled a regulation or a restoration effect on main aging-associated disorders. Thus, they can not only act on tissue architecture, cell-cell interactions and extracellular matrix protection but also on inflammation, cell longevity, skin immune system protection, skin radiance and stem cell survey. Finally, a clinical trial performed on Caucasian women confirmed AI anti-wrinkle efficacy, which was superior to that of a market reference ingredient. In the future, complementary experiments enabling a better understanding of the aging-induced decline of epidermal stem cells would be of a great interest.

Dunstan, R. W., et al. (2021). "Histologic progression of acne inversa/hidradenitis suppurativa: Implications for future investigations and therapeutic intervention." Exp Dermatol **30**(6): 820-830.

Since first recognized in 1839, the pathogenesis of acne inversa (AI) has undergone repeated revisions. Although there is agreement that AI involves occlusion of hair follicles with subsequent inflammation and the formation of tracts, the histologic progression of this disease still requires refinement. The objective of this study was to examine the histologic progression of AI based on the examination of a large cohort of punch biopsies and excisional samples that were examined first by hematoxylin and eosin staining. The most informative of these samples were step-sectioned and stained by immunohistochemistry for epithelial and inflammatory markers. Based on this examination, the following observations were made: 1) AI arises from the epithelium of the infundibulum of terminal and vellus hairs; 2) These form cysts and epithelial tendrils that extend into soft tissue; 3) Immunohistochemical staining demonstrates the epithelium of AI is disordered with infundibular and isthmic differentiation and de novo expression of stem cell markers; 4) The inflammatory response in AI is heterogeneous and largely due to cyst rupture. The conclusions of this investigation were that AI is an epithelial-driven disease caused by infiltrative, cyst forming tendrils and most of the inflammation is due to cyst rupture and release of cornified debris and bacteria. Cyst rupture often occurs below the depths of punch biopsy samples indicating their use for analysis may give an incomplete picture of the disease. Finally, our data suggest that unless therapies inhibit tendril development, it is unlikely they will cause prolonged treatment-induced remission in AI.

Ekert, J. E., et al. (2020). "Recommended Guidelines for Developing, Qualifying, and Implementing Complex In Vitro Models (CIVMs) for Drug Discovery." SLAS Discov **25**(10): 1174-1190.

The pharmaceutical industry is continuing to face high research and development (R&D) costs and low overall success rates of clinical compounds during drug development. There is an increasing demand for development and validation of healthy or disease-relevant and physiological human cellular models that can be implemented in early-stage discovery, thereby shifting attrition of future therapeutics to a point in discovery at which the costs are significantly lower. There needs to be a paradigm shift in the early drug discovery phase (which is lengthy and costly), away from simplistic cellular models that show an inability to effectively and efficiently reproduce healthy or human disease-relevant states to steer target and compound selection for safety, pharmacology, and efficacy questions. This perspective article covers the various stages of early drug discovery from target identification (ID) and validation to the hit/lead discovery phase, lead optimization, and preclinical safety. We outline key aspects that should be considered when developing, qualifying, and implementing complex in vitro models (CIVMs) during these phases, because criteria such as cell types (e.g., cell lines, primary cells, stem cells, and tissue), platform (e.g., spheroids, scaffolds or hydrogels, organoids, microphysiological systems, and bioprinting), throughput, automation, and single and multiplexing endpoints will vary. The article emphasizes the need to adequately qualify these CIVMs such that they are suitable for various

applications (e.g., context of use) of drug discovery and translational research. The article ends looking to the future, in which there is an increase in combining computational modeling, artificial intelligence and machine learning (AI/ML), and CIVMs.

Esmail, S. and W. R. Danter (2019). "DeepNEU: Artificially Induced Stem Cell (aiPSC) and Differentiated Skeletal Muscle Cell (aiSkMC) Simulations of Infantile Onset POMPE Disease (IOPD) for Potential Biomarker Identification and Drug Discovery." Front Cell Dev Biol **7**: 325.

Infantile onset Pompe disease (IOPD) is a rare and lethal genetic disorder caused by the deletion of the acid alpha-glucosidase (GAA) gene. This gene encodes an essential lysosomal enzyme that converts glycogen to glucose. While enzyme replacement therapy helps some, our understanding of disease pathophysiology is limited. In this project we develop computer simulated stem cells (aiPSC) and differentiated skeletal muscle cells (aiSkMC) to empower IOPD research and drug discovery. Our Artificial Intelligence (AI) platform, DeepNEU v3.6 was used to generate aiPSC and aiSkMC simulations with and without GAA expression. These simulations were validated using peer reviewed results from the recent literature. Once the aiSkMC simulations (IOPD and WT) were validated they were used to evaluate calcium homeostasis and mitochondrial function in IOPD. Lastly, we used aiSkMC IOPD simulations to identify known and novel biomarkers and potential therapeutic targets. The aiSkMC simulations of IOPD correctly predicted genotypic and phenotypic features that were reported in recent literature. The probability that these features were accurately predicted by chance alone using the binomial test is 0.0025. The aiSkMC IOPD simulation correctly identified L-type calcium channels (VDCC) as a biomarker and confirmed the positive effects of calcium channel blockade (CCB) on calcium homeostasis and mitochondrial function. These published data were extended by the aiSkMC simulations to identify calpain(s) as a novel potential biomarker and therapeutic target for IOPD. This is the first time that computer simulations of iPSC and differentiated skeletal muscle cells have been used to study IOPD. The simulations are robust and accurate based on available published literature. We also demonstrated that the IOPD simulations can be used for potential biomarker identification leading to targeted drug discovery. We will continue to explore the potential for calpain inhibitors with and without CCB as effective therapy for IOPD.

Feng, Y., et al. (2010). "Hepatocyte-specific ABCA1 transfer increases HDL cholesterol but impairs HDL function and accelerates atherosclerosis." Cardiovasc Res **88**(2): 376-385.

AIMS: The ATP-binding cassette transporter A1 (ABCA1) lipidates apolipoprotein (apo) A-I. The hypothesis that hepatocyte-specific ABCA1 overexpression results in high-density lipoprotein (HDL) dysfunction was evaluated by comparing the effects of murine ABCA1 (AdABCA1) and human apo A-I (AdA-I) transfer on lipoprotein profile, HDL function, and progression of atherosclerosis. METHODS AND RESULTS: Gene transfer in male and female C57BL/6 apo E(-/-) mice was performed at the age of 3 months with E1E3E4-deleted adenoviral vectors containing hepatocyte-specific expression cassettes. Atherosclerosis was quantified at baseline and 56 days later in AdABCA1, AdA-I, and control mice. HDL cholesterol after AdA-I transfer was 1.7-fold ($P < 0.001$) and 1.8-fold ($P < 0.001$) higher in male and female mice, respectively, and potently inhibited atherosclerosis progression compared with respective controls. Notwithstanding a 1.4-fold ($P < 0.01$) and a 1.7-fold ($P < 0.01$) increase of HDL cholesterol in male and female mice, respectively, after AdABCA1 transfer, the intima was 2.2-fold ($P < 0.001$) larger in male and 1.3-fold (P = NS) larger in female mice compared with respective controls. HDL isolated from control and AdA-I mice but not from AdABCA1 mice enhanced endothelial progenitor cell (EPC) migration in vitro and reduced endothelial cell death in vitro after serum and growth factor withdrawal. Scavenger receptor class B type I (SR-BI) protein level in the liver was significantly lower in AdABCA1 mice than in control and AdA-I mice. CONCLUSION: Hepatocyte-specific ABCA1 transfer decreases SR-BI protein level in the liver and abrogates beneficial effects of HDL on EPCs and endothelial cells. Decreased HDL function may underlie accelerated atherosclerosis in AdABCA1 apo E(-/-)mice.

Feng, Y., et al. (2009). "Critical role of scavenger receptor-BI-expressing bone marrow-derived endothelial progenitor cells in the attenuation of allograft vasculopathy after human apo A-I transfer." Blood **113**(3): 755-764.

Allograft vasculopathy is the leading cause of death in patients with heart transplantation. Accelerated endothelial regeneration mediated by enhanced endothelial progenitor cell (EPC) incorporation may attenuate the development of allograft vasculopathy. We investigated the hypothesis that modulation of EPC biology and attenuation of allograft vasculopathy by increased high-density lipoprotein cholesterol after human apo A-I (AdA-I) transfer requires scavenger receptor (SR)-BI expression in bone marrow-derived EPCs.

After AdA-I transfer, the number of circulating EPCs increased 2.0-fold (P < .001) at different time points in C57BL/6 mice transplanted with SR-BI(+/+) bone marrow but remained unaltered in mice with SR-BI(-/-) bone marrow. The effect of high-density lipoprotein on EPC migration in vitro requires signaling via SR-BI and extracellular signal-regulated kinases and is dependent on increased nitric oxide (NO) production in EPCs. Human apo A-I transfer 2 weeks before paratopic artery transplantation reduced intimal area at day 21 3.7-fold (P < .001) in mice with SR-BI(+/+) bone marrow but had no effect in mice with SR-BI(-/-) bone marrow. AdA-I transfer potently stimulated EPC incorporation and accelerated endothelial regeneration in chimeric SR-BI(+/+) mice but not in chimeric SR-BI(-/-) mice. In conclusion, human apo A-I transfer accelerates endothelial regeneration mediated via SR-BI expressing bone marrow-derived EPCs, thereby preventing allograft vasculopathy.

Foote, R. H. (1996). "Review: dairy cattle reproductive physiology research and management--past progress and future prospects." J Dairy Sci **79**(6): 980-990.

Artificial insemination developed as the solution for two important problems in the dairy cattle industry during the past 50 yr: 1) the need for genetic improvement and 2) the elimination of costly venereal diseases. Cooperation among researchers, extension workers, veterinarians, dairy producers, and emerging AI organizations in pooling their expertise, was instrumental to the remarkably rapid development of AI. The cooperation of universities, government, and producers to fund teams of reproductive specialists to collaborate and transfer findings quickly to potential users was a major component of this successful venture. Money invested in these experiments was estimated to have returned about $100 for each $1 invested. Successful freezing of sperm led to the development of the field of cryobiology, and AI paved the way for embryo transfer. The development of ultrasound equipment; various types of rapid hormone assays; prostaglandins, progestogens, and GnRH; and computerization made possible various alternative management plans for controlling reproduction. Multidisciplinary, multigeographical teams that gather basic needed information have the potential for making excellent progress. As herd size increases, new programs for efficient reproductive management and for identifying needed research through computer modeling are a must. Sexed embryos from elite cows and bulls will be used selectively. When embryonic stem cell technology becomes practical, it will revolutionize cattle breeding.

Francois, S., et al. (2006). "Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: a study of their quantitative distribution after irradiation damage." Stem Cells **24**(4): 1020-1029.

Mesenchymal stem cells (MSCs) have been shown to migrate to various tissues. There is little information on the fate and potential therapeutic efficacy of the reinfusion of MSCs following total body irradiation (TBI). We addressed this question using human MSC (hMSCs) infused to nonobese diabetic/ severe combined immunodeficient (NOD/SCID) mice submitted to TBI. Further, we tested the impact of additional local irradiation (ALI) superimposed to TBI, as a model of accidental irradiation. NOD/SCID mice were transplanted with hM-SCs. Group 1 was not irradiated before receiving hMSC infusion. Group 2 received only TBI at a dose of 3.5 Gy, group 3 received local irradiation to the abdomen at a dose of 4.5 Gy in addition to TBI, and group 4 received local irradiation to the leg at 26.5 Gy in addition to TBI. Fifteen days after irradiation, quantitative and spatial distribution of the hMSCs were studied. Histological analysis of mouse tissues confirmed the presence of radio-induced lesions in the irradiated fields. Following their infusion into nonirradiated animals, hMSCs homed at a very low level to various tissues (lung, bone marrow, and muscles) and no significant engraftment was found in other organs. TBI induced an increase of engraftment levels of hMSCs in the brain, heart, bone marrow, and muscles. Abdominal irradiation (AI) as compared with leg irradiation (LI) increased hMSC engraftment in the exposed area (the gut, liver, and spleen). Hind LI as compared with AI increased hMSC engraftment in the exposed area (skin, quadriceps, and muscles). An increase of hMSC engraftment in organs outside the fields of the ALI was also observed. Conversely, following LI, hMSC engraftment was increased in the brain as compared with AI. This study shows that engraftment of hMSCs in NOD/ SCID mice with significantly increased in response to tissue injuries following TBI with or without ALI. ALI induced an increase of the level of engraftment at sites outside the local irradiation field, thus suggesting a distant (abscopal) effect of radiation damage. This work supports the use of MSCs to repair damaged normal tissues following accidental irradiation and possibly in patients submitted to radiotherapy.

Freyer, C. W. and A. W. Loren (2022). "Fluconazole-Induced adrenal insufficiency following allogeneic hematopoietic cell transplant." J Oncol Pharm Pract **28**(8): 1922-1925.

INTRODUCTION: Adrenal insufficiency (AI) is a potentially life-threatening endocrine abnormality rarely associated with azole antifungals. Patients undergoing allogeneic hematopoietic cell transplantation (alloHCT) are at high risk of invasive fungal infection and frequently receive azoles. Signs and symptoms of AI, such as gastrointestinal symptoms, lethargy, and electrolyte disturbances frequently overlap with common alloHCT toxicities, such that azole-induced AI may be under-reported in this population. CASE REPORT: We report the first published case of azole-induced AI following alloHCT. The patient presented with orthostasis and nonspecific gastrointestinal and failure to thrive symptoms in the setting of roughly 6 weeks of fluconazole prophylaxis. The patient was found to have primary AI diagnosed via low serum cortisol and inadequate response to cosyntropin. MANAGEMENT & OUTCOME: AI symptoms resolved with hydrocortisone supplementation and recurred upon rechallenge with fluconazole. The patient had fluconazole permanently discontinued with resolution of symptoms. We rate this case as a probable adverse drug reaction on the Naranjo scale. DISCUSSION: AI may be underreported and misdiagnosed in the alloHCT population given the presence of multiple toxicities with overlapping features. Clinicians must be diligent in investigating adrenal function in patients undergoing alloHCT on azole antifungals who present with symptoms of AI.

Gao, M., et al. (2014). "Regulation of high-density lipoprotein on hematopoietic stem/progenitor cells in atherosclerosis requires scavenger receptor type BI expression." Arterioscler Thromb Vasc Biol **34**(9): 1900-1909.

OBJECTIVE: Recently, we demonstrated that scavenger receptor type BI (SR-BI), a high-density lipoprotein (HDL) receptor, was expressed on murine hematopoietic stem/progenitor cells (HSPC) and infusion of reconstituted HDL and purified human apolipoprotein A-I (apoA-I) suppressed HSPC proliferation. We hypothesized that SR-B1 expression is required for the observed antiproliferative effects of HDL on HSPC. APPROACH AND RESULTS: SR-BI-deficient (SR-BI(-/-)) mice and wild-type controls were fed on chow or high-fat diet (HFD) for 8 to 10 weeks. Under chow diet, a significant increase in Lin(-) Sca1(+) cKit(+) cells (LSK cells, so-called HSPC) was found in the bone marrow of SR-BI(-/-) mice when compared with wild-type mice. HFD induced a further expansion of CD150(+)CD48(-) LSK cells (HSC), HSPC, and granulocyte monocyte progenitors in SR-BI(-/-) mice. Injection of reactive oxygen species inhibitor N-acetylcysteine attenuated HFD-induced HSPC expansion, leukocytosis, and atherosclerosis in SR-BI(-/-) mice. ApoA-I infusion inhibited HSPC cell proliferation, Akt phosphorylation and reactive oxygen species production in HSPC and plaque progression in low-density lipoprotein receptor knockout (LDLr(-/-)) apoA-I(-/-) mice on HFD but had no effect on SR-BI(-/-) mice on HFD. Transplantation of SR-BI(-/-) bone marrow cells into irradiated LDLr(-/-) recipients resulted in enhanced white blood cells reconstitution, inflammatory cell production, and plaque development. In patients with coronary heart disease, HDL levels were negatively correlated with white blood cells count and HSPC frequency in the peripheral blood. By flow cytometry, SR-BI expression was detected on human HSPC. CONCLUSIONS: SR-BI plays a critical role in the HDL-mediated regulation HSPC proliferation and differentiation, which is associated with atherosclerosis progression.

Gare, G. R., et al. (2022). "W-Net: Dense and diagnostic semantic segmentation of subcutaneous and breast tissue in ultrasound images by incorporating ultrasound RF waveform data." Med Image Anal **76**: 102326.

We study the use of raw ultrasound waveforms, often referred to as the "Radio Frequency" (RF) data, for the semantic segmentation of ultrasound scans to carry out dense and diagnostic labeling. We present W-Net, a novel Convolution Neural Network (CNN) framework that employs the raw ultrasound waveforms in addition to the grey ultrasound image to semantically segment and label tissues for anatomical, pathological, or other diagnostic purposes. To the best of our knowledge, this is also the first deep-learning or CNN approach for segmentation that analyzes ultrasound raw RF data along with the grey image. We chose subcutaneous tissue (SubQ) segmentation as our initial clinical goal for dense segmentation since it has diverse intermixed tissues, is challenging to segment, and is an underrepresented research area. SubQ potential applications include plastic surgery, adipose stem-cell harvesting, lymphatic monitoring, and possibly detection/treatment of certain types of tumors. Unlike prior work, we seek to label every pixel in the image, without the use of a background class. A custom dataset consisting of hand-labeled images by an expert clinician and trainees are used for the experimentation, currently labeled into the following categories: skin, fat, fat fascia/stroma, muscle, and muscle fascia. We compared W-Net and attention variant of W-Net (AW-Net) with U-Net and Attention U-Net (AU-Net). Our novel W-Net's RF-Waveform encoding architecture outperformed regular U-Net and AU-Net, achieving the best mIoU

accuracy (averaged across all tissue classes). We study the impact of RF data on dense labeling of the SubQ region, which is followed by the analyses of the generalization capability of the networks to patients and analysis on the SubQ tissue classes, determining that fascia tissues, especially muscle fascia in particular, are the most difficult anatomic class to recognize for both humans and AI algorithms. We present diagnostic semantic segmentation, which is semantic segmentation carried out for the purposes of direct diagnostic pixel labeling, and apply it to breast tumor detection task on a publicly available dataset to segment pixels into malignant tumor, benign tumor, and background tissue class. Using the segmented image we diagnose the patient by classifying the breast lesion as either benign or malignant. We demonstrate the diagnostic capability of RF data with the use of W-Net, which achieves the best segmentation scores across all classes.

Giassetti, M. I., et al. (2019). "Spermatogonial Stem Cell Transplantation: Insights and Outlook for Domestic Animals." Annu Rev Anim Biosci **7**: 385-401.

The demand for food will increase to an unprecedented level over the next 30 years owing to human population expansion, thus necessitating an evolution that improves the efficiency of livestock production. Genetic gain to improve production traits of domestic animal populations is most effectively achieved via selective use of gametes from animals deemed to be elite, and this principle has been the basis of selective breeding strategies employed by humans for thousands of years. In modern-day animal agriculture, artificial insemination (AI) has been the staple of selective breeding programs, but it has inherent limitations for applications in beef cattle and pig production systems. In this review, we discuss the potential and current state of development for a concept termed Surrogate Sires as a next-generation breeding tool in livestock production. The scheme capitalizes on the capacity of spermatogonial stem cells to regenerate sperm production after isolation from donor testicular tissue and transfer into the testes of a recipient male that lacks endogenous germline, thereby allowing the surrogate male to produce offspring with the donor haplotype via natural mating. This concept provides an effective selective breeding tool to achieve genetic gain that is conducive for livestock production systems in which AI is difficult to implement.

Gilani, R. A., et al. (2012). "The importance of HER2 signaling in the tumor-initiating cell population in aromatase inhibitor-resistant breast cancer." Breast Cancer Res Treat **135**(3): 681-692.

Aromatase inhibitors (AIs) are an effective therapy in treating estrogen receptor-positive breast cancer. Nonetheless, a significant percentage of patients either do not respond or become resistant to AIs. Decreased dependence on ER-signaling and increased dependence on growth factor receptor signaling pathways, particularly human epidermal growth factor receptor 2 (EGFR2/HER2), have been implicated in AI resistance. However, the role of growth factor signaling remains unclear. This current study investigates the possibility that signaling either through HER2 alone or through interplay between epidermal growth factor receptor 1 (EGFR/HER1) and HER2 mediates AI resistance by increasing the tumor initiating cell (TIC) subpopulation in AI-resistant cells via regulation of stem cell markers, such as breast cancer resistance protein (BCRP). TICs and BCRP are both known to be involved in drug resistance. Results from in vitro analyses of AI-resistant versus AI-sensitive cells and HER2-versus HER2+ cells, as well as from in vivo xenograft tumors, indicate that (1) AI-resistant cells overexpress both HER2 and BCRP and exhibit increased TIC characteristics compared to AI-sensitive cells; (2) inhibition of HER2 and/or BCRP decrease TIC characteristics in letrozole-resistant cells; and (3) HER2 and its dimerization partner EGFR/HER1 are involved in the regulation of BCRP. Overall, these results suggest that reducing or eliminating the TIC subpopulation with agents that target BCRP, HER2, EGFR/HER1, and/or their downstream kinase pathways could be effective in preventing and/or treating acquired AI resistance.

Goktas, P. and R. Simon Carbajo (2023). "PPSW-SHAP: Towards Interpretable Cell Classification Using Tree-Based SHAP Image Decomposition and Restoration for High-Throughput Bright-Field Imaging." Cells **12**(10).

Advancements in high-throughput microscopy imaging have transformed cell analytics, enabling functionally relevant, rapid, and in-depth bioanalytics with Artificial Intelligence (AI) as a powerful driving force in cell therapy (CT) manufacturing. High-content microscopy screening often suffers from systematic noise, such as uneven illumination or vignetting artifacts, which can result in false-negative findings in AI models. Traditionally, AI models have been expected to learn to deal with these artifacts, but success in an inductive framework depends on sufficient training examples. To address this challenge, we propose a two-fold approach: (1) reducing noise through an image decomposition and restoration technique called the Periodic Plus Smooth Wavelet transform (PPSW) and (2) developing an interpretable machine learning (ML) platform using

tree-based Shapley Additive exPlanations (SHAP) to enhance end-user understanding. By correcting artifacts during pre-processing, we lower the inductive learning load on the AI and improve end-user acceptance through a more interpretable heuristic approach to problem solving. Using a dataset of human Mesenchymal Stem Cells (MSCs) cultured under diverse density and media environment conditions, we demonstrate supervised clustering with mean SHAP values, derived from the 'DFT Modulus' applied to the decomposition of bright-field images, in the trained tree-based ML model. Our innovative ML framework offers end-to-end interpretability, leading to improved precision in cell characterization during CT manufacturing.

Gonzalez-Pecchi, V., et al. (2015). "Apolipoprotein A-I enhances proliferation of human endothelial progenitor cells and promotes angiogenesis through the cell surface ATP synthase." Microvasc Res **98**: 9-15.

BACKGROUND: Human endothelial progenitor cells (hEPC) correspond to a subtype of stem cells which, in the presence of angiogenic stimuli, can be mobilized from bone marrow to circulation and then recruited to the damaged endothelium, where they differentiate into mature endothelial cells. High-density lipoproteins (HDL) increase the level and functionality (proliferation, migration, differentiation, angiogenesis capacity) of circulating hEPC; however, the contribution of receptors for HDL and/or apolipoprotein A-I (apoA-I), the main HDL apolipoprotein, in these effects is still unclear. On mature endothelial cells, the cell surface F1-ATP synthase has been previously characterized as a high affinity receptor of apoA-I, whereas the scavenger receptor SR-BI mainly binds with fully lipidated HDL and displays a poor affinity for lipid-free apoA-I. Furthermore, it was shown that apoA-I binding to surface ATP synthase on mature endothelial cells promotes cell proliferation, whereas inhibits apoptosis. In this work, we aimed to determine the effect of apoA-I in the proliferation and the angiogenic capacity of early hEPC, and the contribution of the cell surface ATP synthase in these events. RESULTS: We first evidenced that early hEPC express the ATP synthase at the surface of nonpermeabilized cells, where it is not colocalized with MitoTracker, a mitochondria marker. ApoA-I (50 mug/mL) increases hEPC proliferation (+14.5%, $p<0.001$) and potentiates the effect of hEPC on a cellular model of angiogenesis, with an increase of +31% ($p<0.01$) in branch point counting and in tubule length. These effects of apoA-I were totally reversed in the presence of ATP synthase inhibitors, such as IF1 or oligomycin, whereas the inhibition of the HDL receptor, SR-BI, partially inhibits these events. CONCLUSIONS: These results provide the first evidence that surface ATP synthase is expressed on early hEPC, where it mediates apoA-I effects in hEPC proliferation and in angiogenesis. This knowledge could be helpful for future investigations focused on the regulation of the number and functionality of these cells and in the development of new therapies for the treatment of diseases, such as cardiovascular disease.

Gordts, S. C., et al. (2012). "Lipid lowering and HDL raising gene transfer increase endothelial progenitor cells, enhance myocardial vascularity, and improve diastolic function." PLoS One **7**(10): e46849.

BACKGROUND: Hypercholesterolemia and low high density lipoprotein (HDL) cholesterol contribute to coronary heart disease but little is known about their direct effects on myocardial function. Low HDL and raised non-HDL cholesterol levels carried increased risk for heart failure development in the Framingham study, independent of any association with myocardial infarction. The objective of this study was to test the hypothesis that increased endothelial progenitor cell (EPC) number and function after lipid lowering or HDL raising gene transfer in C57BL/6 low density lipoprotein receptor deficient (LDLr(-/-)) mice may be associated with an enhanced relative vascularity in the myocardium and an improved cardiac function. METHODOLOGY/PRINCIPAL FINDINGS: Lipid lowering and HDL raising gene transfer were performed using the E1E3E4-deleted LDLr expressing adenoviral vector AdLDLr and the human apolipoprotein A-I expressing vector AdA-I, respectively. AdLDLr transfer in C57BL/6 LDLr(-/-) mice resulted in a 2.0-fold ($p<0.05$) increase of the circulating number of EPCs and in an improvement of EPC function as assessed by ex vivo EPC migration and EPC adhesion. Capillary density and relative vascularity in the myocardium were 28% ($p<0.01$) and 22% ($p<0.05$) higher, respectively, in AdLDLr mice compared to control mice. The peak rate of isovolumetric relaxation was increased by 12% ($p<0.05$) and the time constant of isovolumetric relaxation was decreased by 14% ($p<0.05$) after AdLDLr transfer. Similarly, HDL raising gene transfer increased EPC number and function and raised both capillary density and relative vascularity in the myocardium by 24% ($p<0.05$). The peak rate of isovolumetric relaxation was increased by 16% ($p<0.05$) in AdA-I mice compared to control mice. CONCLUSIONS/SIGNIFICANCE: Both lipid lowering and HDL raising gene transfer have beneficial effects on EPC biology, relative myocardial vascularity, and diastolic function. These

findings raise concerns over the external validity of studies evaluating myocardial biology and cardiac repair in normocholesterolemic animals.

Groschel, M., et al. (2010). "Differential impact of temporary and permanent noise-induced hearing loss on neuronal cell density in the mouse central auditory pathway." J Neurotrauma **27**(8): 1499-1507.

Although acoustic overstimulation has a major pathophysiological influence on the inner ear, central components of the auditory pathway can also be affected by noise-induced hearing loss (NIHL). The present study investigates the influence of a noise-induced temporary threshold shift (TTS) and/or permanent threshold shift (PTS) on neuronal cell densities in key structures of the central auditory pathway. Mice were noise-exposed (3 h, 5-20 kHz) at 115 dB sound pressure level (SPL) under anesthesia, and were investigated immediately (TTS group, n = 5) after the exposure, or 1 week later (PTS group, n = 6). Unexposed animals were used as controls (n = 7). Frequency-specific auditory brainstem responses (ABR) were recorded to examine auditory thresholds. Cell density was determined within the dorsal (DCN) and ventral (VCN) cochlear nucleus; the central nucleus of the inferior colliculus (ICC); the dorsal, ventral, and medial subdivisions of the medial geniculate body (MGBd, MGBv, and MGBm); and layer I to VI of the primary auditory cortex (AI I-VI). ABR thresholds were significantly elevated in the TTS group (52-69 dB SPL) and in the PTS group (33-42 dB SPL) compared to controls. There was a significant decrease in cell density only in the VCN of the TTS group (-10%), most likely induced by the acute overstimulation of neurons. Cell density was significantly reduced in all investigated auditory structures at 1 week post-exposure (PTS group), except in layer II of the AI (VCN: -30% and DCN: -30% (high-frequency); -39% (low-frequency); ICC: -31%; MGBd: -31%; MGBm: -28%; MGBv: -31%; AI: -10 to 14%). Thus there were dramatic changes within the neuronal cytoarchitecture of the central auditory pathway following a single noise exposure. The present findings should help clinicians to better understand the complex psychoacoustic phenomena of NIHL.

Guilbaud, E., et al. (2023). "Cholesterol efflux pathways hinder KRAS-driven lung tumor progenitor cell expansion." Cell Stem Cell **30**(6): 800-817 e809.

Cholesterol efflux pathways could be exploited in tumor biology to unravel cancer vulnerabilities. A mouse model of lung-tumor-bearing KRAS(G12D) mutation with specific disruption of cholesterol efflux pathways in epithelial progenitor cells promoted tumor growth. Defective cholesterol efflux in epithelial progenitor cells governed their transcriptional landscape to support their expansion and create a pro-tolerogenic tumor microenvironment (TME). Overexpression of the apolipoprotein A-I, to raise HDL levels, protected these mice from tumor development and dire pathologic consequences. Mechanistically, HDL blunted a positive feedback loop between growth factor signaling pathways and cholesterol efflux pathways that cancer cells hijack to expand. Cholesterol removal therapy with cyclodextrin reduced tumor burden in progressing tumor by suppressing the proliferation and expansion of epithelial progenitor cells of tumor origin. Local and systemic perturbations of cholesterol efflux pathways were confirmed in human lung adenocarcinoma (LUAD). Our results position cholesterol removal therapy as a putative metabolic target in lung cancer progenitor cells.

Gundgurthi, A., et al. (2013). "Endocrine complications after busulphan and cyclophosphamide based hematopoietic stem cell transplant: A single tertiary care centre experience." Indian J Endocrinol Metab **17**(5): 855-863.

INTRODUCTION: Endocrine complications are common after hematopoietic stem cell transplant (HSCT). Although HSCT is performed at various centers in India, no study is available for endocrine dysfunctions among them. This study was carried out with the objective to evaluate endocrine dysfunction among patients undergone HSCT in the past. MATERIALS AND METHODS: We carried out a cross-sectional study in a 50 post-HSCT recipients (39 allogenic, 11 autologous). All relevant data were collected from patient's records. Samples for hormonal estimation were collected and stimulation tests for cortisol and growth hormone were interpreted based on peak values achieved during insulin tolerance test. RESULTS: The mean age of patients was 26.3 +/- 16.9 years (range 4-74). Adrenal insufficiency (AI) was present in 60%, hypergonadotropic hypogonadism (HH) in 60%, growth hormone deficiency (GHD) in 54%, hypothyroidism in 4%, hyperprolactinemia in 4%, new onset diabetes after transplant in 4%, and impaired fasting glucose in 6%. Multiple endocrine complications were common. GHD was present in 77% of children (n = 22) although height standard deviation score was not statistically different compared to those who didn't have GHD. HH was present in 36% of children. In adults (n = 28), 36% had GHD, all females had HH, and 89% of males had HH. Germ cell dysfunction with compensated Leydig cell dysfunction was the most common pattern of HH in males. Fifteen patients had graft versus host disease (GVHD). GVHD had no bearing on

development of endocrine deficiencies. AI was related to duration after and type of transplant, but was unrelated to steroid intake. CONCLUSIONS: Endocrine manifestations are common after HSCT; they can occur as early or late complications. All HSCT recipients should have endocrine evaluation as per prevailing guidelines.

Gupta, A., et al. (2013). "Efficacy and mechanism of action of Proellex, an antiprogestin in aromatase overexpressing and Letrozole resistant T47D breast cancer cells." J Steroid Biochem Mol Biol **133**: 30-42.

Aromatase inhibitors (AI) are considered as a first line therapy for ER+PR+ breast cancers. However, many patients acquire resistance to AI. In this study, we determined the response of antiprogestin CDB-4124 (Proellex) on the aromatase overexpressing and Letrozole resistant cell lines and also studies its mechanism of action in inhibition of breast cancer cell proliferation. For these studies we generated aromatase overexpressing T47D (T47Darom) and respective control (T47Dcon) breast cancer cell lines by stable transfection with plasmid containing CYP19A1 gene, or empty vector respectively. Letrozole resistant cell line (T47DaromLR) was generated by incubating T47Darom for 75 weeks in the presence of 10 muM Letrozole. Cell proliferation was determined by MTT or crystal violet assays. Gene expressions were quantified by QRT-PCR whereas proteins were identified by western blot analyses, flow cytometry and immunofluorescence staining. Aromatase activity was determined by estradiol ELISA. The effects of Proellex on the anchorage independent growth were measured by soft agar colony formation. Statistical differences between the various groups were determined by Student's 't' test or ANOVA followed by Bonferroni's post hoc test. Results showed that T47Darom and T47DaromLR cell lines had significantly higher aromatase expression (mRNA; 80-90 fold and protein) and as a result exhibited increased aromatization of testosterone to estradiol as compared to T47Dcon. Both these cell lines showed enhanced growth in the presence of Testosterone (50-60%). In T47DaromLR cells increased PR-B and EGFR expression as compared to T47Dcon cells was observed. Proellex and other known aromatase inhibitors (Letrozole, Anastrozole, and Exemestane) inhibited testosterone induced cell proliferation and anchorage independent growth of T47Darom cells. Cell growth inhibition was significantly greater when cells were treated with Proellex alone or in combination with other AIs as compared to AIs alone. Proellex inhibited mRNA and protein levels of PR-B, reduced PRB/p300 complex formation in the nuclei and significantly reduced EGFR expression in T47Darom cells. Our results in the present study indicate that antiproliferative effect of Proellex is probably due to PR-B/EGFR modulation in ER+PR+, aromatase expressing cells. Overall these results suggest that antiprogestin, Proellex can be developed as a possible treatment strategy for aromatase overexpressing ER+/PR+ breast cancer patients as well as for aromatase inhibitor resistant breast cancer patients.

Guth, S., et al. (2020). "Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses." Arch Toxicol **94**(5): 1375-1415.

Recently, epidemiological studies have suggested that fluoride is a human developmental neurotoxicant that reduces measures of intelligence in children, placing it into the same category as toxic metals (lead, methylmercury, arsenic) and polychlorinated biphenyls. If true, this assessment would be highly relevant considering the widespread fluoridation of drinking water and the worldwide use of fluoride in oral hygiene products such as toothpaste. To gain a deeper understanding of these assertions, we reviewed the levels of human exposure, as well as results from animal experiments, particularly focusing on developmental toxicity, and the molecular mechanisms by which fluoride can cause adverse effects. Moreover, in vitro studies investigating fluoride in neuronal cells and precursor/stem cells were analyzed, and 23 epidemiological studies published since 2012 were considered. The results show that the margin of exposure (MoE) between no observed adverse effect levels (NOAELs) in animal studies and the current adequate intake (AI) of fluoride (50 microg/kg b.w./day) in humans ranges between 50 and 210, depending on the specific animal experiment used as reference. Even for unusually high fluoride exposure levels, an MoE of at least ten was obtained. Furthermore, concentrations of fluoride in human plasma are much lower than fluoride concentrations, causing effects in cell cultures. In contrast, 21 of 23 recent epidemiological studies report an association between high fluoride exposure and reduced intelligence. The discrepancy between experimental and epidemiological evidence may be reconciled with deficiencies inherent in most of these epidemiological studies on a putative association between fluoride and intelligence, especially with respect to adequate consideration of potential confounding factors, e.g., socioeconomic status, residence, breast feeding, low birth weight, maternal intelligence, and exposure to other neurotoxic chemicals. In conclusion, based on the totality of

currently available scientific evidence, the present review does not support the presumption that fluoride should be assessed as a human developmental neurotoxicant at the current exposure levels in Europe.

Han, S. Y., et al. (2014). "Marsdenia tenacissima extract inhibits gefitinib metabolism in vitro by interfering with human hepatic CYP3A4 and CYP2D6 enzymes." J Ethnopharmacol **151**(1): 210-217.

ETHNOPHARMACOLOGICAL RELEVANCE: The stem of Marsdenia tenacissima (Roxb.) Wight et Arn. is mainly produced in Yunnan China and has long been used as a medicine to treat cancer in China. Xiao-Ai-Ping injection, the water-soluble part of the stem of Marsdenia tenacissima, is administrated as an anti-cancer agent in clinics for decades. Our previous study showed that Marsdenia tenacissima extract (MTE) restored gefitinib sensitivity in gefitinib-resistant non-small cell lung cancer (NSCLC) cells, but the mechanism involved is unknown. Gefitinib undergoes hepatic metabolism predominantly through human cytochrome P450 (CYP) 3A4 and CYP2D6 enzymes. This study aims to evaluate whether MTE interferes with gefitinib metabolism via human hepatic P450 enzymes. MATERIAL AND METHODS: A cocktail-substrate assay was used to test the effect of MTE on major CYP enzyme activities by incubation of pooled human liver microsomes with specific substrate probes of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in the absence and presence of MTE. Recombinant human CYP450 enzymes were used to predict in vitro gefitinib metabolic clearance in the absence and presence of MTE. The metabolites of the substrate probes and gefitinib were detected by high-performance liquid chromatographic tandem mass spectrometry (HPLC-MS/MS). Human hepatoma HepG2 cells were used to investigate the effect of gefitinib alone or in combination with MTE on CYP3A4 and CYP2D6 mRNA and protein expression. RESULTS: The cocktail-substrate assay showed that MTE inhibited CYP450 activities in human liver microsomes with the inhibition rate of 3A4>2C9>2C19>1A2>2D6. The co-administration of MTE with gefitinib significantly decreased the in vitro intrinsic clearance (Clint) of gefitinib by 2.6 and 4.0-fold for CYP2D6 and CYP3A4, respectively, but did not affect other CYP450s. CYP2D6 and CYP3A4 mRNA and protein expression in human hepatoma HepG2 cells were greatly reduced in the combined gefitinib and MTE treatment. CONCLUSION: We demonstrate that MTE inhibits gefitinib metabolism by interfering with CYP3A4 and CYP2D6. Meanwhile, MTE combined with gefitinib down-regulates the mRNA and protein expression of CYP3A4 and CYP2D6 in the HepG2 cells. Thus, these data suggest that MTE is a promising herbal medicine to enhance gefitinib efficacy through improving its metabolic stability.

Hanai, Y., et al. (2022). "Temporal and Locational Values of Images Affecting the Deep Learning of Cancer Stem Cell Morphology." Biomedicines **10**(5).

Deep learning is being increasingly applied for obtaining digital microscopy image data of cells. Well-defined annotated cell images have contributed to the development of the technology. Cell morphology is an inherent characteristic of each cell type. Moreover, the morphology of a cell changes during its lifetime because of cellular activity. Artificial intelligence (AI) capable of recognizing a mouse-induced pluripotent stem (miPS) cell cultured in a medium containing Lewis lung cancer (LLC) cell culture-conditioned medium (cm), miPS-LLCcm cell, which is a cancer stem cell (CSC) derived from miPS cell, would be suitable for basic and applied science. This study aims to clarify the limitation of AI models constructed using different datasets and the versatility improvement of AI models. The trained AI was used to segment CSC in phase-contrast images using conditional generative adversarial networks (CGAN). The dataset included blank cell images that were used for training the AI but they did not affect the quality of predicting CSC in phase contrast images compared with the dataset without the blank cell images. AI models trained using images of 1-day culture could predict CSC in images of 2-day culture; however, the quality of the CSC prediction was reduced. Convolutional neural network (CNN) classification indicated that miPS-LLCcm cell image classification was done based on cultivation day. By using a dataset that included images of each cell culture day, the prediction of CSC remains to be improved. This is useful because cells do not change the characteristics of stem cells owing to stem cell marker expression, even if the cell morphology changes during culture.

Harraz, A. M., et al. (2011). "The effect of adipose-derived stem cells on augmentation ileocystoplasty: A pilot study." Arab J Urol **9**(2): 139-145.

OBJECTIVES: Incorporation of intestinal tissue into urinary tract elicits many metabolic and mechanical complications due to anatomical and physiological differences. Adipose-derived stem cells (ADSCs) improve vascularity and functional outcomes by a paracrine mechanism. In a pilot study we investigated whether ADSCs can survive in the augmented bladder and improve its function. MATERIALS AND METHODS: Autologous ADSCs were harvested from rat paragonadal fat and cultured

before injection into a rat model of augmentation ileocystoplasty (study group). Control augmented bladders were injected with cell-free saline. Eight weeks later, rats underwent abdominal ultrasonography for upper tract changes and were examined by conscious cystometry to determine bladder function. After extirpation, augmented bladders were examined using Masson trichrome staining for connective tissue and muscle content, immunohistochemistry for alpha-smooth muscle actin, and rat endothelial cell antigen staining for endothelial cells. Changes in the extracellular matrix were assessed by determining the elastin content. ADSCs were labelled and tracked by 5-ethynyl-2-deoxyuridine nuclear staining. RESULTS: Abdominal ultrasonography showed better preservation of upper tract function in the ADSC group than in the saline-treated group (P = 0.007). After 2 months there were no differences in the variables assessed by conscious cystometry between the ADSC and saline-treated groups. However, the bladder weight was significantly greater in the ADSC-treated group. On immunohistochemistry, the implanted ADSCs survived up to 8 weeks but did not transdifferentiate into smooth muscle or endothelial cells. CONCLUSION: These results suggested a potential role of ADSCs in modifying the intestinal segment in augmented bladders; this role has to be further elucidated.

Hasanzadeh, E., et al. (2023). "The Role of Advanced Technologies against COVID-19: Prevention, Detection, and Treatments." Curr Stem Cell Res Ther **18**(6): 800-828.

Concurrent with the global outbreak of COVID-19, the race began among scientists to generate effective therapeutics for the treatment of COVID-19. In this regard, advanced technology such as nanotechnology, cell-based therapies, tissue engineering and regenerative medicine, nerve stimulation and artificial intelligence (AI) are attractive because they can offer new solutions for the prevention, diagnosis and treatment of COVID-19. Nanotechnology can design rapid and specific tests with high sensitivity for detecting infection and synthases new drugs and vaccines based on nanomaterials to directly deliver the intended antiviral agent to the desired site in the body and also provide new surfaces that do not allow virus adhesion. Mesenchymal stem cells and exosomes secreted from them apply in regenerative medicine and regulate inflammatory responses. Cell therapy and tissue engineering are combined to repair or substitute damaged tissues or cells. Tissue engineering using biomaterials, cells, and signaling molecules can develop new therapeutic and diagnostic platforms and help scientists fight viral diseases. Nerve stimulation technology can augment body's natural ability to modulate the inflammatory response and inhibit pro-inflammatory cytokines and consequently suppress cytokine storm. People can access free online health counseling services through AI and it helps very fast for screening and diagnosis of COVID-19 patients. This study is aimed first to give brief information about COVID-19 and the epidemiology of the disease. After that, we highlight important developments in the field of advanced technologies relevant to the prevention, detection, and treatment of the current pandemic.

Herrid, M. and J. R. McFarlane (2013). "Application of testis germ cell transplantation in breeding systems of food producing species: a review." Anim Biotechnol **24**(4): 293-306.

A major benefit of advanced reproduction technologies (ART) in animal breeding is the ability to produce more progeny per individual parent. This is particularly useful with animals of high genetic merit. Testis germ cell transplantation (TGCT) is emerging as a novel reproductive technology with application in animal breeding systems, including the potential for use as an alternative to artificial insemination (AI), an alternative to transgenesis, part of an approach to reducing generation intervals, or an approach toward development of interspecies hybrids. There is one major difference in TGCT between rodents and some other species associated with immunotolerance in heterologous transplantation. In particular, livestock and aquatic species do not require an immunesuppression procedure to allow donor cell survival in recipient testis. Testicular stem cells from a genetically elite individual transplanted into others can develop and produce a surrogate male-an animal that produces the functional sperm of the original individual. Spermatozoa produced from testis stem cells are the only cells in the body of males that can transmit genetic information to the offspring. The isolation and genetic manipulation of testis stem cells prior to transplantation has been shown to create transgenic animals. However, the current success rate of the transplantation procedure in livestock and aquatic species is low, with a corresponding small proportion of donor spermatozoa in the recipient's semen. The propagation of donor cells in culture and preparation of recipient animals are the two main factors that limit the commercial application of this technique. The current paper reviews and compares recent progress and examines the difficulties of TGCT in both livestock and aquatic species, thereby providing new insights into the application of TGCT in food producing animals.

Hidaka, T., et al. (2020). "Prediction of Compound Bioactivities Using Heat-Diffusion Equation." Patterns (N Y) **1**(9): 100140.

Machine learning is expected to improve low throughput and high assay cost in cell-based phenotypic screening. However, it is still a challenge to apply machine learning to achieving sufficiently complex phenotypic screening due to imbalanced datasets, non-linear prediction, and unpredictability of new chemotypes. Here, we developed a prediction model based on the heat-diffusion equation (PM-HDE) to address this issue. The algorithm was verified as feasible for virtual compound screening using biotest data of 946 assay systems registered with PubChem. PM-HDE was then applied to actual screening. Based on supervised learning of the data of about 50,000 compounds from biological phenotypic screening with motor neurons derived from ALS-patient-induced pluripotent stem cells, virtual screening of >1.6 million compounds was implemented. We confirmed that PM-HDE enriched the hit compounds and identified new chemotypes. This prediction model could overcome the inflexibility in machine learning, and our approach could provide a novel platform for drug discovery.

Hill, J. R. and I. Dobrinski (2006). "Male germ cell transplantation in livestock." Reprod Fertil Dev **18**(1-2): 13-18.

Male germ cell transplantation is a powerful approach to study the control of spermatogenesis with the ultimate goal to enhance or suppress male fertility. In livestock animals, applications can be expanded to provide an alternative method of transgenesis and an alternative means of artificial insemination (AI). The transplantation technique uses testis stem cells, harvested from the donor animal. These donor stem cells are injected into seminiferous tubules, migrate from the lumen to relocate to the basement membrane and, amazingly, they can retain the capability to produce donor sperm in their new host. Adaptation of the mouse technique for livestock is progressing, with gradual gains in efficiency. Germ cell transfer in goats has produced offspring, but not yet in cattle and pigs. In goats and pigs, the applications of germ cell transplantation are mainly in facilitating transgenic animal production. In cattle, successful male germ cell transfer could create an alternative to AI in areas where it is impractical. Large-scale culture of testis stem cells would enhance the use of elite bulls by providing a renewable source of stem cells for transfer. Although still in a developmental state, germ cell transplantation is an emerging technology with the potential to create new opportunities in livestock production.

Hochereau-de Reviers, M. T. and C. Perreau (1993). "In vitro culture of embryonic disc cells from porcine blastocysts." Reprod Nutr Dev **33**(5): 475-483.

The aim of the present study was to define the conditions of preparation and in vitro culture of embryonic discs allowing proliferation of ES-like cells. G5-6 porcine blastocysts (G0 = day of AI) were cultured in toto; in G10-11 blastocysts, trophectoderm and primitive endoderm were microsurgically removed from embryonic discs (ED) which were cultured either on plastic or on a feeder layer. Feeder cells were foetal G30 porcine fibroblasts which had been previously irradiated. Culture medium was DMEM supplemented with 0.1 mM beta-mercaptoethanol, 5% foetal calf serum, 5% Ultroser G and 10(3) IU LIF; cultures were performed at 38 degrees C. Colonies were reseeded weekly. Few embryonic discs from G5-6 and no elongating blastocysts gave rise to ES-like cells. At least 50% G10-11 ED attached and developed multilayered colonies (100 cells) of small ovoid ES-like cells. Colonies from 4 sows were maintained in culture for at least 8 wk. Addition of PDGF, insulin or both, induced a transitory stimulation of growth in G6 or G10-11 ED; TGF beta did not modify growth of G6 ICM. Uterine G10-11 flushing medium or retinol induced differentiation of ES-like cells. These cells introduced in nude mice induced teratoma.

Hoffmann, J., et al. (2024). "Development of an explainable AI system using routine clinical parameters for rapid differentiation of inflammatory conditions." Front Immunol **15**: 1364954.

INTRODUCTION: Inflammatory conditions in patients have various causes and require different treatments. Bacterial infections are treated with antibiotics, while these medications are ineffective against viral infections. Autoimmune diseases and graft-versus-host disease (GVHD) after allogeneic stem cell transplantation, require immunosuppressive therapies such as glucocorticoids, which may be contraindicated in other inflammatory states. In this study, we employ a combination of straightforward blood tests to devise an explainable artificial intelligence (XAI) for distinguishing between bacterial infections, viral infections, and autoimmune diseases/graft-versus-host disease. PATIENTS AND METHODS: We analysed peripheral blood from 80 patients with inflammatory conditions and 38 controls. Complete blood count, CRP analysis, and a rapid flow cytometric test for myeloid activation markers CD169, CD64, and HLA-DR were utilized. A two-step XAI distinguished firstly with C5.0 rules pruned by ABC analysis between controls and inflammatory conditions and secondly between the types of inflammatory conditions with a new

bivariate decision tree using the Simpson impurity function. RESULTS: Inflammatory conditions were distinguished using an XAI, achieving an overall accuracy of 81.0% (95%CI 72 - 87%). Bacterial infection (N = 30), viral infection (N = 26), and autoimmune diseases/GVHD (N = 24) were differentiated with accuracies of 90.3%, 80.0%, and 79.0%, respectively. The most critical parameter for distinguishing between controls and inflammatory conditions was the expression of CD64 on neutrophils. Monocyte count and expression of CD169 were most crucial for the classification within the inflammatory conditions. CONCLUSION: Treatment decisions for inflammatory conditions can be effectively guided by XAI rules, straightforward to implement and based on promptly acquired blood parameters.

Hoshino, K., et al. (2006). "Three catheter-based strategies for cardiac delivery of therapeutic gelatin microspheres." Gene Ther **13**(18): 1320-1327.

Gelatin hydrogel microspheres (GHMs) have been reported as novel non-viral vectors for gene or protein delivery (GHM therapy). However, the components of an effective catheter-based delivery strategy for GHM therapy are unknown. We evaluated the effectiveness of three catheter-based strategies for cardiac GHM therapy: (1) antegrade injection (AI) via coronary arteries; (2) retrograde injection (RI) via coronary veins; and (3) direct myocardial injection (DI) via the coronary sinus. AI distributed microspheres homogeneously throughout the target area with 73+/-11% retention. RI scattered microspheres non-homogenously with 22+/-8% retention. DI distributed microspheres in the needle-advanced area with 47+/-14% retention. However, despite high efficiency, AI did not show biological effects of inducing angiogenesis from basic fibroblast growth factor bound to GHMs. Furthermore, focal micro-infarctions, owing to micro-embolism of aggregated GHMs into small coronary arterioles, were detected in the AI group. Conversely, only RI and DI groups displayed increased coronary flow reserve. DI groups also demonstrated increased capillary density. These results suggest that RI and DI are effective for cardiac GHM therapy, while AI appears inappropriate owing to the risk of focal infarctions.

Hossain, M. M., et al. (2014). "Massive deregulation of miRNAs from nuclear reprogramming errors during trophoblast differentiation for placentogenesis in cloned pregnancy." BMC Genomics **15**: 43.

BACKGROUND: Low efficiency of Somatic Cell Nuclear Transfer (NT) has been widely addressed with high incidence of placental abnormalities due to genetic and epigenetic modifications. MiRNAs are shown to be major regulators of such modifications. The present study has been carried out to identify the expression patterns of 377 miRNAs, their functional associations and mechanism of regulation in bovine placentas derived from artificial insemination (AI), in vitro production (IVP) and NT pregnancies. RESULTS: This study reveals a massive deregulation of miRNAs as chromosomal cluster or miRNA families without sex-linkage in NT and in-vitro derived IVP placentas. Cell specific localization miRNAs in blastocysts and expression profiling of embryos and placentas at different developmental stages identified that the major deregulation of miRNAs exhibited in placentas at day 50 of pregnancies is found to be less dependent on global DNA methylation, rather than on aberrant miRNA biogenesis molecules. Among them, aberrant AGO2 expression due to hypermethylation of its promoter was evident. Along with other factors, aberrant AGO2 expression was observed to be associated with multiple defects in trophoblast differentiation through deregulation of miRNAs mediated mechanisms. CONCLUSION: These aberrant miRNA activities might be associated with genetic and epigenetic modifications in abnormal placentogenesis due to maldifferentiation of early trophoblast cell lineage in NT and IVP pregnancies. This study provides the first insight into genome wide miRNA expression, their role in regulation of trophoblast differentiation as well as abnormal placental development in Somatic Cell Nuclear Transfer pregnancies to pave the way to improve the efficiency of cloning by nuclear transfer.

Hsieh, T. C., et al. (2002). "Effects of herbal preparation Equiguard on hormone-responsive and hormone-refractory prostate carcinoma cells: mechanistic studies." Int J Oncol **20**(4): 681-689.

The Equiguard is a dietary supplement comprised of standardized extracts from nine herbs, respectively, Herba epimedium brevicornum Maxim (stem and leaves), Radix morindae officinalis (root), Fructus rosa laevigatae michx (fruit), Rubus chingii Hu (fruit), Schisandra chinensis (Turz.) Baill (fruit), Ligustrum lucidum Ait (fruit), Cuscuta chinensis Lam (seed), Psoralea corylifolia L. (fruit), and Astragalus membranaceus (Fisch.) Bge (root). This proprietary product, formulated according to Chinese traditional medicinal concepts, is aimed at restoring harmony in the <primordial (original) ying-yang> of the kidney, an organ which Chinese medicinal principles consider to be vital for invigorating as well as maintaining balance of the entire urological system. As the prostate is an integral component of the urological system, we performed in vitro studies to

test the effects of ethanol extracts of Equiguard to modulate prostate growth and gene expression. These studies used prostate cancer cells mimicking the androgen-dependent (AD) and androgen-independent (AI) states of prostate carcinogenesis. Results show that Equiguard significantly reduced cancer cell growth, induced apoptosis, suppressed expression of the androgen receptor (AR) and lowered intracellular and secreted prostate specific antigen (PSA), and almost completely abolished colony forming abilities of prostate cancer cells. These data support the interpretation that this herbal formulation contains ingredients that collectively may be efficacious in preventing or treating AD and AI prostate carcinoma. The anti-prostatic activities of Equiguard may stem from its complex composition capable of targeting multiple signal transduction/metabolic pathways, to effectively correct, counteract or circumvent the impaired or dysfunctional mechanisms accompanying different stages of prostate carcinogenesis.

Hu, L. and C. Chen (2024). "BMSCs-EVs Alleviate Pelvic Floor Dysfunction in Mice by Reducing Inflammation and Promoting Tissue Regeneration." In Vivo **38**(6): 2680-2687.

BACKGROUND/AIM: Pelvic floor dysfunctions (PFDs), which encompass pelvic organ prolapse (POP), stress urinary incontinence (SUI), and anal incontinence (AI), are common degenerative diseases in women. Bone marrow mesenchymal stem cells (BMSCs) hold promise for the treatment of PFDs. Extracellular vesicles (EVs) derived from BMSCs, have displayed an extensive role in intercellular communication and tissue repair. However, efficacy of the treatment using EVs originated from BMSCs on mouse models of PFD remains unknown. This study investigated the therapeutic potential of BMSC-derived EVs in a female PFD mouse model induced by vaginal distension (VD). MATERIALS AND METHODS/RESULTS: Flow cytometry analysis confirmed the positive expression of BMSC-related markers, and successful induction of multilineage differentiation further validated their characteristics. As expected, the EVs extracted from BMSCs exhibited typical cup-shaped and circular-shaped structures. In the PFD model, BMSC-derived EVs significantly reduced the levels of inflammatory cytokines ($p<0.05$), improved tissue repair, and mitigated neutrophil infiltration. Furthermore, EVs promoted cell proliferation, decreased expression of relaxin receptors, increased expression of elastin, and elevated collagen content in the anterior vaginal wall tissue ($p<0.05$), suggesting beneficial effects on tissue regeneration and connective tissue restoration in PFD. CONCLUSION: BMSC-derived EVs effectively reduce tissue inflammation, promote tissue regeneration and connective tissue reconstruction, and improve pelvic support deficiency, thereby alleviating PFD induced by vaginal distension (VD) in vivo.

Huang, L., et al. (2023). "The combination of early identification, chemotherapy, and autologous stem cell transplantation obtained favorable outcomes in unilateral primary adrenal lymphoma: A case report." Endocrine **79**(1): 49-54.

PURPOSE: Primary adrenal lymphoma (PAL) is an extremely rare entity, there were few cases have been reported. We report a 52-year-old female with unilateral PAL. METHODS: Case report. RESULTS: A rapid biopsy resulted in the diagnosis of diffuse large B-cell lymphoma after excluding pheochromocytoma. R-CHOP combined with CNS prophylaxis and autologous stem cell transplant (ASCT) has produced an excellent outcome. CONCLUSIONS: Primary adrenal lymphoma (PAL) is a sporadic and highly invasive malignant disease. Symptoms are atypical, making it difficult to obtain an accurate early diagnosis. Adrenal incidentaloma is usually the first clinical manifestation. Some patients may have fever, night sweats, weight loss, and lumbar and abdominal pain. Adrenal insufficiency (AI) may occur in a subset of patients. The identification of other adrenal malignancies, especially catecholamine-secreting tumors, is particularly important for early diagnosis.

Illiaquer, M., et al. (2017). "Impact of stem cell graft on early viral infections and immune reconstitution after allogeneic transplantation in adults." J Clin Virol **93**: 30-36.

BACKGROUND: Viral infections are well-known complications after allogeneic stem cell transplant (allo-SCT). OBJECTIVES: We compared prospectively incidences of DNAemia and active infections (AI) for five opportunistic viruses (Human Herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), BK polyomavirus (BKPyV), Cytomegalovirus (CMV) and Adenovirus (ADV)) and kinetics of immune reconstitution (IR) in adults receiving either double umbilical cord blood (dUCB group) or unrelated peripheral blood stem cell (uPBSC group) allo-SCT after a reduced-intensity conditioning (RIC) regimen. STUDY DESIGN: Whole blood samples were collected at transplant, every 15days during the first 3 months and at 4, 5 and 6 months post-transplant. RESULTS: Sixty-five patients were enrolled (uPBSC n=34; dUCB n=31). Incidences of HHV-6 and BKPyV DNAemia were significantly higher for dUCB (97% vs 23.5% and 58% vs 32%, respectively)

while EBV DNAemia was more frequently detected in uPBSC (71% vs 26%). The incidence of CMV DNAemia was similar between both groups. ADV AI developed only in dUCB. HHV-6 AI were also higher in dUCB (84% vs 21%). In multivariate analysis, dUCB graft was the only independent factor associated with HHV-6 DNAemia (OR: 19.0; 95%CI: 5.2-69.1; p<0.0001) while EBV DNAemia were significantly associated with uPBSC (OR: 29.9; 95%CI: 5.68-158; p <0.0001). dUCB graft was also the only factor associated with HHV-6 AI. Finally, higher counts and faster recoveries of B lymphocytes (p<0.0001) and monocytes (p=0.0007) were observed in the dUCB group. CONCLUSION: We demonstrate a strong correlation between sources of graft and patterns of viral DNAemia and AI and IR after RIC allo-SCT.

Imboden, S., et al. (2021). "Investigating heterogeneities of live mesenchymal stromal cells using AI-based label-free imaging." Sci Rep **11**(1): 6728.

Mesenchymal stromal cells (MSCs) are multipotent cells that have great potential for regenerative medicine, tissue repair, and immunotherapy. Unfortunately, the outcomes of MSC-based research and therapies can be highly inconsistent and difficult to reproduce, largely due to the inherently significant heterogeneity in MSCs, which has not been well investigated. To quantify cell heterogeneity, a standard approach is to measure marker expression on the protein level via immunochemistry assays. Performing such measurements non-invasively and at scale has remained challenging as conventional methods such as flow cytometry and immunofluorescence microscopy typically require cell fixation and laborious sample preparation. Here, we developed an artificial intelligence (AI)-based method that converts transmitted light microscopy images of MSCs into quantitative measurements of protein expression levels. By training a U-Net+ conditional generative adversarial network (cGAN) model that accurately (mean [Formula: see text] = 0.77) predicts expression of 8 MSC-specific markers, we showed that expression of surface markers provides a heterogeneity characterization that is complementary to conventional cell-level morphological analyses. Using this label-free imaging method, we also observed a multi-marker temporal-spatial fluctuation of protein distributions in live MSCs. These demonstrations suggest that our AI-based microscopy can be utilized to perform quantitative, non-invasive, single-cell, and multi-marker characterizations of heterogeneous live MSC culture. Our method provides a foundational step toward the instant integrative assessment of MSC properties, which is critical for high-throughput screening and quality control in cellular therapies.

Inaba, Y., et al. (1998). "The apoptotic changes of testicular germ cells in the obstructive azoospermia models of prepubertal and adult rats." J Urol **160**(2): 540-544.

PURPOSE: It has been suggested that prepubertal obstruction of the seminal tract may result in irreversible damage to spermatogenesis. We examined whether accelerated apoptosis in prepubertal obstruction has a deleterious effect on spermatogenesis in adulthood. MATERIALS AND METHODS: We studied apoptotic changes of both prepubertal and adult obstructive azoospermia rat models by means of an in situ end-labeling technique and electron microscopy, and by examination of the pathological changes. Four groups were designed as follows. Group 1: bilateral vasectomies performed at ten days of age (prepubertal vasectomy model); Group 2: sham operation performed at ten days of age; Group 3: bilateral vasectomies performed at eight weeks of age (adult vasectomy model); Group 4: sham operation performed at eight weeks of age. Three rats in each group were killed weekly, and the testes and epididymides removed and weighed. Germ cell apoptosis was detected by in situ end-labeling, and the apoptotic index (AI) was calculated by dividing the number of in situ labeled cells by the total number of seminiferous tubules. The developmental change of testis and epididymis, the diameter of seminiferous tubules, and the number of spermatogonia were also examined. Histopathological examination of tubular diameter and the number of spermatogonia and Sertoli cells was done by PAS staining. The number of spermatogonia divided by the number of Sertoli cells per tubular cross section was expressed as spermatogonia-Sertoli cell ratio (S-S ratio). RESULTS: At 3 and 4 weeks of age, rats of group 1 demonstrated a significantly higher apoptotic index of germ cells than did the sham-operated rats of group 2 (p <0.05). No significant differences were seen between groups 3 and 4. The increased apoptosis in group 1 seemed to be reduced by the formation of epididymal granulomas. The tubular diameter of group 1 at 16 weeks of age was significantly smaller than that of groups 2, 3, or 4. The S-S ratios were lower at stages IV, V and VI in group 1 at 16 weeks-of-age following vasectomy at 10 days of age compared with that in group 2. CONCLUSIONS: We conclude that an increase of apoptotic degeneration of germ cells in the prepubertal period may cause irreversible changes in germinal stem cells, resulting in

hypospermatogenesis in adulthood.

Issa, J., et al. (2022). "Artificial-Intelligence-Based Imaging Analysis of Stem Cells: A Systematic Scoping Review." Biology (Basel) **11**(10).

This systematic scoping review aims to map and identify the available artificial-intelligence-based techniques for imaging analysis, the characterization of stem cell differentiation, and trans-differentiation pathways. On the ninth of March 2022, data were collected from five electronic databases (PubMed, Medline, Web of Science, Cochrane, and Scopus) and manual citation searching; all data were gathered in Zotero 5.0. A total of 4422 articles were collected after deduplication; only twenty-seven studies were included in this systematic scoping review after a two-phase screening against inclusion criteria by two independent reviewers. The amount of research in this field is significantly increasing over the years. While the current state of artificial intelligence (AI) can tackle a multitude of medical problems, the consensus amongst researchers remains that AI still falls short in multiple ways that investigators should examine, ranging from the quality of images used in training sets and appropriate sample size, as well as the unexpected events that may occur which the algorithm cannot predict.

Jayawickrama, S. M., et al. (2024). "Developments and future prospects of personalized medicine in head and neck squamous cell carcinoma diagnoses and treatments." Cancer Rep (Hoboken) **7**(3): e2045.

BACKGROUND: Precision healthcare has entered a new era because of the developments in personalized medicine, especially in the diagnosis and treatment of head and neck squamous cell carcinoma (HNSCC). This paper explores the dynamic landscape of personalized medicine as applied to HNSCC, encompassing both current developments and future prospects. RECENT FINDINGS: The integration of personalized medicine strategies into HNSCC diagnosis is driven by the utilization of genetic data and biomarkers. Epigenetic biomarkers, which reflect modifications to DNA that can influence gene expression, have emerged as valuable indicators for early detection and risk assessment. Treatment approaches within the personalized medicine framework are equally promising. Immunotherapy, gene silencing, and editing techniques, including RNA interference and CRISPR/Cas9, offer innovative means to modulate gene expression and correct genetic aberrations driving HNSCC. The integration of stem cell research with personalized medicine presents opportunities for tailored regenerative approaches. The synergy between personalized medicine and technological advancements is exemplified by artificial intelligence (AI) and machine learning (ML) applications. These tools empower clinicians to analyze vast datasets, predict patient responses, and optimize treatment strategies with unprecedented accuracy. CONCLUSION: The developments and prospects of personalized medicine in HNSCC diagnosis and treatment offer a transformative approach to managing this complex malignancy. By harnessing genetic insights, biomarkers, immunotherapy, gene editing, stem cell therapies, and advanced technologies like AI and ML, personalized medicine holds the key to enhancing patient outcomes and ushering in a new era of precision oncology.

Jiang, Z., et al. (2008). "Local effects of retrovirally transduced endostatin-expressing human umbilical cord blood CD34+ cells on transplanted malignancy in a mouse model of hepatic cancer." Cell Transplant **17**(8): 969-975.

Antiangiogenesis has been exploited as an effective approach to inhibit the growth of solid tumors. This technique has been evaluated using various vectors in several xenograft animal models to demonstrate the efficacy of endostatin gene therapy against cancer growth. However, previous studies have not examined the use of cord blood CD34+ cells as endostatin-producing cells for gene therapy against hepatoma. This exploratory study was done to investigate the local effects of CD34+ cells transduced with the endostatin gene on a mouse xenograft tumor model. The human endostatin gene was transferred into CD34+ cells using the recombinant retrovirus plasmid, pLncx/endo. Expression was verified by RT-PCR and Western blot analyses, confirming the stable expression and secretion of endostatin from the transferred CD34+ cells. The proliferation of vascular endothelial cells was evaluated by MTT assay and found to decrease by about 59.9% when treated with the supernatant of cultured transfected CD34+ cells in vitro. These genetically modified cord blood CD34+ cells were implanted intratumorally and tumor regression was evaluated after 2 weeks. The average size of a xenograft tumor in the CD34+/endo group was reduced 31.39% compared to that in the untreated mice or those transplanted with CD34+ cells transduced with a control vector. The microvascular density of the tumor decreased 62.45% in the treated group. The expression of proliferation cell nuclear antigen (PCNA) also decreased significantly in the treated group. Moreover, the apoptotic index (AI) of tumors, as evaluated by TUNEL staining, was significantly enhanced in the treatment group. Our findings indicate that angiogenesis of the xenograft tumor in mice may be inhibited by local

administration of genetically modified CD34+ cells expressing the endostatin gene. This novel approach may lead to a new direction of cell-based gene therapy for malignancy.

Kale, G., et al. (2024). "A snapshot on introspection of autism spectrum disorder." Mol Biol Rep **51**(1): 610.

Autism spectrum disorder is a neurodevelopmental condition marked by restricted interests and difficulty with social communication. ASD is characterized by heightened neuroinflammation and irregular neuronal connections. ASD is more frequent in male than female with male-female ratio of around 4:1. ASD affects 2.8% or 1 in 36 8-year-olds, based on the CDC's Morbidity and Mortality Weekly Report. Various factors like Environmental, Genetic, Epigenetic and Developmental factors are linked with genesis of ASD. Repetitive behaviors, Impaired communication skills, difficulty with social interaction are some of the clinical features of ASD. Current Pharmacotherapy of ASD limits to management of symptoms only, not cure. The stem cell therapy has a promising potential to be a breakthrough in treating ASD. Various types of stem cells have been successfully tested in children with ASD. AI has a potential to emerge as a tool for early detection of ASD. Robotics can assist the children with ASD to overcome the challenges associated with ASD.

Kameda, H., et al. (2024). "Deep Learning of Cancer Stem Cell Morphology." Methods Mol Biol **2777**: 231-256.

Knowledge regarding cancer stem cell (CSC) morphology is limited, and more extensive studies are therefore required. Image recognition technologies using artificial intelligence (AI) require no previous expertise in image annotation. Herein, we describe the construction of AI models that recognize the CSC morphology in cultures and tumor tissues. The visualization of the AI deep learning process enables insight to be obtained regarding unrecognized structures in an image.

Kanda, G. N., et al. (2022). "Robotic search for optimal cell culture in regenerative medicine." Elife **11**.

Induced differentiation is one of the most experience- and skill-dependent experimental processes in regenerative medicine, and establishing optimal conditions often takes years. We developed a robotic AI system with a batch Bayesian optimization algorithm that autonomously induces the differentiation of induced pluripotent stem cell-derived retinal pigment epithelial (iPSC-RPE) cells. From 200 million possible parameter combinations, the system performed cell culture in 143 different conditions in 111 days, resulting in 88% better iPSC-RPE production than that obtained by the pre-optimized culture in terms of the pigmentation scores. Our work demonstrates that the use of autonomous robotic AI systems drastically accelerates systematic and unbiased exploration of experimental search space, suggesting immense use in medicine and research.

Kandula, A. K. R., et al. (2024). "Generative AI for Cell Type-Specific Fluorescence Image Generation of hPSC-derived Cardiac Organoid." bioRxiv.

Human pluripotent stem cell (hPSC)-derived cardiac organoid is the most recent three-dimensional tissue structure that mimics the structure and functionality of the human heart and plays a pivotal role in modeling heart development and disease. The hPSC-derived cardiac organoids are commonly characterized by bright-field microscopic imaging for tracking daily organoid differentiation and morphology formation. Although the brightfield microscope provides essential information about hPSC-derived cardiac organoids, such as morphology, size, and general structure, it does not extend our understanding of cardiac organoids on cell type-specific distribution and structure. Then, fluorescence microscopic imaging is required to identify the specific cardiovascular cell types in the hPSC-derived cardiac organoids by fluorescence immunostaining fixed organoid samples or fluorescence reporter imaging of live organoids. Both approaches require extra steps of experiments and techniques and do not provide general information on hPSC-derived cardiac organoids from different batches of differentiation and characterization, which limits the biomedical applications of hPSC-derived cardiac organoids. This research addresses this limitation by proposing a comprehensive workflow for colorizing phase contrast images of cardiac organoids from brightfield microscopic imaging using conditional Generative Adversarial Networks (GANs) to provide cardiovascular cell type-specific information in hPSC-derived cardiac organoids. By infusing these phase contrast images with accurate fluorescence colorization, our approach aims to unlock the hidden wealth of cell type, structure, and further quantifications of fluorescence intensity and area, for better characterizing hPSC-derived cardiac organoids.

Kashiyama, N., et al. (2019). "MHC-mismatched Allotransplantation of Induced Pluripotent Stem Cell-derived Cardiomyocyte Sheets to Improve Cardiac

Function in a Primate Ischemic Cardiomyopathy Model." Transplantation **103**(8): 1582-1590.

BACKGROUND: Although allogeneic-induced pluripotent stem cell (iPSC)-derived cardiomyocytes (CMs) exhibit potential in cardiomyogenesis for heart failure, whether major histocompatibility complex (MHC)-matched allogenic iPSC implantation (MMAI) minimizes immune rejection for cell survival or functional recovery remains unknown. We herein explored whether MMAI with an iPSC-CM sheet is stable for a longer period and therapeutically more effective than MHC-mismatched AI in a primate ischemic cardiomyopathy model. METHODS: Green fluorescent protein-transfected iPSC-CM sheets, derived from cynomolgus macaques with homozygous MHC haplotypes "HT1," were transplanted on the left ventricle, generated by ligating the left anterior descending artery for 2 weeks in an ischemic model with or without heterozygous HT1 as MMAI and MHC-mismatched AI. Sham models were made by opening the chest at 14 days after left anterior descending ligation without any treatment. RESULTS: Stereomicroscopy revealed that at 4 months after transplantation, green fluorescent protein intensity was higher in the MMAI group than in the MHC-mismatched AI group and the sham group. Immunohistochemistry staining revealed that host immune reaction with CD3-positive cells was stronger in MHC-mismatched AI than in MMAI at 3 months. Cardiac function improved both in MMAI and MHC-mismatched AI at 1 month after transplantation and was preserved until 6 months, whereas in the sham group, functional deterioration progressed over time. CONCLUSIONS: Although MHC-homo-iPSCs are preferred to avoid immune rejection, MHC-mismatched iPSC-CMs can also induce comparable cardiac functional recovery at late follow-up, suggesting that MHC-mismatched iPSC-based cardiac regenerative therapy with immunosuppressants is a feasible option for treating heart failure in clinical settings.

Kazi, A. A., et al. (2014). "Nonhypoxic regulation and role of hypoxia-inducible factor 1 in aromatase inhibitor resistant breast cancer." Breast Cancer Res **16**(1): R15.

INTRODUCTION: Although aromatase inhibitors (AIs; for example, letrozole) are highly effective in treating estrogen receptor positive (ER+) breast cancer, a significant percentage of patients either do not respond to AIs or become resistant to them. Previous studies suggest that acquired resistance to AIs involves a switch from dependence on ER signaling to dependence on growth factor-mediated pathways, such as human epidermal growth factor receptor-2 (HER2). However, the role of HER2, and the identity of other relevant factors that may be used as biomarkers or therapeutic targets remain unknown. This study investigated the potential role of transcription factor hypoxia inducible factor 1 (HIF-1) in acquired AI resistance, and its regulation by HER2. METHODS: In vitro studies using AI (letrozole or exemestane)-resistant and AI-sensitive cells were conducted to investigate the regulation and role of HIF-1 in AI resistance. Western blot and RT-PCR analyses were conducted to compare protein and mRNA expression, respectively, of ERalpha, HER2, and HIF-1alpha (inducible HIF-1 subunit) in AI-resistant versus AI-sensitive cells. Similar expression analyses were also done, along with chromatin immunoprecipitation (ChIP), to identify previously known HIF-1 target genes, such as breast cancer resistance protein (BCRP), that may also play a role in AI resistance. Letrozole-resistant cells were treated with inhibitors to HER2, kinase pathways, and ERalpha to elucidate the regulation of HIF-1 and BCRP. Lastly, cells were treated with inhibitors or inducers of HIF-1alpha to determine its importance. RESULTS: Basal HIF-1alpha protein and BCRP mRNA and protein are higher in AI-resistant and HER2-transfected cells than in AI-sensitive, HER2-parental cells under nonhypoxic conditions. HIF-1alpha expression in AI-resistant cells is likely regulated by HER2 activated-phosphatidylinositide-3-kinase/Akt-protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, as its expression was inhibited by HER2 inhibitors and kinase pathway inhibitors. Inhibition or upregulation of HIF-1alpha affects breast cancer cell expression of BCRP; AI responsiveness; and expression of cancer stem cell characteristics, partially through BCRP. CONCLUSIONS: One of the mechanisms of AI resistance may be through regulation of nonhypoxic HIF-1 target genes, such as BCRP, implicated in chemoresistance. Thus, HIF-1 should be explored further for its potential as a biomarker of and therapeutic target.

Khan, M. A. Z. and J. C. Konje (2019). "Ethical and religious dilemmas of modern reproductive choices and the Islamic perspective." Eur J Obstet Gynecol Reprod Biol **232**: 5-9.

Advances in the field of Assisted Reproductive Technologies (ART) are constantly evolving, starting from Artificial Insemination (AI) and in-vitro fertilization (IVF), to the current state of the art technologies that enable embryo biopsy for Pre-implantation Genetic Testing (PGT). The future includes gene mapping and DNA replacement technologies with the potential for the so-called "designer babies." In other words, shortly, a modern

couple may be in a position to decide how to procreate and with whom; which pregnancy to keep and which one to terminate depending on their prior knowledge about the pregnancy and the available choices. This article addresses the moral, ethical, legal and religious dilemmas as a result of these technological advances in the field of ART and how these new challenges are addressed theologically in the Islamic world where the state law is strongly influenced by religion. This article sets out to discuss relevant issues and dilemmas but does not seek to prioritize or promote any opinion or view over any other religion/sect, ethical or legal opinion or view.

Khatri, M., et al. (2010). "Isolation and characterization of chicken lung mesenchymal stromal cells and their susceptibility to avian influenza virus." Dev Comp Immunol **34**(4): 474-479.

In this study, we isolated and characterized mesenchymal stromal cells (MSCs) from the lungs of 1- to 2-week-old chickens. Microscopically, the cultured cells showed fibroblast-like morphology. Phenotypically these cells expressed CD44, CD90, CD105 and the transcription factor PouV, which has been shown to be critical for stem cell self-renewal and pluripotency. The multipotency of chicken MSCs was demonstrated by their ability to undergo adipogenic and osteogenic differentiation. Like chicken bone marrow MSCs and mammalian MSCs, chicken lung MSCs had immunoregulatory activity and profoundly suppressed the proliferative capacity of T cells in response to a mitogenic stimulus. Next, we examined the susceptibility of these cells to H1N1 and H9N5 avian influenza (AI) viruses. The lung MSCs were shown to express known influenza virus alpha-2,3 and alpha-2,6 sialic acid receptors and to support replication of both the avian H1N1 and avian H9N5 influenza strains. Viral infection of MSCs resulted in cell lysis and cytokine and chemokine production. Further characterization of lung MSCs in chicken and other mammalian species may help in understanding the pathogenesis of infectious and non-infectious lung diseases and the mechanisms of lung injury repair.

Kidder, B. L., et al. (2024). "Novel high throughput screen reports that benzo(a)pyrene overrides mouse trophoblast stem cell multipotency, inducing SAPK activity, HAND1 and differentiated trophoblast giant cells." Placenta **152**: 72-85.

INTRODUCTION: Cultured mouse trophoblast stem cells (mTSC) maintain proliferation/normal stemness (NS) under FGF4, which when removed, causes normal differentiation (ND). Hypoxic, or hyperosmotic stress forces trophoblast giant cells (TGC) differentiate. Hypoxic, hyperosmotic, and genotoxic benzo(a)pyrene (BaP), which is found in tobacco smoke, force down-regulation of inhibitor of differentiation (Id)2, enabling TGC differentiation. Hypoxic and hyperosmotic stress induce TGC by SAPK-dependent HAND1 increase. Here we test whether BaP forces mTSC-to-TGC while inducing SAPK and HAND1. METHODS: Hand1 and SAPK activity were assayed by immunoblot, mTSC-to-TGC growth and differentiation were assayed at Tfinal after 72hr exposure of BaP, NS, ND, Retinoic acid (RA), or sorbitol. Nuclear-stained cells were micrographed automatically by a live imager, and assayed by ImageJ/FIJI, Biotek Gen 5, AIVIA proprietary artificial intelligence (AI) software or open source, CellPose artificial intelligence/AI software. RESULTS: BaP (0.05-1muM) activated SAPK and HAND1 without diminishing growth. TSC-to-TGC differentiation was assayed with increasingly accuracy for 2-4 N cycling nuclei and >4 N differentiating TGC nuclei, using ImageJ/FIJI, Gen 5, AIVIA, or CellPose AI software. The AIVIA and Cellpose AI software matches human accuracy. The lowest BaP effects on SAPK activation/HAND1 increase are >10-fold more sensitive than similar effects for mESC. RA induces 44-47% 1st lineage TGC differentiation, but the same RA dose induces only 1% 1st lineage mESC differentiation. DISCUSSION: First, these pilot data suggest that mTSC can be used in high throughput screens (HTS) to predict toxicant exposures that force TGC differentiation. Second, mTSC differentiated more cells than mESC for similar stress exposures, Third, open source AI can replace human micrograph quantitation and enable a miscarriage-predicting HTS.

Kim, H., et al. (2022). "Predicting multipotency of human adult stem cells derived from various donors through deep learning." Sci Rep **12**(1): 21614.

Adult stem cell-based therapeutic approaches have great potential in regenerative medicine because of their immunoregulatory properties and multidifferentiation capacity. Nevertheless, the outcomes of stem cell-based therapies to date have shown inconsistent efficacy owing to donor variation, thwarting the expectation of clinical effects. However, such donor dependency has been elucidated by biological consequences that current research could not predict. Here, we introduce cellular morphology-based prediction to determine the multipotency rate of human nasal turbinate stem cells (hNTSCs), aiming to predict the differentiation rate of keratocyte progenitors. We characterized the overall genes and morphologies of hNTSCs from five donors and compared stemness-related properties, including multipotency and specific lineages, using

mRNA sequencing. It was demonstrated that transformation factors affecting the principal components were highly related to cell morphology. We then performed a convolutional neural network-based analysis, which enabled us to assess the multipotency level of each cell group based on their morphologies with 85.98% accuracy. Surprisingly, the trend in expression levels after ex vivo differentiation matched well with the deep learning prediction. These results suggest that AI-assisted cellular behavioral prediction can be utilized to perform quantitative, non-invasive, single-cell, and multimarker characterizations of live stem cells for improved quality control in clinical cell therapies.

Kim, M., et al. (2023). "Differentiation of Adipose-Derived Stem Cells into Smooth Muscle Cells in an Internal Anal Sphincter-Targeting Anal Incontinence Rat Model." J Clin Med **12**(4).

OBJECTIVE: Studies on development of an anal incontinence (AI) model targeting smooth muscle cells (SMCs) of the internal anal sphincter (IAS) have not been reported. The differentiation of implanted human adipose-derived stem cells (hADScs) into SMCs in an IAS-targeting AI model has also not been demonstrated. We aimed to develop an IAS-targeting AI animal model and to determine the differentiation of hADScs into SMCs in an established model. MATERIALS AND METHODS: The IAS-targeting AI model was developed by inducing cryoinjury at the inner side of the muscular layer via posterior intersphincteric dissection in Sprague-Dawley rats. Dil-stained hADScs were implanted at the IAS injury site. Multiple markers for SMCs were used to confirm molecular changes before and after cell implantation. Analyses were performed using H&E, immunofluorescence, Masson's trichrome staining, and quantitative RT-PCR. RESULTS: Impaired smooth muscle layers accompanying other intact layers were identified in the cryoinjury group. Specific SMC markers, including SM22alpha, calponin, caldesmon, SMMHC, smoothelin, and SDF-1 were significantly decreased in the cryoinjured group compared with levels in the control group. However, CoL1A1 was increased significantly in the cryoinjured group. In the hADSc-treated group, higher levels of SMMHC, smoothelin, SM22alpha, and alpha-SMA were observed at two weeks after implantation than at one week after implantation. Cell tracking revealed that Dil-stained cells were located at the site of augmented SMCs. CONCLUSIONS: This study first demonstrated that implanted hADSc restored impaired SMCs at the injury site, showing stem cell fate corresponding to the established IAS-specific AI model.

Kimura, H. (1998). "[Usefulness of micronucleus assay in radiosensitivity tests using human cancer cell lines]." Nihon Hinyokika Gakkai Zasshi **89**(8): 712-720.

BACKGROUND: Recently, micronucleus assay is expected to be one of the radiosensitivity tests. The usefulness of micronucleus assay was compared with MTT assay and clonogenic assay using 5 human derived urological cancer cell lines, NBT-2, T24, PC3, OS-RC-2, and RERF-LC-AI in vitro. The correlation between the results in vitro assay and the radiation effects of nude mouse in vivo was investigated. METHODS: In vitro, the micronucleus frequency of 2 Gy radiation was scored in micronucleus assay. The survival fraction of 2 Gy radiation was obtained in MTT assay and clonogenic assay. The correlation between 3 assays was investigated. In vivo, cancer cells was inoculated to nude mouse and the tumor volume was measured at 3-7 days interval in control group and 10 Gy irradiated group. The tumor volume ratio in irradiated group to control group was calculated as a radiation effect in each cell lines, the correlation between this ratio in vivo and each value of 2 Gy radiation in vitro was studied. RESULTS: The correlation between micronucleus frequency and survival fraction in clonogenic assay was statistically significant ($r = 0.941$, $p = 0.0169$). But the correlation of the survival fraction between MTT assay and clonogenic assay is not statistically significant. The correlation between micronucleus frequency and the tumor volume ratio in vivo was statistically significant ($r = 0.990$, $p = 0.0011$). The correlation between survival fraction in clonogenic assay and the tumor volume ratio in vivo was also statistically significant ($r = 0.914$, $p = 0.0298$). However, the correlation between survival fraction in MTT assay and the tumor volume ratio in vivo was not statistically significant ($r = 0.782$, $p = 0.118$). CONCLUSION: In this 5 cell lines, micronucleus assay was most correlated to nude mouse radiation effect. This result suggested the possibility of micronucleus assay to be a better predictive method than clonogenic assay for radiosensitivity test.

Koenuma, M., et al. (1995). "Pharmacokinetic correlation between experimental and clinical effects on human non-small cell lung cancers of cis-diammineglycolatoplatinum (254-S) and cis-diamminedichloroplatinum." Anticancer Res **15**(2): 417-421.

We attempted to correlate the in vitro and in vivo antitumor activities of cis-diammineglycolatoplatinum (254-S), a novel platinum complex, and cis-diamminedichloro-platinum (CDDP) against the established culture cell

lines and xenografts of human non-small cell lung cancer (NSCLC) with their clinical effects, based on the previous finding that the cytotoxicity of CDDP depends on the area under the curve (AUC). The concentration of 254-S and CDDP inhibiting the in vitro growth of 4 cultured NSCLC lines by 50% (IC50) was 0.82-7.8 and 0.53-4.2 micrograms/ml, respectively, showing a similar level. Of the 4 cell lines, only the most sensitive line, RERF-LC-AI, showed an IC50 close to a specific concentration (0.50 for 254-S and 0.32 micrograms/ml for CDDP) that reproduces in vitro the clinical AUCfree (24.8 and 5.34 micrograms-hr/ml) of the respective drugs. We treated 6 lines of human NSCLC xenografts implanted in nude mice with 254-S and CDDP at a particular dose (13.2 and 3.7 mg/kg) that is equivalent to the clinical doses with respect to the plasma AUCfree. 254-S and CDDP exhibited significant antitumor effects on 2 and 1 of the 6 lines, respectively. These in vitro and in vivo findings were considered to be relatively well correlated with the reported clinical response rates of 15-19% for 254-S and 14-15% for CDDP.

Komatani, T. S. (2017). "Upcoming challenges in intellectual property presented by emerging pharmaceutical technologies." Pharm Pat Anal **6**(1): 1-4.

Komsa-Penkova, R., et al. (2022). "Morphological and Quantitative Evidence for Altered Mesenchymal Stem Cell Remodeling of Collagen in an Oxidative Environment-Peculiar Effect of Epigallocatechin-3-Gallate." Polymers (Basel) **14**(19).

Mesenchymal stem cells (MSCs) are involved in the process of extracellular matrix (ECM) remodeling where collagens play a pivotal role. We recently demonstrated that the remodeling of adsorbed collagen type I might be disordered upon oxidation following its fate in the presence of human adipose-derived MSC (ADMSCs). With the present study we intended to learn more about the effect of polyphenolic antioxidant Epigallocatechin-3-gallate (EGCG), attempting to mimic the conditions of oxidative stress in vivo and its putative prevention by antioxidants. Collagen Type I was isolated from mouse tail tendon (MTC) and labelled with FITC before being oxidized according to Fe(2+)/H(2)O(2) protocol. FITC-collagen remodeling by ADMSC was assessed morphologically before and after EGCG pretreatment and confirmed via detailed morphometric analysis measuring the anisotropy index (AI) and fluorescence intensity (FI) in selected regions of interest (ROI), namely: outside the cells, over the cells, and central (nuclear/perinuclear) region, whereas the pericellular proteolytic activity was measured by de-quenching fluorescent collagen probes (FRET effect). Here we provide morphological evidence that MTC undergoes significant reorganization by the adhering ADMSC and is accompanied by a substantial activation of pericellular proteolysis, and further confirm that both processes are suppressed upon collagen oxidation. An important observation was that this abrogated remodeling cannot be prevented by the EGCG pretreatment. Conversely, the detailed morphometric analysis showed that oxidized FITC-collagen tends to accumulate beneath cells and around cell nuclei, suggesting the activation of alternative routes for its removal, such as internalization and/or transcytosis. Morphometric analysis also revealed that both processes are supported by EGCG pretreatment.

Kowalczewski, A., et al. (2024). "Design optimization of geometrically confined cardiac organoids enabled by machine learning techniques." Cell Rep Methods **4**(6): 100798.

Stem cell organoids are powerful models for studying organ development, disease modeling, drug screening, and regenerative medicine applications. The convergence of organoid technology, tissue engineering, and artificial intelligence (AI) could potentially enhance our understanding of the design principles for organoid engineering. In this study, we utilized micropatterning techniques to create a designer library of 230 cardiac organoids with 7 geometric designs. We employed manifold learning techniques to analyze single organoid heterogeneity based on 10 physiological parameters. We clustered and refined the cardiac organoids based on their functional similarity using unsupervised machine learning approaches, thus elucidating unique functionalities associated with geometric designs. We also highlighted the critical role of calcium transient rising time in distinguishing organoids based on geometric patterns and clustering results. This integration of organoid engineering and machine learning enhances our understanding of structure-function relationships in cardiac organoids, paving the way for more controlled and optimized organoid design.

Krater, M., et al. (2021). "AIDeveloper: Deep Learning Image Classification in Life Science and Beyond." Adv Sci (Weinh) **8**(11): e2003743.

Artificial intelligence (AI)-based image analysis has increased drastically in recent years. However, all applications use individual solutions, highly specialized for a particular task. Here, an easy-to-use, adaptable, and open source software, called AIDeveloper (AID) to train neural nets (NN) for image classification without the need for

programming is presented. AID provides a variety of NN-architectures, allowing to apply trained models on new data, obtain performance metrics, and export final models to different formats. AID is benchmarked on large image datasets (CIFAR-10 and Fashion-MNIST). Furthermore, models are trained to distinguish areas of differentiated stem cells in images of cell culture. A conventional blood cell count and a blood count obtained using an NN are compared, trained on >1.2 million images, and demonstrated how AID can be used for label-free classification of B- and T-cells. All models are generated by non-programmers on generic computers, allowing for an interdisciplinary use.

Kubasova, N., et al. (2022). "In Vivo Clonal Analysis Reveals Random Monoallelic Expression in Lymphocytes That Traces Back to Hematopoietic Stem Cells." Front Cell Dev Biol **10**: 827774.

Evaluating the epigenetic landscape in the stem cell compartment at the single-cell level is essential to assess the cells' heterogeneity and predict their fate. Here, using a genome-wide transcriptomics approach in vivo, we evaluated the allelic expression imbalance in the progeny of single hematopoietic cells (HSCs) as a read-out of epigenetic marking. After 4 months of extensive proliferation and differentiation, we found that X-chromosome inactivation (XCI) is tightly maintained in all single-HSC derived hematopoietic cells. In contrast, the vast majority of the autosomal genes did not show clonal patterns of random monoallelic expression (RME). However, a persistent allele-specific autosomal transcription in HSCs and their progeny was found in a rare number of cases, none of which has been previously reported. These data show that: 1) XCI and RME in the autosomal chromosomes are driven by different mechanisms; 2) the previously reported high frequency of genes under RME in clones expanded in vitro (up to 15%) is not found in clones undergoing multiple differentiation steps in vivo; 3) prior to differentiation, HSCs have stable patterns of autosomal RME. We propose that most RME patterns in autosomal chromosomes are erased and established de novo during cell lineage differentiation.

Kumar, R. and W. S. Wassif (2022). "Adrenal insufficiency." J Clin Pathol **75**(7): 435-442.

Adrenal insufficiency (AI), first described by Thomas Addison in 1855, is characterised by inadequate hormonal production by the adrenal gland, which could either be primary, due to destruction of the adrenal cortex, or secondary/tertiary, due to lack of adrenocorticotropic hormone or its stimulation by corticotropin-releasing hormone. This was an invariably fatal condition in Addison's days with most patients dying within a few years of diagnosis. However, discovery of cortisone in the 1940s not only improved the life expectancy of these patients but also had a dramatic effect on their overall quality of life. The diagnosis, easily confirmed by demonstrating inappropriately low cortisol secretion, is often delayed by months, and many patients present with acute adrenal crisis. Sudden withdrawal from chronic glucocorticoid therapy is the most common cause of AI. Currently, there remains a wide variation in the management of this condition across Europe. As primary AI is a relatively rare condition, most medical specialists will only manage a handful of these patients in their career. Despite many advances in recent years, there is currently no curative option, and modern cortisol replacement regimens fail to adequately mimic physiological cortisol rhythm. A number of new approaches including allograft of adrenocortical tissue and stem cell therapy are being tried but remain largely experimental.

Kusumoto, D., et al. (2022). "Induced Pluripotent Stem Cell-Based Drug Screening by Use of Artificial Intelligence." Pharmaceuticals (Basel) **15**(5).

Induced pluripotent stem cells (iPSCs) are terminally differentiated somatic cells that differentiate into various cell types. iPSCs are expected to be used for disease modeling and for developing novel treatments because differentiated cells from iPSCs can recapitulate the cellular pathology of patients with genetic mutations. However, a barrier to using iPSCs for comprehensive drug screening is the difficulty of evaluating their pathophysiology. Recently, the accuracy of image analysis has dramatically improved with the development of artificial intelligence (AI) technology. In the field of cell biology, it has become possible to estimate cell types and states by examining cellular morphology obtained from simple microscopic images. AI can evaluate disease-specific phenotypes of iPS-derived cells from label-free microscopic images; thus, AI can be utilized for disease-specific drug screening using iPSCs. In addition to image analysis, various AI-based methods can be applied to drug development, including phenotype prediction by analyzing genomic data and virtual screening by analyzing structural formulas and protein-protein interactions of compounds. In the future, combining AI methods may rapidly accelerate drug discovery using iPSCs. In this review, we explain the details of AI technology and the application of AI for iPSC-based drug screening.

Laine, J., et al. (2018). "Development of the excitation-contraction coupling machinery and its

relation to myofibrillogenesis in human iPSC-derived skeletal myocytes." Skelet Muscle **8**(1): 1.

BACKGROUND: Human induced pluripotent stem cells-derived myogenic progenitors develop functional and ultrastructural features typical of skeletal muscle when differentiated in culture. Besides disease-modeling, such a system can be used to clarify basic aspects of human skeletal muscle development. In the present study, we focus on the development of the excitation-contraction (E-C) coupling, a process that is essential both in muscle physiology and as a tool to differentiate between the skeletal and cardiac muscle. The occurrence and maturation of E-C coupling structures (Sarcoplasmic Reticulum-Transverse Tubule (SR-TT) junctions), key molecular components, and Ca(2+) signaling were examined, along with myofibrillogenesis. METHODS: Pax7(+)-myogenic progenitors were differentiated in culture, and developmental changes were examined from a few days up to several weeks. Ion channels directly involved in the skeletal muscle E-C coupling (RyR1 and Cav1.1 voltage-gated Ca(2+) channels) were labeled using indirect immunofluorescence. Ultrastructural changes of differentiating cells were visualized by transmission electron microscopy. On the functional side, depolarization-induced intracellular Ca(2+) transients mediating E-C coupling were recorded using Fura-2 ratiometric Ca(2+) imaging, and myocyte contraction was captured by digital photomicrography. RESULTS: We show that the E-C coupling machinery occurs and operates within a few days post-differentiation, as soon as the myofilaments align. However, Ca(2+) transients become effective in triggering myocyte contraction after 1 week of differentiation, when nascent myofibrils show alternate A-I bands. At later stages, myofibrils become fully organized into adult-like sarcomeres but SR-TT junctions do not reach their triadic structure and typical A-I location. This is mirrored by the absence of cross-striated distribution pattern of both RyR1 and Cav1.1 channels. CONCLUSIONS: The E-C coupling machinery occurs and operates within the first week of muscle cells differentiation. However, while early development of SR-TT junctions is coordinated with that of nascent myofibrils, their respective maturation is not. Formation of typical triads requires other factors/conditions, and this should be taken into account when using in-vitro models to explore skeletal muscle diseases, especially those affecting E-C coupling.

Lalefar, N. R., et al. (2016). "Wnt3a nanodisks promote ex vivo expansion of hematopoietic stem and progenitor cells." J Nanobiotechnology **14**(1): 66.

BACKGROUND: Wnt proteins modulate development, stem cell fate and cancer through interactions with cell surface receptors. Wnts are cysteine-rich, glycosylated, lipid modified, two domain proteins that are prone to aggregation. The culprit responsible for this behavior is a covalently bound palmitoleoyl moiety in the N-terminal domain. RESULTS: By combining murine Wnt3a with phospholipid and apolipoprotein A-I, ternary complexes termed nanodisks (ND) were generated. ND-associated Wnt3a is soluble in the absence of detergent micelles and gel filtration chromatography revealed that Wnt3a co-elutes with ND. In signaling assays, Wnt3a ND induced beta-catenin stabilization in mouse fibroblasts as well as hematopoietic stem and progenitor cells (HSPC). Prolonged exposure of HSPC to Wnt3a ND stimulated proliferation and expansion of Lin(-) Sca-1(+) c-Kit(+) cells. Surprisingly, ND lacking Wnt3a contributed to Lin(-) Sca-1(+) c-Kit(+) cell expansion, an effect that was not mediated through beta-catenin. CONCLUSIONS: The data indicate Wnt3a ND constitute a water-soluble transport vehicle capable of promoting ex vivo expansion of HSPC.

Ledvina, A. R., et al. (2013). "Activated ion ETD performed in a modified collision cell on a hybrid QLT-Oribtrap mass spectrometer." J Am Soc Mass Spectrom **24**(11): 1623-1633.

We describe the implementation and characterization of activated ion electron transfer dissociation (AI-ETD) on a hybrid QLT-Orbitrap mass spectrometer. AI-ETD was performed using a collision cell that was modified to enable ETD reactions, in addition to normal collisional activation. The instrument manifold was modified to enable irradiation of ions along the axis of this modified cell with IR photons from a CO2 laser. Laser power settings were optimized for both charge (z) and mass to charge (m/z) and the instrument control firmware was updated to allow for automated adjustments to the level of irradiation. This implementation of AI-ETD yielded 1.6-fold more unique identifications than ETD in an nLC-MS/MS analysis of tryptic yeast peptides. Furthermore, we investigated the application of AI-ETD on large scale analysis of phosphopeptides, where laser power aids ETD, but can produce b- and y-type ions because of the phosphoryl moiety's high IR adsorption. nLC-MS/MS analysis of phosphopeptides derived from human embryonic stem cells using AI-ETD yielded 2.4-fold more unique identifications than ETD alone, demonstrating a promising advance in ETD sequencing of PTM containing peptides.

Lee, S. B., et al. (2024). "Efficient improvement of

the proliferation, differentiation, and anti-arthritic capacity of mesenchymal stem cells by simply culturing on the immobilized FGF2 derived peptide, 44-ERGVVSIKGV-53." J Adv Res **62**: 119-141.

INTRODUCTION: The stem cell microenvironment has been evidenced to robustly affect its biological functions and clinical grade. Natural or synthetic growth factors, especially, are essential for modulating stem cell proliferation, metabolism, and differentiation via the interaction with specific extracellular receptors. Fibroblast growth factor-2 (FGF-2) possesses pleiotropic functions in various tissues and organs. It interacts with the FGF receptor (FGFR) and activates FGFR signaling pathways, which involve numerous biological functions, such as angiogenesis, wound healing, cell proliferation, and differentiation. OBJECTIVES: Here, we aim to explore the molecular functions, mode of action, and therapeutic activity of yet undetermined function, FGF-2-derived peptide, FP2 (44-ERGVVSIKGV-53) in promoting the proliferation, differentiation, and therapeutic application of human Wharton's jelly mesenchymal stem cells (hWJ-MSCs) in comparison to other test peptides, canofin1 (FP1), hexafin2 (FP3), and canofin3 (FP4) with known functions. METHODS: The immobilization of test peptides that are fused with mussel adhesive proteins (MAP) on the culture plate was carried out via EDC/NHS chemistry. Cell Proliferation assay, colony-forming unit, western blotting analysis, gene expression analysis, RNA-Seq. analysis, osteogenic, and chondrogenic differentiation capacity were applied to test the activity of the test peptides. We additionally utilized three-dimensional (3D) structural analysis and artificial intelligence (AI)-based AlphaFold2 and CABS-dock programs for receptor interaction prediction of the peptide receptor. We also verified the in vivo therapeutic capacity of FP2-cultured hWJ-MSCs using an osteoarthritis mice model. RESULTS: Culture of hWJ-MSC onto an FP2-immobilized culture plate showed a significant increase in cell proliferation ($n = 3$; $*p < 0.05$, $**p < 0.01$) and the colony-forming unit ($n = 3$; $*p < 0.05$, $**p < 0.01$) compared with the test peptides. FP2 showed a significantly upregulated phosphorylation of FRS2alpha and FGFR1 and activated the AKT and ERK signaling pathways ($n = 3$; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$). Interestingly, we detected efficient FP2 receptor binding that was predicted using AI-based tools. Treatment with an AKT inhibitor significantly abrogated the FP2-mediated enhancement of cell differentiation ($n = 3$; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$). Intra-articular injection of FP2-cultured MSCs significantly mitigated arthritis symptoms in an osteoarthritis mouse model, as shown through the functional tests ($n = 10$; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$), modulation of the expression level of the pro-inflammatory and anti-inflammatory genes, and improved osteochondral regeneration as demonstrated by tissue sections. CONCLUSION: Our study identified the FGF-2-derived peptide FP2 as a promising candidate peptide to improve the therapeutic potential of hWJ-MSCs, especially in bone and cartilage regeneration.

Lee, Y. N., et al. (2020). "Evaluation of Multi-Layered Pancreatic Islets and Adipose-Derived Stem Cell Sheets Transplanted on Various Sites for Diabetes Treatment." Cells **9**(9).

Islet cell transplantation is considered an ideal treatment for insulin-deficient diabetes, but implantation sites are limited and show low graft survival. Cell sheet technology and adipose-derived stem cells (ADSCs) can be useful tools for improving islet cell transplantation outcomes since both can increase implantation efficacy and graft survival. Herein, the optimal transplantation site in diabetic mice was investigated using islets and stem cell sheets. We constructed multi-layered cell sheets using rat/human islets and human ADSCs. Cell sheets were fabricated using temperature-responsive culture dishes. Islet/ADSC sheet (AI sheet) group showed higher viability and glucose-stimulated insulin secretion than islet-only group. Compared to islet transplantation alone, subcutaneous AI sheet transplantation showed better blood glucose control and CD31+ vascular traits. Because of the adhesive properties of cell sheets, AI sheets were easily applied on liver and peritoneal surfaces. Liver or peritoneal surface grafts showed better glucose control, weight gain, and intraperitoneal glucose tolerance test (IPGTT) profiles than subcutaneous site grafts using both rat and human islets. Stem cell sheets increased the therapeutic efficacy of islets in vivo because mesenchymal stem cells enhance islet function and induce neovascularization around transplanted islets. The liver and peritoneal surface can be used more effectively than the subcutaneous site in future clinical applications.

Levy, S. and H. Ruohola-Baker (2023). "AI-driven designed protein epigenomics." Clin Res Oncol **1**(1): 1-3.

The biological revolutions of computationally designed proteins, induced pluripotent stem cells (iPSCs), and the CRISPR-Cas9 system finally enables modifications that can spur deep understanding of spatial requirement of epigenetic information. This commentary describes the utility of a computationally designed protein, EED Binder (EB), when fused to dCas9 (EBdCas9)

for identifying critical sites of PRC2 dependent histone H3K27me3 marks in the chromatin. By using EBdCas9 and gRNA, PRC2 function can be inhibited at specific loci, resulting in precise reduction of EZH2 and H3K27me3 marks, and in some (but not all) locations, activation of the gene and functional outcomes (such as regulation of cell cycle or trophoblast transdifferentiation). Interestingly, a functional TATA box located more than 500bp upstream of a TBX18 TSS was found to be repressed by PRC2, supporting the theory that epigenetic regulators control the repression of transcriptional elements on the promoter region. The EBdCas9 technology may provide a useful tool for controlling gene regulation through epigenomic control.

Leyton, J. V., et al. (2008). "Humanized radioiodinated minibody for imaging of prostate stem cell antigen-expressing tumors." Clin Cancer Res **14**(22): 7488-7496.

PURPOSE: Prostate stem cell antigen (PSCA) is a cell surface glycoprotein that is overexpressed in prostate cancer, including hormone refractory disease. Previous preclinical studies showed the intact anti-PSCA antibodies, 1G8 and hu1G8, localized specifically to PSCA-expressing xenografts. Optimal micro positron emission tomography (microPET) imaging using hu1G8, however, required a delay of 168 hours postinjection. In this study, the 2B3 minibody (an 80-kDa engineered antibody fragment) has been produced for rapid targeting and imaging. EXPERIMENTAL DESIGN: A gene encoding a PSCA-specific minibody, V(L)-linker-V(H)-hinge-huIgG1 C(H)3, was assembled. The minibody was expressed by secretion from mammalian cells and purified by cation exchange chromatography. Relative affinity and specificity were determined by competition ELISA and flow cytometry. Serial microPET imaging using a 124I-labeled minibody was conducted at 4 and 21 hours in mice bearing LAPC-9 AD, LAPC-9 AI, PC-3, and LNCaP-PSCA human prostate cancer xenografts. Tumor and tissue biodistribution was determined, and region of interest analysis of the images was conducted. RESULTS: Yields of 20 mg/L purified 2B3 minibody were obtained that showed specific binding to LNCaP-PSCA cells. Purified 2B3 minibody showed specific binding to LNCaP-PSCA cells with an apparent affinity of 46 nmol/L. Radioiodinated 2B3 minibody showed rapid nontarget tissue and blood clearance kinetics (t1/2beta = 11.2 hours). MicroPET scanning using the 124I-2B3 minibody showed both androgen-dependent and -independent tumors as early as 4 hours and excellent high contrast images at 21 hours postinjection. CONCLUSIONS: Imaging PSCA-positive prostate cancer is feasible using an intermediate size antibody fragment at 21 hours.

Li, F., et al. (2019). "Bone Marrow Mesenchymal Stem Cells Decrease the Expression of RANKL in Collagen-Induced Arthritis Rats via Reducing the Levels of IL-22." J Immunol Res **2019**: 8459281.

OBJECTIVE: To investigate the transplantation effect of bone marrow mesenchymal stem cells (MSCs) on the expression of interlukin-22 (IL-22) and RANKL in collagen-induced arthritis (CIA) rats. METHODS: 32 CIA models were established. 16 CIA rats were transplanted with MSCs, and others were used as nontreatment CIA controls. The concentrations of IL-22 and RANKL in serum were detected by ELISA and those in synovial tissue of rats' joints by immunohistochemical staining. In addition, the expression of RANKL mRNA was measured by RT-PCR in the fibroblast-like synoviocytes (FLSs), cultured with IL-22 in vitro, which were delivered from the joints of CIA rats treated with or without MSCs. RESULTS: The transplantation of MSCs into CIA rats relieved the destruction of joints, measured by AI score, X-ray, and histopathology. MSCs also reduced the expression of IL-22 and RANKL in serum by ELISA ($P < 0.001$) and similarly in FLSs by immunohistochemical staining. In vitro, IL-22 induced significantly the expression of RANKL mRNA in cultured FLSs in a dose-dependent manner, whereas this induction was significantly reduced in FLSs derived from CIA rats transplanted with MSCs (normal controls: $F = 79.33$, $P < 0.001$; CIA controls: $F = 712.72$, $P < 0.001$; and CIA-MSC rats: $F = 139.04$, $P < 0.001$). CONCLUSION: Our results suggest that the transplantation of MSCs can reduce the expression of RANKL in vivo by downregulating the levels of IL-22, thereby ameliorating the degree of RA bone destruction. This study provides a theoretical basis for a potential therapy of RA with MSCs, and IL-22 and RANKL may become two new targets to treat RA.

Li, J., et al. (2015). "Effect of SDF-1/CXCR4 axis on the migration of transplanted bone mesenchymal stem cells mobilized by erythropoietin toward lesion sites following spinal cord injury." Int J Mol Med **36**(5): 1205-1214.

Accumulating evidence has indicated that the stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) axis plays a crucial role in the recruitment of bone marrow-derived mesenchymal stem cells (BMSCs) into lesion sites in animal models. The aim of this study was to investigate the effects of the SDF-1/CXCR4 axis on the migration of transplanted BMSCs mobilized by

erythropoietin (EPO) toward the lesion site following spinal cord injury (SCI). A model of SCI was established in rats using the modified Allen's test. In the EPO group, EPO was administered at a distance of 2 mm cranially and then 2 mm caudally from the site of injury. In the BMSC group, 10 microl of BMSC suspension was administered in the same manner. In the BMSC + EPO group, both BMSCs and EPO were administered as described above. In the BMSC + EPO + AMD3100 group, in addition to the injection of BMSCs and EPO, AMD3100 (a chemokine receptor antagonist) was administered. The Basso-Beattie-Bresnahan (BBB) Locomotor Rating Scale and a grid walk test were used to estimate the neurological recovery following SCI. Enzyme-linked immunosorbent assay (ELISA) was performed to assess the tumor necrosis factor-alpha (TNF-alpha) and SDF-1 expression levels. An immunofluorescence assay was performed to identify the distribution of the BMSCs in the injured spinal cord. A Transwell migration assay was performed to examine BMSC migration. A terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay was performed to detect the apoptotic index (AI). Western blot analysis was performed to measure the expression levels of erythropoietin receptor (EPOR) and CXCR4. Significant improvements in locomotor function were detected in the BMSC + EPO group compared with the BMSC group ($P<0.05$). GFP-labeled BMSCs were observed and were located at the lesion sites. Additionally, EPO significantly decreased the TNF-alpha levels and increased the SDF-1 levels in the injured spinal cord ($P<0.05$).The AI in the BMSC + EPO group was significantly lower compared with that in the other groups ($P<0.05$). Furthermore, EPO significantly upregulated the protein expression of CXCR4 in the BMSCs and promoted the migration of the BMSCs, whereas these effects were markedly inhibited when the BMSCs were co-transplanted with AMD3100. The findings of the present study confirm that EPO mobilizes BMSCs to the lesion site following SCI and enhances the anti-apoptotic effects of the BMSCs by upregulating the expression of SDF-1/CXCR4 axis.

Li, L., et al. (2006). "[A potential role for the bone marrow mesenchymal stem cell in the pathogenesis of osteoporosis by ovariectomy in rat]." Sheng Wu Yi Xue Gong Cheng Xue Za Zhi **23**(1): 129-135.

The purpose of this paper is to investigate the osteogenesis and adipogenesis in bone marrow mesenchymal stem cells (MSCs) isolated from normal rats and osteoporotic rats by ovariectomy. Osteoporotic animal model was established in 3 month-old and 6 month-old female Sprague-Dawley (SD) rats by ovariectomy. Animal experiments were divided into 4 groups: 1) control-3 group; 2) ovx-3 group; 3) control-6 group and 4) ovx-6 group. MSCs were isolated by means of the density-gradient centrifugation method from each group, respectively. Colony-forming unit-fibroblast (CFU-Fs) number, CFU-Fs size distribution and cell density in CFU-Fs of primary passage MSCs were measured at the inverted phase contrast microscope. The cell cycle and proliferation index (PI) as well as apoptosis idex (AI) of MSCs were studied by (FCM). After osteogenic induction (OSI), calcium nodes of MSCs were marked by alizarin red staining (ARS); The expression level of alkaline phosphatase(ALP) was detected by dynamics method with substrate of phosphoric acid para-Nitro benzene and the content of osteocalcin (OCN) was detected with the isotope labelling method. After adipogenic induction (ADI), lipid droplet in MSCs were detected by oil red O staining and the mRNA level of lipoprotein lipase (LPL) was measured by RT-PCR. The results showed that CFU-Fs and PI are obviously decresed and AI are increased of MSCs in OVX-3 and OVX-6 groups ($P<0.05$). The secretory volume of ALP and BGP of MSCs and the content of calcium nods of MSCs are lower in OVX-3 and OVX-6 groups than that in control-3 and control-6 groups after osteogenic induction ($P<0.05$). The number of lipid droplet and the expression level of LPL mRNA are higher in OVX-3 and OVX-6 groups than that in control-3 and control-6 ($P<0.05$). The result in our study suggested that depress of osteogenesis and the up-regulation of adipogenesis of MSCs in osteoporotic rats by ovariectomy may be relate close to the pathogenesis of osteoporosis.

Li, S., et al. (2011). "Biphasic effect of EGb761 on simulated ischemia-induced rat BMSC survival in vitro and in vivo." Life Sci **88**(19-20): 853-863.

AIMS: The standardized extract from the leaves of Ginkgo biloba (EGb761) is applied as a phyto-pharmacon in therapy of diverse cardiovascular disorders. However, the effects of EGb761 on bone-marrow mesenchymal stem cells (BMSCs) transplanted into the ischemic myocardium currently remain uncertain. In this study, the dosage-effects of EGb761 on BMSC survival in vitro and in vivo were investigated. MAIN METHODS: The ischemic microenvironment of rat BMSCs was simulated by hypoxia/serum deprivation (SD) and the rat myocardial infarction model was established. The rat BMSCs were cultured under hypoxia/SD or transplanted into the animal ischemic heart. The BMSC apoptosis was determined by FACS and TUNEL assay. Each apoptotic signal molecule's activity was assayed by immunoblot. KEY

FINDINGS: EGb761 showed a biphasic effect on the hypoxia/SD-induced BMSC apoptosis. Low concentration of EGb761 (10-100mug/ml) aggravated hypoxia/SD-induced apoptosis via Akt inactivation and an enhancement of caspase-9 and caspase-3 expressions, whereas high concentration of EGb761 (500-2000mug/ml) significantly prevented hypoxia/SD-induced BMSC apoptosis via the activated Akt and the inactivated caspase-9 and caspase-3. The animal study also indicated that the apoptotic index (AI) in the high concentration of EGb761 group was significantly lower than the low concentration of EGb761 group. SIGNIFICANCE: The biphasic effect of EGb761 is closely related to the PI3K-Akt and caspase-9 signaling pathways. The therapeutic concentration of EGb761 may be one of the vital factors determining the specific action of EGb761 on cell apoptosis. It is of significant clinical implication to investigate the mechanisms of the biphasic effect of EGb761.

Li, X., et al. (2022). "Establishment of a 13 genes-based molecular prediction score model to discriminate the neurotoxic potential of food relevant-chemicals." Toxicol Lett **355**: 1-18.

Although many neurotoxicity prediction studies of food additives have been developed, they are applicable in a qualitative way. We aimed to develop a novel prediction score that is described quantitatively and precisely. We examined cell viability, reactive oxygen species activity, intracellular calcium and RNA transcription level of potential prediction related genes to develop a high-throughput neurotoxicity test method in vitro to screen the neurotoxicity of hazardous factors in food using AI-based machine learning. We trained artificial intelligence models (random forest and neural network) to predict neurotoxicity precisely, establishing a universal classification assessment score (CA-Score) that relies on the expression status of only 13 of prediction related genes. The CA-Score system is almost universally applicable to food risk factors ($p<0.05$) in a manner independent of platform (microarray or RNA sequencing) by being compared with cut-off value 23.487 to judge whether it's neurotoxic or not. We finally validated our prediction with the external validation of CA-Score on neural precursor cells derived from embryonic stem cells. Therefore, we draw a conclusion that the AI-based machine learning including neural network and random forest is likely to provide a useful tool for large-scale screening of neurotoxicity in food risk factors.

Li, X., et al. (2023). "DART: Distance Assisted Recursive Testing." J Mach Learn Res **24**.

Multiple testing is a commonly used tool in modern data science. Sometimes, the hypotheses are embedded in a space; the distances between the hypotheses reflect their co-null/co-alternative patterns. Properly incorporating the distance information in testing will boost testing power. Hence, we developed a new multiple testing framework named Distance Assisted Recursive Testing (DART). DART features in joint artificial intelligence (AI) and statistics modeling. It has two stages. The first stage uses AI models to construct an aggregation tree that reflects the distance information. The second stage uses statistical models to embed the testing on the tree and control the false discovery rate. Theoretical analysis and numerical experiments demonstrated that DART generates valid, robust, and powerful results. We applied DART to a clinical trial in the allogeneic stem cell transplantation study to identify the gut microbiota whose abundance was impacted by post-transplant care.

Li, Y., et al. (2024). "The molecular mechanisms of cardiac development and related diseases." Signal Transduct Target Ther **9**(1): 368.

Cardiac development is a complex and intricate process involving numerous molecular signals and pathways. Researchers have explored cardiac development through a long journey, starting with early studies observing morphological changes and progressing to the exploration of molecular mechanisms using various molecular biology methods. Currently, advancements in stem cell technology and sequencing technology, such as the generation of human pluripotent stem cells and cardiac organoids, multi-omics sequencing, and artificial intelligence (AI) technology, have enabled researchers to understand the molecular mechanisms of cardiac development better. Many molecular signals regulate cardiac development, including various growth and transcription factors and signaling pathways, such as WNT signaling, retinoic acid signaling, and Notch signaling pathways. In addition, cilia, the extracellular matrix, epigenetic modifications, and hypoxia conditions also play important roles in cardiac development. These factors play crucial roles at one or even multiple stages of cardiac development. Recent studies have also identified roles for autophagy, metabolic transition, and macrophages in cardiac development. Deficiencies or abnormal expression of these factors can lead to various types of cardiac development abnormalities. Nowadays, congenital heart disease (CHD) management requires lifelong care, primarily involving surgical and pharmacological treatments. Advances in surgical techniques and the development of clinical genetic testing have enabled earlier

diagnosis and treatment of CHD. However, these technologies still have significant limitations. The development of new technologies, such as sequencing and AI technologies, will help us better understand the molecular mechanisms of cardiac development and promote earlier prevention and treatment of CHD in the future.

Li, Z., et al. (2024). "AI identifies potent inducers of breast cancer stem cell differentiation based on adversarial learning from gene expression data." Brief Bioinform **25**(3).

Cancer stem cells (CSCs) are a subpopulation of cancer cells within tumors that exhibit stem-like properties and represent a potentially effective therapeutic target toward long-term remission by means of differentiation induction. By leveraging an artificial intelligence approach solely based on transcriptomics data, this study scored a large library of small molecules based on their predicted ability to induce differentiation in stem-like cells. In particular, a deep neural network model was trained using publicly available single-cell RNA-Seq data obtained from untreated human-induced pluripotent stem cells at various differentiation stages and subsequently utilized to screen drug-induced gene expression profiles from the Library of Integrated Network-based Cellular Signatures (LINCS) database. The challenge of adapting such different data domains was tackled by devising an adversarial learning approach that was able to effectively identify and remove domain-specific bias during the training phase. Experimental validation in MDA-MB-231 and MCF7 cells demonstrated the efficacy of five out of six tested molecules among those scored highest by the model. In particular, the efficacy of triptolide, OTS-167, quinacrine, granisetron and A-443654 offer a potential avenue for targeted therapies against breast CSCs.

Liao, M., et al. (2021). "Autophagy Blockade by Ai Du Qing Formula Promotes Chemosensitivity of Breast Cancer Stem Cells Via GRP78/beta-Catenin/ABCG2 Axis." Front Pharmacol **12**: 659297.

Accumulating evidence suggests that the root of drug chemoresistance in breast cancer is tightly associated with subpopulations of cancer stem cells (CSCs), whose activation is largely dependent on taxol-promoting autophagy. Our pilot study identified GRP78 as a specific marker for chemoresistance potential of breast CSCs by regulating Wnt/beta-catenin signaling. Ai Du Qing (ADQ) is a traditional Chinese medicine formula that has been utilized in the treatment cancer, particularly during the consolidation phase. In the present study, we investigated the regulatory effects and molecular mechanisms of ADQ in promoting autophagy-related breast cancer chemosensitivity. ADQ with taxol decreasing the cell proliferation and colony formation of breast cancer cells, which was accompanied by suppressed breast CSC ratio, limited self-renewal capability, as well as attenuated multi-differentiation. Furthermore, autophagy in ADQ-treated breast CSCs was blocked by taxol via regulation of beta-catenin/ABCG2 signaling. We also validated that autophagy suppression and chemosensitizing activity of this formula was GRP78-dependent. In addition, GRP78 overexpression promoted autophagy-inducing chemoresistance in breast cancer cells by stabilizing beta-catenin, while ADQ treatment downregulated GRP78, activated the Akt/GSK3beta-mediated proteasome degradation of beta-catenin via ubiquitination activation, and consequently attenuated the chemoresistance-promoted effect of GRP78. In addition, both mouse breast cancer xenograft and zebrafish xenotransplantation models demonstrated that ADQ inhibited mammary tumor growth, and the breast CSC subpopulation showed obscure adverse effects. Collectively, this study not only reveals the chemosensitizating mechanism of ADQ in breast CSCs, but also highlights the importance of GRP78 in mediating autophagy-promoting drug resistance via beta-catenin/ABCG2 signaling.

Lien, C. Y., et al. (2023). "Recognizing the Differentiation Degree of Human Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium Cells Using Machine Learning and Deep Learning-Based Approaches." Cells **12**(2).

Induced pluripotent stem cells (iPSCs) can be differentiated into mesenchymal stem cells (iPSC-MSCs), retinal ganglion cells (iPSC-RGCs), and retinal pigmental epithelium cells (iPSC-RPEs) to meet the demand of regeneration medicine. Since the production of iPSCs and iPSC-derived cell lineages generally requires massive and time-consuming laboratory work, artificial intelligence (AI)-assisted approach that can facilitate the cell classification and recognize the cell differentiation degree is of critical demand. In this study, we propose the multi-slice tensor model, a modified convolutional neural network (CNN) designed to classify iPSC-derived cells and evaluate the differentiation efficiency of iPSC-RPEs. We removed the fully connected layers and projected the features using principle component analysis (PCA), and subsequently classified iPSC-RPEs according to various differentiation degree. With the assistance of the support vector machine (SVM), this model further showed capabilities to classify iPSCs, iPSC-MSCs, iPSC-RPEs, and iPSC-

RGCs with an accuracy of 97.8%. In addition, the proposed model accurately recognized the differentiation of iPSC-RPEs and showed the potential to identify the candidate cells with ideal features and simultaneously exclude cells with immature/abnormal phenotypes. This rapid screening/classification system may facilitate the translation of iPSC-based technologies into clinical uses, such as cell transplantation therapy.

Liman, T. G., et al. (2016). "Stromal Cell-Derived Factor-1 Alpha Is Decreased in Women With Migraine With Aura." Headache **56**(8): 1274-1279.

BACKGROUND: Endothelial dysfunction may contribute to the pathophysiology of migraine with aura. Stromal cell-derived factor-1 alpha (SDF-1alpha) is involved in the maintenance of endothelial integrity via mobilization of vascular stem cells. OBJECTIVES: We sought to determine whether SDF-1alpha levels are decreased in women with MA. METHODS: In this post hoc analysis of a case-cohort study, levels of SDF-1alpha were determined by enzyme-linked immunosorbent assay. Endothelial function was assessed using peripheral arterial tonometry. Arterial stiffness was assessed by fingertip tonometry derived and heart-rate-adjusted augmentation index (AI). RESULTS: Twenty-eight women with MA and 27 age-matched healthy women were included in this study. Levels of SDF-1alpha were significantly lower in women with MA compared to age- and risk factor-matched healthy women (1763 +/- 281 vs 2013 +/- 263 pg/mL, P = 0.006). SDF-1alpha levels were positively correlated with AI in healthy women (r = 0.49, P = 0.009), but not in women with MA (r = 0.05, P = 0.78). SDF-1alpha levels were negatively correlated with CD144-positive endothelial microparticles (EMP; r = -0.31, P = .02), and activated CD62E-positive EMP (r = -0.35, P = .01). CONCLUSION: Levels of SDF-1alpha are decreased in women with MA and are associated with EMPs as a surrogate marker of endothelial dysfunction. This might contribute to the pathophysiology and vascular risk in MA, but evidence from larger prospective studies is warranted.

Lin, C. M., et al. (2012). "[Effect of UC-MSCs on inflammation and thrombosis of the rats with collagen type II induced arthritis]." Zhonghua Xue Ye Xue Za Zhi **33**(3): 215-219.

OBJECTIVE: To investigate the immunoregulation effects of umbilical cord mesenchymal stem cells (UC-MSCs) on the rats with collagen II induced arthritis (CIA). METHODS: The rats were first immunized by intradermal injection of chicken collagen type II emulsified with complete Freund's adjuvant (CFA) to monitor their swelling of foot, hair color and action state. After injected UC-MSC by caudal vein, the rats were scored with the arthritis index (AI) once a week. Then, the concentration of interleukin (IL-6), tumor necrosis factor-alpha (TNF-alpha) in serum and D-dimer (D-D), antithrombin-III (AT-III), thrombomodulin (TM) in plasma were detected by ELISA. RESULTS: Obvious swellings of the feet were found in the experiment group compared with normal one. ELISA analysis showed that the concentrations of IL-6, TNF-alpha, D-D and TM in plasma of the experiment group as of (200.48 +/- 15.04) ng/L, (450.25 +/- 45.39) ng/L, (274.26 +/- 67.93) ng/L and (9.18 +/- 0.84) microg/L, respectively were higher than of(167.62 +/- 0.97) ng/L, (371.44 +/- 21.26) ng/L, (193.95 +/- 8.22) ng/L and (6.30 +/- 0.32) microg/L respectively in normal group (P < 0.05), but the concentration of AT-III \[(89.57 +/- 6.40) ng/L\] was lower than normal group \[(112.82 +/- 1.74) ng/L\] (P < 0.05). The levels of cytokines through the UC-MSCs treatment were significantly different from the model group (P < 0.05). After 9 weeks, these cytokines in the UC-MSCs group were mostly the same as the normal group. CONCLUSION: The thrombophilia status of the CIA rats was caused by immune injury. The UC-MSCs reduced the production of inflammatory cytokines and regulated and repaired the balance of coagulation and anticoagulation system of the body to cure the immune-related thrombophilia.

Lin, K. C., et al. (1996). "Isolation and expression of a host response gene family encoding thaumatin-like proteins in incompatible oat-stem rust fungus interactions." Mol Plant Microbe Interact **9**(6): 511-522.

Four cDNA clones (corresponding to tlp-1, -2, -3, and -4 genes) encoding thaumatin-like (TL), pathogenesis-related proteins were isolated from oat (Avena sativa) infected by an incompatible isolate Pga-1H of the oat stem rust fungus (Puccinia graminis f. sp. avenae). All four cDNA clones contained an open reading frame predicted to encode a 169-amino acid polypeptide with a signal peptide of 21 amino acids at the N-terminus, suggesting that these proteins are transported through a secretory pathway. The amino acid sequences revealed high homology among the four cDNA clones, 80 to 99% identity and 86 to 100% similarity. The tlp genes and several TL protein genes of certain cereals are clustered into a small group that is phylogenetically separate from the major group of TL protein genes of several plant species. In plants infected with the incompatible isolate Pga-1H, or an inappropriate isolate Pgt-8D of P. graminis f. sp. tritici, high levels of tlp gene transcripts accumulated at 42 to 48 h AI

and thereafter when hypersensitive host cell death occurred and hyphal growth was inhibited, whereas in plants infected with a compatible isolate Pga-6A, relatively lower amounts of transcripts were detected. Overall, transcript levels were higher with tlp-1 than with the three other genes. Spray with a light mineral oil used as a spore carrier induced transient expression of tlp-1, -2, and -3 genes at 16 to 30 h AI which obscured the initial induction of the tlp genes in response to infection by the pathogens. In contrast, tlp-4 was induced very little by oil spray, so that induction was clearly observed in response to either compatible, incompatible, or inappropriate isolates at 24 to 30 h AI. Wounding leaves by either slicing or puncturing them strongly induced tlp-1 and tlp-3, moderately induced tlp-2, but had no effect on tlp-4. Taken together, the results showed that tlp genes displayed differential responses to oil spray, mechanical wounding, and pathogen infection and that the expression of tlp genes, especially tlp-1, in oat is associated with resistance reactions in response to infection by incompatible and inappropriate isolates of the stem rust fungi.

Liu, H. M., et al. (2015). "MSCs relieve lung injury of COPD mice through promoting proliferation of endogenous lung stem cells." J Huazhong Univ Sci Technolog Med Sci **35**(6): 828-833.

Bone marrow mesenchymal stem cells (MSCs) transplantation could repair injury tissue, but no study confirms whether MSCs can promote the proliferation of endogenous lung stem cells to repair alveolar epithelial cells of mice with chronic obstructive pulmonary disease (COPD). This study was designed to investigate the effect of MSCs on the proliferation of endogenous lung stem cells in COPD mice to confirm the repair mechanism of MSCs. The mice were divided into control group, COPD group, and COPD+MSCs group. The following indexes were detected: HE staining of lung tissue, the mean linear intercept (MLI) and alveolar destructive index (DI), the total cell number in bronchoalveolar lavage fluid (BALF), pulmonary function, alveolar wall apoptosis index (AI) and proliferation index (PI), the number of CD45(-)/CD31(-)/Sca-1(+) cells by flow cytometry (FCM), and the number of bronchoalveolar stem cells (BASCs) in bronchoalveolar duct junction (BADJ) by immunofluorescence. As compared with control group, the number of inflammatory cells in lung tissue was increased, alveolar septa was destroyed and the emphysema-like changes were seen, and the changes of lung function were in line with COPD in COPD group; AI of alveolar wall was significantly increased and PI significantly decreased in COPD group. There was no significant difference in the number of CD45(-)/CD31(-)/Sca-1(+) cells and BASCs between control group and COPD group. As compared with COPD group, the number of inflammatory cells in BALF was decreased, the number of CD45(-)/CD31(-)/Sca-1(+) cells and BASCs was increased, AI of alveolar wall was decreased and PI was increased, and emphysema-like changes were relieved in COPD+MSCs group. These findings suggested that MSCs transplantation can relieve lung injury by promoting proliferation of endogenous lung stem cells in the cigarette smoke-induced COPD mice.

Liu, R., et al. (2024). "An AI-Cyborg System for Adaptive Intelligent Modulation of Organoid Maturation." bioRxiv.

Recent advancements in flexible bioelectronics have enabled continuous, long-term stable interrogation and intervention of biological systems. However, effectively utilizing the interrogated data to modulate biological systems to achieve specific biomedical and biological goals remains a challenge. In this study, we introduce an AI-driven bioelectronics system that integrates tissue-like, flexible bioelectronics with cyber learning algorithms to create a long-term, real-time bidirectional b ioelectronic interface with o ptimized a daptive intelligent m odulation (BIO-AIM). When integrated with biological systems as an AI-cyborg system, BIO-AIM continuously adapts and optimizes stimulation parameters based on stable cell state mapping, allowing for real-time, closed-loop feedback through tissue-embedded flexible electrode arrays. Applied to human pluripotent stem cell-derived cardiac organoids, BIO-AIM identifies optimized stimulation conditions that accelerate functional maturation. The effectiveness of this approach is validated through enhanced extracellular spike waveforms, increased conduction velocity, and improved sarcomere organization, outperforming both fixed and no stimulation conditions.

Lonergan, P. (2018). "Review: Historical and futuristic developments in bovine semen technology." Animal **12**(s1): s4-s18.

Up to the 18th century, the prevailing view of reproduction, or 'generation' as it was referred to, was that organisms develop from miniatures of themselves, termed preformation. The alternative theory, epigenesis, proposed that the structure of an animal emerges gradually from a relatively formless egg. The teachings of the Ancient Greeks who argued either that both sexes each contributed 'semen' to form the embryo, or held a more male-centred view that the female merely provided fertile ground for the male seed to grow, dominated thinking until the 17th

century, when the combined work of numerous scholars led to the theory that all female organisms, including humans, produced eggs. The sequence of events leading to the commercial use of artificial insemination (AI) date back to the discovery of sperm in 1678, although it took almost 100 years to demonstrate that sperm were the agents of fertilisation and a further 100 years for the detailed events associated with fertilisation to be elucidated. The first successful AI, carried out in the dog, dates back to 1780 while it was not until the early to mid-1900s that practical methods for AI were described in Russia. Inspired by the Russian success, the first AI cooperative was established in Denmark in 1936 and later in the United States in 1938. The next major advances involved development of semen extenders, addition of antibiotics to semen, and the discovery in 1949 that glycerol protected sperm during cryopreservation. Almost four decades later, the flow cytometric separation of X- and Y-bearing sperm opened a new chapter in the application of AI for cattle breeding. As we look forward today, developments in imaging sperm and breakthroughs in gene editing and stem cell technology are opening up new possibilities to manipulate reproduction in a way never thought possible by the pioneers of the past. This review highlights some of the main milestones and individuals in the history of sperm biology and the development of technologies associated with AI in cattle.

Lu, X., et al. (2003). "Inhibition of proliferation and expression of AR/PSA by herbal supplement Equiguard in LNCaP cells cultured in androgen-proficient FBS and androgen-deficient charcoal-stripped FBS is correlated with increased serine-15 phosphorylation of the tumor suppressor gene p53." Anticancer Res **23**(3B): 2489-2498.

Use of dietary supplements and botanical products is widely accepted by patients diagnosed with prostate cancer (CaP) as a primary or complementary form of treatment for their medical conditions in the U.S. Yet, the majority of these products have not been rigorously studied with regard to scientific mechanism(s). Because many of the available products are mixtures of multiple extracts derived from plants, some of which are not necessarily native to the U.S., we consider mechanistic studies under defined laboratory conditions to be valuable and essential, not only from the standpoint of standardization and possible contamination with the products, but also in providing insights and scientific evidence for the clinical efficacy some of these products purportedly demonstrate. In previous studies from this laboratory, Equiguard, a composite supplement consisting of standardized extracts from nine Chinese herbs, which was originally formulated to correct physiological decline in kidney functions associated with age, was fortuitously found to display anti-CaP properties. Using a panel of CaP cells, we showed that ethanol extracts of Equiguard significantly inhibited cancer cell growth, induced apoptosis, lowered expression of the androgen receptor (AR), decreased intracellular and secreted prostate-specific antigen (PSA) levels and completely abolished the colony forming activities of CaP cells. Since responsiveness to Equiguard was observed in cells mimicking the androgen-dependent (AD) and androgen-independent (AI) states of CaP, our results raise the interesting possibility that this herbal supplement may potentially prevent, delay or circumvent the onset of AI, and thereby induce chronic instead of terminal CaP. Since androgen ablation therapy (chemical or surgical castration) is the mainstay for localized CaP, we questioned whether Equiguard might still exert the aforementioned activities in experimental settings modeled after androgen ablation. Accordingly, we studied the effects of Equiguard in LNCaP cells, cultured in androgen-proficient (FBS) or -deficient (CS-FBS) media that simulate the hormonal status pre- and post-castration in vivo. Extracts of Equiguard were effective in reducing colony formation, proliferation and PCNA expression of cells cultured in CS-FBS. Moreover, within a concentration range of Equiguard, the prostate-specific genes, PSA and AR, were affected to a similar extent in cells cultured either in FBS or CS-FBS, and were correlated with increased phosphorylation at serine-15 of the tumor suppressor gene p53. These results are consistent with the interpretation that the anti-proliferative and gene modulatory properties of Equiguard are largely independent of the status of androgens in the culture media.

Ma, J., et al. (2015). "Neural stem cell transplantation promotes behavioral recovery in a photothrombosis stroke model." Int J Clin Exp Pathol **8**(7): 7838-7848.

Stem cell-based therapy provides a promising approach for treat stroke. Neural stem cells isolated from mice hippocampus possessing the capacity of differentiate into neurons and astrocytes both in vitro and vivo. Here, we investigated the capability of neural stem cell transplantation in photothrombosis stroke model. Nissl staining revealed that the cortical infarct significantly decreased by 16.32% (Vehicle: 27.93le: an mm(3), n=6, NSC: 23.37le: ai mm(3), n=6, $P<0.05$) in the NSC group compared with the vehicle. More over transplantation of neural stem cells significantly ($P<0.01$) improved neurological performance

compared with vehicle. These results indicate that transplantation of neural stem cell is an effective therapy in ischemic stroke.

Mackay, B. S., et al. (2021). "The future of bone regeneration: integrating AI into tissue engineering." Biomed Phys Eng Express **7**(5).

Tissue engineering is a branch of regenerative medicine that harnesses biomaterial and stem cell research to utilise the body's natural healing responses to regenerate tissue and organs. There remain many unanswered questions in tissue engineering, with optimal biomaterial designs still to be developed and a lack of adequate stem cell knowledge limiting successful application. Advances in artificial intelligence (AI), and deep learning specifically, offer the potential to improve both scientific understanding and clinical outcomes in regenerative medicine. With enhanced perception of how to integrate artificial intelligence into current research and clinical practice, AI offers an invaluable tool to improve patient outcome.

Maertens, J., et al. (2016). "ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients." J Antimicrob Chemother **71**(9): 2397-2404.

The 5th European Conference on Infections in Leukaemia (ECIL-5) meeting aimed to establish evidence-based recommendations for the prophylaxis of Pneumocystis jirovecii pneumonia (PCP) in non-HIV-infected patients with an underlying haematological condition, including allogeneic HSCT recipients. Recommendations were based on the grading system of the IDSA. Trimethoprim/sulfamethoxazole given 2-3 times weekly is the drug of choice for the primary prophylaxis of PCP in adults (A-II:) and children (A-I:) and should be given during the entire period at risk. Recent data indicate that children may benefit equally from a once-weekly regimen (B-II:). All other drugs, including pentamidine, atovaquone and dapsone, are considered second-line alternatives when trimethoprim/sulfamethoxazole is poorly tolerated or contraindicated. The main indications of PCP prophylaxis are ALL, allogeneic HSCT, treatment with alemtuzumab, fludarabine/cyclophosphamide/rituximab combinations, >4 weeks of treatment with corticosteroids and well-defined primary immune deficiencies in children. Additional indications are proposed depending on the treatment regimen.

Mallick, S., et al. (2022). "Engineered Nanotechnology: An Effective Therapeutic Platform for the Chronic Cutaneous Wound." Nanomaterials (Basel) **12**(5).

The healing of chronic wound infections, especially cutaneous wounds, involves a complex cascade of events demanding mutual interaction between immunity and other natural host processes. Wound infections are caused by the consortia of microbial species that keep on proliferating and produce various types of virulence factors that cause the development of chronic infections. The mono- or polymicrobial nature of surface wound infections is best characterized by its ability to form biofilm that renders antimicrobial resistance to commonly administered drugs due to poor biofilm matrix permeability. With an increasing incidence of chronic wound biofilm infections, there is an urgent need for non-conventional antimicrobial approaches, such as developing nanomaterials that have intrinsic antimicrobial-antibiofilm properties modulating the biochemical or biophysical parameters in the wound microenvironment in order to cause disruption and removal of biofilms, such as designing nanomaterials as efficient drug-delivery vehicles carrying antibiotics, bioactive compounds, growth factor antioxidants or stem cells reaching the infection sites and having a distinct mechanism of action in comparison to antibiotics-functionalized nanoparticles (NPs) for better incursion through the biofilm matrix. NPs are thought to act by modulating the microbial colonization and biofilm formation in wounds due to their differential particle size, shape, surface charge and composition through alterations in bacterial cell membrane composition, as well as their conductivity, loss of respiratory activity, generation of reactive oxygen species (ROS), nitrosation of cysteines of proteins, lipid peroxidation, DNA unwinding and modulation of metabolic pathways. For the treatment of chronic wounds, extensive research is ongoing to explore a variety of nanoplatforms, including metallic and nonmetallic NPs, nanofibers and self-accumulating nanocarriers. As the use of the magnetic nanoparticle (MNP)-entrenched pre-designed hydrogel sheet (MPS) is found to enhance wound healing, the bio-nanocomposites consisting of bacterial cellulose and magnetic nanoparticles (magnetite) are now successfully used for the healing of chronic wounds. With the objective of precise targeting, some kinds of "intelligent" nanoparticles are constructed to react according to the required environment, which are later incorporated in the dressings, so that the wound can be treated with nano-impregnated dressing material in situ. For the effective healing of skin wounds, high-expressing, transiently modified stem cells, controlled by nano 3D architectures, have been developed to encourage angiogenesis and tissue

regeneration. In order to overcome the challenge of time and dose constraints during drug administration, the approach of combinatorial nano therapy is adopted, whereby AI will help to exploit the full potential of nanomedicine to treat chronic wounds.

Mambelli, L. I., et al. (2013). "A novel strategy of mesenchymal stem cells delivery in the uterus of mares with endometrosis." Theriogenology **79**(5): 744-750.

Mesenchymal stem cells (MSCs), because of their immunomodulation and trophic activities, in addition to their capacity to regenerate damaged tissues, have potential for treatment of many diseases. The success of stem cell therapies depends, in part, on the method of cell delivery, which should provide wide cell distribution and homing in to injured sites. The objective of the present study was to developing a novel strategy for delivery of MSCs into the uterus of mares with endometrosis (degenerative alteration of uterine glands and surrounding stroma). Endometrosis was confirmed in all mares (N = 6) used in this study. To trace multipotent equine adipose tissue-derived MSCs (eAT-MSCs) in endometrial tissue, before transplantation, cells were stained with a fluorescent dye. During a synchronized estrus, the eAT-MSCs (2 x 10(7) diluted in 20 mL of sodium chloride 0.9%) were inoculated into uterus using a simple technique, similar to artificial insemination (AI) in mares. At 7 and 21 days after transplantation, homing of fluorescently labeled eAT-MSCs was observed by confocal microscopy of uterine biopsies collected from the uterine body and in both uterine horns, including glandular and periglandular spaces, in three of four treated mares. Herein, we propose a new method of MSCs delivery in uterus of mares with endometrosis, which was minimally invasive and technically simple.

Mandava, M., et al. (2023). "Thyroid and Adrenal Dysfunction in Hemoglobinopathies Before and After Allogeneic Hematopoietic Cell Transplant." J Endocr Soc **7**(12): bvad134.

PURPOSE: To determine the rate and clinical characteristics associated with abnormal thyroid and adrenal function in recipients of nonmyeloablative hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) and beta-thalassemia. METHODS: We retrospectively reviewed patients who enrolled in 4 nonmyeloablative HCT regimens with alemtuzumab and total body irradiation (TBI). Baseline and annual post-HCT data were compared, which included age, sex, sickle phenotype, thyroid panel (total T3, free T4, thyroid stimulating hormone, antithyroid antibodies), cortisol level, ACTH stimulation testing, ferritin, medications, and other relevant medical history. RESULTS: Among 43 patients in haploidentical transplant and 84 patients in the matched related donor protocols with mostly SCD, the rate of any thyroid disorder pre-HCT was 3.1% (all subclinical hypothyroidism) and post-HCT was 29% (10 hypothyroidism, 4 Grave's disease, and 22 subclinical hypothyroidism). Ninety-two (72%) patients had ferritin >1000 ng/dL, of which 33 patients (35.8%) had thyroid dysfunction. Iron overload was noted in 6 of 10 patients with hypothyroidism and 12 of 22 patients with subclinical hypothyroidism.Sixty-one percent were on narcotics for pain control. With respect to adrenal insufficiency (AI) pre-HCT, 2 patients were maintained on corticosteroids for underlying rheumatologic disorder and 8 had AI diagnosed during pre-HCT ACTH stimulation testing (total 10, 7.9%). Post-HCT, an additional 4 (3%) developed AI from corticosteroid use for acute graft vs host disease, Evans syndrome, or hemolytic anemia. CONCLUSION: Although iron overload was common in SCD, thyroid dysfunction pre-HCT related to excess iron was less common. Exposure to alemtuzumab or TBI increased the rates of thyroid dysfunction post-HCT. In contrast, AI was more common pre-HCT, but no risk factor was identified. AI post-HCT was infrequent and associated with corticosteroid use for HCT-related complications.

Mao, S., et al. (2022). "MiR-183-5p overexpression in bone mesenchymal stem cell-derived exosomes protects against myocardial ischemia/reperfusion injury by targeting FOXO1." Immunobiology **227**(3): 152204.

OBJECTIVE: Exosomes have been suggested to serve as possible drug delivery vehicles due to their nanometer-size range and capability of transferring biological materials to recipient cells. Thus, whether miR-183-5p-overexpressing bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos) could protect against myocardial ischemia/reperfusion (MI/R) injury by targeting FOXO1 was investigated. METHODS: Exosomes were isolated from rat BMSCs, and ischemia/reperfusion (I/R) rat models were established. I/R rats were treated with Exo/NC-Exo/miR-183-5p-Exo/anti-miR-183-5p-Exo. Cardiac function, serum biochemical indices, apoptosis, myocardial infarction size, and the expression of miR-183-5p, FOXO1 and cleaved caspase 3 were assessed. Primary cardiomyocytes were isolated to establish hypoxia/reoxygenation (H/R) models to observe the function of miR-183-5p-Exo in vitro. RESULTS: Rats in the I/R group exhibited a decreased left ventricular ejection fraction (LVEF), left ventricular fraction shortening (LVFS) and left

ventricular systolic pressure (LVSP) but an increased left ventricular end-diastolic pressure (LVEDP), myocardial infarct size and apoptosis index (AI). In addition, in I/R rats, miR-183-5p expression was decreased, but FOXO1 and cleaved caspase 3 expression was increased. Both Exo and miR-183-5p-Exo improved the above indices in I/R rats, but miR-183-5p-Exo showed better effects. However, anti-miR-183-5p-Exo reversed the protective effect of Exo. FOXO1 was a target gene of miR-183-5p. Experiments in vitro revealed that Exo and miR-183-5p-Exo suppressed apoptosis and oxidative stress injury in H/R-induced cardiomyocytes, whereas overexpressed FOXO1 reversed the protective role of miR-183-5p-Exo. CONCLUSION: BMSC-derived exosomal miR-183-5p could target FOXO1 to reduce apoptosis and oxidative stress in I/R cardiomyocytes and improve cardiac function, thereby protecting against MI/R injury.

Maramraju, S., et al. (2024). "AI-organoid integrated systems for biomedical studies and applications." Bioeng Transl Med **9**(2): e10641.

In this review, we explore the growing role of artificial intelligence (AI) in advancing the biomedical applications of human pluripotent stem cell (hPSC)-derived organoids. Stem cell-derived organoids, these miniature organ replicas, have become essential tools for disease modeling, drug discovery, and regenerative medicine. However, analyzing the vast and intricate datasets generated from these organoids can be inefficient and error-prone. AI techniques offer a promising solution to efficiently extract insights and make predictions from diverse data types generated from microscopy images, transcriptomics, metabolomics, and proteomics. This review offers a brief overview of organoid characterization and fundamental concepts in AI while focusing on a comprehensive exploration of AI applications in organoid-based disease modeling and drug evaluation. It provides insights into the future possibilities of AI in enhancing the quality control of organoid fabrication, label-free organoid recognition, and three-dimensional image reconstruction of complex organoid structures. This review presents the challenges and potential solutions in AI-organoid integration, focusing on the establishment of reliable AI model decision-making processes and the standardization of organoid research.

Marrache, S. and S. Dhar (2013). "Biodegradable synthetic high-density lipoprotein nanoparticles for atherosclerosis." Proc Natl Acad Sci U S A **110**(23): 9445-9450.

Atherosclerosis remains one of the most common causes of death in the United States and throughout the world because of the lack of early detection. Macrophage apoptosis is a major contributor to the instability of atherosclerotic lesions. Development of an apoptosis targeted high-density lipoprotein (HDL)-mimicking nanoparticle (NP) to carry contrast agents for early detection of vulnerable plaques and the initiation of preventative therapies that exploit the vascular protective effects of HDL can be attractive for atherosclerosis. Here, we report the construction of a synthetic, biodegradable HDL-NP platform for detection of vulnerable plaques by targeting the collapse of mitochondrial membrane potential that occurs during apoptosis. This HDL mimic contains a core of biodegradable poly(lactic-co-glycolic acid), cholesteryl oleate, and a phospholipid bilayer coat that is decorated with triphenylphosphonium (TPP) cations for detection of mitochondrial membrane potential collapse. The lipid layer provides the surface for adsorption of apolipoprotein (apo) A-I mimetic 4F peptide, and the core contains diagnostically active quantum dots (QDs) for optical imaging. In vitro uptake, detection of apoptosis, and cholesterol binding studies indicated promising detection ability and therapeutic potential of TPP-HDL-apoA-I-QD NPs. In vitro studies indicated the potential of these NPs in reverse cholesterol transport. In vivo biodistribution and pharmacokinetics indicated favorable tissue distribution, controlled pharmacokinetic parameters, and significant triglyceride reduction for i.v.-injected TPP-HDL-apoA-I-QD NPs in rats. These HDL NPs demonstrate excellent biocompatibility, stability, nontoxic, and nonimmunogenic properties, which prove to be promising for future translation in early plaque diagnosis and might find applications to prevent vulnerable plaque progression.

Marzec-Schmidt, K., et al. (2023). "Artificial Intelligence Supports Automated Characterization of Differentiated Human Pluripotent Stem Cells." Stem Cells **41**(9): 850-861.

Revolutionary advances in AI and deep learning in recent years have resulted in an upsurge of papers exploring applications within the biomedical field. Within stem cell research, promising results have been reported from analyses of microscopy images to, that is, distinguish between pluripotent stem cells and differentiated cell types derived from stem cells. In this work, we investigated the possibility of using a deep learning model to predict the differentiation stage of pluripotent stem cells undergoing differentiation toward hepatocytes, based on morphological features of cell cultures. We were able to achieve close to perfect classification of images from early and late time points during differentiation, and this aligned very well with the

experimental validation of cell identity and function. Our results suggest that deep learning models can distinguish between different cell morphologies, and provide alternative means of semi-automated functional characterization of stem cell cultures.

Matsuda, N., et al. (2022). "Raster plots machine learning to predict the seizure liability of drugs and to identify drugs." Sci Rep **12**(1): 2281.

In vitro microelectrode array (MEA) assessment using human induced pluripotent stem cell (iPSC)-derived neurons holds promise as a method of seizure and toxicity evaluation. However, there are still issues surrounding the analysis methods used to predict seizure and toxicity liability as well as drug mechanisms of action. In the present study, we developed an artificial intelligence (AI) capable of predicting the seizure liability of drugs and identifying drugs using deep learning based on raster plots of neural network activity. The seizure liability prediction AI had a prediction accuracy of 98.4% for the drugs used to train it, classifying them correctly based on their responses as either seizure-causing compounds or seizure-free compounds. The AI also made concentration-dependent judgments of the seizure liability of drugs that it was not trained on. In addition, the drug identification AI implemented using the leave-one-sample-out scheme could distinguish among 13 seizure-causing compounds as well as seizure-free compound responses, with a mean accuracy of 99.9 +/- 0.1% for all drugs. These AI prediction models are able to identify seizure liability concentration-dependence, rank the level of seizure liability based on the seizure liability probability, and identify the mechanism of the action of compounds. This holds promise for the future of in vitro MEA assessment as a powerful, high-accuracy new seizure liability prediction method.

Matsumoto, R., et al. (2021). "Complex Organ Construction from Human Pluripotent Stem Cells for Biological Research and Disease Modeling with New Emerging Techniques." Int J Mol Sci **22**(19).

Human pluripotent stem cells (hPSCs) are grouped into two cell types; embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs). hESCs have provided multiple powerful platforms to study human biology, including human development and diseases; however, there were difficulties in the establishment of hESCs from human embryo and concerns over its ethical issues. The discovery of hiPSCs has expanded to various applications in no time because hiPSCs had already overcome these problems. Many hPSC-based studies have been performed using two-dimensional monocellular culture methods at the cellular level. However, in many physiological and pathophysiological conditions, intra- and inter-organ interactions play an essential role, which has hampered the establishment of an appropriate study model. Therefore, the application of recently developed technologies, such as three-dimensional organoids, bioengineering, and organ-on-a-chip technology, has great potential for constructing multicellular tissues, generating the functional organs from hPSCs, and recapitulating complex tissue functions for better biological research and disease modeling. Moreover, emerging techniques, such as single-cell transcriptomics, spatial transcriptomics, and artificial intelligence (AI) allowed for a denser and more precise analysis of such heterogeneous and complex tissues. Here, we review the applications of hPSCs to construct complex organs and discuss further prospects of disease modeling and drug discovery based on these PSC-derived organs.

McInerney, C. E., et al. (2022). "Using AI-Based Evolutionary Algorithms to Elucidate Adult Brain Tumor (Glioma) Etiology Associated with IDH1 for Therapeutic Target Identification." Curr Issues Mol Biol **44**(7): 2982-3000.

Adult brain tumors (glioma) represent a cancer of unmet need where standard-of-care is non-curative; thus, new therapies are urgently needed. It is unclear whether isocitrate dehydrogenases (IDH1/2) when not mutated have any role in gliomagenesis or tumor growth. Nevertheless, IDH1 is overexpressed in glioblastoma (GBM), which could impact upon cellular metabolism and epigenetic reprogramming. This study characterizes IDH1 expression and associated genes and pathways. A novel biomarker discovery pipeline using artificial intelligence (evolutionary algorithms) was employed to analyze IDH-wildtype adult gliomas from the TCGA LGG-GBM cohort. Ninety genes whose expression correlated with IDH1 expression were identified from: (1) All gliomas, (2) primary GBM, and (3) recurrent GBM tumors. Genes were overrepresented in ubiquitin-mediated proteolysis, focal adhesion, mTOR signaling, and pyruvate metabolism pathways. Other non-enriched pathways included O-glycan biosynthesis, notch signaling, and signaling regulating stem cell pluripotency (PCGF3). Potential prognostic (TSPYL2, JAKMIP1, CIT, TMTC1) and two diagnostic (MINK1, PLEKHM3) biomarkers were downregulated in GBM. Their gene expression and methylation were negatively and positively correlated with IDH1 expression, respectively. Two diagnostic biomarkers (BZW1, RCF2) showed the opposite trend. Prognostic genes were not impacted by high frequencies of molecular alterations and only one (TMTC1) could be validated in another cohort.

Genes with mechanistic links to IDH1 were involved in brain neuronal development, cell proliferation, cytokinesis, and O-mannosylation as well as tumor suppression and anaplerosis. Results highlight metabolic vulnerabilities and therapeutic targets for use in future clinical trials.

McNeish, J., et al. (2000). "High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1." Proc Natl Acad Sci U S A **97**(8): 4245-4250.

Recently, the human ATP-binding cassette transporter-1 (ABC1) gene has been demonstrated to be mutated in patients with Tangier disease. To investigate the role of the ABC1 protein in an experimental in vivo model, we used gene targeting in DBA-1J embryonic stem cells to produce an ABC1-deficient mouse. Expression of the murine Abc1 gene was ablated by using a nonisogenic targeting construct that deletes six exons coding for the first nucleotide-binding fold. Lipid profiles from Abc1 knockout (-/-) mice revealed an approximately 70% reduction in cholesterol, markedly reduced plasma phospholipids, and an almost complete lack of high density lipoproteins (HDL) when compared with wild-type littermates (+/+). Fractionation of lipoproteins by FPLC demonstrated dramatic alterations in HDL cholesterol (HDL-C), including the near absence of apolipoprotein AI. Low density lipoprotein (LDL) cholesterol (LDL-C) and apolipoprotein B were also significantly reduced in +/- and -/- compared with their littermate controls. The inactivation of the Abc1 gene led to an increase in the absorption of cholesterol in mice fed a chow or a high-fat and -cholesterol diet. Histopathologic examination of Abc1-/- mice at ages 7, 12, and 18 mo demonstrated a striking accumulation of lipid-laden macrophages and type II pneumocytes in the lungs. Taken together, these findings demonstrate that Abc1-/- mice display pathophysiologic hallmarks similar to human Tangier disease and highlight the capacity of ABC1 transporters to participate in the regulation of dietary cholesterol absorption.

Mellinghoff, S. C., et al. (2018). "Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO)." Ann Hematol **97**(2): 197-207.

Immunocompromised patients are at high risk of invasive fungal infections (IFI), in particular those with haematological malignancies undergoing remission-induction chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) and recipients of allogeneic haematopoietic stem cell transplants (HSCT). Despite the development of new treatment options in the past decades, IFI remains a concern due to substantial morbidity and mortality in these patient populations. In addition, the increasing use of new immune modulating drugs in cancer therapy has opened an entirely new spectrum of at risk periods. Since the last edition of antifungal prophylaxis recommendations of the German Society for Haematology and Medical Oncology in 2014, seven clinical trials regarding antifungal prophylaxis in patients with haematological malignancies have been published, comprising 1227 patients. This update assesses the impact of this additional evidence and effective revisions. Our key recommendations are the following: prophylaxis should be performed with posaconazole delayed release tablets during remission induction chemotherapy for AML and MDS (AI). Posaconazole iv can be used when the oral route is contraindicated or not feasible. Intravenous liposomal amphotericin B did not significantly decrease IFI rates in acute lymphoblastic leukaemia (ALL) patients during induction chemotherapy, and there is poor evidence to recommend it for prophylaxis in these patients (CI). Despite substantial risk of IFI, we cannot provide a stronger recommendation for these patients. There is poor evidence regarding voriconazole prophylaxis in patients with neutropenia (CII). Therapeutic drug monitoring TDM should be performed within 2 to 5 days of initiating voriconazole prophylaxis and should be repeated in case of suspicious adverse events or of dose changes of interacting drugs (BIItu). General TDM during posaconazole prophylaxis is not recommended (CIItu), but may be helpful in cases of clinical failure such as breakthrough IFI for verification of compliance or absorption.

Milford, S. R., et al. (2023). "Playing Brains: The Ethical Challenges Posed by Silicon Sentience and Hybrid Intelligence in DishBrain." Sci Eng Ethics **29**(6): 38.

The convergence of human and artificial intelligence is currently receiving considerable scholarly attention. Much debate about the resulting Hybrid Minds focuses on the integration of artificial intelligence into the human brain through intelligent brain-computer interfaces as they enter clinical use. In this contribution we discuss a complementary development: the integration of a functional in vitro network of human neurons into an in silico computing environment.To do so, we draw on a recent experiment reporting the creation of silico-biological intelligence as a case study (Kagan et al.,

2022b). In this experiment, multielectrode arrays were plated with stem cell-derived human neurons, creating a system which the authors call DishBrain. By embedding the system into a virtual game-world, neural clusters were able to receive electrical input signals from the game-world and to respond appropriately with output signals from pre-assigned motor regions. Using this design, the authors demonstrate how the DishBrain self-organises and successfully learns to play the computer game 'Pong', exhibiting 'sentient' and intelligent behaviour in its virtual environment.The creation of such hybrid, silico-biological intelligence raises numerous ethical challenges. Following the neuroscientific framework embraced by the authors themselves, we discuss the arising ethical challenges in the context of Karl Friston's Free Energy Principle, focusing on the risk of creating synthetic phenomenology. Following the DishBrain's creator's neuroscientific assumptions, we highlight how DishBrain's design may risk bringing about artificial suffering and argue for a congruently cautious approach to such synthetic biological intelligence.

Mimeault, M., et al. (2013). "Marked improvement of cytotoxic effects induced by docetaxel on highly metastatic and androgen-independent prostate cancer cells by downregulating macrophage inhibitory cytokine-1." Br J Cancer **108**(5): 1079-1091.

BACKGROUND: Overexpression of macrophage inhibitory cytokine-1 (MIC-1) frequently occurs during the progression of prostate cancer (PC) to androgen-independent (AI) and metastatic disease states and is associated with a poor outcome of patients. METHODS: The gain- and loss-of-function analyses of MIC-1 were performed to establish its implications for aggressive and chemoresistant phenotypes of metastatic and AI PC cells and the benefit of its downregulation for reversing docetaxel resistance. RESULTS: The results have indicated that an enhanced level of secreted MIC-1 protein in PC3 cells is associated with their acquisition of epithelial-mesenchymal transition features and higher invasive capacity and docetaxel resistance. Importantly, the downregulation of MIC-1 in LNCaP-LN3 and PC3M-LN4 cells significantly decreased their invasive capacity and promoted the antiproliferative, anti-invasive and mitochrondrial- and caspase-dependent apoptotic effects induced by docetaxel. The downregulation of MIC-1 in PC3M-LN4 cells was also effective in promoting the cytotoxic effects induced by docetaxel on the side population (SP) endowed with stem cell-like properties and the non-SP cell fraction from PC3M-LN4 cells. CONCLUSION: These data suggest that the downregulation of MIC-1 may constitute a potential therapeutic strategy for improving the efficacy of current docetaxel-based chemotherapies, eradicating the total mass of PC cells and thereby preventing disease relapse and the death of PC patients.

Minarik, J., et al. (2009). "Monitoring of plasma cell proliferative and apoptotic indices in the course of multiple myeloma." Leuk Lymphoma **50**(12): 1983-1991.

In a group of 310 patients with multiple myeloma (MM) we assessed the proliferative (PC-PI) and apoptotic indices (PC-AI). Patients were divided according to the disease state, i.e. at the time of diagnosis, in relapse, and in MM remission. We assessed the behavior of both indices with respect to therapy response and activity of the disease. In patients who reached remission, there was a significant decrease of PC-PI together with an increase of PC-AI in comparison with initial measurements. In non-responders, there was a reverse trend with increasing PC-PI and decreasing PC-AI. The values of PC-PI and PC-AI in residual myeloma population were similar regardless of treatment, i.e. in patients treated using conventional chemotherapy and after high-dosed chemotherapy with autologous stem cell transplant. Patients in long-lasting remission phase maintained stable low values of PC-PI with high PC-AI without a significant change, whereas in the group of progressing/relapsing patients, there was a significant increase of PC-PI together with a decrease of PC-AI. Our results suggest that longitudinal measurement of proliferative and apoptotic indices in MM plasmocytes helps to estimate the behavior of the tumor population and may thus become a convenient auxiliary parameter for prognosis and a targeted, individualized treatment approach.

Miroshnichenko, S., et al. (2020). "Apolipoprotein A-I Supports MSCs Survival under Stress Conditions." Int J Mol Sci **21**(11).

Clinical trials have shown the safety of mesenchymal stem/stromal cells (MSCs) transplantation, but the effectiveness of these treatments is limited. Since, transplanted MSCs will undergo metabolic disturbances in the bloodstream, we investigated the influence of blood plasmas of type 2 diabetes (T2D) patients on MSCs viability and examined whether apolipoprotein A-I (apoA-I) could protect cells from stressful conditions of serum deprivation (SD), hypoxia, and elevated concentrations of reactive oxygen species (ROS). ApoA-I exhibits anti-inflammatory, immune activities, improves glycemic control, and is suitable for T2D patients but its influence on MSCs remains

unknown. For the first time we have shown that apoA-I decreases intracellular ROS and supports proliferative rate of MSCs, thereby increasing cell count in oxidation conditions. ApoA-I did not influence cell cycle when MSCs were predominantly in the G0/G1 phases under conditions of SD/hypoxia, activated proliferation rapidly, and reduced apoptosis during MSCs transition to the oxygenation or oxidation conditions. Finally, it was found that the blood plasma of T2D individuals had a cytotoxic effect on MScapital ES, Cyrillics in 39% of cases and had a wide variability of antioxidant properties. ApoA-I protects cells under all adverse conditions and can increase the efficiency of MSCs transplantation in T2D patients.

Morrell, J. M. and M. Wallgren (2011). "Removal of bacteria from boar ejaculates by Single Layer Centrifugation can reduce the use of antibiotics in semen extenders." Anim Reprod Sci **123**(1-2): 64-69.

There is considerable interest world-wide in reducing the use of antibiotics to stem the development of antibiotic-resistant strains of bacteria. An alternative to the routine addition of antibiotics to semen extenders in livestock breeding would be to separate the spermatozoa from bacterial contaminants in the semen immediately after collection. The present study was designed to determine whether such separation was possible by Single Layer Centrifugation (SLC) using the colloid Androcoll-P. The results showed that complete removal (6 out of 10 samples), or considerable reduction of bacterial contaminants (4 out of 10 samples) was possible with this method. The type of bacteria and/or the length of time between collection and SLC-processing affected the removal of bacteria, with motile flagellated bacteria being more likely to be present after SLC than non-flagellated bacteria. Although further studies are necessary, these preliminary results suggest that the use of SLC when processing boar semen for AI doses might enable antibiotic usage in semen extenders to be reduced.

Morschhauser, F., et al. (2007). "Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation." Blood **110**(1): 54-58.

A prospective, multicenter, nonrandomized phase 2 trial was conducted to evaluate the efficacy and safety of a single dose of yttrium-90 ((90)Y) ibritumomab tiuxetan in elderly patients in first relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) ineligible for stem-cell transplantation. Patients had been previously treated with chemotherapy (group A, n = 76) or chemotherapy plus rituximab (group B, n = 28). Patients in group A were further divided into patients in whom induction therapy had failed (stratum AI, n = 33) and patients who had relapsed after achieving complete response (CR; stratum AII, n = 43). The overall response rate (ORR) was 52% and 53% in strata AI and AII, respectively, and 19% in group B, with CR/CRu rates of 24%, 39.5%, and 12%, respectively. Median progression-free survival was 5.9 months and 3.5 months in strata AI and AII, respectively, and 1.6 months in group B. Median overall survival was 21.4, 22.4, and 4.6 months in stratum AI, stratum AII, and group B, respectively. Two patients died from thrombocytopenic cerebral bleeding following administration of therapy. Nonhematologic adverse events were mild to moderate. (90)Y-ibritumomab is active in patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL) and its further evaluation in phase 3 studies is ongoing.

Mou, L., et al. (2024). "Advancing diabetes treatment: the role of mesenchymal stem cells in islet transplantation." Front Immunol **15**: 1389134.

Diabetes mellitus, a prevalent global health challenge, significantly impacts societal and economic well-being. Islet transplantation is increasingly recognized as a viable treatment for type 1 diabetes that aims to restore endogenous insulin production and mitigate complications associated with exogenous insulin dependence. We review the role of mesenchymal stem cells (MSCs) in enhancing the efficacy of islet transplantation. MSCs, characterized by their immunomodulatory properties and differentiation potential, are increasingly seen as valuable in enhancing islet graft survival, reducing immune-mediated rejection, and supporting angiogenesis and tissue repair. The utilization of MSC-derived extracellular vesicles further exemplifies innovative approaches to improve transplantation outcomes. However, challenges such as MSC heterogeneity and the optimization of therapeutic applications persist. Advanced methodologies, including artificial intelligence (AI) and single-cell RNA sequencing (scRNA-seq), are highlighted as potential technologies for addressing these challenges, potentially steering MSC therapy toward more effective, personalized treatment modalities for diabetes. This review revealed that MSCs are important for advancing diabetes treatment strategies, particularly through islet transplantation. This highlights the importance of MSCs in the field of regenerative medicine, acknowledging both their potential and the challenges that must be navigated to fully realize their therapeutic promise.

Mozaffari, E., et al. (2024). "Remdesivir-Associated Survival Outcomes Among Immunocompromised Patients Hospitalized for COVID-19: Real-world Evidence From the Omicron-Dominant Era." Clin Infect Dis **79**(Supplement_4): S149-S159.

BACKGROUND: Patients with immunocompromising conditions are at increased risk for coronavirus disease 2019 (COVID-19)-related hospitalizations and deaths. Randomized clinical trials provide limited enrollment, if any, to provide information on the outcomes in such patients treated with remdesivir. METHODS: Using the US PINC AI Healthcare Database, we identified adult patients with immunocompromising conditions, hospitalized for COVID-19 between December 2021 and February 2024. The primary outcome was all-cause inpatient mortality examined in propensity score-matched patients in remdesivir vs nonremdesivir groups. Subgroup analyses were performed for patients with cancer, hematological malignancies, and solid organ or hematopoietic stem cell transplant recipients. RESULTS: Of 28 966 patients included in the study, 16 730 (58%) received remdesivir during the first 2 days of hospitalization. After propensity score matching, 8822 patients in the remdesivir and 8822 patients in the nonremdesivir group were analyzed. Remdesivir was associated with a significantly lower mortality rate among patients with no supplemental oxygen (adjusted hazard ratio [95% confidence interval], 0.73 [.62-.86] at 14 days and 0.79 [.68-.91] at 28 days) and among those with supplemental oxygen (0.75 [.67-.85] and 0.78 [.70-.86], respectively). Remdesivir was also associated with lower mortality rates in subgroups of patients with cancer, hematological malignancies (leukemia, lymphoma, or multiple myeloma), and solid organ or hematopoietic stem cell transplants. CONCLUSIONS: In this large cohort of patients with immunocompromising conditions hospitalized for COVID-19, remdesivir was associated with significant improvement in survival, including patients with varied underlying immunocompromising conditions. The integration of current real-world evidence into clinical guideline recommendations can inform clinical communities to optimize treatment decisions in the evolving COVID-19 era, extending beyond the conclusion of the public health emergency declaration.

Muhsen, I. N., et al. (2018). "Artificial Intelligence Approaches in Hematopoietic Cell Transplantation: A Review of the Current Status and Future Directions." Turk J Haematol **35**(3): 152-157.

The evidence-based literature on healthcare is currently expanding exponentially. The opportunities provided by the advancement in artificial intelligence (AI) tools such as machine learning are appealing in tackling many of the current healthcare challenges. Thus, AI integration is expanding in most fields of healthcare, including the field of hematology. This study aims to review the current applications of AI in the field of hematopoietic cell transplantation (HCT). A literature search was done involving the following databases: Ovid MEDLINE, including In-Process and other non-indexed citations, and Google Scholar. The abstracts of the following professional societies were also screened: American Society of Hematology, American Society for Blood and Marrow Transplantation, and European Society for Blood and Marrow Transplantation. The literature review showed that the integration of AI in the field of HCT has grown remarkably in the last decade and offers promising avenues in diagnosis and prognosis in HCT populations targeting both pre- and post-transplant challenges. Studies of AI integration in HCT have many limitations that include poorly tested algorithms, lack of generalizability, and limited use of different AI tools. Machine learning techniques in HCT are an intense area of research that needs much development and extensive support from hematology and HCT societies and organizations globally as we believe that this will be the future practice paradigm.

Mundle, S., et al. (1999). "The relative extent and propensity of CD34+ vs. CD34- cells to undergo apoptosis in myelodysplastic marrows." Int J Hematol **69**(3): 152-159.

The paradox of peripheral cytopenias despite cellular bone marrow (BM) observed in myelodysplastic syndromes (MDS) has been associated with excessive intramedullary apoptosis of hematopoietic cells. Since MDS is regarded as a stem cell disorder, the present studies were undertaken to examine the relative susceptibility and propensity of early progenitor CD34+ cells to undergo apoptosis as compared to more maturing/matured CD34- cells. Five serial studies were performed on 4 independent groups of 36 newly diagnosed MDS patients. First, in 2 separate groups of 16 and 8 patients each, measurement of the extent of apoptosis in CD34+ and CD34- fractions of the BM aspirate mononuclear cells was carried out using independent biparametric flow cytometry methods, CD34 labeling/terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) (n = 16), and CD34 labeling/reduced uptake of nucleic acid staining dye LDS751 (n = 8). The difference in the median degrees of apoptosis in CD34+ vs. CD34- cells was not statistically significant by either technique (P = 0.583 and P = 0.674 for TUNEL and LDS751, respectively). In the next group of 4 MDS patients, a

double-labeling was performed on plastic embedded marrow biopsy sections, to detect CD34 antigen with specific monoclonal antibody and apoptosis by in situ end labeling (ISEL) of fragmented DNA. Despite high overall apoptosis (56.2% +/- 18.4%), only an occasional CD34+ cell was found to be simultaneously labeled with ISEL. Finally, in the last group of 8 MDS patients, CD34+ cells were separated from CD34- cells on affinity column and cultured in serum containing medium for 4 hours. At 0- and 4-hour time points, ISEL was carried out to label apoptotic cells. In addition, a fluorometric assay was employed to estimate the activity of a proapoptotic enzyme, Caspase 3. Both the net increase in % ISEL labeled cells (apoptotic index or AI) and Caspase-3 activity were significantly lower in CD34+ cells as compared to CD34- cells (AI, 0.87% +/- 0.5% vs. 3.97% +/- 1.4%, n = 6, P = 0.028 and Caspase-3 Units/mg protein, 46.9 +/- 25.0 vs. 71.7 +/- 23.03, n = 5, P = 0.042, respectively). We conclude that when estimated in a total population of mononuclear cells, CD34+ cells and CD34- cells show comparable degrees of apoptosis. However, once separated the CD34+ fraction demonstrates lower propensity to undergo apoptosis, thereby suggesting the CD34- fraction as being a possible source for proapoptotic signaling.

Murphy, A. J., et al. (2013). "Pegylation of high-density lipoprotein decreases plasma clearance and enhances antiatherogenic activity." Circ Res **113**(1): e1-e9.

RATIONALE: Infusions of apolipoprotein AI (apoAI), mimetic peptides, or high-density lipoprotein (HDL) remain a promising approach for the treatment of atherosclerotic coronary disease. However, rapid clearance leads to a requirement for repeated administration of large amounts of material and limits effective plasma concentrations. OBJECTIVE: Because pegylation of purified proteins is commonly used as a method to increase their half-life in the circulation, we determined whether pegylation of apoAI or HDL would increase its plasma half-life and in turn its antiatherogenic potential. METHODS AND RESULTS: Initial pegylation attempts using lipid-poor apoAI showed a marked tendency to form multi-pegylated (PEG) species with reduced ability to promote cholesterol efflux from macrophage foam cells. However, pegylation of human holo-HDL or reconstituted phospholipid/apoAI particles (rHDL) led to selective N-terminal monopegylation of apoAI with full preservation of cholesterol efflux activity. The plasma clearance of PEG-rHDL was estimated after injection into hypercholesterolemic Apoe-/- mice; the half-life of pegylated PEG-apoAI after injection of PEG-rHDL was increased approximately 7-fold compared with apoAI in nonpegylated rHDL. In comparison with nonpegylated rHDL, infusion of PEG-rHDL (40 mg/kg) into hypercholesterolemic Apoe-/- mice led to more pronounced suppression of bone marrow myeloid progenitor cell proliferation and monocytosis, as well as reduced atherosclerosis and a stable plaque phenotype. CONCLUSIONS: We describe a novel method for effective monopegylation of apoAI in HDL particles, in which lipid binding seems to protect against pegylation of key functional residues. Pegylation of apoAI in rHDL markedly increases its plasma half-life and enhances antiatherogenic properties in vivo.

Murphy, A. J., et al. (2012). "Anti-atherogenic mechanisms of high density lipoprotein: effects on myeloid cells." Biochim Biophys Acta **1821**(3): 513-521.

In some settings increasing high density lipoprotein (HDL) levels has been associated with a reduction in experimental atherosclerosis. This has been most clearly seen in apolipoprotein A-I (apoA-I) transgenic mice or in animals infused with HDL or its apolipoproteins. A major mechanism by which these treatments are thought to delay progression or cause regression of atherosclerosis is by promoting efflux of cholesterol from macrophage foam cells. In addition, HDL has been described as having anti-inflammatory and other beneficial effects. Some recent research has linked anti-inflammatory effects to cholesterol efflux pathways but likely multiple mechanisms are involved. Macrophage cholesterol efflux may have a role in facilitating emigration of macrophages from lesions during regression. While macrophages can mediate cholesterol efflux by several pathways, studies in knockout mice or cells point to the importance of active efflux mediated by ATP binding cassette transporter (ABC) A1 and G1. In addition to traditional roles in macrophages, these transporters have been implicated in the control of hematopoietic stem cell proliferation, monocytosis and neutrophilia, as well as activation of monocytes and neutrophils. Thus, HDL and cholesterol efflux pathways may have important anti-atherogenic effects at all stages of the myeloid cell/monocyte/dendritic cell/macrophage lifecycle. This article is part of a Special Issue entitled Advances in High Density Lipoprotein Formation and Metabolism: A Tribute to John F. Oram (1945-2010).

Mushtaq, A. H., et al. (2023). "Machine learning applications and challenges in graft-versus-host disease: a scoping review." Curr Opin Oncol **35**(6): 594-600.

PURPOSE OF REVIEW: This review delves into the potential of artificial intelligence (AI), particularly machine learning (ML), in enhancing graft-versus-host disease (GVHD) risk assessment, diagnosis, and personalized treatment. RECENT FINDINGS: Recent studies have demonstrated the superiority of ML algorithms over traditional multivariate statistical models in donor selection for allogeneic hematopoietic stem cell transplantation. ML has recently enabled dynamic risk assessment by modeling time-series data, an upgrade from the static, "snapshot" assessment of patients that conventional statistical models and older ML algorithms offer. Regarding diagnosis, a deep learning model, a subset of ML, can accurately identify skin segments affected with chronic GVHD with satisfactory results. ML methods such as Q-learning and deep reinforcement learning have been utilized to develop adaptive treatment strategies (ATS) for the personalized prevention and treatment of acute and chronic GVHD. SUMMARY: To capitalize on these promising advancements, there is a need for large-scale, multicenter collaborations to develop generalizable ML models. Furthermore, addressing pertinent issues such as the implementation of stringent ethical guidelines is crucial before the widespread introduction of AI into GVHD care.

Musial, K., et al. (2024). "Assessment of Risk Factors for Acute Kidney Injury with Machine Learning Tools in Children Undergoing Hematopoietic Stem Cell Transplantation." J Clin Med **13**(8).

Background: Although acute kidney injury (AKI) is a common complication in patients undergoing hematopoietic stem cell transplantation (HSCT), its prophylaxis remains a clinical challenge. Attempts at prevention or early diagnosis focus on various methods for the identification of factors influencing the incidence of AKI. Our aim was to test the artificial intelligence (AI) potential in the construction of a model defining parameters predicting AKI development. Methods: The analysis covered the clinical data of children followed up for 6 months after HSCT. Kidney function was assessed before conditioning therapy, 24 h after HSCT, 1, 2, 3, 4, and 8 weeks after transplantation, and, finally, 3 and 6 months post-transplant. The type of donor, conditioning protocol, and complications were incorporated into the model. Results: A random forest classifier (RFC) labeled the 93 patients according to presence or absence of AKI. The RFC model revealed that the values of the estimated glomerular filtration rate (eGFR) before and just after HSCT, as well as methotrexate use, acute graft versus host disease (GvHD), and viral infection occurrence, were the major determinants of AKI incidence within the 6-month post-transplant observation period. Conclusions: Artificial intelligence seems a promising tool in predicting the potential risk of developing AKI, even before HSCT or just after the procedure.

Mussetti, A., et al. (2024). "Artificial intelligence methods to estimate overall mortality and non-relapse mortality following allogeneic HCT in the modern era: an EBMT-TCWP study." Bone Marrow Transplant **59**(2): 232-238.

Allogeneic haematopoietic cell transplantation (alloHCT) has curative potential counterbalanced by its toxicity. Prognostic scores fail to include current era patients and alternative donors. We examined adult patients from the EBMT registry who underwent alloHCT between 2010 and 2019 for oncohaematological disease. Our primary objective was to develop a new prognostic score for overall mortality (OM), with a secondary objective of predicting non-relapse mortality (NRM) using the OM score. AI techniques were employed. The model for OM was trained, optimized, and validated using 70%, 15%, and 15% of the data set, respectively. The top models, "gradient boosting" for OM (AUC = 0.64) and "elasticnet" for NRM (AUC = 0.62), were selected. The analysis included 33,927 patients. In the final prognostic model, patients with the lowest score had a 2-year OM and NRM of 18 and 13%, respectively, while those with the highest score had a 2-year OM and NRM of 82 and 93%, respectively. The results were consistent in the subset of the haploidentical cohort (n = 4386). Our score effectively stratifies the risk of OM and NRM in the current era but do not significantly improve mortality prediction. Future prognostic scores can benefit from identifying biological or dynamic markers post alloHCT.

Mythreye, K., et al. (2008). "ApoA-I induced CD31 in bone marrow-derived vascular progenitor cells increases adhesion: implications for vascular repair." Biochim Biophys Acta **1781**(11-12): 703-709.

Transgenic over expression of apolipoprotein A-I (ApoA-I) the major structural apolipoprotein of HDL appears to convey the most consistent and strongest anti atherogenic effect observed in animal models so far. We tested the hypothesis that ApoA-I mediates its cardio protective effects additionally through ApoA-I induced differentiation of bone marrow-derived progenitor cells in vitro. This study demonstrates that lineage negative bone marrow cells (lin(-) BMCs) alter and differentiate in response to free ApoA-I. We find that lin(-) BMCs in culture treated with recombinant free

ApoA-I at a concentration of 0.4 microM are twice as large in size and have altered cell morphology compared to untreated cells; untreated cells retain the original spheroid morphology. Further, the total number of CD31 positive cells in the ApoA-I treated population consistently increased by two fold. This phenotype was significantly reduced in untreated cells and points towards a novel ApoA-I dependent differentiation. A protein lacking its best lipid-binding region (ApoA-I Delta 10) did not stimulate any changes in the lin(-)BMCs indicating that ApoA-I may mediate its effects by regulating cholesterol efflux. The increased CD31 correlates with an increased ability of the lin(-) BMCs to adhere to both fibronectin and mouse brain endothelial cells. Our results provide the first evidence that exogenous free ApoA-I has the capacity to change the characteristics of progenitor cell populations and suggests a novel mechanism by which HDL may mediate its cardiovascular benefits.

Nakami, W., et al. (2021). "Culture of spermatogonial stem cells and use of surrogate sires as a breeding technology to propagate superior genetics in livestock production: A systematic review." Vet World **14**(12): 3235-3248.

BACKGROUND AND AIM: Spermatogonial stem cells (SSCs) have previously been isolated from animals' testes, cultured in vitro, and successfully transplanted into compatible recipients. The SSC unique characteristic has potential for exploitation as a reproductive tool and this can be achieved through SSC intratesticular transplantation to surrogate sires. Here, we aimed at comprehensively analyzing published data on in vitro maintenance of SSC isolated from the testes of livestock animals and their applications. MATERIALS AND METHODS: The literature search was performed in PubMed, Science Direct, and Google Scholar electronic databases. Data screening was conducted using Rayyan Intelligent Systematic Review software (https://www.rayyan.ai/). Duplicate papers were excluded from the study. Abstracts were read and relevant full papers were reviewed for data extraction. RESULTS: From a total of 4786 full papers screened, data were extracted from 93 relevant papers. Of these, eight papers reported on long-term culture conditions (>1 month) for SSC in different livestock species, 22 papers on short-term cultures (5-15 days), 10 papers on transfection protocols, 18 papers on transplantation using different methods of preparation of livestock recipients, and five papers on donor-derived spermatogenesis. CONCLUSION: Optimization of SSC long-term culture systems has renewed the possibilities of utilization of these cells in gene-editing technologies to develop transgenic animals. Further, the development of genetically deficient recipients in the endogenous germline layer lends to a future possibility for the utilization of germ cell transplantation in livestock systems.

Nardone, S., et al. (2024). "A spatially-resolved transcriptional atlas of the murine dorsal pons at single-cell resolution." Nat Commun **15**(1): 1966.

The "dorsal pons", or "dorsal pontine tegmentum" (dPnTg), is part of the brainstem. It is a complex, densely packed region whose nuclei are involved in regulating many vital functions. Notable among them are the parabrachial nucleus, the Kolliker Fuse, the Barrington nucleus, the locus coeruleus, and the dorsal, laterodorsal, and ventral tegmental nuclei. In this study, we applied single-nucleus RNA-seq (snRNA-seq) to resolve neuronal subtypes based on their unique transcriptional profiles and then used multiplexed error robust fluorescence in situ hybridization (MERFISH) to map them spatially. We sampled ~1 million cells across the dPnTg and defined the spatial distribution of over 120 neuronal subtypes. Our analysis identified an unpredicted high transcriptional diversity in this region and pinpointed the unique marker genes of many neuronal subtypes. We also demonstrated that many neuronal subtypes are transcriptionally similar between humans and mice, enhancing this study's translational value. Finally, we developed a freely accessible, GPU and CPU-powered dashboard (http://harvard.heavy.ai:6273/) that combines interactive visual analytics and hardware-accelerated SQL into a data science framework to allow the scientific community to query and gain insights into the data.

Nguyen, T., et al. (2023). "Analysis of cardiac single-cell RNA-sequencing data can be improved by the use of artificial-intelligence-based tools." Sci Rep **13**(1): 6821.

Single-cell RNA sequencing (scRNAseq) enables researchers to identify and characterize populations and subpopulations of different cell types in hearts recovering from myocardial infarction (MI) by characterizing the transcriptomes in thousands of individual cells. However, the effectiveness of the currently available tools for processing and interpreting these immense datasets is limited. We incorporated three Artificial Intelligence (AI) techniques into a toolkit for evaluating scRNAseq data: AI Autoencoding separates data from different cell types and subpopulations of cell types (cluster analysis); AI Sparse Modeling identifies genes and signaling mechanisms that are differentially activated between subpopulations (pathway/gene set

enrichment analysis), and AI Semisupervised Learning tracks the transformation of cells from one subpopulation into another (trajectory analysis). Autoencoding was often used in data denoising; yet, in our pipeline, Autoencoding was exclusively used for cell embedding and clustering. The performance of our AI scRNAseq toolkit and other highly cited non-AI tools was evaluated with three scRNAseq datasets obtained from the Gene Expression Omnibus database. Autoencoder was the only tool to identify differences between the cardiomyocyte subpopulations found in mice that underwent MI or sham-MI surgery on postnatal day (P) 1. Statistically significant differences between cardiomyocytes from P1-MI mice and mice that underwent MI on P8 were identified for six cell-cycle phases and five signaling pathways when the data were analyzed via Sparse Modeling, compared to just one cell-cycle phase and one pathway when the data were analyzed with non-AI techniques. Only Semisupervised Learning detected trajectories between the predominant cardiomyocyte clusters in hearts collected on P28 from pigs that underwent apical resection (AR) on P1, and on P30 from pigs that underwent AR on P1 and MI on P28. In another dataset, the pig scRNAseq data were collected after the injection of CCND2-overexpression Human-induced Pluripotent Stem Cell-derived cardiomyocytes ((CCND2)hiPSC) into injured P28 pig heart; only the AI-based technique could demonstrate that the host cardiomyocytes increase proliferating by through the HIPPO/YAP and MAPK signaling pathways. For the cluster, pathway/gene set enrichment, and trajectory analysis of scRNAseq datasets generated from studies of myocardial regeneration in mice and pigs, our AI-based toolkit identified results that non-AI techniques did not discover. These different results were validated and were important in explaining myocardial regeneration.

Nosrati, H. and M. Nosrati (2023). "Artificial Intelligence in Regenerative Medicine: Applications and Implications." Biomimetics (Basel) **8**(5).

The field of regenerative medicine is constantly advancing and aims to repair, regenerate, or substitute impaired or unhealthy tissues and organs using cutting-edge approaches such as stem cell-based therapies, gene therapy, and tissue engineering. Nevertheless, incorporating artificial intelligence (AI) technologies has opened new doors for research in this field. AI refers to the ability of machines to perform tasks that typically require human intelligence in ways such as learning the patterns in the data and applying that to the new data without being explicitly programmed. AI has the potential to improve and accelerate various aspects of regenerative medicine research and development, particularly, although not exclusively, when complex patterns are involved. This review paper provides an overview of AI in the context of regenerative medicine, discusses its potential applications with a focus on personalized medicine, and highlights the challenges and opportunities in this field.

Obradovic, D., et al. (2016). "Autologous hematopoietic stem cell transplantation in combination with immunoablative protocol in secondary progressive multiple sclerosis--A 10-year follow-up of the first transplanted patient." Vojnosanit Pregl **73**(5): 504-508.

INTRODUCTION: Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that affects young individuals and leads to severe disability. High dose immunoablation followed by autologous hemopoietic stem cell transplantation (AHSCT) has been considered in the last 15 years as potentialy effective therapeutic approach for aggressive MS. The most recent long-time follow-up results suggest that AHSCT is not only effective for highly-aggressive MS, but for relapsing-remitting MS as well, providing long-term remission, or maybe even cure. We presented a 10-year follow-up of the first MS patient being treated by immunoablation therapy and AHSCT. CASE REPORT: A 27-year-old male experienced the first symptoms--intermitent numbness and paresthesia of arms and legs of what was treated for two years by psychiatrist as anxiety disorder. After he developed severe paraparesis he was admitted to the Neurology Clinic and diagnosed with MS. Our patient developed aggressive MS with frequent relapses, rapid disability progression and transition to secondary progressive form 6 years after MS onset[the Expanded Disability Status Scale (EDSS) 7.0 Ambulation Index (AI) 7]. AHSCT was performed, cyclophosphamide was used for hemopoietic stem cell mobilization and the BEAM protocol was used as conditionig regimen. No major adverse events followed the AHSCT. Neurological impairment improved, EDSS 6.5, AI 6 and during a 10-year follow-up remained unchanged. Brain MRI follow-up showed the absence of gadolinium enhancing lesions and a mild progression of brain atrophy. CONCLUSION: The patient with rapidly evolving, aggressive, noninflammatory MS initialy improved and remained stable, without disability progression for 10 years, after AHSCT. This kind of treatment should be considered in aggressive MS, or in disease modifying treatment nonresponsive MS patients, since appropriately timed AHSCT treatment may not only prevent disability progression but reduce the achieved level of disability, as well.

Okamoto, T., et al. (2022). "Integration of human inspection and artificial intelligence-based morphological typing of patient-derived organoids reveals interpatient heterogeneity of colorectal cancer." Cancer Sci **113**(8): 2693-2703.

Colorectal cancer (CRC) is a heterogenous disease, and patients have differences in therapeutic response. However, the mechanisms underlying interpatient heterogeneity in the response to chemotherapeutic agents remain to be elucidated, and molecular tumor characteristics are required to select patients for specific therapies. Patient-derived organoids (PDOs) established from CRCs recapitulate various biological characteristics of tumor tissues, including cellular heterogeneity and the response to chemotherapy. Patient-derived organoids established from CRCs show various morphologies, but there are no criteria for defining these morphologies, which hampers the analysis of their biological significance. Here, we developed an artificial intelligence (AI)-based classifier to categorize PDOs based on microscopic images according to their similarity in appearance and classified tubular adenocarcinoma-derived PDOs into six types. Transcriptome analysis identified differential expression of genes related to cell adhesion in some of the morphological types. Genes involved in ribosome biogenesis were also differentially expressed and were most highly expressed in morphological types showing CRC stem cell properties. We identified an RNA polymerase I inhibitor, CX-5641, to be an upstream regulator of these type-specific gene sets. Notably, PDO types with increased expression of genes involved in ribosome biogenesis were resistant to CX-5461 treatment. Taken together, these results uncover the biological significance of the morphology of PDOs and provide novel indicators by which to categorize CRCs. Therefore, the AI-based classifier is a useful tool to support PDO-based cancer research.

Olivera, R., et al. (2018). "Bone marrow mesenchymal stem cells as nuclear donors improve viability and health of cloned horses." Stem Cells Cloning **11**: 13-22.

INTRODUCTION: Cell plasticity is crucial in cloning to allow an efficient nuclear reprogramming and healthy offspring. Hence, cells with high plasticity, such as multipotent mesenchymal stem cells (MSCs), may be a promising alternative for horse cloning. In this study, we evaluated the use of bone marrow-MSCs (BM-MSCs) as nuclear donors in horse cloning, and we compared the in vitro and in vivo embryo development with respect to fibroblasts. MATERIALS AND METHODS: Zona-free nuclear transfer was performed using BM-MSCs (MSC group, n=3432) or adult fibroblasts (AF group, n=4527). Embryos produced by artificial insemination (AI) recovered by uterine flushing and transferred to recipient mares were used as controls (AI group). RESULTS: Blastocyst development was higher in the MSC group than in the AF group (18.1% vs 10.9%, respectively; $p<0.05$). However, pregnancy rates and delivery rates were similar in both cloning groups, although they were lower than in the AI group (pregnancy rates: 17.7% [41/232] for MSC, 12.5% [37/297] for AF and 80.7% [71/88] for AI; delivery rates: 56.8% [21/37], 41.5% [17/41] and 90.1% [64/71], respectively). Remarkably, the gestation length of the AF group was significantly longer than the control (361.7+/-10.9 vs 333.9+/-8.7 days), in contrast to the MSC group (340.6+/-8.89 days). Of the total deliveries, 95.2% (20/21) of the MSC-foals were viable, compared to 52.9% (9/17) of the AF-foals ($p<0.05$). In addition, the AF-foals had more physiological abnormalities at birth than the MSC-foals; 90.5% (19/21) of the MSC-delivered foals were completely normal and healthy, compared to 35.3% (6/17) in the AF group. The abnormalities included flexural or angular limb deformities, umbilical cord enlargement, placental alterations and signs of syndrome of neonatal maladjustment, which were treated in most cases. CONCLUSION: In summary, we obtained 29 viable cloned foals and found that MSCs are suitable donor cells in horse cloning. Even more, these cells could be more efficiently reprogrammed compared to fibroblasts.

Otterstrom, J. J., et al. (2022). "Technologies bringing young Zebrafish from a niche field to the limelight." SLAS Technol **27**(2): 109-120.

Fundamental life science and pharmaceutical research are continually striving to provide physiologically relevant context for their biological studies. Zebrafish present an opportunity for high-content screening (HCS) to bring a true in vivo model system to screening studies. Zebrafish embryos and young larvae are an economical, human-relevant model organism that are amenable to both genetic engineering and modification, and direct inspection via microscopy. The use of these organisms entails unique challenges that new technologies are overcoming, including artificial intelligence (AI). In this perspective article, we describe the state-of-the-art in terms of automated sample handling, imaging, and data analysis with zebrafish during early developmental stages. We highlight advances in orienting the embryos, including the use of robots, microfluidics, and creative multi-well plate solutions. Analyzing the

micrographs in a fast, reliable fashion that maintains the anatomical context of the fluorescently labeled cells is a crucial step. Existing software solutions range from AI-driven commercial solutions to bespoke analysis algorithms. Deep learning appears to be a critical tool that researchers are only beginning to apply, but already facilitates many automated steps in the experimental workflow. Currently, such work has permitted the cellular quantification of multiple cell types in vivo, including stem cell responses to stress and drugs, neuronal myelination and macrophage behavior during inflammation and infection. We evaluate pro and cons of proprietary versus open-source methodologies for combining technologies into fully automated workflows of zebrafish studies. Zebrafish are poised to charge into HCS with ever-greater presence, bringing a new level of physiological context.

Padi, S., et al. (2020). "Comparison of Artificial Intelligence based approaches to cell function prediction." Inform Med Unlocked **18**.

Predicting Retinal Pigment Epithelium (RPE) cell functions in stem cell implants using non-invasive bright field microscopy imaging is a critical task for clinical deployment of stem cell therapies. Such cell function predictions can be carried out using Artificial Intelligence (AI) based models. In this paper we used Traditional Machine Learning (TML) and Deep Learning (DL) based AI models for cell function prediction tasks. TML models depend on feature engineering and DL models perform feature engineering automatically but have higher modeling complexity. This work aims at exploring the tradeoffs between three approaches using TML and DL based models for RPE cell function prediction from microscopy images and at understanding the accuracy relationship between pixel-, cell feature-, and implant label-level accuracies of models. Among the three compared approaches to cell function prediction, the direct approach to cell function prediction from images is slightly more accurate in comparison to indirect approaches using intermediate segmentation and/or feature engineering steps. We also evaluated accuracy variations with respect to model selections (five TML models and two DL models) and model configurations (with and without transfer learning). Finally, we quantified the relationships between segmentation accuracy and the number of samples used for training a model, segmentation accuracy and cell feature error, and cell feature error and accuracy of implant labels. We concluded that for the RPE cell data set, there is a monotonic relationship between the number of training samples and image segmentation accuracy, and between segmentation accuracy and cell feature error, but there is no such a relationship between segmentation accuracy and accuracy of RPE implant labels.

Papa, P. M., et al. (2020). "Clinical safety of intratesticular transplantation of allogeneic bone marrow multipotent stromal cells in stallions." Reprod Domest Anim **55**(4): 429-437.

Although stem cell therapy is a promising alternative for treatment of degenerative diseases, there are just few reports on the use of stem cells therapy in horse's reproductive system. This study aims to evaluate the effect of intratesticular injection of bone marrow mesenchymal stromal/stem cells (MSCs) in healthy stallions, and its outcome on seminal parameters and fertility. In Experiment 1, 24 stallions were divided into treatment group (TG) and control group (CG). In the TG, an intratesticular application of MSC was performed, and in the CG, only PBS was used. Measurements of testicular volume, surface temperature and Doppler ultrasonography were performed 24 and 48 hr after treatments. Fifteen days after application, the testicles were removed and submitted to histological analysis. In Experiment 2, 3 fertile stallions received similarly treatment with MSCs. Physical examination and sperm analysis were performed weekly during 60 days after treatment, and at the end, semen from one of them was used for artificial inseminations of 6 healthy mares. In Experiment 1, clinical examinations showed no signals of acute inflammation on both groups according to the analysed variables ($p > .05$). Also, no signal of chronic inflammation was observed on histological evaluation. In Experiment 2, stallions presented no physical alterations or changes in sperm parameters, and a satisfactory fertility rate (83%; 5/6) was observed after AI. The results support the hypothesis that intratesticular application of bone marrow MSCs is a safe procedure, and this could be a promising alternative to treat testicular degenerative conditions.

Parihar, A. S., et al. (2024). "Diabetes and Oral Health: Advancements in Prevention, Screening and Treatment of Periodontal Diseases." J Pharm Bioallied Sci **16**(Suppl 3): S1968-S1970.

Diabetes is a pervasive metabolic disorder that notably impacts various body systems, including oral health. One of the critical manifestations of diabetes in oral health is its exacerbating effect on periodontal diseases. Recent advancements in the prevention, screening, and treatment of periodontal diseases have become increasingly significant due to the bidirectional link between periodontal health and diabetes management. This review explores

contemporary strategies and technological innovations in the comprehensive management of periodontal diseases among diabetic patients. It highlights the integration of digital dentistry tools such as artificial intelligence (AI) and teledentistry in enhancing diagnostic precision and treatment outcomes. Preventive measures, including new pharmacological formulations and lifestyle interventions tailored for diabetic individuals, are discussed. Additionally, the review underscores the importance of routine screening protocols that incorporate glycemic control status to refine treatment plans for periodontal therapies. Furthermore, advancements in regenerative therapies, including the application of growth factors and stem cell therapy, are examined for their potential to restore periodontal tissue integrity, offering promising directions for future research and clinical practice. Through a synthesis of recent literature, this review aims to provide insights into effective periodontal disease management strategies that are critical for improving the overall health and quality of life of individuals with diabetes.

Patel, J. R., et al. (2023). "Novel Therapeutic Combination Targets the Growth of Letrozole-Resistant Breast Cancer through Decreased Cyclin B1." Nutrients **15**(7).

As breast cancer cells transition from letrozole-sensitive to letrozole-resistant, they over-express epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), and human epidermal growth factor receptor 2 (HER2) while acquiring enhanced motility and epithelial-to-mesenchymal transition (EMT)-like characteristics that are attenuated and reversed by glyceollin treatment, respectively. Interestingly, glyceollin inhibits the proliferation and tumor progression of triple-negative breast cancer (TNBC) and estrogen-independent breast cancer cells; however, it is unlikely that a single phytochemical would effectively target aromatase-inhibitor (AI)-resistant metastatic breast cancer in the clinical setting. Since our previous report indicated that the combination of lapatinib and glyceollin induced apoptosis in hormone-dependent AI-resistant breast cancer cells, we hypothesized that combination therapy would also be beneficial for hormone independent letrozole-resistant breast cancer cells (LTLT-Ca) compared to AI-sensitive breast cancer cells (AC-1) by decreasing the expression of proteins associated with proliferation and cell cycle progression. While glyceollin + lapatinib treatment caused comparable inhibitory effects on the proliferation and migration in both cell lines, combination treatment selectively induced S and G2/M phase cell cycle arrest of the LTLT-Ca cells, which was mediated by decreased cyclin B1. This phenomenon may represent a unique opportunity to design novel combinatorial therapeutic approaches to target hormone-refractory breast tumors.

Patel, J. R., et al. (2021). "Mammospheres of letrozole-resistant breast cancer cells enhance breast cancer aggressiveness." Oncol Lett **22**(2): 620.

Aromatase inhibitors (AIs), such as letrozole, are considered as first-line treatment for estrogen receptor-positive breast cancer in postmenopausal women. Despite the successful use of letrozole, resistance to therapy, tumor relapse and metastasis remain principal causes of patient mortality. Although there is no therapy currently available for AI-resistant breast cancer, previous reports have demonstrated that AI resistance is associated with hormone independence, increased growth factor signaling, enhanced cellular motility and epithelial to mesenchymal transition (EMT). This suggests a convergence of EMT and cancer stem cells (CSCs) in endocrine resistance. The present study evaluated the contribution of mammospheres in letrozole-resistant breast cancer by characterizing mammospheres and their potential impact on cellular motility. Ovariectomized immunocompromised female mice were inoculated in the mammary fat pad with either letrozole-resistant MCF-7 cells (LTLT-Ca) or letrozole-sensitive MCF-7 cells (AC-1). Subsequently, intratumoral CSC marker expression was assessed by immunohistochemistry. The results indicated that LTLT-Ca tumors were CD44(+)/CD24(+), while AC-1 tumors presented low CD44/CD24 expression. Since mammosphere formation depends on CSCs, both cell lines were cultured either adherently (2D) or as mammospheres (3D) to assess the CD44/CD24 protein expression profile. When 3D culturing both cell lines, higher expression levels of CD44 and CD24 were observed when compared with their adherent counterparts, with the most robust change observed in the LTLT-Ca cell line. To quantitate the breast cancer stem cell activity, mammosphere formation assays were performed, and the LTLT-Ca cells formed mammospheres at a 3.4-fold higher index compared with AC-1 cells. Additionally, targeted gene expression arrays were conducted to compare the LTLT-Ca 3D and 2D cells, revealing that LTLT-Ca 3D cells displayed decreased expression levels of genes involved in cell adhesion and tumor suppression (e. g., E-cadherin, caveolin 1 and beta-catenin). To validate this finding, wound healing assays were performed, and LTLT-Ca mammospheres exhibited a 70% wound closure, whereas AC-1 mammospheres exhibited a 39% wound closure. Collectively, the present findings demonstrated a

strong association between AI-resistant mammospheres and an increased propensity for migration, which may be indicative of a poor prognosis.

Patino, C. A., et al. (2021). "Deep Learning and Computer Vision Strategies for Automated Gene Editing with a Single-Cell Electroporation Platform." SLAS Technol **26**(1): 26-36.

Single-cell delivery platforms like microinjection and nanoprobe electroporation enable unparalleled control over cell manipulation tasks but are generally limited in throughput. Here, we present an automated single-cell electroporation system capable of automatically detecting cells with artificial intelligence (AI) software and delivering exogenous cargoes of different sizes with uniform dosage. We implemented a fully convolutional network (FCN) architecture to precisely locate the nuclei and cytosol of six cell types with various shapes and sizes, using phase contrast microscopy. Nuclear staining or reporter fluorescence was used along with phase contrast images of cells within the same field of view to facilitate the manual annotation process. Furthermore, we leveraged the near-human inference capabilities of the FCN network in detecting stained nuclei to automatically generate ground-truth labels of thousands of cells within seconds, and observed no statistically significant difference in performance compared to training with manual annotations. The average detection sensitivity and precision of the FCN network were 95+/-1.7% and 90+/-1.8%, respectively, outperforming a traditional image-processing algorithm (72+/-7.2% and 72+/-5.5%) used for comparison. To test the platform, we delivered fluorescent-labeled proteins into adhered cells and measured a delivery efficiency of 90%. As a demonstration, we used the automated single-cell electroporation platform to deliver Cas9-guide RNA (gRNA) complexes into an induced pluripotent stem cell (iPSC) line to knock out a green fluorescent protein-encoding gene in a population of ~200 cells. The results demonstrate that automated single-cell delivery is a useful cell manipulation tool for applications that demand throughput, control, and precision.

Pereira, G. C. (2023). "Novel Nanotechnology-Driven Prototypes for AI-Enriched Implanted Prosthetics Following Organ Failure." Methods Mol Biol **2575**: 195-237.

Meeting medical challenges posed by global burdens is proven to be of primary interest. One example is the COVID-19 epidemic that humankind is currently experiencing, since around December 2019. Innovation is key to respond rapidly and effectively to sanitary and health emergencies, when human lives are severely threatened. In this scenery, medical devices that can be rapidly launched in the market and manufactured at scale are crucial for saving lives. One example is a lifesaving respiratory device launched in about 10 days (Mercedes F1 team's new device based on continuous positive airway pressure devices) and rapidly approved by international agencies responsible for assuring drug and medical devices safety, in response to the COVID-19 burden. Remarkably, it is the first time in history that mankind observes disease spread reaching such high proportions, globally, in such short time scale. However, while this epidemic had, in March 2020, reached the critical figures of about 38,000 deaths and c. 738,000 infected, organ donation and transplantation patients are suffering for years, accounting for an increasing number of affected, annually. These patients are invisible for the general public. Therefore, this chapter approaches the organ donation and transplantation burden, proposing effective solutions to leverage the suffering, improving life quality of patients enduring several underlying issues, from hemodialysis complications and critical organ failure to lacking compatible donors. This, on the basis of technology repurposing, to speed up approval processes followed by international agencies responsible for assuring drug and medical devices safety, while adding innovative methods to existing technology and reducing invasiveness.

Piralla, A., et al. (2015). "Persistent rhinovirus infection in pediatric hematopoietic stem cell transplant recipients with impaired cellular immunity." J Clin Virol **67**: 38-42.

BACKGROUND: HRV infections are generally self-limiting in healthy subjects, whereas in immunocompromised hosts HRV infections can lead to severe complications and persistent infections. The persistence of HRV shedding could be due to the inefficient immunological control of a single infectious episode. OBJECTIVES: To investigate the clinical, virologic and immunologic characteristics of pediatric HSCT recipients with HRV-PI infection. STUDY DESIGN: During the period 2006-2012, eight hematopoietic stem cell transplant (HSCT) recipients presented with persistent rhinovirus infection (HRV-PI, >/=30 days). Viral load and T-CD4(+), T-CD8(+), B and NK lymphocyte counts at the onset of infection were compared with those of fourteen HSCT recipients with acute HRV infection (HRV-AI, </=15 days). RESULTS: The median duration of HRV positivity in patients with HRV-PI was 61 days (range 30-174 days) and phylogenetic analysis showed the persistence of a single HRV type

in all patients (100%). In HSCT recipients with HRV-PI, T-CD4(+), T-CD8(+) and NK cell counts at the onset of infection were significantly lower than those observed in recipients with HRV-AI ($p<0.01$), while B cell counts were similar in the two groups ($p= 0.25$). A decrease in HRV load was associated with a significant increase in T-CD4(+), T-CD8(+)and NK lymphocyte counts in HRV-PI patients ($p<0.01$). CONCLUSIONS: This study suggests a role for cellular immunity in HRV clearance and highlights the importance of its recovery for the control of HRV infection in HSCT recipients.

Plump, A. S., et al. (1996). "Apolipoprotein A-I is required for cholesteryl ester accumulation in steroidogenic cells and for normal adrenal steroid production." J Clin Invest **97**(11): 2660-2671.

In addition to its ability to remove cholesterol from cells, HDL also delivers cholesterol to cells through a poorly defined process in which cholesteryl esters are selectively transferred from HDL particles into the cell without the uptake and degradation of the lipoprotein particle. The HDL-cholesteryl ester selective uptake pathway is known to occur in human, rabbit, and rodent hepatocytes where it may contribute to the clearance of plasma cholesteryl ester. The selective uptake pathway has been studied most extensively in steroidogenic cells of rodents in which it accounts for 90% or more of the cholesterol destined for steroid production or cholesteryl ester accumulation. In this study we have used apo A-I-, apo A-II-, and apo E-deficient mice created by gene targeting in embryonic stem cells to test the importance of the three major HDL proteins in determining cholesteryl ester accumulation in steroidogenic cells of the adrenal gland, ovary, and testis. apo E and apo A-II deficiencies were found to have only modest effects on cholesteryl ester accumulation. In contrast, apo A-I deficiency caused an almost complete failure to accumulate cholesteryl ester in steroidogenic cells. These results suggest that apo A-I is essential for the selective uptake of HDL-cholesteryl esters. The lack of apo A-I has a major impact on adrenal gland physiology causing diminished basal corticosteroid production, a blunted steroidogenic response to stress, and increased expression of compensatory pathways to provide cholesterol substrate for steroid production.

Polgreen, L. E., et al. (2011). "Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes." Eur J Pediatr **170**(8): 1049-1054.

Approximately one third of boys with X-linked adrenoleukodystophy (X-ALD) develop an acute, progressive inflammatory process of the central nervous system, resulting in rapid neurologic deterioration and death. Hematopoietic cell transplantation (HCT) can halt the progression of neurologic disease if performed early in the course of the cerebral form of X-ALD. We describe a retrospective cohort study of 90 boys with X-ALD evaluated at our institution between 2000 and 2009, to determine if early diagnosis of X-ALD following the diagnosis of unexplained adrenal insufficiency (AI) improves outcomes. We describe seven cases with a delay in the diagnosis of X-ALD and compare their outcomes to ten controls with the diagnosis of ALD made within 12 months following diagnosis of AI. At the time of evaluation for HCT, boys with a delay in the diagnosis of X-ALD had more extensive cerebral involvement and more limited functioning. These boys also were 3.9 times more likely to die and had significant advancement of cerebral disease after HCT, compared with boys with a timely diagnosis of X-ALD. In conclusion, the early diagnosis of cerebral X-ALD following the diagnosis of unexplained AI, and subsequent treatment with HCT improves both neurological outcomes and survival in boys with cerebral X-ALD.

Pollock, N. I., et al. (2024). "Exploring height outcomes with adjuvant aromatase inhibition in growth hormone-deficient male survivors of childhood cancer." Pediatr Blood Cancer **71**(8): e31117.

BACKGROUND: Aromatase inhibitors (AI) may improve height in short stature conditions; however, the effect in childhood cancer survivors (CCS) is unknown. We assessed final adult height (FAH) in CCS treated with AI and GH compared with those treated with GH alone. METHODS: Retrospective cohort study of GH-deficient male CCS treated between 2007 and 2023. FAH was noted as the height at the fusion of growth plates or 18 years of age. Multivariable linear regression was used to examine treatment association with FAH, adjusting for other risk factors. RESULTS: Ninety-two patients were included; 70 were treated with GH and 22 with combination AI/GH. The mean age at GH initiation did not differ between groups. The mean age at AI initiation was 13.7 +/- 1.9 years. A greater proportion of patients in the AI/GH group were treated with stem cell transplantation, abdominal radiation, total body irradiation, and cis-retinoic acid ($p < .01$). Multivariable linear regression demonstrated no significant treatment association with FAH Z-score (beta = 0.04, 95% CI: -0.9 to 0.9). History of spinal radiation (beta = -0.93, 95% CI: -1.7 to -0.2), lower starting height Z-score (beta = -0.8, 95% CI: -1.2 to -0.4), and greater difference between bone age and chronological age (beta = -0.3, 95% CI: -0.5 to -0.07)

were associated with lower FAH Z-score. CONCLUSIONS: Adjuvant AI was not associated with increased FAH in male CCS compared with GH monotherapy. Future work is needed to determine the optimal adjunctive treatment to maximize FAH for this population.

Popescu, V., et al. (2023). "Chronic Wound Management: From Gauze to Homologous Cellular Matrix." Biomedicines **11**(9).

BACKGROUND: Chronic wounds are a significant health problem with devastating consequences for patients' physical, social, and mental health, increasing healthcare systems' costs. Their prolonged healing times, economic burden, diminished quality of life, increased infection risk, and impact on patients' mobility and functionality make them a major concern for healthcare professionals. PURPOSE: This review offers a multi-perspective analysis of the medical literature focusing on chronic wound management. METHODS USED: We evaluated 48 articles from the last 21 years registered in the MEDLINE and Global Health databases. The articles included in our study had a minimum of 20 citations, patients > 18 years old, and focused on chronic, complex, and hard-to-heal wounds. Extracted data were summarized into a narrative synthesis using the same health-related quality of life instrument. RESULTS: We evaluated the efficacy of existing wound care therapies from classical methods to modern concepts, and wound care products to regenerative medicine that uses a patient's pluripotent stem cells and growth factors. Regenerative medicine and stem cell therapies, biologic dressings and scaffolds, negative pressure wound therapy (NPWT), electrical stimulation, topical growth factors and cytokines, hyperbaric oxygen therapy (HBOT), advanced wound dressings, artificial intelligence (AI), and digital wound management are all part of the new arsenal of wound healing. CONCLUSION: Periodic medical evaluation and proper use of modern wound care therapies, including the use of plasma-derived products [such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF)] combined with proper systemic support (adequate protein levels, blood sugar, vitamins involved in tissue regeneration, etc.) are the key to a faster wound healing, and, with the help of AI, can reach the fastest healing rate possible.

Porwit, A., et al. (2022). "Unsupervised cluster analysis and subset characterization of abnormal erythropoiesis using the bioinformatic Flow-Self Organizing Maps algorithm." Cytometry B Clin Cytom **102**(2): 134-142.

BACKGROUND: The Flow-Self Organizing Maps (FlowSOM) artificial intelligence (AI) program, available within the Bioconductor open-source R-project, allows for an unsupervised visualization and interpretation of multiparameter flow cytometry (MFC) data. METHODS: Applied to a reference merged file from 11 normal bone marrows (BM) analyzed with an MFC panel targeting erythropoiesis, FlowSOM allowed to identify six subpopulations of erythropoietic precursors (EPs). In order to find out how this program would help in the characterization of abnormalities in erythropoiesis, MFC data from list-mode files of 16 patients (5 with non-clonal anemia and 11 with myelodysplastic syndrome [MDS] at diagnosis) were analyzed. RESULTS: Unsupervised FlowSOM analysis identified 18 additional subsets of EPs not present in the merged normal BM samples. Most of them involved subtle unexpected and previously unreported modifications in CD36 and/or CD71 antigen expression and in side scatter characteristics. Three patterns were observed in MDS patient samples: i) EPs with decreased proliferation and abnormal proliferating precursors, ii) EPs with a normal proliferating fraction and maturation defects in late precursors, and iii) EPs with a reduced erythropoietic fraction but mostly normal patterns suggesting that erythropoiesis was less affected. Additionally, analysis of sequential samples from an MDS patient under treatment showed a decrease of abnormal subsets after azacytidine treatment and near normalization after allogeneic hematopoietic stem-cell transplantation. CONCLUSION: Unsupervised clustering analysis of MFC data discloses subtle alterations in erythropoiesis not detectable by cytology nor FCM supervised analysis. This novel AI analytical approach sheds some new light on the pathophysiology of these conditions.

Potten, C. S., et al. (1977). "Circadian rhythms of presumptive stem cells in three different epithelia of the mouse." Cell Tissue Kinet **10**(6): 557-568.

Variation in the percentage of labelled cells (LI), mitoses (MI) and apoptosis (AI: i.e. shrinkage necrosis) have been studied throughout a 24 hr period (40 min after labelling with 3H-TdR) for tongue epithelium, epidermis and intestinal epithelium in the mouse. A room with reversed light cycle was used to obtain data for half of the 24 hr period. All three tissues showed marked variations in LI with peak values between 24.00 and 03.00 hours. In the intestine a maximum value for MI was observed 3-6 hr after that for LI and with a maximum value for AI slightly later. In all three epithelia the circadian rhythm was most striking in cells at positions which can be correlated with presumptive stem cell activity; e.g. in the crypts the labelling and mitotic peaks

reflecting a circadian rhythm were most clearly distinguishable at the basal part of the crypts. These observations are discussed in relation to the validity of various proliferative models.

Poupardin, R., et al. (2024). "Advances in Extracellular Vesicle Research Over the Past Decade: Source and Isolation Method are Connected with Cargo and Function." Adv Healthc Mater **13**(19): e2303941.

The evolution of extracellular vesicle (EV) research has introduced nanotechnology into biomedical cell communication science while recognizing what is formerly considered cell "dust" as constituting an entirely new universe of cell signaling particles. To display the global EV research landscape, a systematic review of 20 364 original research articles selected from all 40 684 EV-related records identified in PubMed 2013-2022 is performed. Machine-learning is used to categorize the high-dimensional data and further dissected significant associations between EV source, isolation method, cargo, and function. Unexpected correlations between these four categories indicate prevalent experimental strategies based on cargo connectivity with function of interest being associated with certain EV sources or isolation strategies. Conceptually relevant association of size-based EV isolation with protein cargo and uptake function will guide strategic conclusions enhancing future EV research and product development. Based on this study, an open-source database is built to facilitate further analysis with conventional or AI tools to identify additional causative associations of interest.

Raina, R., et al. (2024). "Application of artificial intelligence and machine learning for risk stratification acute kidney injury among hematopoietic stem cell transplantation patients: PCRRT ICONIC AI Initiative Group Meeting Proceedings." Clin Nephrol.

Acute kidney injury (AKI) is a frequent, severe complication of hematopoietic stem cell transplantation (HSCT) and is associated with an increased risk of morbidity and mortality. Recent advances in artificial intelligence (AI) and machine learning (ML) have showcased their proficiency in predicting AKI, projecting disease progression, and accurately identifying underlying etiologies. This review examines the central aspects of AKI post-HSCT, veno-occlusive disease (VOD) in HSCT recipients, discusses present-day applications of artificial intelligence in AKI, and introduces a proposed ML framework for the early detection of AKI risk.

Ramakrishna, R. R., et al. (2020). "Stem cell imaging through convolutional neural networks: current issues and future directions in artificial intelligence technology." PeerJ **8**: e10346.

Stem cells are primitive and precursor cells with the potential to reproduce into diverse mature and functional cell types in the body throughout the developmental stages of life. Their remarkable potential has led to numerous medical discoveries and breakthroughs in science. As a result, stem cell-based therapy has emerged as a new subspecialty in medicine. One promising stem cell being investigated is the induced pluripotent stem cell (iPSC), which is obtained by genetically reprogramming mature cells to convert them into embryonic-like stem cells. These iPSCs are used to study the onset of disease, drug development, and medical therapies. However, functional studies on iPSCs involve the analysis of iPSC-derived colonies through manual identification, which is time-consuming, error-prone, and training-dependent. Thus, an automated instrument for the analysis of iPSC colonies is needed. Recently, artificial intelligence (AI) has emerged as a novel technology to tackle this challenge. In particular, deep learning, a subfield of AI, offers an automated platform for analyzing iPSC colonies and other colony-forming stem cells. Deep learning rectifies data features using a convolutional neural network (CNN), a type of multi-layered neural network that can play an innovative role in image recognition. CNNs are able to distinguish cells with high accuracy based on morphologic and textural changes. Therefore, CNNs have the potential to create a future field of deep learning tasks aimed at solving various challenges in stem cell studies. This review discusses the progress and future of CNNs in stem cell imaging for therapy and research.

Ray-Coquard, I., et al. (2001). "[High-dose chemotherapy in soft tissue sarcomas of adults]." Bull Cancer **88**(9): 858-862.

Few cytotoxic agents are active for the treatment of soft tissue sarcomas of adults: drugs active in monotherapy are doxorubicin, ifosfamide, dacarbazine and ET743. In patients with advanced stage soft tissue sarcomas (ASTS), a dose-response relationship has been established for doxorubicin and ifosfamide. Intensive combination chemotherapy regimens at conventional doses (MAID, or AI) yield higher objective response rates than monochemotherapy regimens, ranging between 25% and 44%, but failed improve survival rates as comparted to less intensive regimens. Recently, several phase I or II studies have investigated the use of high dose chemotherapy regimens as consolidation therapy in ASTS in response to conventional

regimens. HDCT regimens have been reported to yield response rates ranging between 18% and 66%. Some of these patients with ASTS achieved long term complete remission, in particular in the subgroup of patients in complete remission after conventional chemotherapy in advanced phase. Phase III studies are required to confirm that survival may be improved by HDCT in subgroups of patients with ASTS.

Rehbach, K., et al. (2020). "Integrating CRISPR Engineering and hiPSC-Derived 2D Disease Modeling Systems." J Neurosci **40**(6): 1176-1185.

Human induced pluripotent stem cells (hiPSCs) have revolutionized research on human diseases, particularly neurodegenerative and psychiatric disorders, making it possible to study mechanisms of disease risk and initiation in otherwise inaccessible patient-specific cells. Today, the integration of CRISPR engineering approaches with hiPSC-based models permits precise isogenic comparisons of human neurons and glia. This review is intended as a guideline for neuroscientists and clinicians interested in translating their research to hiPSC-based studies. It offers state-of-the-art approaches to tackling the challenges that are unique to human in vitro disease models, particularly interdonor and intradonor variability, and limitations in neuronal maturity and circuit complexity. Finally, we provide a detailed overview of the immense possibilities the field has to offer, highlighting efficient neural differentiation and induction strategies for the major brain cell types and providing perspective into integrating CRISPR-based methods into study design. The combination of hiPSC-based disease modeling, CRISPR technology, and high-throughput approaches promises to advance our scientific knowledge and accelerate progress in drug discovery.Dual Perspectives Companion Paper: Studying Human Neurodevelopment and Diseases Using 3D Brain Organoids, by Ai Tian, Julien Muffat, and Yun Li.

Reiter, R. E., et al. (2000). "Coamplification of prostate stem cell antigen (PSCA) and MYC in locally advanced prostate cancer." Genes Chromosomes Cancer **27**(1): 95-103.

Gain of sequences on chromosome arm 8q is a common feature of prostate cancer that may correlate with metastatic and androgen-independent progression. The target gene(s) for this gain is not known, although MYC is amplified in a subset of advanced tumors and is one potential candidate. Prostate stem cell antigen (PSCA) is a prostate-specific cell surface protein that maps to chromosome region 8q24.2 and is overexpressed in prostate cancer. Our aim in this study was to test the hypothesis that PSCA overexpression may result from overrepresentation of chromosome arm 8q. Twenty locally advanced prostate cancers were analyzed by dual-probe fluorescence in situ hybridization (FISH) for alterations of MYC and PSCA. Extra copies of MYC were found in 12/20 (60%) tumors, including 5 (25%) with simple gain (no increase in MYC copy number relative to the chromosome 8 centromere) and 7 (35%) with an additional increase (AI or overrepresentation) in MYC copy number relative to the centromere. In the five cases with simple gain of MYC, there was a concomitant gain of PSCA. PSCA was overrepresented in 5/7 (71%) cases with AI of MYC. Immunohistochemical staining of the 20 tumors with monoclonal antibodies specific for PSCA showed a high degree of correlation between PSCA gene overrepresentation and protein overexpression. Four of 5 tumors with AI of PSCA overexpressed PSCA protein, compared with only 2/15 tumors with a normal PSCA copy number or simple gain of PSCA (P = 0.014). These results demonstrate that PSCA is co-overrepresented with MYC in a majority of cases, but may not be a necessary part of the 8q amplicon. PSCA protein overexpression can result from AI of PSCA and might be useful as a cell surface marker on prostate cancer cells with 8q overrepresentation. Genes Chromosomes Cancer 27:95-103, 2000.

Rennie, P. S., et al. (1990). "Loss of androgen dependence is associated with an increase in tumorigenic stem cells and resistance to cell-death genes." J Steroid Biochem Mol Biol **37**(6): 843-847.

Complete remissions of the androgen-dependent Shionogi mouse mammary carcinoma are observed after androgen withdrawal but invariably the disease recurs and is refractory to further hormonal manipulations. To determine the proportions of androgen-dependent (AD) and -independent (AI) tumorigenic stem cells in parent and recurrent tumors an in vivo limiting dilution assay was developed. There was a marked enrichment of stem cells in the recurrent tumors (1/200 tumor cells) relative to the parent tumors (1/4000 tumor cells) when assayed in male hosts. By assaying tumor takes in female mice, the proportion of AI stem cells was found to be 1/370,000 tumor cells in the parent vs 1/800 tumor cells in the recurrent carcinoma; a 500-fold increase in AI stem cells resulting from androgen-withdrawal. Unexpectedly, no enrichment of AI stem cells was evident in regressing parent tumors; rather, the proportion of such cells was very small (1/2,200,000 tumor cells). This finding implies that the AI cells which survive androgen withdrawal may result from

the ability of small number of initially AD stem cells to adapt to an altered hormonal environment. This adaptive process was further defined in terms of the disappearance of androgen receptors from the nucleus and the expression of androgen-repressed genes including the proto-oncogenes, c-fos and c-myc, and the cell death gene, TRPM-2; all of which are constitutively active in recurrent AI tumor cells. Overall, our results indicate: (1) the tumor mass consists mainly of differentiated cells; (2) stem cells initially are AD but at most the killing effect of androgen-withdrawal will be limited to 2-3 logarithms before compensatory adaptive mechanisms supervene; and (3) progression of stem cells to an AI state, in which they are resistant to the killing effects of cell death genes, might be prevented by the inhibition of androgen-repressed adaptive mechanisms which come into play when androgens are withdrawn.

Royce, S. G., et al. (2019). "iPSC- and mesenchymoangioblast-derived mesenchymal stem cells provide greater protection against experimental chronic allergic airways disease compared with a clinically used corticosteroid." FASEB J **33**(5): 6402-6411.

The airway remodeling (AWR) associated with chronic allergic airways disease (AAD)/asthma contributes to irreversible airway obstruction. This study compared and combined the antiremodeling and other effects of induced pluripotent stem cell and mesenchymoangioblast-derived mesenchymal stem cells (MCA-MSCs) with the corticosteroid dexamethasone (Dex) in experimental chronic AAD/asthma. Female BALB/c mice subjected to 11 wk of ovalbumin (Ova)-induced chronic AAD were intranasally administered MCA-MSCs (1 x 10(6) cells/mouse; once weekly on wk 10 and 11), Dex (0.5 mg/ml; once daily for 2 wk), or both combined. MCA-MSC detection and changes in airway inflammation (AI), AWR, and airway hyperresponsiveness (AHR) were measured at the end of wk 11. Mice with chronic AAD had significant AI, goblet cell metaplasia, epithelial damage/thickening, aberrant TGF-beta1 levels, subepithelial myofibroblast accumulation, airway/lung fibrosis, and AHR (all $P < 0.001$ vs. healthy controls). MCA-MSCs were detected in the lungs up to 5-7 d postadministration and demonstrated modest anti-inflammatory but striking antifibrotic effects against Ova-induced AAD, effectively decreasing AHR by 70-75% (all $P < 0.05$ vs. Ova alone). In comparison, Dex predominantly demonstrated anti-inflammatory effects, decreasing AHR by approximately 30%. Combining MCA-MSCs with Dex provided equivalent protection to that offered by either therapy alone. MCA-MSCs reduce chronic AAD-induced AWR and AHR to a greater extent than Dex and may act as a suitable adjunct therapy to corticosteroid treatment of asthma.-Royce, S. G., Mao, W., Lim, R., Kelly, K., Samuel, C. S. iPSC- and mesenchymoangioblast-derived mesenchymal stem cells provide greater protection against experimental chronic allergic airways disease compared with a clinically used corticosteroid.

Royce, S. G., et al. (2017). "Intranasal administration of mesenchymoangioblast-derived mesenchymal stem cells abrogates airway fibrosis and airway hyperresponsiveness associated with chronic allergic airways disease." FASEB J **31**(9): 4168-4178.

Structural changes known as airway remodeling (AWR) characterize chronic/severe asthma and contribute to lung dysfunction. Thus, we assessed the in vivo efficacy of induced pluripotent stem cell and mesenchymoangioblast-derived mesenchymal stem cells (MCA-MSCs) on AWR in a murine model of chronic allergic airways disease (AAD)/asthma. Female Balb/c mice were subjected to a 9-wk model of ovalbumin (Ova)-induced chronic AAD and treated intravenously or intranasally with MCA-MSCs from weeks 9 to 11. Changes in airway inflammation (AI), AWR, and airway hyperresponsiveness (AHR) were assessed. Ova-injured mice presented with AI, goblet cell metaplasia, epithelial thickening, increased airway TGF-beta1 levels, subepithelial myofibroblast and collagen accumulation, total lung collagen concentration, and AHR (all $P < 0.001$ vs. uninjured control group). Apart from epithelial thickness, all other parameters measured were significantly, although not totally, decreased by intravenous delivery of MCA-MSCs to Ova-injured mice. In comparison, intranasal delivery of MCA-MSCs to Ova-injured mice significantly decreased all parameters measured (all $P < 0.05$ vs. Ova group) and, most notably, normalized aberrant airway TGF-beta1 levels, airway/lung fibrosis, and AHR to values measured in uninjured animals. MCA-MSCs also increased collagen-degrading gelatinase levels. Hence, direct delivery of MCA-MSCs offers great therapeutic benefit for the AWR and AHR associated with chronic AAD.-Royce, S. G., Rele, S., Broughton, B. R. S., Kelly, K., Samuel, C. S. Intranasal administration of mesenchymoangioblast-derived mesenchymal stem cells abrogates airway fibrosis and airway hyperresponsiveness associated with chronic allergic airways disease.

Royce, S. G., et al. (2015). "Mesenchymal stem cells and serelaxin synergistically abrogate established

airway fibrosis in an experimental model of chronic allergic airways disease." Stem Cell Res **15**(3): 495-505.

This study determined if the anti-fibrotic drug, serelaxin (RLN), could augment human bone marrow-derived mesenchymal stem cell (MSC)-mediated reversal of airway remodeling and airway hyperresponsiveness (AHR) associated with chronic allergic airways disease (AAD/asthma). Female Balb/c mice subjected to the 9-week model of ovalbumin (OVA)-induced chronic AAD were either untreated or treated with MSCs alone, RLN alone or both combined from weeks 9-11. Changes in airway inflammation (AI), epithelial thickness, goblet cell metaplasia, transforming growth factor (TGF)-beta1 expression, myofibroblast differentiation, subepithelial and total lung collagen deposition, matrix metalloproteinase (MMP) expression, and AHR were then assessed. MSCs alone modestly reversed OVA-induced subepithelial and total collagen deposition, and increased MMP-9 levels above that induced by OVA alone (all $p<0.05$ vs OVA group). RLN alone more broadly reversed OVA-induced epithelial thickening, TGF-beta1 expression, myofibroblast differentiation, airway fibrosis and AHR (all $p<0.05$ vs OVA group). Combination treatment further reversed OVA-induced AI and airway/lung fibrosis compared to either treatment alone (all $p<0.05$ vs either treatment alone), and further increased MMP-9 levels. RLN appeared to enhance the therapeutic effects of MSCs in a chronic disease setting; most likely a consequence of the ability of RLN to limit TGF-beta1-induced matrix synthesis complemented by the MMP-promoting effects of MSCs.

Royce, S. G., et al. (2016). "Serelaxin improves the therapeutic efficacy of RXFP1-expressing human amnion epithelial cells in experimental allergic airway disease." Clin Sci (Lond) **130**(23): 2151-2165.

Current asthma therapies primarily target airway inflammation (AI) and suppress episodes of airway hyperresponsiveness (AHR) but fail to treat airway remodelling (AWR), which can develop independently of AI and contribute to irreversible airway obstruction. The present study compared the anti-remodelling and therapeutic efficacy of human bone marrow-derived mesenchymal stem cells (MSCs) to that of human amnion epithelial stem cells (AECs) in the setting of chronic allergic airways disease (AAD), in the absence or presence of an anti-fibrotic (serelaxin; RLX). Female Balb/c mice subjected to the 9-week model of ovalbumin (OVA)-induced chronic AAD, were either vehicle-treated (OVA alone) or treated with MSCs or AECs alone [intranasally (i.n.)-administered with 1x10(6) cells once weekly], RLX alone (i.n.-administered with 0.8 mg/ml daily) or a combination of MSCs or AECs and RLX from weeks 9-11 (n=6/group). Measures of AI, AWR and AHR were then assessed. OVA alone exacerbated AI, epithelial damage/thickness, sub-epithelial extracellular matrix (ECM) and total collagen deposition, markers of collagen turnover and AHR compared with that in saline-treated counterparts (all $P<0.01$ compared with saline-treated controls). RLX or AECs (but not MSCs) alone normalized epithelial thickness and partially diminished the OVA-induced fibrosis and AHR by approximately 40-50% (all $P<0.05$ compared with OVA alone). Furthermore, the combination treatments normalized epithelial thickness, measures of fibrosis and AHR to that in normal mice, and significantly decreased AI. Although AECs alone demonstrated greater protection against the AAD-induced AI, AWR and AHR, compared with that of MSCs alone, combining RLX with MSCs or AECs reversed airway fibrosis and AHR to an even greater extent.

Ruan, Q., et al. (2007). "The effects of different auditory activity on the expression of phosphorylated c-Jun in the auditory system." Acta Otolaryngol **127**(6): 594-604.

CONCLUSION: The data revealed that calcium influx via the NMDA receptor up-regulated the expression of phosphorylated c-Jun in the primary auditory cortices following sensory stimulation and after different neural injury stimulations which guide activity-dependent changes in gene expression and neural plasticity. OBJECTIVES: Activator protein-1 (AP-1) transcription factor, which is mainly composed of c-Fos and c-Jun proteins, is believed to be a key participant in molecular processes that guide activity-dependent changes in gene expression. Our previous study had shown that the expression of NMDAR2A gene on synaptosomes membrane of auditory cortical neurons varied by electrical intracochlear stimulation (EIS) and neural injury induced by acoustic trauma. In this study, we investigated the role of the NMDA receptor (NMDAR) in regulating the expression of phosphorylated c-Jun in the primary auditory cortex (AI). The modulation factors observed for gene expression included EIS and noise traumas. MATERIALS AND METHODS: EIS was applied in rats with early postnatal auditory deprivation. The impact of the noise traumas on the ultrastructures of spiral ganglion neurons (SGNs) and their innervations to inner hair cells (IHCs) were verified by transmission electron microscopy (EM). These changes include a decrease in subcellular organelles, the swelling of mitochondria and endoplasmic

reticulum, the morphological changes in cell nuclei, and damage in the afferent synapse. RESULTS: Immunohistochemistry observations showed that the expression of phosphorylated c-jun and active caspase-3 in hair cells and SGNs varied with amount of noise. Immunocytochemistry and Western blotting showed that the auditory cortex began to express phosphorylated c-jun 24 h after 2 h of EIS. However, this expression was not changed by EIS if NMDAR antagonist was applied. The level of phosphorylated c-Jun was remarkably increased in AI after noise overstimulation at 115 dB SPL for 3 h. Again, such an increase was not seen if NMDAR antagonist 3-(2 carboxypiperazin-4yl) propyl-1-phosphonic acid (CPP, 10 mg/kg, i.p.) was applied 30 min before the noise exposure.

Sababathy, M., et al. (2024). "Multipotent mesenchymal stromal/stem cell-based therapies for acute respiratory distress syndrome: current progress, challenges, and future frontiers." Braz J Med Biol Res **57**: e13219.

Acute respiratory distress syndrome (ARDS) is a critical, life-threatening condition marked by severe inflammation and impaired lung function. Mesenchymal stromal/stem cells (MSCs) present a promising therapeutic avenue due to their immunomodulatory, anti-inflammatory, and regenerative capabilities. This review comprehensively evaluates MSC-based strategies for ARDS treatment, including direct administration, tissue engineering, extracellular vesicles (EVs), nanoparticles, natural products, artificial intelligence (AI), gene modification, and MSC preconditioning. Direct MSC administration has demonstrated therapeutic potential but necessitates optimization to overcome challenges related to effective cell delivery, homing, and integration into damaged lung tissue. Tissue engineering methods, such as 3D-printed scaffolds and MSC sheets, enhance MSC survival and functionality within lung tissue. EVs and MSC-derived nanoparticles offer scalable and safer alternatives to cell-based therapies. Likewise, natural products and bioactive compounds derived from plants can augment MSC function and resilience, offering complementary strategies to enhance therapeutic outcomes. In addition, AI technologies could aid in optimizing MSC delivery and dosing, and gene editing tools like CRISPR/Cas9 allow precise modification of MSCs to enhance their therapeutic properties and target specific ARDS mechanisms. Preconditioning MSCs with hypoxia, growth factors, or pharmacological agents further enhances their therapeutic potential. While MSC therapies hold significant promise for ARDS, extensive research and clinical trials are essential to determine optimal protocols and ensure long-term safety and effectiveness.

Saberian, E., et al. (2024). "Applications of artificial intelligence in regenerative dentistry: promoting stem cell therapy and the scaffold development." Front Cell Dev Biol **12**: 1497457.

Tissue repair represents a critical concern within the domain of dentistry. On a daily basis, countless individuals seek dental clinic services due to inadequate dental care. Many of the treatments that patients receive have unfavorable side effects. The employment of innovative methodologies, including gene therapy, tissue engineering, and stem cell (SCs) applications for regenerative purposes, has garnered significant interest over the past years. In recent times, artificial intelligence, particularly neural networks, has emerged as a topic of considerable attention among many medical professionals. Artificial intelligence possesses the capability to analyze data patterns through learning algorithms. Research opportunities in the rapidly expanding field of health sciences have been made possible by the use of artificial intelligence (AI) technologies. Though its uses are not restricted to these situations, artificial intelligence (AI) has the potential to improve and accelerate many aspects of regenerative medicine research and development, especially when working with complicated patterns. This review article is to investigate how artificial intelligence might be used to enhance regenerative processes in dentistry by using scaffolds and stem cells, in light of the continuous advances in artificial intelligence in the fields of medicine and tissue regeneration. It highlights the difficulties that still exist in this developing sector and explores the possible uses of AI with a particular emphasis on dentistry practices.

Sahoo, D., et al. (2021). "AI-guided discovery of the invariant host response to viral pandemics." EBioMedicine **68**: 103390.

BACKGROUND: Coronavirus Disease 2019 (Covid-19) continues to challenge the limits of our knowledge and our healthcare system. Here we sought to define the host immune response, a.k.a, the "cytokine storm" that has been implicated in fatal COVID-19 using an AI-based approach. METHOD: Over 45,000 transcriptomic datasets of viral pandemics were analyzed to extract a 166-gene signature using ACE2 as a 'seed' gene; ACE2 was rationalized because it encodes the receptor that facilitates the entry of SARS-CoV-2 (the virus that causes COVID-19) into host cells. An AI-based approach was used to explore the utility of the signature in navigating the uncharted territory of Covid-19, setting therapeutic goals, and finding

therapeutic solutions. FINDINGS: The 166-gene signature was surprisingly conserved across all viral pandemics, including COVID-19, and a subset of 20-genes classified disease severity, inspiring the nomenclatures ViP and severe-ViP signatures, respectively. The ViP signatures pinpointed a paradoxical phenomenon wherein lung epithelial and myeloid cells mount an IL15 cytokine storm, and epithelial and NK cell senescence and apoptosis determine severity/fatality. Precise therapeutic goals could be formulated; these goals were met in high-dose SARS-CoV-2-challenged hamsters using either neutralizing antibodies that abrogate SARS-CoV-2*ACE2 engagement or a directly acting antiviral agent, EIDD-2801. IL15/IL15RA were elevated in the lungs of patients with fatal disease, and plasma levels of the cytokine prognosticated disease severity. INTERPRETATION: The ViP signatures provide a quantitative and qualitative framework for titrating the immune response in viral pandemics and may serve as a powerful unbiased tool to rapidly assess disease severity and vet candidate drugs. FUNDING: This work was supported by the National Institutes for Health (NIH) [grants CA151673 and GM138385 (to DS) and AI141630 (to P.G), DK107585-05S1 (SD) and AI155696 (to P.G, D.S and S.D), U19-AI142742 (to S. C, CCHI: Cooperative Centers for Human Immunology)]; Research Grants Program Office (RGPO) from the University of California Office of the President (UCOP) (R00RG2628 & R00RG2642 to P.G, D.S and S.D); the UC San Diego Sanford Stem Cell Clinical Center (to P.G, D.S and S.D); LJI Institutional Funds (to S.C); the VA San Diego Healthcare System Institutional funds (to L.C.A). GDK was supported through The American Association of Immunologists Intersect Fellowship Program for Computational Scientists and Immunologists. ONE SENTENCE SUMMARY: The host immune response in COVID-19.

Schlemmer, M., et al. (2006). "Efficacy of consolidation high-dose chemotherapy with ifosfamide, carboplatin and etoposide (HD-ICE) followed by autologous peripheral blood stem cell rescue in chemosensitive patients with metastatic soft tissue sarcomas." Oncology **71**(1-2): 32-39.

BACKGROUND: Prognosis of patients with metastatic soft tissue sarcomas (MSTS) is poor even after response to doxorubicin-based chemotherapy. We report phase II data of high-dose chemotherapy and peripheral blood stem cell (PBSC) rescue in patients with MSTS responding to AI-G chemotherapy. PATIENTS AND METHODS: From 1997 to 2002, 55 patients with MSTS were prospectively treated with 4 cycles of AI-G (doxorubicin 75 mg/m(2), ifosfamide 6 g/m(2) with G-CSF support). Responders received 2 further cycles of AI-G with collection of PBSCs. High-dose chemotherapy consisted of ifosfamide 12 g/m(2), carboplatin 1.2 g/m(2) and etoposide 1.2 g/m(2) (HD-ICE) followed by reinfusion of PBSCs. RESULTS: Twenty-one of 55 patients (38%) were assessed as responders (3 complete response, 18 partial response). All but 2 patients refusing treatment received high-dose chemotherapy with PBSC rescue leading to grade IV hematologic toxicity without severe infections in all patients. No toxic death occurred. After a median follow-up time of 30 months, the median progression-free time was 12 months and survival time was 22 months for the entire group. By intent-to-treat analysis the probability of 5-year progression-free survival was significantly higher for patients allocated to HD-ICE compared to patients receiving second-line chemotherapy after failure of AI-G (14 vs. 3%; p = 0.003). The estimated 5-year overall survival between the 2 groups was different (27% vs. not reached) but did not reach significance (p = 0.08). CONCLUSION: HD-ICE is feasible and promising in patients with chemosensitive MSTS. A randomized phase III trial is warranted to further define the role of HD-ICE as consolidation treatment in these patients.

Scholz, S., et al. (2023). "Listen to the patients! Identifying CML patients' needs analyzing patient-generated content with AI-driven methodologies." Front Digit Health **5**: 1243215.

BACKGROUND: Various patient support programs exist to provide successful therapy options for patients. Pharmaceutical companies are increasingly recognizing the importance of actively supporting patients in their long-term treatment. In order to effectively assist patients, it is crucial to understand their current needs by taking a look at the patients' opinions. OBJECTIVE: This study focuses specifically on chronic myeloid leukemia (CML) and aims to determine if the current patient engagement offerings from pharmaceutical companies adequately address the needs of CML patients. To achieve this, the study uses content generated by CML patients to assess the patient engagement strategies of selected pharmaceutical companies, explore the relevance of medication, their products, and services, and analyze key concerns from the perspective of the patients. METHODS: To address the research questions, various methodologies were employed. Initially, desk research was conducted to identify relevant pharmaceutical companies and internet forums related to CML. Subsequently, content generated by patients was acquired and AI-driven techniques such as topic modeling and topic evolution analyses were used to examine this user-generated content (UGC)

within the identified public forums. This involved analyzing topic models and tracking topic changes over time. RESULTS: The desk research revealed that pharmaceutical companies primarily offer information about the disease and available treatment options. The UGC analysis confirmed the significant role played by the industry in supporting CML patients. Key areas of interest for patients include the disease itself, potential treatment methods and associated side effects, dosage of active substances, and the possibility of switching therapies due to treatment failure or resistance. Stem cell transplantation was also discussed. CONCLUSIONS: Overall, the pharmaceutical industry adequately addresses the needs of CML patients. However, there is room for improvement in educating patients about treatment options, drugs, and their side effects. Psychological support should not be neglected. Since CML patients frequently engage with clinical trial outcomes, there is potential for increased patient involvement in such trials. Further research in this area is recommended.

Sebastian, S. A., et al. (2023). "Precision Medicine and Cardiac Channelopathies: Human iPSCs Take the Lead." Curr Probl Cardiol **48**(12): 101990.

Sudden cardiac death (SCD) is one of the leading causes of death worldwide, usually involving young people. SCD remains a critical public health problem accounting for 185,000-450,000 deaths annually, representing around 7%-18% of all deaths globally. As per evidence, approximately 2%-54% of sudden unexpected deaths in people under the age of 35 years fail to show evidence of structural cardiac abnormalities at autopsy, making ion channelopathies the probable causes in such cases. The most generally recognized cardiac ion channelopathies with genetic testing are long QT syndrome (LQTS), Brugada syndrome (BrS), short QT syndrome (SQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). The substantial progress in understanding the genetics of ion channelopathies in the last 2 decades has obliged the early diagnosis and prevention of SCD to a certain extent. In this review, we analyze the critical challenges and recent advancements in the identification, risk stratification, and clinical management of potentially fatal cardiac ion channel disorders. We also emphasize the application of precision medicine (PM) and artificial intelligence (AI) for comprehending the underlying genetic mechanisms, especially the role of human induced pluripotent stem cell (iPSC) based platforms to unravel the primary refractory clinical problems associated with channelopathies.

Sequeda-Castaneda, L. G., et al. (2024). "Evaluation of Ilex guayusa and Piper marginatum Extract Cytotoxicity on Human Dental Pulp Mesenchymal Stem Cells." Dent J (Basel) **12**(6).

BACKGROUND: Amelogenesis imperfecta is a hereditary disorder affecting dental enamel. Among its phenotypes, hypocalcified AI is characterized by mineral deficiency, leading to tissue wear and, consequently, dental sensitivity. Excessive fluoride intake (through drinking water, fluoride supplements, toothpaste, or by ingesting products such as pesticides or insecticides) can lead to a condition known as dental fluorosis, which manifests as stains and teeth discoloration affecting their structure. Our recent studies have shown that extracts from Colombian native plants, Ilex guayusa and Piper marginatum, deposit mineral ions such as phosphate and orthophosphate into the dental enamel structure; however, it is unknown whether these extracts produce toxic effects on the dental pulp. OBJECTIVE: To assess cytotoxicity effects on human dental pulp stem cells (hDPSCs) exposed to extracts isolated from I. guayusa and P. marginatum and, hence, their safety for clinical use. METHODS: Raman spectroscopy, fluorescence microscopy, and flow cytometry techniques were employed. For Raman spectroscopy, hDPSCs were seeded onto nanobiochips designed to provide surface-enhanced Raman spectroscopy (SERS effect), which enhances their Raman signal by several orders of magnitude. After eight days in culture, I. guayusa and P. marginatum extracts at different concentrations (10, 50, and 100 ppm) were added. Raman measurements were performed at 0, 12, and 24 h following extract application. Fluorescence microscopy was conducted using an OLIMPUS fv1000 microscope, a live-dead assay was performed using a kit employing a BD FACS Canto TM II flow cytometer, and data analysis was determined using a FlowJo program. RESULTS: The Raman spectroscopy results showed spectra consistent with viable cells. These findings were corroborated using fluorescence microscopy and flow cytometry techniques, confirming high cellular viability. CONCLUSIONS: The analyzed extracts exhibited low cytotoxicity, suggesting that they could be safely applied on enamel for remineralization purposes. The use of nanobiochips for SERS effect improved the cell viability assessment.

Shaffer, B. C., et al. (2024). "Artificial intelligence enabled interpretation of ECG images to predict hematopoietic cell transplantation toxicity." Blood Adv **8**(21): 5603-5611.

Artificial intelligence (AI)-enabled interpretation of electrocardiogram (ECG) images (AI-ECGs) can identify patterns predictive of future adverse cardiac events. We hypothesized that such an

approach would provide prognostic information for the risk of cardiac complications and mortality in patients undergoing hematopoietic cell transplantation (HCT). We retrospectively subjected ECGs obtained before HCT to an externally trained, deep-learning model designed to predict the risk of atrial fibrillation (AF). Included were 1377 patients (849 autologous [auto] HCT and 528 allogeneic [allo] HCT recipients). The median follow-up was 2.9 years. The 3-year cumulative incidence of AF was 9% (95% confidence interval [CI], 7-12) in patients who underwent auto HCT and 13% (10%-16%) in patients who underwent allo HCT. In the entire cohort, pre-HCT AI-ECG estimate of AF risk correlated highly with the development of clinical AF (hazard ratio [HR], 7.37; 95% CI, 3.53-15.4; P < .001), inferior survival (HR, 2.4; 95% CI, 1.3-4.5; P = .004), and greater risk of nonrelapse mortality (NRM; HR, 95% CI, 3.36; 1.39-8.13; P = .007), without increased risk of relapse. Association with mortality was only noted in allo HCT recipients, where the risk of NRM was greater. The use of cyclophosphamide after transplantation resulted in greater 90-day incidence of AF (13% vs 5%; P = .01) compared to calcineurin inhibitor-based graft-versus-host disease prophylaxis, corresponding to temporal changes in AI-ECG AF prediction after HCT. In summary, AI-ECG can inform risk of posttransplant cardiac outcomes and survival in HCT patients and represents a novel strategy for personalized risk assessment.

Shah, K., et al. (2022). "Adrenocortical Function in Children With Brain Tumors and Pediatric Hematopoietic Cell Transplantation Recipients." J Pediatr Hematol Oncol **44**(2): e469-e473.

Adrenocortical insufficiency (AI) is a clinical condition defined by deficient production of glucocorticoids that can result in life-threatening complications. We examined the prevalence of AI in children with brain tumors and those undergoing hematopoietic cell transplantation. Adrenocorticotropic hormone stimulation (stim) testing was used for the assessment of adrenocortical function. On the basis of 155 stim tests in 117 patients, AI was diagnosed in 27.4% of patients with brain tumors and in 21% of hematopoietic cell transplantation recipients. A number of risk factors associated with AI were identified. Adrenocorticotropic hormone stim testing led to a definitive diagnosis of AI or recovery of adrenal function and unambiguous medical management.

Sharun, K., et al. (2023). "ChatGPT and artificial hallucinations in stem cell research: assessing the accuracy of generated references - a preliminary study." Ann Med Surg (Lond) **85**(10): 5275-5278.

Stem cell research has the transformative potential to revolutionize medicine. Language models like ChatGPT, which use artificial intelligence (AI) and natural language processing, generate human-like text that can aid researchers. However, it is vital to ensure the accuracy and reliability of AI-generated references. This study assesses Chat Generative Pre-Trained Transformer (ChatGPT)'s utility in stem cell research and evaluates the accuracy of its references. Of the 86 references analyzed, 15.12% were fabricated and 9.30% were erroneous. These errors were due to limitations such as no real-time internet access and reliance on preexisting data. Artificial hallucinations were also observed, where the text seems plausible but deviates from fact. Monitoring, diverse training, and expanding knowledge cut-off can help to reduce fabricated references and hallucinations. Researchers must verify references and consider the limitations of AI models. Further research is needed to enhance the accuracy of such language models. Despite these challenges, ChatGPT has the potential to be a valuable tool for stem cell research. It can help researchers to stay up-to-date on the latest developments in the field and to find relevant information.

She, T., et al. (2011). "[Biological effects of paracrine from insulin stimulated adipose-derived stem cells (ADSC) on human vascular endothelial cells]." Zhonghua Shao Shang Za Zhi **27**(1): 32-36.

OBJECTIVE: To study the biological effects of the paracrine from ADSC after being stimulated by insulin on vascular endothelial cells. METHODS: (1) ADSC was isolated from human adipose tissue and cultured in vitro. The third generation cells were collected and divided into insulin group (I, cultured with serum-free DMEM containing 1 x 10(-7) mol/L insulin) and control group (C, cultured with serum-free DMEM) according to the random number table, with 6 slots in each group. Three days later, ADSC culture medium (ADSC-CM) was collected for determination of levels of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) by ELISA. (2) Human umbilical vein endothelial cells (HUVEC) were cultured to the third generation, and they were cultured with special nutrient solution and divided into ADSC-CM with insulin stimulation group (AI), ADSC-CM without insulin stimulation group (AC), insulin group (I, with same concentration as above), blank control group (BC) according to the random number table. Three days later, proliferation of HUVEC was determined with MTT method (with expression of absorbance value). Another two samples of HUVEC were respectively divided into 4 groups as above for determination of apoptosis rate with Annexin V/FITC

double-staining 12 hours after culture, and HUVEC migration with scratch adhesion test at post scratch hour (PSH) 12, 24, 36, 48. Data were processed with t test. RESULTS: (1) Compared with those in C group [(287 +/- 47), (577 +/- 84) pg/mL, respectively], the secretion levels of VEGF and HGF in I group [(643 +/- 64), (930 +/- 68) pg/mL, respectively] were significantly increased (with t value respectively 18.869, 18.475, P values all below 0.05). (2) The absorbance value of HUVEC in AI and AC groups was 0.847 +/- 0.042, 0.798 +/- 0.022, respectively, which were higher than that in I and BC groups [0.665 +/- 0.028 (with t value respectively 4.579, 3.732), 0.674 +/- 0.031 (with t value respectively 3.761, 4.073), P values all below 0.01], and that in AI group was higher than that in AC group ($t = 2.576$, $P < 0.05$). The apoptosis rates of HUVEC in AI and AC groups [(5.8 +/- 1.9)%, (9.0 +/- 2.0)%, respectively] were obviously lower as compared with that in I and BC groups [(30.4 +/- 6.0)% (with t value respectively 12.891, 10.417), (31.4 +/- 7.4)% (with t value respectively 11.474, 9.783), P values all below 0.05], and that in AC group was higher than that in AI group ($t = 8.548$, $P < 0.05$). The distance of migration of HUVEC in AI and AC groups were greater than that in I and BC groups at PSH 36, 48, and that in AI group was greater as compared with that in AC group (with t value respectively 4.076, 4.573, P values all below 0.05). CONCLUSIONS: Paracrine from ADSC after being stimulated by insulin can promote proliferation and migration of HUVEC, and suppress its apoptosis, and it is beneficial for tissue vascularization.

Shende, P. and N. P. Devlekar (2021). "A Review on the Role of Artificial Intelligence in Stem Cell Therapy: An Initiative for Modern Medicines." Curr Pharm Biotechnol **22**(9): 1156-1163.

Stem Cells (SCs) show a wide range of applications in the treatment of numerous diseases, including neurodegenerative diseases, diabetes, cardiovascular diseases, cancer, etc. SC related research has gained popularity owing to the unique characteristics of self-renewal and differentiation. Artificial Intelligence (AI), an emerging field of computer science and engineering, has shown potential applications in different fields like robotics, agriculture, home automation, healthcare, banking, and transportation since its invention. This review aims to describe the various applications of AI in SC biology, including understanding the behavior of SCs, recognizing individual cell type before undergoing differentiation, characterization of SCs using mathematical models and prediction of mortality risk associated with SC transplantation. This review emphasizes the role of neural networks in SC biology and further elucidates the concepts of machine learning and deep learning and their applications in SC research.

Shenoy, S. (2020). "Cell plasticity in cancer: A complex interplay of genetic, epigenetic mechanisms and tumor micro-environment." Surg Oncol **34**: 154-162.

Cell plasticity, also known as lineage plasticity is defined as the ability of a cell to reprogram and change its phenotype identity. Cell plasticity is context dependent and occurs during the development of an embryo, tissue regeneration, wound healing. However when deregulated and aberrant it also contributes to cancer initiation, progression, metastases and resistance to therapies. Tumors cells exhibit varying forms of cell plasticity in each stage of the disease to evade normal regulation as would have occurred in normal cell division and homeostasis. Current evidence demonstrates complex interplay between the genes, epigenes, tumor microenvironment and the EMT in cell reprogramming and cancer cell plasticity. Herein we present experimental evidence and evolving new developments in cell plasticity in cancer cells. Additionally "Deregulated/aberrant/hijacked cell plasticity" could be considered as an additional hallmark of a cancer. In the future, combining the advances in next generation sequencing and single cell RNA techniques with evolving AI (artificial intelligence) technologies such as deep learning techniques may predict the trajectories of cancer cells and assist in navigating through the complex intricacies of the cancers. A durable, precise, personalized oncologic treatment could be a reality.

Shi, Q., et al. (2024). "Early Predicting Osteogenic Differentiation of Mesenchymal Stem Cells Based on Deep Learning Within One Day." Ann Biomed Eng **52**(6): 1706-1718.

Osteogenic differentiation of mesenchymal stem cells (MSCs) is proposed to be critical for bone tissue engineering and regenerative medicine. However, the current approach for evaluating osteogenic differentiation mainly involves immunohistochemical staining of specific markers which often can be detected at day 5-7 of osteogenic inducing. Deep learning (DL) is a significant technology for realizing artificial intelligence (AI). Computer vision, a branch of AI, has been proved to achieve high-precision image recognition using convolutional neural networks (CNNs). Our goal was to train CNNs to quantitatively measure the osteogenic differentiation of MSCs. To this end, bright-field images of MSCs during early osteogenic differentiation (day 0, 1, 3, 5, and 7) were captured

using a simple optical phase contrast microscope to train CNNs. The results showed that the CNNs could be trained to recognize undifferentiated cells and differentiating cells with an accuracy of 0.961 on the independent test set. In addition, we found that CNNs successfully distinguished differentiated cells at a very early stage (only 1 day). Further analysis showed that overall morphological features of MSCs were the main basis for the CNN classification. In conclusion, MSCs differentiation detection can be achieved early and accurately through simple bright-field images and DL networks, which may also provide a potential and novel method for the field of cell detection in the near future.

Silva-Sousa, T., et al. (2024). "The global evolution and impact of systems biology and artificial intelligence in stem cell research and therapeutics development: a scoping review." Stem Cells **42**(11): 929-944.

Advanced bioinformatics analysis, such as systems biology (SysBio) and artificial intelligence (AI) approaches, including machine learning (ML) and deep learning (DL), is increasingly present in stem cell (SC) research. An approximate timeline on these developments and their global impact is still lacking. We conducted a scoping review on the contribution of SysBio and AI analysis to SC research and therapy development based on literature published in PubMed between 2000 and 2024. We identified an 8 to 10-fold increase in research output related to all 3 search terms between 2000 and 2021, with a 10-fold increase in AI-related production since 2010. Use of SysBio and AI still predominates in preclinical basic research with increasing use in clinically oriented translational medicine since 2010. SysBio- and AI-related research was found all over the globe, with SysBio output led by the (US, n = 1487), (UK, n = 1094), Germany (n = 355), The Netherlands (n = 339), Russia (n = 215), and France (n = 149), while for AI-related research the US (n = 853) and UK (n = 258) take a strong lead, followed by Switzerland (n = 69), The Netherlands (n = 37), and Germany (n = 19). The US and UK are most active in SCs publications related to AI/ML and AI/DL. The prominent use of SysBio in ESC research was recently overtaken by prominent use of AI in iPSC and MSC research. This study reveals the global evolution and growing intersection among AI, SysBio, and SC research over the past 2 decades, with substantial growth in all 3 fields and exponential increases in AI-related research in the past decade.

Sivalingam, A. M. (2024). "Advances in understanding biomarkers and treating neurological diseases - Role of the cerebellar dysfunction and emerging therapies." Ageing Res Rev **101**: 102519.

Cerebellar dysfunction is increasingly recognized as a critical factor in various neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Research has revealed distinct cerebellar atrophy patterns in conditions such as AD and multiple system atrophy, and studies in mice have highlighted its impact on motor control and cognitive functions. Emerging research into autism spectrum disorder (ASD) has identified key targets, such as elevated levels of chemokine receptors and ZIC family genes. Biomarkers, including cerebrospinal fluid (CSF), genetic markers, and advances in AI and bioinformatics, are enhancing early diagnosis and personalized treatment across neurodegenerative disorders. Notable advancements include improved diagnostic tools, gene therapy, and novel clinical trials. Despite progress, challenges such as the bloodbrain barrier and neuroinflammation persist. Current therapies for AD, PD, HD, and ALS, including antisense oligonucleotides and stem cell treatments, show promise but require further investigation. A comprehensive approach that integrates diagnostic methods and innovative therapies is essential for effective management and improved patient outcomes.

Smirnova, L., et al. (2023). "Organoid intelligence (OI) - The ultimate functionality of a brain microphysiological system." ALTEX **40**(2): 191-203.

Understanding brain function remains challenging as work with human and animal models is complicated by compensatory mechanisms, while in vitro models have been too simple until now. With the advent of human stem cells and the bioengineering of brain microphysiological systems (MPS), understanding how both cognition and long-term memory arise is now coming into reach. We suggest combining cutting-edge AI with MPS research to spearhead organoid intelligence (OI) as synthetic biological intelligence. The vision is to realize cognitive functions in brain MPS and scale them to achieve relevant short- and long-term memory capabilities and basic information processing as the ultimate functional experimental models for neurodevelopment and neurological function and as cell-based assays for drug and chemical testing. By advancing the frontiers of biological computing, we aim to (a) create models of intelligence-in-a-dish to study the basis of human cognitive functions, (b) provide models to advance the search for toxicants contributing to neurological diseases and identify remedies for neurological maladies, and (c) achieve relevant biological computational capacities to complement traditional

computing. Increased understanding of brain functionality, in some respects still superior to today's supercomputers, may allow to imitate this in neuromorphic computer architectures or might even open up biological computing to complement silicon computers. At the same time, this raises ethical questions such as where sentience and consciousness start and what the relationship between a stem cell donor and the respective OI system is. Such ethical discussions will be critical for the socially acceptable advance of brain organoid models of cognition.

Sniecinski, I. and J. Seghatchian (2018). "Artificial intelligence: A joint narrative on potential use in pediatric stem and immune cell therapies and regenerative medicine." Transfus Apher Sci **57**(3): 422-424.

Artificial Intelligence (AI) reflects the intelligence exhibited by machines and software. It is a highly desirable academic field of many current fields of studies. Leading AI researchers describe the field as "the study and design of intelligent agents". McCarthy invented this term in 1955 and defined it as "the science and engineering of making intelligent machines". The central goals of AI research are reasoning, knowledge, planning, learning, natural language processing (communication), perception and the ability to move and manipulate objects. In fact the multidisplinary AI field is considered to be rather interdisciplinary covering numerous number of sciences and professions, including computer science, psychology, linguistics, philosophy and neurosciences. The field was founded on the claim that a central intellectual property of humans, intelligence-the sapience of Homo Sapiens "can be so precisely described that a machine can be made to simulate it". This raises philosophical issues about the nature of the mind and the ethics of creating artificial beings endowed with human-like intelligence. Artificial Intelligence has been the subject of tremendous optimism but has also suffered stunning setbacks. The goal of this narrative is to review the potential use of AI approaches and their integration into pediatric cellular therapies and regenerative medicine. Emphasis is placed on recognition and application of AI techniques in the development of predictive models for personalized treatments with engineered stem cells, immune cells and regenerated tissues in adults and children. These intelligent machines could dissect the whole genome and isolate the immune particularities of individual patient's disease in a matter of minutes and create the treatment that is customized to patient's genetic specificity and immune system capability. AI techniques could be used for optimization of clinical trials of innovative stem cell and gene therapies in pediatric patients by precise planning of treatments, predicting clinical outcomes, simplifying recruitment and retention of patients, learning from input data and applying to new data, thus lowering their complexity and costs. Complementing human intelligence with machine intelligence could have an exponentially high impact on continual progress in many fields of pediatrics. However how long before we could see the real impact still remains the big question. The most pertinent question that remains to be answered therefore, is can AI effectively and accurately predict properties of newer DDR strategies? The goal of this article is to review the use of AI method for cellular therapy and regenerative medicine and emphasize its potential to further the progress in these fields of medicine.

Sordini, L., et al. (2021). "Effect of Electrical Stimulation Conditions on Neural Stem Cells Differentiation on Cross-Linked PEDOT:PSS Films." Front Bioeng Biotechnol **9**: 591838.

The ability to culture and differentiate neural stem cells (NSCs) to generate functional neural populations is attracting increasing attention due to its potential to enable cell-therapies to treat neurodegenerative diseases. Recent studies have shown that electrical stimulation improves neuronal differentiation of stem cells populations, highlighting the importance of the development of electroconductive biocompatible materials for NSC culture and differentiation for tissue engineering and regenerative medicine. Here, we report the use of the conjugated polymer poly(3,4-ethylenedioxythiophene) doped with polystyrene sulfonate (PEDOT:PSS CLEVIOS P AI 4083) for the manufacture of conductive substrates. Two different protocols, using different cross-linkers (3-glycidyloxypropyl)trimethoxysilane (GOPS) and divinyl sulfone (DVS) were tested to enhance their stability in aqueous environments. Both cross-linking treatments influence PEDOT:PSS properties, namely conductivity and contact angle. However, only GOPS-cross-linked films demonstrated to maintain conductivity and thickness during their incubation in water for 15 days. GOPS-cross-linked films were used to culture ReNcell-VM under different electrical stimulation conditions (AC, DC, and pulsed DC electrical fields). The polymeric substrate exhibits adequate physicochemical properties to promote cell adhesion and growth, as assessed by Alamar Blue(R) assay, both with and without the application of electric fields. NSCs differentiation was studied by immunofluorescence and quantitative real-time polymerase chain reaction. This study demonstrates that the pulsed DC stimulation (1 V/cm for 12 days), is the most efficient at enhancing the differentiation

of NSCs into neurons.

Srinivasan, M., et al. (2021). "Exploring the Current Trends of Artificial Intelligence in Stem Cell Therapy: A Systematic Review." Cureus **13**(12): e20083.

The concept of healing in medicine has been taking a new form where scientists and researchers are in pursuance of regenerative medicine. Until now, doctors have "reacted" to disease by treating the symptoms; however, modern medicine is transforming toward regeneration rather than reactive treatment, which is where stem cell therapy comes into the play-the concept of replacing damaged cells with brand new cells that perform the same function better. Stem cell treatment is currently being used to treat autoimmune, inflammatory, neurological, orthopedic, and traumatic disorders, with various research being undertaken for a wide range of diseases. It could also be the answer to anti-aging and a disease-free state. Despite the benefits, numerous errors could prevail in treating patients with stem cells. With the advancement of technology and research in the modern period, medicine is beginning to turn to artificial intelligence (AI) to address the complicated errors that could occur in regenerative medicine. For successful treatment, one must achieve precision and accuracy when analyzing healthy and productive stem cells that possess all the properties of a native cell. This review intends to discuss and study the application of AI in stem cell therapy and how it influences how medicine is practiced, thus creating a path to a regenerative future with negligible adverse effects. The following databases were used for a literature search: PubMed, Google Scholar, PubMed Central, and Institute of Electrical and Electronics Engineers (IEEE) Xplore. After a thorough analysis, studies were chosen, keeping in mind the inclusion and exclusion criteria set by the authors of this review, which comprised reports published within the last six years in the English language. The authors also made sure to include studies that sufficed the quality of each report assessed using appropriate quality appraisal tools, after which eight reports were found to be eligible and were included in this review. This research mainly revolves around machine learning, deep neural networks (DNN), and other subclasses of AI encompassed in these categories. While there are concerns and limitations in implementing various mediums of AI in stem cell therapy, the analysis of the eligible studies concluded that artificial intelligence provides significant benefits to the global healthcare ecosystem in numerous ways, such as determining the viability, functionality, biosafety, and bioefficacy of stem cells, as well as appropriate patient selection. Applying AI to this novelty brings out the precision, accuracy, and a revolution in regenerative medicine. In addition, stem cell therapy is not currently FDA approved (except for the blood-forming stem cells) and, to date, is considered experimental with no clear outline of risks and benefits. Given this limitation, studies are conducted regularly around the world in hopes for a concrete conclusion where technological advances such as AI could help in shaping the future of regenerative medicine.

Sugita, K., et al. (1986). "Use of a cocktail of monoclonal antibodies and human complement in selective killing of acute lymphocytic leukemia cells." Int J Cancer **37**(3): 351-357.

Autologous remission bone marrow is a potential source of repopulative stem cells after ablative chemoradiotherapy of tumor patients. Even with remission bone marrow, one major obstacle to use of autologous bone-marrow support is the danger of reinfusing viable tumor cells. This report describes a purging protocol with human complement, which seems suitable for eliminating acute lymphatic leukemia (ALL) cells of the common ALL type. Lysis of ALL blasts is induced with a cocktail of 3 monoclonal antibodies of IgM type (termed VIB-pool). These are directed against the CALLA (CD 10) antigen (VIL-AI antibody) and against 2 different epitopes of the CD24 surface structure (VIB-C5 and VIB-E3 antibodies). The purging efficiency was evaluated with leukemic cell lines of the common ALL type (Reh-6 and Nalm-6) and with blast cells from common ALL patients. Optimal lysis was obtained with antibody and human serum concentrations as low as 1 microgram/ml and 7% respectively. As a standard purging protocol we propose one 20-min incubation at room temperature with antibody followed by two 30-min incubations at 37 degrees C with 25% human complement. In dye exclusion test 99% purging efficiency and in clonogenic assays detecting elimination of up to 5 logs of clonogenic tumor cells 99.99% (= 4 logs) purging efficiency were achieved. Treatment with VIB-pool and human complement had no negative effect on the growth of the normal hemopoietic progenitor cells CFU-GM, CFU-E and BFU-E.

Sukandar, E. R., et al. (2019). "Tetrandraxanthones A-I, Prenylated and Geranylated Xanthones from the Stem Bark of Garcinia tetrandra." J Nat Prod **82**(5): 1312-1318.

Nine new xanthones, tetrandraxanthones A-I (1-9), and 22 known xanthones (10-31) were isolated from Garcinia tetrandra stem bark. The structures of 1-9 were characterized through detailed spectroscopic analysis, including HRESIMS and 2D NMR data. Among the compounds tested for their cytotoxicity,

26 showed significant cytotoxic effects against five human cancer cell lines, including MCF-7, HT-29, KB, Hep G2, and HeLa S3, with IC(50) values in the range of 1.6-3.4 muM, while 10 and 11 were cytotoxic against the MCF-7, HeLa S3, and KB cell lines, with IC(50) values of 4.3-9.0 muM.

Suzuki, I. (2020). "[Approach to drug efficacy and safety assessment based on functions of a human iPSC-derived neuronal network]." Nihon Yakurigaku Zasshi **155**(5): 289-294.

Development of an in vitro drug efficacy and safety assessment based on the function of the neural network is required in preclinical studies. A microelectrode array (MEA), which can simultaneously measure the electrical activity of a human induced pluripotent stem cell-derived neural network at multiple points, is an effective assay system. In this study, we focused on seizure liability and clarified the responsiveness to seizure-positive compounds depending on the excitatory and inhibitory balance (E/I balance) of each evaluation sample. In addition, it has been shown that multivariate analysis and AI analysis methods are effective for detecting toxicity and predicting drug mechanisms of action. The future challenge is to approach in vitro-to-in vivo extrapolation (IVIVE) for in vitro assessment. An assessment using brain organoids and low-frequency component analysis, in which enable comparison with in vivo ECoG are effective approaches to IVIVE. MEA can be applied to the central nervous system and the peripheral nervous system; therefore, MEA is also expected to become a highly useful assessment tool for peripheral neuropathy.

Tacke, D., et al. (2014). "Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology." Ann Hematol **93**(9): 1449-1456.

Invasive fungal infections cause substantial morbidity and mortality in immunocompromised patients, particularly in those with haematological malignancies and recipients of allogeneic haematopoietic stem cell transplantation. Difficulties in diagnosing invasive fungal infections and subsequent delays in treatment initiation lead to unfavourable outcomes and emphasise the importance of prophylaxis. Since the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology in 2009, results of 14 additional clinical studies have been published comprising 2,899 patients and initiating this update. Key recommendations for adult patients are as follows: Posaconazole remains the drug of choice during remission-induction chemotherapy in acute myeloid leukaemia, myelodysplastic syndrome and allogeneic haematopoietic stem cell transplantation with graft versus host disease (AI). In the pre-engraftment period of allogeneic transplantation, several antifungals are appropriate and can be recommended with equal strength: voriconazole (BI), micafungin (BI), fluconazole (BI) and posaconazole (BII). There is poor evidence regarding antifungal prophylaxis in the post-engraftment period of allogeneic haematopoietic stem cell transplantation if no steroids for treatment of graft versus host disease are required. Aerosolised liposomal amphotericin B inhalation in conjunction with fluconazole can be used in patients with prolonged neutropenia (BII).

Tanveer, Y., et al. (2023). "Revolutionizing Heart Transplantation: A Multidisciplinary Approach to Xenotransplantation, Immunosuppression, Regenerative Medicine, Artificial Intelligence, and Economic Sustainability." Cureus **15**(9): e46176.

Heart transplantation (HTx) stands as a life-saving intervention for patients with end-stage heart disease, but the field is fraught with numerous challenges that span from the scarcity of donor organs to long-term complications arising from immunosuppressive therapies. This comprehensive review article offers an in-depth exploration of the multifaceted aspects of HTx. The review covers groundbreaking advancements in xenotransplantation, enabled by cutting-edge genetic engineering techniques, and the promising role of stem cell therapies, particularly porcine mesenchymal stem cells, in cardiac regeneration. It also delves into the evolution and limitations of immunosuppressive therapies and the revolutionary potential of artificial intelligence (AI) and machine learning (ML) in enhancing donor-recipient matching and predicting patient outcomes. Economic considerations, especially in the context of rising healthcare costs, are examined to assess the sustainability of these advancements. The article further discusses the significant improvements in patient outcomes over the years, while highlighting persisting challenges, such as graft failure, rejection, and infection. It underscores the importance of experience and specialized training, evidenced by the presence of an institutional learning curve. The review concludes by advocating for a multifaceted, collaborative approach involving clinicians, researchers, and policymakers to overcome existing challenges. Through coordinated efforts that consider medical, ethical, and economic factors, the field of HTx is poised for further evolution, offering renewed hope for improved

patient care and outcomes.

Tao, G., et al. (2024). "Global research trends and hotspots of artificial intelligence research in spinal cord neural injury and restoration-a bibliometrics and visualization analysis." Front Neurol **15**: 1361235.

BACKGROUND: Artificial intelligence (AI) technology has made breakthroughs in spinal cord neural injury and restoration in recent years. It has a positive impact on clinical treatment. This study explores AI research's progress and hotspots in spinal cord neural injury and restoration. It also analyzes research shortcomings related to this area and proposes potential solutions. METHODS: We used CiteSpace 6.1.R6 and VOSviewer 1.6.19 to research WOS articles on AI research in spinal cord neural injury and restoration. RESULTS: A total of 1,502 articles were screened, in which the United States dominated; Kadone, Hideki (13 articles, University of Tsukuba, JAPAN) was the author with the highest number of publications; ARCH PHYS MED REHAB (IF = 4.3) was the most cited journal, and topics included molecular biology, immunology, neurology, sports, among other related areas. CONCLUSION: We pinpointed three research hotspots for AI research in spinal cord neural injury and restoration: (1) intelligent robots and limb exoskeletons to assist rehabilitation training; (2) brain-computer interfaces; and (3) neuromodulation and noninvasive electrical stimulation. In addition, many new hotspots were discussed: (1) starting with image segmentation models based on convolutional neural networks; (2) the use of AI to fabricate polymeric biomaterials to provide the microenvironment required for neural stem cell-derived neural network tissues; (3) AI survival prediction tools, and transcription factor regulatory networks in the field of genetics were discussed. Although AI research in spinal cord neural injury and restoration has many benefits, the technology has several limitations (data and ethical issues). The data-gathering problem should be addressed in future research, which requires a significant sample of quality clinical data to build valid AI models. At the same time, research on genomics and other mechanisms in this field is fragile. In the future, machine learning techniques, such as AI survival prediction tools and transcription factor regulatory networks, can be utilized for studies related to the up-regulation of regeneration-related genes and the production of structural proteins for axonal growth.

Telang, N. (2015). "Putative cancer-initiating stem cells in cell culture models for molecular subtypes of clinical breast cancer." Oncol Lett **10**(6): 3840-3846.

Cancer-initiating stem cells (CISC) represent a minor subpopulation of heterogeneous breast cancer. CISC are responsible for the acquired resistance to conventional chemoendocrine therapy and eventual relapse observed in patients with breast cancer. Certain molecular subtypes of clinical breast cancer that exhibit differential expression of genes coding for hormone and growth factor receptors differ in their response to conventional chemoendocrine therapy and targeted therapeutic inhibitors. Thus, the development of reliable cell culture models for CISC may provide a valuable experimental approach for the study of stem cell-targeted therapy for the treatment of breast cancer. The present study utilized optimized cell culture systems as experimental models for different molecular subtypes of clinical breast cancer, including luminal A, human epidermal growth factor receptor (HER)-2-enriched and triple negative breast cancer. Biomarker end points, including control of homeostatic growth, cancer risk and drug resistance, were quantitatively analyzed in the selected models. The results of the analyses indicated that, compared with the non-tumorigenic controls, the cell models representing the aforementioned molecular subtypes of clinical breast cancer exhibited aberrant cell cycle progression, downregulated cellular apoptosis and loss of control of homeostatic growth, as evidenced by hyperproliferation. Additionally, these models displayed persistent cancer risk, as indicated by their high incidence and frequency of anchorage-independent (AI) colony formation in vitro and their tumor development capacity in vivo. Furthermore, in the presence of maximum cytostatic drug concentrations, the drug-resistant phenotypes isolated from the parental drug-sensitive cell lines representing luminal A, HER-2-enriched and triple negative breast cancer exhibited an 11.5, 5.0 and 6.2 fold increase in cell growth, and a 5.6, 5.4 and 4.4 fold increase in the number of AI colonies, respectively, compared with the drug-sensitive controls. Collectively, the data of the present study demonstrated the presence of putative CISC in these breast cancer models.

Tindle, C., et al. (2021). "Adult stem cell-derived complete lung organoid models emulate lung disease in COVID-19." Elife **10**.

BACKGROUND: SARS-CoV-2, the virus responsible for COVID-19, causes widespread damage in the lungs in the setting of an overzealous immune response whose origin remains unclear. METHODS: We present a scalable, propagable, personalized, cost-effective adult stem cell-derived human lung organoid model that is complete with both proximal and distal airway epithelia. Monolayers derived from adult lung organoids

(ALOs), primary airway cells, or hiPSC-derived alveolar type II (AT2) pneumocytes were infected with SARS-CoV-2 to create in vitro lung models of COVID-19. RESULTS: Infected ALO monolayers best recapitulated the transcriptomic signatures in diverse cohorts of COVID-19 patient-derived respiratory samples. The airway (proximal) cells were critical for sustained viral infection, whereas distal alveolar differentiation (AT2-->AT1) was critical for mounting the overzealous host immune response in fatal disease; ALO monolayers with well-mixed proximodistal airway components recapitulated both. CONCLUSIONS: Findings validate a human lung model of COVID-19, which can be immediately utilized to investigate COVID-19 pathogenesis and vet new therapies and vaccines. FUNDING: This work was supported by the National Institutes for Health (NIH) grants 1R01DK107585-01A1, 3R01DK107585-05S1 (to SD); R01-AI141630, CA100768 and CA160911 (to PG) and R01-AI 155696 (to PG, DS and SD); R00-CA151673 and R01-GM138385 (to DS), R01- HL32225 (to PT), UCOP-R00RG2642 (to SD and PG), UCOP-R01RG3780 (to P.G. and D.S) and a pilot award from the Sanford Stem Cell Clinical Center at UC San Diego Health (P.G, S.D, D.S). GDK was supported through The American Association of Immunologists Intersect Fellowship Program for Computational Scientists and Immunologists. L.C.A's salary was supported in part by the VA San Diego Healthcare System. This manuscript includes data generated at the UC San Diego Institute of Genomic Medicine (IGC) using an Illumina NovaSeq 6000 that was purchased with funding from a National Institutes of Health SIG grant (#S10 OD026929).

Toader, C., et al. (2023). "Frontiers of Cranial Base Surgery: Integrating Technique, Technology, and Teamwork for the Future of Neurosurgery." Brain Sci **13**(10).

The landscape of cranial base surgery has undergone monumental transformations over the past several decades. This article serves as a comprehensive survey, detailing both the historical and current techniques and technologies that have propelled this field into an era of unprecedented capabilities and sophistication. In the prologue, we traverse the historical evolution from rudimentary interventions to the state-of-the-art neurosurgical methodologies that define today's practice. Subsequent sections delve into the anatomical complexities of the anterior, middle, and posterior cranial fossa, shedding light on the intricacies that dictate surgical approaches. In a section dedicated to advanced techniques and modalities, we explore cutting-edge evolutions in minimally invasive procedures, pituitary surgery, and cranial base reconstruction. Here, we highlight the seamless integration of endocrinology, biomaterial science, and engineering into neurosurgical craftsmanship. The article emphasizes the paradigm shift towards "Functionally" Guided Surgery facilitated by intraoperative neuromonitoring. We explore its historical origins, current technologies, and its invaluable role in tailoring surgical interventions across diverse pathologies. Additionally, the digital era's contributions to cranial base surgery are examined. This includes breakthroughs in endoscopic technology, robotics, augmented reality, and the potential of machine learning and AI-assisted diagnostic and surgical planning. The discussion extends to radiosurgery and radiotherapy, focusing on the harmonization of precision and efficacy through advanced modalities such as Gamma Knife and CyberKnife. The article also evaluates newer protocols that optimize tumor control while preserving neural structures. In acknowledging the holistic nature of cranial base surgery, we advocate for an interdisciplinary approach. The ecosystem of this surgical field is presented as an amalgamation of various medical disciplines, including neurology, radiology, oncology, and rehabilitation, and is further enriched by insights from patient narratives and quality-of-life metrics. The epilogue contemplates future challenges and opportunities, pinpointing potential breakthroughs in stem cell research, regenerative medicine, and genomic tailoring. Ultimately, the article reaffirms the ethos of continuous learning, global collaboration, and patient-first principles, projecting an optimistic trajectory for the field of cranial base surgery in the coming decade.

Tucker, B. A., et al. (2020). "Autologous cell replacement: a noninvasive AI approach to clinical release testing." J Clin Invest **130**(2): 608-611.

The advent of human induced pluripotent stem cells (iPSCs) provided a means for avoiding ethical concerns associated with the use of cells isolated from human embryos. The number of labs now using iPSCs to generate photoreceptor, retinal pigmented epithelial (RPE), and-more recently-choroidal endothelial cells has grown exponentially. However, for autologous cell replacement to be effective, manufacturing strategies will need to change. Many tasks carried out by hand will need simplifying and automating. In this issue of the JCI, Schaub and colleagues combined quantitative bright-field microscopy and artificial intelligence (deep neural networks and traditional machine learning) to noninvasively monitor iPSC-derived graft maturation, predict donor cell identity, and evaluate graft function

prior to transplantation. This approach allowed the authors to preemptively identify and remove abnormal grafts. Notably, the method is (a) transferable, (b) cost and time effective, (c) high throughput, and (d) useful for primary product validation.

Uchiumi, K., et al. (2019). "Cancer stem-like properties of hormonal therapy-resistant breast cancer cells." Breast Cancer **26**(4): 459-470.

BACKGROUND: Presently, hormonal therapy targeting estrogen receptors is the most effective treatment available for luminal breast cancer. However, many patients relapse after the therapy. It has been suggested that cancer stem-like cells are involved with hormonal therapy resistance; in the present study, we evaluated this hypothesis. METHODS: In the present study, we used our previously established hormonal therapy-resistant cell lines, including aromatase inhibitor (AI)-resistant cells (Type 1 and Type 2) and fulvestrant-resistant cells (MFR). RESULTS: AI-resistant cell lines expressing ER (Type 1 V1 and V2) showed high cancer stemness in terms of their CD44/CD24 expression and side populations, which were stimulated by the addition of estrogen and inhibited by fulvestrant. However, ALDH activity was lower than in the ER-negative resistant cells, suggesting that the stemness of luminal cells is distinct from that of basal-like breast cancer cells. The migration and invasion activity of the ER-positive Type 1 V1 and V2 cells were higher than in the ER-negative cell lines, Type 2 and MFR. CONCLUSIONS: Fractionation of parental cells based on CD44/CD24 expression and colony formation assay indicated that CD44+/CD24+ cells might be the origin of hormonal therapy-resistant cells. This population reconstituted various other subpopulations under estrogen deprivation. These results indicate that hormonal therapy resistance is closely related to the cancer stem cell-like properties of luminal breast cancer.

Ullmann, A. J., et al. (2012). "ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)." Clin Microbiol Infect **18 Suppl 7**: 53-67.

Fungal diseases still play a major role in morbidity and mortality in patients with haematological malignancies, including those undergoing haematopoietic stem cell transplantation. Although Aspergillus and other filamentous fungal diseases remain a major concern, Candida infections are still a major cause of mortality. This part of the ESCMID guidelines focuses on this patient population and reviews pertaining to prophylaxis, empirical/pre-emptive and targeted therapy of Candida diseases. Anti-Candida prophylaxis is only recommended for patients receiving allogeneic stem cell transplantation. The authors recognize that the recommendations would have most likely been different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). In targeted treatment of candidaemia, recommendations for treatment are available for all echinocandins, that is anidulafungin (AI), caspofungin (AI) and micafungin (AI), although a warning for resistance is expressed. Liposomal amphotericin B received a BI recommendation due to higher number of reported adverse events in the trials. Amphotericin B deoxycholate should not be used (DII); and fluconazole was rated CI because of a change in epidemiology in some areas in Europe. Removal of central venous catheters is recommended during candidaemia but if catheter retention is a clinical necessity, treatment with an echinocandin is an option (CII(t)). In chronic disseminated candidiasis therapy, recommendations are liposomal amphotericin B for 8 weeks (AIII), fluconazole for >3 months or other azoles (BIII). Granulocyte transfusions are only an option in desperate cases of patients with Candida disease and neutropenia (CIII).

Usynin, I. F., et al. (2018). "Apolipoprotein A-I Stimulates Cell Proliferation in Bone Marrow Cell Culture." Bull Exp Biol Med **164**(3): 308-311.

Culturing of bone marrow cells in serum-free RPMI-1640 medium led to a decrease in the rate of DNA biosynthesis. Addition of HDL or their main protein component apolipoprotein A-I to the culture medium dose-dependently increased the rate of [3H]-thymidine incorporation into DNA. The maximum stimulation was achieved at HDL concentration of 80 mug/ml and apolipoprotein A-I concentration of 20 mug/ml. To identify the target-cells of apolipoprotein A-I, we used thymidine analogue 5-ethynyl-2'-deoxyuridine (EdU) that incorporates into cell DNA at the stage of replicative DNA synthesis (S phase) and can be detected by fluorescence microscopy. In bone marrow cell culture, apolipoprotein A-I stimulates the proliferation of monocyte (monoblasts, promonocytes) and granulocyte (myeloblasts, promyelocytes) progenitor cells, as well as bone marrow stromal cells.

Vaishya, R., et al. (2024). "Artificial Intelligence (AI): A Potential Game Changer in Regenerative Orthopedics-A Scoping Review." Indian J Orthop **58**(10): 1362-1374.

BACKGROUND AND AIMS: Regenerative orthopedics involves approaches like stem cell

therapy, platelet-rich plasma (PRP) therapy, the use of biological scaffold implants, tissue engineering, etc. We aim to present a scoping review of the role of artificial intelligence (AI) in different treatment approaches of regenerative orthopedics. METHODS: Using the PRISMA guidelines, a search for articles for the last ten years (2013-2024) on PubMed was done, using several keywords. We have discussed the state-of-the-art, strengths/benefits, and limitations of the published research, and provide a useful resource for the way ahead in future for researchers working in this area. RESULTS: Using the eligibility criteria out of 82 initially screened publications, we included 18 studies for this review. We noticed that the treatment responses to regenerative treatments depend on several factors; hence, to facilitate better comprehensive and patient-specific treatments, AI technology is very useful. Machine learning (ML) and deep learning (DL) are a few of the most frequently used AI techniques. They use a data-driven approach for training models to make human-like decisions. Data are fed to the ML/DL algorithm and the trained model makes classifications or predictions based on its learning. CONCLUSION: The area of regenerative orthopedics is highly sophisticated and significantly aids in providing cost-effective and non-invasive treatments to patients suffering from orthopedic ailments and injuries. Due to its promising future, the use of AI in regenerative orthopedics is an emerging and promising research field; however, its universal clinical applications are associated with some ethical considerations, which need addressing. SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1007/s43465-024-01189-1.

Van Linthout, S., et al. (2015). "Therapeutic potential of HDL in cardioprotection and tissue repair." Handb Exp Pharmacol **224**: 527-565.

Epidemiological studies support a strong association between high-density lipoprotein (HDL) cholesterol levels and heart failure incidence. Experimental evidence from different angles supports the view that low HDL is unlikely an innocent bystander in the development of heart failure. HDL exerts direct cardioprotective effects, which are mediated via its interactions with the myocardium and more specifically with cardiomyocytes. HDL may improve cardiac function in several ways. Firstly, HDL may protect the heart against ischaemia/reperfusion injury resulting in a reduction of infarct size and thus in myocardial salvage. Secondly, HDL can improve cardiac function in the absence of ischaemic heart disease as illustrated by beneficial effects conferred by these lipoproteins in diabetic cardiomyopathy. Thirdly, HDL may improve cardiac function by reducing infarct expansion and by attenuating ventricular remodelling post-myocardial infarction. These different mechanisms are substantiated by in vitro, ex vivo, and in vivo intervention studies that applied treatment with native HDL, treatment with reconstituted HDL, or human apo A-I gene transfer. The effect of human apo A-I gene transfer on infarct expansion and ventricular remodelling post-myocardial infarction illustrates the beneficial effects of HDL on tissue repair. The role of HDL in tissue repair is further underpinned by the potent effects of these lipoproteins on endothelial progenitor cell number, function, and incorporation, which may in particular be relevant under conditions of high endothelial cell turnover. Furthermore, topical HDL therapy enhances cutaneous wound healing in different models. In conclusion, the development of HDL-targeted interventions in these strategically chosen therapeutic areas is supported by a strong clinical rationale and significant preclinical data.

Vathipadiekal, V., et al. (2016). "A candidate transacting modulator of fetal hemoglobin gene expression in the Arab-Indian haplotype of sickle cell anemia." Am J Hematol **91**(11): 1118-1122.

Fetal hemoglobin (HbF) levels are higher in the Arab-Indian (AI) beta-globin gene haplotype of sickle cell anemia compared with African-origin haplotypes. To study genetic elements that effect HbF expression in the AI haplotype we completed whole genome sequencing in 14 Saudi AI haplotype sickle hemoglobin homozygotes-seven selected for low HbF (8.2% +/- 1.3%) and seven selected for high HbF (23.5% +/- 2.6%). An intronic single nucleotide polymorphism (SNP) in ANTXR1, an anthrax toxin receptor (chromosome 2p13), was associated with HbF. These results were replicated in two independent Saudi AI haplotype cohorts of 120 and 139 patients, but not in 76 Saudi Benin haplotype, 894 African origin haplotype and 44 AI haplotype patients of Indian origin, suggesting that this association is effective only in the Saudi AI haplotype background. ANTXR1 variants explained 10% of the HbF variability compared with 8% for BCL11A. These two genes had independent, additive effects on HbF and together explained about 15% of HbF variability in Saudi AI sickle cell anemia patients. ANTXR1 was expressed at mRNA and protein levels in erythroid progenitors derived from induced pluripotent stem cells (iPSCs) and CD34(+) cells. As CD34(+) cells matured and their HbF decreased ANTXR1 expression increased; as iPSCs differentiated and their HbF increased, ANTXR1 expression decreased. Along with elements in cis to the HbF genes, ANTXR1 contributes to the variation in HbF in Saudi AI haplotype sickle cell anemia and

is the first gene in trans to HBB that is associated with HbF only in carriers of the Saudi AI haplotype. Am. J. Hematol. 91:1118-1122, 2016. (c) 2016 Wiley Periodicals, Inc.

Vera, C. D., et al. (2022). "Treating Duchenne Muscular Dystrophy: The Promise of Stem Cells, Artificial Intelligence, and Multi-Omics." Front Cardiovasc Med **9**: 851491.

Muscular dystrophies are chronic and debilitating disorders caused by progressive muscle wasting. Duchenne muscular dystrophy (DMD) is the most common type. DMD is a well-characterized genetic disorder caused by the absence of dystrophin. Although some therapies exist to treat the symptoms and there are ongoing efforts to correct the underlying molecular defect, patients with muscular dystrophies would greatly benefit from new therapies that target the specific pathways contributing directly to the muscle disorders. Three new advances are poised to change the landscape of therapies for muscular dystrophies such as DMD. First, the advent of human induced pluripotent stem cells (iPSCs) allows researchers to design effective treatment strategies that make up for the gaps missed by conventional "one size fits all" strategies. By characterizing tissue alterations with single-cell resolution and having molecular profiles for therapeutic treatments for a variety of cell types, clinical researchers can design multi-pronged interventions to not just delay degenerative processes, but regenerate healthy tissues. Second, artificial intelligence (AI) will play a significant role in developing future therapies by allowing the aggregation and synthesis of large and disparate datasets to help reveal underlying molecular mechanisms. Third, disease models using a high volume of multi-omics data gathered from diverse sources carry valuable information about converging and diverging pathways. Using these new tools, the results of previous and emerging studies will catalyze precision medicine-based drug development that can tackle devastating disorders such as DMD.

Vilquin, P., et al. (2015). "MicroRNA-125b upregulation confers aromatase inhibitor resistance and is a novel marker of poor prognosis in breast cancer." Breast Cancer Res **17**(1): 13.

INTRODUCTION: Increasing evidence indicates that microRNAs (miRNAs) are important players in oncogenesis. Considering the widespread use of aromatase inhibitors (AIs) in endocrine therapy as a first-line treatment for postmenopausal estrogen receptor alpha-positive breast cancer patients, identifying deregulated expression levels of miRNAs in association with AI resistance is of utmost importance. METHODS: To gain further insight into the molecular mechanisms underlying the AI resistance, we performed miRNA microarray experiments using a new model of acquired resistance to letrozole (Res-Let cells), obtained by long-term exposure of aromatase-overexpressing MCF-7 cells (MCF-7aro cells) to letrozole, and a model of acquired anastrozole resistance (Res-Ana cells). Three miRNAs (miR-125b, miR-205 and miR-424) similarly deregulated in both AI-resistant cell lines were then investigated in terms of their functional role in AI resistance development and breast cancer cell aggressiveness and their clinical relevance using a cohort of 65 primary breast tumor samples. RESULTS: We identified the deregulated expression of 33 miRNAs in Res-Let cells and of 18 miRNAs in Res-Ana cells compared with the sensitive MCF-7aro cell line. The top-ranked Kyoto Encyclopedia of Genes and Genomes pathways delineated by both miRNA signatures converged on the AKT/mTOR pathway, which was found to be constitutively activated in both AI-resistant cell lines. We report for the first time, to our knowledge, that ectopic overexpression of either miR-125b or miR-205, or the silencing of miR-424 expression, in the sensitive MCF-7aro cell line was sufficient to confer resistance to letrozole and anastrozole, to target and activate the AKT/mTOR pathway and to increase the formation capacity of stem-like and tumor-initiating cells possessing self-renewing properties. Increasing miR-125b expression levels was also sufficient to confer estrogen-independent growth properties to the sensitive MCF-7aro cell line. We also found that elevated miR-125b expression levels were a novel marker for poor prognosis in breast cancer and that targeting miR-125b in Res-Let cells overcame letrozole resistance. CONCLUSION: This study highlights that acquisition of specific deregulated miRNAs is a newly discovered alternative mechanism developed by AI-resistant breast cancer cells to achieve constitutive activation of the AKT/mTOR pathway and to develop AI resistance. It also highlights that miR-125b is a new biomarker of poor prognosis and a candidate therapeutic target in AI-resistant breast cancers.

Vo, Q. D., et al. (2024). "The use of artificial intelligence in induced pluripotent stem cell-based technology over 10-year period: A systematic scoping review." PLoS One **19**(5): e0302537.

BACKGROUND: Stem cell research, particularly in the domain of induced pluripotent stem cell (iPSC) technology, has shown significant progress. The integration of artificial intelligence (AI), especially machine learning (ML) and deep learning (DL), has played a pivotal role in refining

iPSC classification, monitoring cell functionality, and conducting genetic analysis. These enhancements are broadening the applications of iPSC technology in disease modelling, drug screening, and regenerative medicine. This review aims to explore the role of AI in the advancement of iPSC research. METHODS: In December 2023, data were collected from three electronic databases (PubMed, Web of Science, and Science Direct) to investigate the application of AI technology in iPSC processing. RESULTS: This systematic scoping review encompassed 79 studies that met the inclusion criteria. The number of research studies in this area has increased over time, with the United States emerging as a leading contributor in this field. AI technologies have been diversely applied in iPSC technology, encompassing the classification of cell types, assessment of disease-specific phenotypes in iPSC-derived cells, and the facilitation of drug screening using iPSC. The precision of AI methodologies has improved significantly in recent years, creating a foundation for future advancements in iPSC-based technologies. CONCLUSIONS: Our review offers insights into the role of AI in regenerative and personalized medicine, highlighting both challenges and opportunities. Although still in its early stages, AI technologies show significant promise in advancing our understanding of disease progression and development, paving the way for future clinical applications.

Wang, L., et al. (2016). "Bone Marrow Mesenchymal Stem Cells Attenuate Mitochondria Damage Induced by Hypoxia in Mouse Trophoblasts." PLoS One **11**(4): e0153729.

OBJECTIVE: We aimed to observe the change of mitochondrial function and structure as well as the cell function induced by hypoxia in mouse trophoblasts, and moreover, to validate the restoration of these changes after co-culture with bone marrow mesenchymal stem cells (hereinafter referred to as "MSCs"). Further, we explored the mechanism of MSCs attenuating the functional damage of trophoblasts caused by hypoxia. METHODS: Cells were divided into two groups, trophoblasts and MSCs+trophoblasts respectively, and the two groups of cells were incubated with normoxia or hypoxia. Chemiluminescence was used to assay the beta-HCG and progesterone in cell culture supernatants quantitatively. Western blotting and PCR were applied to detect the expression of Mfn2, MMP-2, MMP-9 and integrin beta1 in the two groups. The mitochondrial membrane potential of each group of cells was detected with JC-1 dye and the ATP content was measured by the phosphomolybdic acid colorimetric method. We utilized transmission electron microscopy for observing the ultrastructure of mitochondria in trophoblasts. Finally, we assessed the cell apoptosis with flow cytometry (FCM) and analyzed the expression of the apoptosis related genes-Bcl-2, Bax, Caspase3 and Caspase9 by western blotting. RESULTS: The results showed that the Mfn2 expression was reduced after 4 h in hypoxia compared with that in normoxia, but increased in the co-culture group when compared with that in the separated-culture group ($p<0.05$). In addition, compared with the separated-culture group, thebeta-HCG and progesterone levels in the co-culture group were significantly enhanced ($p<0.05$), and so were the expressions of MMP-2, MMP-9 and integrin beta1 ($p<0.05$). Moreover, it exhibited significantly higher in ATP levels and intensified about the mitochondrial membrane potential in the co-culture group. TEM revealed disorders of the mitochondrial cristae and presented short rod-like structure and spheroids in hypoxia, however, in the co-culture group, the mitochondrial cristae had a relatively regular arrangement and the mitochondrial ultrastructure showed hyperfusion. The expression of Bax, Caspase3 and Caspase9 was decreased in the co-culture group when compared with that in trophoblast cells cultured alone ($p<0.05$), while the Bcl-2 levels and the Apoptosis Index (AI) were markedly increased in the co-culture group ($p<0.05$). CONCLUSION: Bone marrow mesenchymal stem cells can attenuate mitochondria damage and cell apoptosis induced by hypoxia; the mechanism could be upregulating the expression of Mfn2 in mouse trophoblasts and changing mitochondrial structure.

Wang, M., et al. (2016). "Intraperitoneal injection (IP), Intravenous injection (IV) or anal injection (AI)? Best way for mesenchymal stem cells transplantation for colitis." Sci Rep **6**: 30696.

Stem cell transplantation showed promising results in IBD management. However, the therapeutic impacts of cell delivery route that is critical for clinical translation are currently poorly understood. Here, three different MSCs delivery routes: intraperitoneal (IP), intravenous (IV), and anal injection (AI) were compared on DSS-induced colitic mice model. The overall therapeutic factors, MSCs migration and targeting as well as local immunomodulatory cytokines and FoxP3(+) cells infiltration were analyzed. Colitis showed varying degrees of alleviation after three ways of MSCs transplantation, and the IP injection showed the highest survival rate of 87.5% and displayed the less weight loss and quick weight gain. The fecal occult blood test on the day 3 also showed nearly complete absence of occult blood in IP group. The fluorescence imaging disclosed higher intensity of engrafted cells

in inflamed colon and the corresponding mesentery lymph nodes (MLNs) in IP and AI groups than the IV group. Real time-PCR and ELISA also demonstrate lower TNF-alpha and higher IL-10, TSG-6 levels in IP group. The immunohistochemistry indicated higher repair proliferation (Ki-67) and more FoxP3(+) cells accumulation of IP group. IP showed better colitis recovery and might be the optimum MSCs delivery route for the treatment of DSS-induced colitis.

Wang, N. and M. Westerterp (2020). "ABC Transporters, Cholesterol Efflux, and Implications for Cardiovascular Diseases." Adv Exp Med Biol **1276**: 67-83.

Most types of cells in the body have no or very limited capacity of catabolizing cholesterol, so cholesterol efflux is essential for cholesterol homeostasis. There are multiple mechanisms responsible for cellular cholesterol efflux. Among them, the active efflux pathways are mediated primarily by the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1. ABCA1 is essential for cholesterol and phospholipid efflux to apolipoprotein A-I and high density lipoprotein (HDL) biogenesis. ABCG1 promotes cholesterol efflux primarily to HDL particles. Atherosclerotic cardiovascular disease is a chronic inflammatory disease characterized by marked macrophage foam cell accumulation in atherosclerotic plaques and associated pro-inflammatory responses in lesional cells. Findings from both animal and human studies indicate a critical role of disturbed cholesterol homeostasis in pro-inflammatory responses in these cells, particularly in lesional macrophages. ABCA1 and ABCG1 are highly expressed in macrophages, particularly in response to cholesterol accumulation, and are essential in maintenance of cholesterol homeostasis. Functional deficiency of ABCA1 and ABCG1 in macrophage markedly increases atherogenesis, with exacerbated inflammatory responses. ABCA1 and ABCG1 also play a critical role in control of hematopoietic stem and progenitor cell (HSPC) proliferation and extramedullary hematopoiesis. Hematopoietic ABCA1 and ABCG1 deficiencies cause marked HSPC expansion and extramedullary hematopoiesis, particularly in hypercholesterolemia, and lead to marked monocytosis and neutrophilia with exacerbated pro-inflammatory responses. All these contribute to atherosclerosis. In this chapter, we describe these findings and discuss the current understanding of the underlying mechanisms. We also discuss other ABC transporters such as ABCG4, which also promotes cholesterol efflux to HDL and controls megakaryocyte proliferation and platelet biogenesis. By this pathway, ABCG4 also modulates atherogenesis. Therapeutic approaches targeting the pathways and mechanisms described also are discussed.

Wang, P., et al. (2015). "Sensitization to docetaxel in prostate cancer cells by green tea and quercetin." J Nutr Biochem **26**(4): 408-415.

Chemotherapy with docetaxel (Doc) is a standard treatment for metastatic and castration-resistant prostate cancer. However, chemoresistance and side effects of Doc limit its clinical success. We investigated whether natural products green tea (GT) and quercetin (Q), a flavonoid from apples and onions, will enhance the efficacy of Doc in androgen-independent (AI) prostate cancer cells. Two cell lines including LAPC-4-AI and PC-3 were treated in vitro with 40 muM of (-)-epigallocatechin gallate (EGCG), 5 muM of Q, 2 or 5 nM of Doc alone or in combination. The mixture of EGCG+Q+Doc increased the antiproliferative effect by threefold in LAPC-4-AI cells and eightfold in PC-3 cells compared to Doc alone. EGCG, Q and Doc in combination significantly enhanced cell cycle arrest at G2/M phase and increased apoptosis in both LAPC-4-AI and PC-3 cells compared to Doc alone. The mixture increased the inhibition of PI3K/Akt and the signal transducer and activator of transcription (Stat) 3 signaling pathways compared to Doc alone, and decreased the protein expression of multidrug resistance-related protein. In addition, the combination with EGCG and Q increased the inhibition of tumor cell invasion and colony formation in both LAPC-4-AI and PC-3 cells compared to Doc alone, and decreased the percentage of CD44(+)/CD24(-) stem-like LAPC-4-AI cells. In summary, GT and Q enhanced the therapeutic effect of Doc in castration-resistant prostate cancer cells through multiple mechanisms including the down-regulation of chemoresistance-related proteins. This study provides a novel therapeutic modality to enhance the efficacy of Doc in a nontoxic manner.

Wang, S. K., et al. (2023). "FAM20A mutations and transcriptome analyses of dental pulp tissues of enamel renal syndrome." Int Endod J **56**(8): 943-954.

AIM: Biallelic loss-of-function FAM20A mutations cause amelogenesis imperfecta (AI) type IG, better known as enamel renal syndrome (ERS), characterized by severe enamel hypoplasia, delayed/failed tooth eruption, intrapulpal calcifications, gingival hyperplasia and nephrocalcinosis. FAM20A binds to FAM20C, the Golgi casein kinase (GCK) and potentiates its function to phosphorylate secreted proteins critical for biomineralization. While many FAM20A

pathogenic mutations have been reported, the pathogeneses of orodental anomalies in ERS remain to be elucidated. This study aimed to identify disease-causing mutations for patients with ERS phenotypes and to discern the molecular mechanism underlying ERS intrapulpal calcifications. METHODOLOGY: Phenotypic characterization and whole exome analyses were conducted for 8 families and 2 sporadic cases with hypoplastic AI. A minigene assay was performed to investigate the molecular consequences of a FAM20A splice-site variant. RNA sequencing followed by transcription profiling and gene ontology (GO) analyses were carried out for dental pulp tissues of ERS and the control. RESULTS: Biallelic FAM20A mutations were demonstrated for each affected individual, including 7 novel pathogenic variants: c.590-5T>A, c.625T>A (p.Cys209Ser), c.771del (p.Gln258Argfs*28), c.832_835delinsTGTCCGACGGTGTCCGACGGTG TC CA (p.Val278Cysfs*29), c.1232G>A (p.Arg411Gln), c.1297A>G (p.Arg433Gly) and c.1351del (p.Gln451Serfs*4). The c.590-5T>A splice-site mutation caused Exon 3 skipping, which resulted in an in-frame deletion of a unique region of the FAM20A protein, p.(Asp197_Ile214delinsVal). Analyses of differentially expressed genes in ERS pulp tissues demonstrated that genes involved in biomineralization, particularly dentinogenesis, were significantly upregulated, such as DSPP, MMP9, MMP20 and WNT10A. Enrichment analyses indicated overrepresentation of gene sets associated with BMP and SMAD signalling pathways. In contrast, GO terms related to inflammation and axon development were underrepresented. Among BMP signalling genes, BMP agonists GDF7, GDF15, BMP3, BMP8A, BMP8B, BMP4 and BMP6 were upregulated, while BMP antagonists GREM1, BMPER and VWC2 showed decreased expression in ERS dental pulp tissues. CONCLUSIONS: Upregulation of BMP signalling underlies intrapulpal calcifications in ERS. FAM20A plays an essential role in pulp tissue homeostasis and prevention of ectopic mineralization in soft tissues. This critical function probably depends upon MGP (matrix Gla protein), a potent mineralization inhibitor that must be properly phosphorylated by FAM20A-FAM20C kinase complex.

Wang, Y., et al. (2014). "Comparative RNA-seq analysis reveals potential mechanisms mediating the conversion to androgen independence in an LNCaP progression cell model." Cancer Lett **342**(1): 130-138.

The androgen-independent phenotype is an important symptom of refractory prostate cancer. However, the molecular mechanisms underlying this phenotypic conversion remain unclear. Using RNA-seq analysis of androgen-dependent prostate cancer cells (LNCaP) vs. androgen-independent cancer cells (LNCaP-AI-F), we identified 788 differentially expressed genes, 315 alternative splicing events, and eight novel LNCaP-AI-F-specific fusion genes. The fusion genes EIF2AK1-ATR and GLYR1-SLC9A8 were predicted to be damaging and oncogenic. We also observed dramatic changes in androgen receptor (AR)-mediated pathway molecules, including prostate-specific antigen (PSA, a major biomarker of prostate cancer) and AR variants, as well as neuroendocrine-like (NE-like) and tumor stem cell-like characteristics, during androgen-independent phenotype progression. Our findings provide new insights into the regulatory complexities of refractory prostate cancers.

Watanabe, M., et al. (2004). "[A case report: testicular pure seminoma metastasized to costal bone after 2 years post-operatively]." Hinyokika Kiyo **50**(7): 505-509.

A 32-year-old man underwent orchiectomy for his right testicular tumor (pure seminoma, pT1, stage A(I)). Pelvic and para-aortic lymph nodes were irradiated with 18 Gy as adjuvant therapy. Two years later, he developed low back pain. Computed tomography, magnetic resonance imaging and bone scans showed an enhanced mass at the 10th left costa. Aspiration cytology showed seminoma. After administration of chemotherapy with bleomycin, etoposide and cisplatinum, following high dose chemotherapy with peripheral blood stem cell transplantation, the costal lesion was diminished and symptoms relieved. Then radical costectomy was performed. A histopathological study showed non-viable cells of seminoma. Post-operative progress was uneventful. Testicular pure seminoma with bone metastasis is rare, and to our knowledge, only 9 cases have been reported.

Watanabe, T. M., et al. (2020). "[Application of scattering microscopy for evaluation of iPS cell and its differentiated cells]." Nihon Yakurigaku Zasshi **155**(5): 312-318.

Various artificial cells and artificial tissues can be generated from induced pluripotent stem cells (iPS cells). There is now an urgent need to standardize the quality evaluation and management of iPS cells. Recently, artificial intelligence (AI) technology such as machine learning is providing evaluation method for the quality of iPS cells and iPS cell-derived somatic cells based on optical microscopy. Light, which is the principle of optical microscopy, has an interesting and important feature. There are various kinds of interaction between light and molecule, and the scattered light includes internal

information of the molecule. Raman scattering inheres all the vibration mode of molecular bonds composing a molecule, and second harmonic generation (SHG) light, which is one of second-order non-linear scattering light, is derived from electric polarizations in the molecule, in other words, carries structural information within the protein. While states of a cell are usually defined by protein/gene expression patterns, we have proposed to apply Raman spectra for cellular fingerprinting as an alternative for identifying the cell state, and now succeeded in predicting gene-expression of antibiotic resistant bacteria in combination with machine learning technology. Meanwhile, SHG microscopy has been used to visualize fiber structures in living specimens, such as collagen, and microtubules as a label-free modality. By utilizing the feature that SHG senses protein structure change, we developed a new method to measure actomyosin activity in cardiac cells. The most important advantage of the use of the scattering light is their non-labeling and non-invasive capability.

Widemann, A., et al. (2014). "Circulating endothelial cells and progenitors as prognostic factors during autoimmune thrombotic thrombocytopenic purpura: results of a prospective multicenter French study." J Thromb Haemost **12**(10): 1601-1609.

BACKGROUND: Autoimmune thrombotic thrombocytopenic purpura (AI-TTP) is characterized by an excess of circulating ultralarge von Willebrand factor (VWF) caused by anti-ADAMTS-13 autoantibodies. Animal studies, however, have shown that endothelial cell activation may also be an important trigger of AI-TTP. OBJECTIVES: To prospectively study circulating biomarkers of endothelial lesion and activation, such as circulating endothelial cells (CECs), soluble P-selectin (sP-selectin), or VWF, and of endothelial repair, such as circulating progenitor cells (CPCs) and endothelial progenitor cells (EPCs), in AI-TTP, in relation to disease severity and prognosis. RESULTS: Twenty-two patients were included in this study. CEC ($P < 0.01$), VWF ($P < 0.05$) and sP-selectin ($P < 0.01$) levels were significantly increased during crisis, and returned to baseline levels during remission. Both CEC ($P < 0.05$) and sP-selectin ($P < 0.05$) levels were significantly higher in patients who died or developed neurologic sequelae. CPC levels were substantially increased during the acute phase of the disease ($P < 0.001$), and returned to baseline levels during remission. Among CPCs, EPC levels were also increased during crisis ($P < 0.05$) and significantly decreased during remission. Patients who received < 16 plasma exchanges (PEs) had significantly higher EPC counts ($P < 0.05$) than those who needed more numerous PEs to obtain remission, suggesting that initial EPC counts may be associated with faster endothelial repair. CONCLUSION: The profile of circulating endothelial markers shows massive endothelial activation and repair/remodeling during AI-TTP, and suggests that CECs and EPCs may be promising prognostic biomarkers of the disease.

Williamson, R., et al. (1992). "Marked reduction of high density lipoprotein cholesterol in mice genetically modified to lack apolipoprotein A-I." Proc Natl Acad Sci U S A **89**(15): 7134-7138.

Atherosclerosis is a major cause of morbidity and mortality in developed countries. In humans the risk of atherosclerosis is inversely correlated with plasma levels of high density lipoprotein (HDL). As a step in determining whether the experimental reduction of plasma HDL level will increase susceptibility to atherosclerosis, we have used gene targeting in embryonic stem cells to produce mice lacking apolipoprotein A-I, the major protein component of HDL particles. Mice homozygous for the disrupted gene have no plasma apolipoprotein A-I detectable by double immunodiffusion; their total plasma cholesterol and HDL-cholesterol levels after overnight fasting are reduced to about one-third and one-fifth of normal levels, and they are grossly deficient in alpha-migrating HDL particles.

Wongsa, N., et al. (2011). "Cananginones A-I, linear acetogenins from the stem bark of Miliusa velutina [corrected]." Phytochemistry **72**(14-15): 1859-1864.

Nine linear C23 and C21 acetogenins, named cananginones A-I (1-9), were isolated from stem bark of Miliusa velutina [corrected] . Their structures were established by spectroscopic methods. These compounds showed cytotoxicity against three cancer cell lines (KB, MCF7 and NCI-H187) with IC(5)(0) values in the range 16.6-129.7 muM. Only 5 showed weak antimalarial activity against Plasmodium falciparum. In addition, 8 and 9 exhibited weak antifungal activity against Candida albicans.

Xu, L., et al. (2023). "Exosomes derived from mesenchymal stromal cells: a promising treatment for pelvic floor dysfunction." Hum Cell **36**(3): 937-949.

Pelvic floor dysfunction (PFDs), which include pelvic organ prolapse (POP), stress urinary incontinence (SUI) and anal incontinence (AI), are common degenerative diseases in women that have dramatic effects on quality of life. The pathology of PFDs is based on impaired pelvic connective tissue supportive strength due to an imbalance in extracellular matrix (ECM) metabolism, the loss of a

variety of cell types, such as fibroblasts, muscle cells, peripheral nerve cells, and oxidative stress and inflammation in the pelvic environment. Fortunately, exosomes, which are one of the major secretions of mesenchymal stromal cells (MSCs), are involved in intercellular communication and the modulation of molecular activities in recipient cells via their contents, which are bioactive proteins and genetic factors such as mRNAs and miRNAs. These components modify fibroblast activation and secretion, facilitate ECM modelling, and promote cell proliferation to enhance pelvic tissue regeneration. In this review, we focus on the molecular mechanisms and future directions of exosomes derived from MSCs that are of great value in the treatment of PFD.

Xue, E., et al. (2024). "Utility of Large Language Models for Health Care Professionals and Patients in Navigating Hematopoietic Stem Cell Transplantation: Comparison of the Performance of ChatGPT-3.5, ChatGPT-4, and Bard." J Med Internet Res **26**: e54758.

BACKGROUND: Artificial intelligence is increasingly being applied to many workflows. Large language models (LLMs) are publicly accessible platforms trained to understand, interact with, and produce human-readable text; their ability to deliver relevant and reliable information is also of particular interest for the health care providers and the patients. Hematopoietic stem cell transplantation (HSCT) is a complex medical field requiring extensive knowledge, background, and training to practice successfully and can be challenging for the nonspecialist audience to comprehend. OBJECTIVE: We aimed to test the applicability of 3 prominent LLMs, namely ChatGPT-3.5 (OpenAI), ChatGPT-4 (OpenAI), and Bard (Google AI), in guiding nonspecialist health care professionals and advising patients seeking information regarding HSCT. METHODS: We submitted 72 open-ended HSCT-related questions of variable difficulty to the LLMs and rated their responses based on consistency-defined as replicability of the response-response veracity, language comprehensibility, specificity to the topic, and the presence of hallucinations. We then rechallenged the 2 best performing chatbots by resubmitting the most difficult questions and prompting to respond as if communicating with either a health care professional or a patient and to provide verifiable sources of information. Responses were then rerated with the additional criterion of language appropriateness, defined as language adaptation for the intended audience. RESULTS: ChatGPT-4 outperformed both ChatGPT-3.5 and Bard in terms of response consistency (66/72, 92%; 54/72, 75%; and 63/69, 91%, respectively; P=.007), response veracity (58/66, 88%; 40/54, 74%; and 16/63, 25%, respectively; P<.001), and specificity to the topic (60/66, 91%; 43/54, 80%; and 27/63, 43%, respectively; P<.001). Both ChatGPT-4 and ChatGPT-3.5 outperformed Bard in terms of language comprehensibility (64/66, 97%; 53/54, 98%; and 52/63, 83%, respectively; P=.002). All displayed episodes of hallucinations. ChatGPT-3.5 and ChatGPT-4 were then rechallenged with a prompt to adapt their language to the audience and to provide source of information, and responses were rated. ChatGPT-3.5 showed better ability to adapt its language to nonmedical audience than ChatGPT-4 (17/21, 81% and 10/22, 46%, respectively; P=.03); however, both failed to consistently provide correct and up-to-date information resources, reporting either out-of-date materials, incorrect URLs, or unfocused references, making their output not verifiable by the reader. CONCLUSIONS: In conclusion, despite LLMs' potential capability in confronting challenging medical topics such as HSCT, the presence of mistakes and lack of clear references make them not yet appropriate for routine, unsupervised clinical use, or patient counseling. Implementation of LLMs' ability to access and to reference current and updated websites and research papers, as well as development of LLMs trained in specialized domain knowledge data sets, may offer potential solutions for their future clinical application.

Yadalam, P. K., et al. (2024). "Variational Approaches for Drug-Disease-Gene Links in Periodontal Inflammation." Int Dent J.

INTRODUCTION AND OBJECTIVES: Oral diseases, including gingivitis and periodontitis, are linked to the Wnt signaling pathway, vital for bone metabolism, cementum homeostasis, and mesenchymal stem cell differentiation. Advances in generative AI techniques, such as variational autoencoders (VAEs) and quantum variational classifiers (QVCs), offer promising tools for predicting gene associations between drugs and diseases. This study aims to compare the predictive performance of VAEs and QVCs in modeling drug-disease gene networks within the Wnt signaling pathway in periodontal inflammation. METHODS: Genes associated with Wnt-related periodontal inflammation were identified through comprehensive literature reviews and genomic databases. Their roles in various biological processes were evaluated using gene set enrichment analysis, employing tools like Enrichr, which integrates diverse gene sets from sources such as DSigDB, DisGeNET, and Lincs_l1000.drug. The study then applied VAEs and QVCs to predict gene-disease associations related to the Wnt signaling pathway. RESULTS: The analysis

revealed an extensive network comprising 1738 nodes and 1498 edges, averaging 1.992 neighbors per node. The network exhibited a diameter of 2, a radius of 1, and a characteristic path length of 1.992, indicating limited interconnectivity. The VQA model demonstrated a high accuracy rate of 97.5%, although it only detected 50% of anomalies. The VQC model achieved a precision of 78%, with Class 1 samples showing improved recall and a balanced F1 score. CONCLUSION: VQC and VAE models exhibit strong potential for discovering FDA-approved drugs by predicting gene-drug associations in periodontitis based on the Wnt signaling pathway. CLINICAL RELEVANCE: This study highlights the potential of VAEs and QVCs in predicting gene-drug associations for periodontal inflammation. This could lead to more targeted therapies for oral diseases like periodontitis, improving patient outcomes and advancing personalized treatment strategies in clinical practice.

Yakkala, P. A., et al. (2024). "An update on the development on tubulin inhibitors for the treatment of solid tumors." Expert Opin Ther Targets **28**(3): 193-220.

INTRODUCTION: Microtubules play a vital role in cancer therapeutics. They are implicated in tumorigenesis, thus inhibiting tubulin polymerization in cancer cells, and have now become a significant target for anticancer drug development. A plethora of drug molecules has been crafted to influence microtubule dynamics and presently, numerous tubulin inhibitors are being investigated. This review discusses the recently developed inhibitors including natural products, and also examines the preclinical and clinical data of some potential molecules. AREA COVERED: The current review article summarizes the development of tubulin inhibitors while detailing their specific binding sites. It also discusses the newly designed inhibitors that may be useful in the treatment of solid tumors. EXPERT OPINION: Microtubules play a crucial role in cellular processes, especially in cancer therapy where inhibiting tubulin polymerization holds promise. Ongoing trials signify a commitment to revolutionizing cancer treatment and exploring targeted therapies. Challenges in microtubule modulation, like resistance and off-target effects, demand focused efforts, emphasizing combination therapies and personalized treatments. Beyond microtubules, promising avenues in cancer research include immunotherapy, genomic medicine, CRISPR gene editing, liquid biopsies, AI diagnostics, and stem cell therapy, showcasing a holistic approach for future advancements.

Yamaguchi, T., et al. (2012). "Development of an all-in-one inducible lentiviral vector for gene specific analysis of reprogramming." PLoS One **7**(7): e41007.

Fair comparison of reprogramming efficiencies and in vitro differentiation capabilities among induced pluripotent stem cell (iPSC) lines has been hampered by the cellular and genetic heterogeneity of de novo infected somatic cells. In order to address this problem, we constructed a single cassette all-in-one inducible lentiviral vector (Ai-LV) for the expression of three reprogramming factors (Oct3/4, Klf4 and Sox2). To obtain multiple types of somatic cells having the same genetic background, we generated reprogrammable chimeric mice using iPSCs derived from Ai-LV infected somatic cells. Then, hepatic cells, hematopoietic cells and fibroblasts were isolated at different developmental stages from the chimeric mice, and reprogrammed again to generate 2nd iPSCs. The results revealed that somatic cells, especially fetal hepatoblasts were reprogrammed 1200 times more efficiently than adult hepatocytes with maximum reprogramming efficiency reaching 12.5%. However, we found that forced expression of c-Myc compensated for the reduced reprogramming efficiency in aged somatic cells without affecting cell proliferation. All these findings suggest that the Ai-LV system enables us to generate a panel of iPSC clones derived from various tissues with the same genetic background, and thus provides an invaluable tool for iPSC research.

Yan, R., et al. (2015). "[Preparation of magnetic near infrared fluorescent probe and targeted multimodal imaging of human mesenchymal stem cells in vitro]." Zhonghua Yi Xue Za Zhi **95**(1): 56-60.

OBJECTIVE: To prepare the magnetic near infrared fluorescent (NIRF) bifunctional molecular probe with human holo-transferrin (Tf) as a targeted ligand and detect human transferrin receptor (hTfR) actively. METHODS: Molecular probe Tf-cy5.5-IO was prepared and purified by conjugating Tf, superparamagnetic iron oxide (IO) and near infrared fluorescent dye (cy5.5). The particle size and morphology was determined by transmission electron microscopy (TEM), zeta potential and particle sizing analyzer. Human serum albumin (HSA) was used for conjugating with cy5.5 and IO as control. hMSCs and HeLa (as a positive control) were divided into 4 groups: A non-labeled, B Tf-cy5.5-IO, C HSA-cy5.5-IO and D competition assay to confirm the targeted connection. The fluorescent signals from intracellular probe were detected with laser scanning confocal microscope (LSCM) and flow cytometry. Intracellular iron was detected with iron concentration assay and TEM. MRI and NIRF imaging of 2x10(5) cells were performed respectively. Enhancements of R2 value and average intensity (AI)

were analyzed qualitatively. RESULTS: The conjugation between IO, Tf and cy5.5 was confirmed with a molar ratio of 1: 2.89: 7.89. The hyperdense aqueous diameter of probe was 23.39 +/- 2.42 nm. LSCM showed the fluorescence from Tf-cy5.5-IO and cy3-labeled monoclonal antibody against hTfR in cells and two markers were localized in intracellular compartments of similar appearance. After co-incubating with Tf-cy5.5-IO, the intracellular iron and average intensity were significantly higher than cells of other groups ($P < 0.01$). MRI and NIRF images showed that, after incubation, intracellular Tf-cy5.5-IO decreased the T2WI signal of human mesenchymal stem cells (hMSCs) and AI on NIRF image increased. Enhancements of R2 value and AI were higher in B group than those in other groups ($P < 0.05$). CONCLUSION: Tf-cy5.5-IO probe can recognize and conjugate with hTfR specifically. And targeted imaging in vitro of hTfR expressed in hMSCs may be performed by MRI and NIRF multimodal imaging.

Yang, M. S., et al. (1998). "Determination of endogenous trace metal contents in various mouse brain regions after prolonged oral administration of aluminum chloride." J Toxicol Environ Health A **55**(6): 445-453.

Aluminum (Al) has been said to associate with the Alzheimer's-like neurodegeneration in humans. One of the proposed mechanisms for the action of Al is that excess Al might interfere with trace metal metabolism. In this study, the levels of Ca, Mg, Cu, and Zn in blood, liver, and different regions of the brain (separated into the cortex, hippocampus, cerebellum, and brainstem) were measured in mice after daily oral administration of AICI3 (100 mg/kg body weight) for 2 mo. It was found that upon prolonged oral administration of AI, serum Al level was elevated significantly. There was no marked change in serum Ca, Mg, Zn, or Cu content. In the liver, Al content was not increased but there was a significant elevation in Cu and Zn content compared to control animals, probably due to the prolonged administration of the acidic salt solution. In brain, there was a significant twofold increase in Al in the hippocampus and a significant decrease in Al in the cortex. In addition to regional changes in AI content, Zn content in the hippocampus and increased Cu content in the hippocampus, cortex, and brainstem were significantly reduced. Data demonstrated that Al could alter Zn and Cu homeostasis in selected brain regions. The possible relation between Al and neuronal cell injury was discussed.

Yang, N., et al. (2013). "Apolipoprotein A-I mimetic peptide reverse D-4F improves the biological functions of mouse bone marrow-derived late EPCs via PI3K/AKT/eNOS pathway." Mol Cell Biochem **377**(1-2): 229-236.

Apolipoprotein A-I (ApoA-I) mimetic peptide inhibits the development of atherosclerosis (AS) in apolipoprotein E-deficient mice; however, the underlying mechanism remains unclear. Endothelial progenitor cells (EPCs) can prevent AS progression through repairing proatherogenic factors impaired endothelium. In the present study, we examined the effect of reverse D-4F, one of apoA-I mimetic peptide on the proliferation, migration, and tube formation of mouse bone marrow-derived late EPCs. The present study showed that reverse D-4F (10-100 mug/ml) significantly improved the proliferation, migration, and tube formation of EPCs in a dose-dependent manner, and activated phospho-AKT at serine residue 473 and phospho-eNOS at serine residue 1177. LY294002 (PI3-kinase inhibitor) and L-NAME (NOS inhibitor) significantly inhibited reverse D-4F mediated improvement of EPCs biological functions, and LY294002 significantly decreased reverse D-4F stimulated activation of phospho-AKT (473) and phospho-eNOS (1177). The results indicate that reverse D-4F mediated improvement of EPCs functions is dependent on the PI3K/AKT/eNOS pathway.

Yang, X., et al. (2007). "[Effects of recombinant human bone morphogenetic protein 2 and osteogenic agents on proliferation and differentiation of rat mesenchymal stem cells]." Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi **21**(2): 140-144.

OBJECTIVE: To investigate the effects of the recombinant human bone morphogenetic protein 2 (rhBMP-2) and/or the osteogenic agents on proliferation and expression of the osteoblast phenotype differentiation of the SD rat mesenchymal stem cells (MSCs). METHODS: The rat MSCs were cultured in vitro and were randomly divided into the experimental groups (Groups A-I) and the control group. In the experimental group, MSCs were induced by rhBMP-2 in different doses (10, 50, 100 and 200 microg/L) in Groups B-E, the osteogenic agent alone (Group A) and by the combined use of rhBMP-2 [in different doses (10,50, 100 and 200 microg/L)] and the osteogenic agent in Groups F-I. The MTT colorimetric assay was used to evaluate the proliferation, and the activities of alkaline phosphatase (ALP) and osteocalcin (OC) were observed at 3, 6, 9, 12 days, respectively. RESULTS: The inverted phase contrast microscopy showed that MSCs by primary culture for 12 hours were adhibited, with a fusiform shape at 48 hours. At 4 days they were polygonal or atractoid, and were spread gyrately or radiately at 6 days. At 10 days, they were spread at

the bottom of the bottle. The statistical analysis showed that the expression of the osteoblast phenotype differentiation of MSCs could be induced in the experimental groups. The proliferation of MSCs could be enhanced in a dose-dependent manner in Groups B-E. The expression of the osteoblast phenotype differentiation, which was tested by the activities of ALP and OC, was significantly higher in Groups F-I than in Groups A-E. CONCLUSION: The combined use of rhBMP-2 and the osteogenic agents can enhance the MSC proliferation and induce an expression and maintenance of the osteoblast phenotype differentiation of the rat MSCs.

Ye, B., et al. (2024). "Deciphering lung adenocarcinoma prognosis and immunotherapy response through an AI-driven stemness-related gene signature." J Cell Mol Med **28**(14): e18564.

Lung adenocarcinoma (LUAD) is a leading cause of cancer-related deaths, and improving prognostic accuracy is vital for personalised treatment approaches, especially in the context of immunotherapy. In this study, we constructed an artificial intelligence (AI)-driven stemness-related gene signature (SRS) that deciphered LUAD prognosis and immunotherapy response. CytoTRACE analysis of single-cell RNA sequencing data identified genes associated with stemness in LUAD epithelial cells. An AI network integrating traditional regression, machine learning, and deep learning algorithms constructed the SRS based on genes associated with stemness. Subsequently, we conducted a comprehensive exploration of the connection between SRS and both intrinsic and extrinsic immune environments using multi-omics data. Experimental validation through siRNA knockdown in LUAD cell lines, followed by assessments of proliferation, migration, and invasion, confirmed the functional role of CKS1B, a top SRS gene. The SRS demonstrated high precision in predicting LUAD prognosis and likelihood of benefiting from immunotherapy. High-risk groups classified by the SRS exhibited decreased immunogenicity and reduced immune cell infiltration, indicating challenges for immunotherapy. Conversely, in vitro experiments revealed CKS1B knockdown significantly impaired aggressive cancer phenotypes like proliferation, migration, and invasion of LUAD cells, highlighting its pivotal role. These results underscore a close association between stemness and tumour immunity, offering predictive insights into the immune landscape and immunotherapy responses in LUAD. The newly established SRS holds promise as a valuable tool for selecting LUAD populations likely to benefit from future clinical stratification efforts.

Ye, M. N. and H. F. Chen (2008). "[Effects of Astragalus injection on proliferation of basal-like breast cancer cell line MDA-MB-468]." Zhong Xi Yi Jie He Xue Bao **6**(4): 399-404.

OBJECTIVE: To investigate the effects of Astragalus injection (AI) on basal-like breast cancer cell line MDA-MB-468 and murine bone marrow stromal stem cells (mMSCs). METHODS: MDA-MB-468 cells and primary cultured mMSCs were treated by different concentrations of AI, and with untreated MDA-MB-468 cells as blank control. The morphology of cells was observed by phase-contrast inverted microscope and transmission electron microscopy. Cytotoxic effects of AI on MDA-MB-468 cells and mMSCs were evaluated by cell counting kit-8 (CCK-8) assay. Cell cycle and apoptosis of MDA-MB-468 cells induced by AI were measured by flow cytometry. Lactate dehydrogenase (LDH) activity in supernatants was measured by enzymatic colorimetric method. The expressions of epidermal growth factor receptor (EGFR) and p53 protein in MDA-MB-468 cells were evaluated by streptavidin-biotin-peroxidase complex method. RESULTS: A time-dependent cytotoxic effect of 1 g/ml AI was observed in MDA-MB-468 cells. 1 g/ml AI also had cytotoxic effect on mMSCs, but its effect was not better than cisplatin. 0.1 g/ml AI could promote the proliferation of mMSCs. Different concentrations of AI could all induce the apoptosis of MDA-MB-468 cells. There was no significant difference in LDH activity in the supernatants between blank control group and AI-treated and cisplatin-treated groups. AI could down-regulate the expressions of EGFR and p53 protein. CONCLUSION: The effects of AI on MDA-MB-468 cells and mMSCs are related to the concentration of AI, and its mechanism of inhibiting the proliferation of MDA-MB-468 cells may be due to down-regulation of the expressions of EGFR and p53 protein.

Yildirim, Z., et al. (2024). "Next-Gen Therapeutics: Pioneering Drug Discovery with iPSCs, Genomics, AI, and Clinical Trials in a Dish." Annu Rev Pharmacol Toxicol.

In the high-stakes arena of drug discovery, the journey from bench to bedside is hindered by a daunting 92% failure rate, primarily due to unpredicted toxicities and inadequate therapeutic efficacy in clinical trials. The FDA Modernization Act 2.0 heralds a transformative approach, advocating for the integration of alternative methods to conventional animal testing, including cell-based assays that employ human induced pluripotent stem cell (iPSC)-derived organoids, and organ-on-a-chip

technologies, in conjunction with sophisticated artificial intelligence (AI) methodologies. Our review explores the innovative capacity of iPSC-derived clinical trial in a dish models designed for cardiovascular disease research. We also highlight how integrating iPSC technology with AI can accelerate the identification of viable therapeutic candidates, streamline drug screening, and pave the way toward more personalized medicine. Through this, we provide a comprehensive overview of the current landscape and future implications of iPSC and AI applications being navigated by the research community and pharmaceutical industry.

Yilmaz, M., et al. (2013). "Adenoviral infections in adult allogeneic hematopoietic SCT recipients: a single center experience." Bone Marrow Transplant **48**(9): 1218-1223.

Disseminated adenoviral infection (AI) is associated with profound immunosuppression and poor outcome after allogeneic hematopoietic SCT (allo-HSCT). A better understanding of AI in allo-HSCT recipients can serve as a basis to develop more effective management strategies. We evaluated all adult patients who received allo-HSCT at MD Anderson Cancer Center between 1999 and 2008. Among the 2879 allo-HSCT patients, 73 (2.5%) were diagnosed with AI. Enteritis (26%) and pneumonia (24%) were the most common clinical manifestations; pneumonia was the most common cause of adenovirus-associated death. A multivariable Bayesian logistic regression showed that when the joint effects of all covariates were accounted for, cord blood transplant, absolute lymphocyte count (ALC) </= 200/mm(3) and male gender were associated with a higher probability of disseminated AI. The OS was significantly worse for patients with AI that was disseminated rather than localized (median of 5 months vs median of 28 months, P<0.001) and for patients with ALC </= 200/mm(3) (P<0.001). Disseminated AI, in patients who received allo-HSCT, is a significant cause of morbidity and mortality. Strategies for early diagnosis and intervention are essential, especially for high-risk patients.

Yuan, L., et al. (2019). "Systemic and prophylactic intrathecal chemotherapy for primary adrenal lymphoma: A retrospective study of 20 case reports." Medicine (Baltimore) **98**(24): e15662.

Primary adrenal lymphoma (PAL) is a rare entity of lymphoma with dismal prognosis using systemic chemotherapy. More clinical reports are needed to guide the treatment for PAL.We performed a retrospective analysis of 20 patients diagnosed with PAL who presented to our center between January 2005 and January 2014.Median age at presentation was 48 years (range: 27-73) with a male-to-female ratio of 7:3. Bilateral and right-sided adrenal involvement were seen in 11 of 20 and 7 of 20 patients, respectively. Adrenal insufficiency (AI) was seen in 6 of 10 evaluated patients. Diffuse large B cell lymphoma (DLBCL) was the most common immunophenotype (85.0%). Two patients died due to rapid disease progression before treatment. Two patients received autologous stem cell transplantation as consolidation therapy. All patients received prophylactic intrathecal chemotherapy. The estimated 5-year overall survival (OS) and progression-free survival (PFS) were 52.5% [95% confidence interval (95% CI: 28.2-72.0)] and 53.2% (95% CI: 29.0-72.5), respectively.These findings suggest that PAL should always be considered in differential diagnosis of adrenal mass with AI. Despite the contrasting previous reports, long-term prognosis of PAL is not necessarily inferior to that of non-Hodgkin lymphoma in general.

Zammit, M., et al. (2020). "[(18)F]FEPPA PET imaging for monitoring CD68-positive microglia/macrophage neuroinflammation in nonhuman primates." EJNMMI Res **10**(1): 93.

PURPOSE: The aim of this study was to examine whether the translocator protein 18-kDa (TSPO) PET ligand [(18)F]FEPPA has the sensitivity for detecting changes in CD68-positive microglial/macrophage activation in hemiparkinsonian rhesus macaques treated with allogeneic grafts of induced pluripotent stem cell-derived midbrain dopaminergic neurons (iPSC-mDA). METHODS: In vivo positron emission tomography (PET) imaging with [(18)F]FEPPA was used in conjunction with postmortem CD68 immunostaining to evaluate neuroinflammation in the brains of hemiparkinsonian rhesus macaques (n = 6) that received allogeneic iPSC-mDA grafts in the putamen ipsilateral to MPTP administration. RESULTS: Based on assessment of radiotracer uptake and confirmed by visual inspection of the imaging data, nonhuman primates with allogeneic grafts showed increased [(18)F]FEPPA binding at the graft sites relative to the contralateral putamen. From PET asymmetry analysis of the images, the mean asymmetry index of the monkeys was AI = - 0.085 +/- 0.018. Evaluation and scoring of CD68 immunoreactivity by an investigator blind to the treatment identified significantly more neuroinflammation in the grafted areas of the putamen compared to the contralateral putamen (p = 0.0004). [(18)F]FEPPA PET AI showed a positive correlation with CD68 immunoreactivity AI ratings in the monkeys (Spearman's rho = 0.94; p = 0.005). CONCLUSION: These findings reveal that [(18)F]FEPPA PET is an effective marker for

detecting increased CD68-positive microglial/macrophage activation and demonstrates sufficient sensitivity to detect changes in neuroinflammation in vivo following allogeneic cell engraftment.

Zhang, B., et al. (2023). "Therapeutic Efficacy of Mesenchymal Stem/Stromal Cell Small Extracellular Vesicles in Alleviating Arthritic Progression by Restoring Macrophage Balance." Biomolecules **13**(10).

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and damage, often associated with an imbalance in M1/M2 macrophages. Elevated levels of anti-inflammatory M2 macrophages have been linked to a therapeutic response in RA. We have previously demonstrated that mesenchymal stem/stromal cell small extracellular vesicles (MSC-sEVs) promote M2 polarization and hypothesized that MSC-sEVs could alleviate RA severity with a concomitant increase in M2 polarization. Here, we treated a mouse model of collagen-induced arthritis (CIA) with MSC-sEVs. Relative to vehicle-treated CIA mice, both low (1 mug) and high (10 mug) doses of MSC-sEVs were similarly efficacious but not as efficacious as Prednisolone, the positive control. MSC-sEV treatment resulted in statistically significant reductions in disease progression rate and disease severity as measured by arthritic index (AI), anti-CII antibodies, IL-6, and C5b-9 plasma levels. There were no statistically significant differences in the treatment outcome between low (1 mug) and high (10 mug) doses of MSC-sEVs. Furthermore, immunohistochemical analysis revealed that concomitant with the therapeutic efficacy, MSC-sEV treatment increased anti-inflammatory M2 macrophages and decreased pro-inflammatory M1 macrophages in the synovium. Consistent with increased M2 macrophages, histopathological examination also revealed reduced inflammation, pannus formation, cartilage damage, bone resorption, and periosteal new bone formation in the MSC-sEV-treated group compared to the vehicle group. These findings suggest that MSC-sEVs are potential biologic disease-modifying antirheumatic drugs (DMARDs) that can help slow or halt RA joint damage and preserve joint function.

Zhang, H., et al. (2017). "CRISPR/Cas9-Mediated Gene Editing in Human iPSC-Derived Macrophage Reveals Lysosomal Acid Lipase Function in Human Macrophages-Brief Report." Arterioscler Thromb Vasc Biol **37**(11): 2156-2160.

OBJECTIVE: To gain mechanistic insights into the role of LIPA (lipase A), the gene encoding LAL (lysosomal acid lipase) protein, in human macrophages. APPROACH AND RESULTS: We used CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 (CRISPR-associated protein 9) technology to knock out LIPA in human induced pluripotent stem cells and then differentiate to macrophage (human-induced pluripotent stem cells-derived macrophage [IPSDM]) to explore the human macrophage LIPA loss-of-function phenotypes. LIPA was abundantly expressed in monocyte-derived macrophages and was markedly induced on IPSDM differentiation to comparable levels as in human monocyte-derived macrophage. IPSDM with knockout of LIPA (LIPA(-/-)) had barely detectable LAL enzymatic activity. Control and LIPA(-/-) IPSDM were loaded with [(3)H]-cholesteryl oleate-labeled AcLDL (acetylated low-density lipoprotein) followed by efflux to apolipoprotein A-I. Efflux of liberated [(3)H]-cholesterol to apolipoprotein A-I was abolished in LIPA(-/-) IPSDM, indicating deficiency in LAL-mediated lysosomal cholesteryl ester hydrolysis. In cells loaded with [(3)H]-cholesterol-labeled AcLDL, [(3)H]-cholesterol efflux was, however, not different between control and LIPA(-/-) IPSDM. ABCA1 (ATP-binding cassette, subfamily A, member 1) expression was upregulated by AcLDL loading but to a similar extent between control and LIPA(-/-) IPSDM. In nonlipid loaded state, LIPA(-/-) IPSDM had high levels of cholesteryl ester mass compared with minute amounts in control IPSDM. Yet, with AcLDL loading, overall cholesteryl ester mass was increased to similar levels in both control and LIPA(-/-) IPSDM. LIPA(-/-) did not impact lysosomal apolipoprotein-B degradation or expression of IL1B, IL6, and CCL5. CONCLUSIONS: LIPA(-/-) IPSDM reveals macrophage-specific hallmarks of LIPA deficiency. CRISPR/Cas9 and IPSDM provide important tools to study human macrophage biology and more broadly for future studies of disease-associated LIPA genetic variation in human macrophages.

Zhang, H., et al. (2015). "Functional analysis and transcriptomic profiling of iPSC-derived macrophages and their application in modeling Mendelian disease." Circ Res **117**(1): 17-28.

RATIONALE: An efficient and reproducible source of genotype-specific human macrophages is essential for study of human macrophage biology and related diseases. OBJECTIVE: To perform integrated functional and transcriptome analyses of human induced pluripotent stem cell-derived macrophages (IPSDMs) and their isogenic human peripheral blood mononuclear cell-derived macrophage (HMDM) counterparts and assess the application of IPSDM in

modeling macrophage polarization and Mendelian disease. METHODS AND RESULTS: We developed an efficient protocol for differentiation of IPSDM, which expressed macrophage-specific markers and took up modified lipoproteins in a similar manner to HMDM. Like HMDM, IPSDM revealed reduction in phagocytosis, increase in cholesterol efflux capacity and characteristic secretion of inflammatory cytokines in response to M1 (lipopolysaccharide+interferon-gamma) activation. RNA-Seq revealed that nonpolarized (M0) as well as M1 or M2 (interleukin-4) polarized IPSDM shared transcriptomic profiles with their isogenic HMDM counterparts while also revealing novel markers of macrophage polarization. Relative to IPSDM and HMDM of control individuals, patterns of defective cholesterol efflux to apolipoprotein A-I and high-density lipoprotein-3 were qualitatively and quantitatively similar in IPSDM and HMDM of patients with Tangier disease, an autosomal recessive disorder because of mutations in ATP-binding cassette transporter AI. Tangier disease-IPSDM also revealed novel defects of enhanced proinflammatory response to lipopolysaccharide stimulus. CONCLUSIONS: Our protocol-derived IPSDM are comparable with HMDM at phenotypic, functional, and transcriptomic levels. Tangier disease-IPSDM recapitulated hallmark features observed in HMDM and revealed novel inflammatory phenotypes. IPSDMs provide a powerful tool for study of macrophage-specific function in human genetic disorders as well as molecular studies of human macrophage activation and polarization.

Zhang, J., et al. (2020). "5F peptide promotes endothelial differentiation of bone marrow stem cells through activation of ERK1/2 signaling." Eur J Pharmacol **876**: 173051.

Synthetic apolipoprotein A-I (apoA-I) mimetic peptide 5F exhibits anti-atherosclerotic ability with largely unknown mechanism(s). Bone marrow (BM)-derived endothelial progenitor cells (EPCs) play a critical role in vascular integrity and function. The objective of the present study was to evaluate the effect of 5F on endothelial differentiation of BM stem cells and related mechanisms. Murine BM multipotent adult progenitor cells (MAPCs) were induced to differentiate into endothelial cells in vitro with or without 5F. The expression of endothelial markers vWF, Flk-1 and CD31 was significantly increased in the cells treated with 5F with enhanced in vitro vascular tube formation and LDL uptake without significant changes on proliferation and stem cell maker Oct-4 expression. Phosphorylated ERK1/2, not Akt, was significantly increased in 5F-treated cells. Treatment of MAPCs with PD98059 or small interfering RNA against ERK2 substantially attenuated ERK1/2 phosphorylation, and effectively prevented 5F-induced enhancement of endothelial differentiation of MAPCs. In vivo studies revealed that 5F increased EPCs number in the BM in mice after acute hindlimb ischemia that was effectively prevented with PD98059 treatment. These data supported the conclusion that 5F promoted endothelial differentiation of MAPCs through activation of ERK1/2 signaling.

Zhang, X., et al. (2015). "MSCs with ACE II gene affect apoptosis pathway of acute lung injury induced by bleomycin." Exp Lung Res **41**(1): 32-43.

PURPOSE: The aim of this study was to evaluate the effect and related mechanisms of Mesenchymal stem cells (MSCs) and Angiotensin converting enzyme II (ACE II) on acute lung injury (ALI). METHODS: MSCs were separated from umbilical cord cells, and the changes of phenotype before and after ACE II silence were observed using Flow Cytometer. ALI model was induced by 10 mg/mL bleomycin in 60 Balb/c mice, and the rest 8 mice were regarded as the baseline group. The mice were randomly divided into four groups (n = 15): control, ACE II, stem, and stem + ACE II. The apoptotic index (AI) was calculated using TUNEL, and the detection of protein and mRNA of Bax, Bak and p53, Bcl-2, Grp78, CHOP and Caspase 12 were used by western-blot and RT-PCR, respectively. RESULTS: The umbilical cord cells differentiated into stable MSCs about 14 days, and ACE II transfection reached a peak at the 5th day after transfection. ACE II silence did not affect the phenotype of MSCs. All the proteins and mRNAs expression except Bcl-2 in the stem and stem + ACE II were significantly lower than those in control from 8 h ($p < 0.05$, $p < 0.01$), while Bcl-2 exhibited an opposite trend. Stem + ACE II performed a better effect than single stem in most indexes, including AI ($p < 0.05$, $p < 0.01$). CONCLUSIONS: The co-administration of MSCs and ACE II can significantly suppress apoptosis in ALI mice, and may be an effective clinical treatment for ALI.

Zhang, Z., et al. (2023). "Deep Learning of Phase-Contrast Images of Cancer Stem Cells Using a Selected Dataset of High Accuracy Value Using Conditional Generative Adversarial Networks." Int J Mol Sci **24**(6).

Artificial intelligence (AI) technology for image recognition has the potential to identify cancer stem cells (CSCs) in cultures and tissues. CSCs play an important role in the development and relapse of tumors. Although the characteristics of CSCs have been extensively studied, their morphological

features remain elusive. The attempt to obtain an AI model identifying CSCs in culture showed the importance of images from spatially and temporally grown cultures of CSCs for deep learning to improve accuracy, but was insufficient. This study aimed to identify a process that is significantly efficient in increasing the accuracy values of the AI model output for predicting CSCs from phase-contrast images. An AI model of conditional generative adversarial network (CGAN) image translation for CSC identification predicted CSCs with various accuracy levels, and convolutional neural network classification of CSC phase-contrast images showed variation in the images. The accuracy of the AI model of CGAN image translation was increased by the AI model built by deep learning of selected CSC images with high accuracy previously calculated by another AI model. The workflow of building an AI model based on CGAN image translation could be useful for the AI prediction of CSCs.

Zhang, Z., et al. (2012). "Apolipoprotein A-I mimetic peptide D-4F promotes human endothelial progenitor cell proliferation, migration, adhesion though eNOS/NO pathway." Mol Biol Rep **39**(4): 4445-4454.

Circulating endothelial progenitor cells (EPCs) have a critical role in endothelial maintenance and repair. Apolipoprotein A-I mimetic peptide D-4F has been shown to posses anti-atherogenic properties via sequestration of oxidized phospholipids, induction of remodeling of high density lipoprotein and promotion of cholesterol efflux from macrophage-derived foam cells. In this study, we test the effects of D-4F on EPC biology. EPCs were isolated from the peripheral venous blood of healthy male volunteers and characterized by 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine-labeled acetylated LDL uptake and ulex europaeus agglutinin binding and flow cytometry. Cell proliferation, migration, adhesion, nitric oxide production and endothelial nitric oxide synthase (eNOS) expression in the absence and presence of D-4F or simvastatin (as a positive control), were assayed. We demonstrated that D-4F significantly enhanced EPC proliferation, migration and adhesion in a dose-dependent manner compared with vehicle. However, all of the favorable effects of D-4F on EPCs were dramatically attenuated by preincubation with NOS inhibitor L-NAME. Further, D-4F also increased nitric oxide production in culture supernatant and the levels of eNOS expression and phosphorylation. The stimulatory effects of D-4F (10 mug/ml) on EPC biology were comparable to 0.5 muM simvastatin. These results suggest that eNOS/NO pathway mediates the functional modulation of EPC biology in response to D-4F treatment and support the notion that the beneficial role of D-4F on EPCs may be one of the important components of its anti-atherogenic potential.

Zhao, J., et al. (2023). "PhaseFIT: live-organoid phase-fluorescent image transformation via generative AI." Light Sci Appl **12**(1): 297.

Organoid models have provided a powerful platform for mechanistic investigations into fundamental biological processes involved in the development and function of organs. Despite the potential for image-based phenotypic quantification of organoids, their complex 3D structure, and the time-consuming and labor-intensive nature of immunofluorescent staining present significant challenges. In this work, we developed a virtual painting system, PhaseFIT (phase-fluorescent image transformation) utilizing customized and morphologically rich 2.5D intestinal organoids, which generate virtual fluorescent images for phenotypic quantification via accessible and low-cost organoid phase images. This system is driven by a novel segmentation-informed deep generative model that specializes in segmenting overlap and proximity between objects. The model enables an annotation-free digital transformation from phase-contrast to multi-channel fluorescent images. The virtual painting results of nuclei, secretory cell markers, and stem cells demonstrate that PhaseFIT outperforms the existing deep learning-based stain transformation models by generating fine-grained visual content. We further validated the efficiency and accuracy of PhaseFIT to quantify the impacts of three compounds on crypt formation, cell population, and cell stemness. PhaseFIT is the first deep learning-enabled virtual painting system focused on live organoids, enabling large-scale, informative, and efficient organoid phenotypic quantification. PhaseFIT would enable the use of organoids in high-throughput drug screening applications.

Zheng, X., et al. (2023). "Organoid cell fate dynamics in space and time." Sci Adv **9**(33): eadd6480.

Organoids are a major new tool to study tissue renewal. However, characterizing the underlying differentiation dynamics remains challenging. Here, we developed TypeTracker, which identifies cell fates by AI-enabled cell tracking and propagating end point fates back along the branched lineage trees. Cells that ultimately migrate to the villus commit to their new type early, when still deep inside the crypt, with important consequences: (i) Secretory cells commit before terminal division, with secretory fates emerging symmetrically in sister cells. (ii) Different secretory types descend from distinct stem cell lineages rather than an omnipotent secretory

progenitor. (iii) The ratio between secretory and absorptive cells is strongly affected by proliferation after commitment. (iv) Spatial patterning occurs after commitment through type-dependent cell rearrangements. This "commit-then-sort" model contrasts with the conventional conveyor belt picture, where cells differentiate by moving up the crypt-villus axis and hence raises new questions about the underlying commitment and sorting mechanisms.

Zheng, Z., et al. (2011). "Removal of autologous activated CD4-positive T lymphocytes also results in increased colony-forming units in patients with low and intermediate-1 risk myelodysplastic syndromes." Eur J Haematol **86**(1): 47-56.

Autologous activated CD4(+) T lymphocytes (CD4(+) /CCR5(+) double-positive cells) that derived from BMNCs of patients with low and intermediate-1 risk myelodysplastic syndrome were depleted or added to in vitro cultures. The BMNCs depleted of CD4(+) /CCR5(+) T cells exhibited significantly increased numbers of colony-forming units (CFUs). Conversely, the bone marrow mononuclear cells cultures with a fourfold augmentation of CD4(+) /CCR5(+) T lymphocytes exhibited no colonies in cultures in vitro. The apoptotic index (AI) of colony cells was decreased compared with that of preculture counterparts. After depletion of CD4(+) /CCR5(+) in vitro cultures, the clonal cells increased in patients with chromosome 5q- or 20q- abnormalities but remained unchanged in patients with trisomy 8. In addition, after removal of CD4(+) /CCR5(+) T cells, the number of CFUs was increased in those patients with a higher number of BM Th1 (CD4(+) / IFN-gamma(+)) cells, hypocellularity, or bearing the DR15 allele. We concluded that the selective removal of autologous activated CD4(+) T cells can increase the generation of CFUs. However, whether the increased CFUs consisted of cells derived from residual normal hemopoiesis or clonal hemopoiesis remains unknown.

Zhou, T., et al. (2023). "Artificial intelligence-based comprehensive analysis of immune-stemness-tumor budding profile to predict survival of patients with pancreatic adenocarcinoma." Cancer Biol Med **20**(3): 196-217.

OBJECTIVE: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy. CD8(+) T cells, cancer stem cells (CSCs), and tumor budding (TB) have been significantly correlated with the outcome of patients with PDAC, but the correlations have been independently reported. In addition, no integrated immune-CSC-TB profile for predicting survival in patients with PDAC has been established. METHODS: Multiplexed immunofluorescence and artificial intelligence (AI)-based comprehensive analyses were used for quantification and spatial distribution analysis of CD8(+) T cells, CD133(+) CSCs, and TB. In vivo humanized patient-derived xenograft (PDX) models were established. Nomogram analysis, calibration curve, time-dependent receiver operating characteristic curve, and decision curve analyses were performed using R software. RESULTS: The established 'anti-/pro-tumor' models showed that the CD8(+) T cell/TB, CD8(+) T cell/CD133(+) CSC, TB-adjacent CD8(+) T cell, and CD133(+) CSC-adjacent CD8(+) T cell indices were positively associated with survival of patients with PDAC. These findings were validated using PDX-transplanted humanized mouse models. An integrated nomogram-based immune-CSC-TB profile that included the CD8(+) T cell/TB and CD8(+) T cell/CD133(+) CSC indices was established and shown to be superior to the tumor-node-metastasis stage model in predicting survival of patients with PDAC. CONCLUSIONS: 'Anti-/pro-tumor' models and the spatial relationship among CD8(+) T cells, CSCs, and TB within the tumor microenvironment were investigated. Novel strategies to predict the prognosis of patients with PDAC were established using AI-based comprehensive analysis and machine learning workflow. The nomogram-based immune-CSC-TB profile can provide accurate prognosis prediction for patients with PDAC.

Zhou, T., et al. (2021). "Challenges and advances in clinical applications of mesenchymal stromal cells." J Hematol Oncol **14**(1): 24.

Mesenchymal stromal cells (MSCs), also known as mesenchymal stem cells, have been intensely investigated for clinical applications within the last decades. However, the majority of registered clinical trials applying MSC therapy for diverse human diseases have fallen short of expectations, despite the encouraging pre-clinical outcomes in varied animal disease models. This can be attributable to inconsistent criteria for MSCs identity across studies and their inherited heterogeneity. Nowadays, with the emergence of advanced biological techniques and substantial improvements in bio-engineered materials, strategies have been developed to overcome clinical challenges in MSC application. Here in this review, we will discuss the major challenges of MSC therapies in clinical application, the factors impacting the diversity of MSCs, the potential approaches that modify MSC products with the highest therapeutic potential, and finally the usage of MSCs for COVID-19 pandemic disease.

Zhu, C. J., et al. (2011). "Preliminary study on the mechanism of acupoint injection of bone marrow mesenchymal stem cells in improving blood flow in the rat of hind limb ischemia." J Tradit Chin Med **31**(3): 241-245.

OBJECTIVE: To explore the mechanism of acupoint injection of bone marrow mesenchymal stem cells (BM-MSCs) in improving blood flow in the rat with hind limb ischemia. METHODS: Twenty-four SD rats were randomly divided into 4 groups: normal control group (n = 6), model group (n = 6), BM-MSCs acupoint injection group (AI group, n = 6) and BM-MSC intramuscular injection group (MI group, n = 6). Sanyinjiao (SP 6), Housanli (ST 36), Zhaohai (KI 6), Huantiao (GB 30) and Yanglingquan (GB 34) were selected for the AI group, and five non-acupoints were selected on gastrocnemius and adductor of ischemic hind limbs in the MI group. BM-MSCs were injected to the latter two groups. The rat hind limb ischemia model was established with the method of blocking the femoral artery and its branches. Three weeks after injection of BM-MSCs, in each group, hindlimb adductor and gastrocnemius were taken from the ischemic side. Expressions of vascular endothelial growth factor (VEGF) and transfer growth factor-beta1 (TGF-beta1) in the skeletal muscle were determined with immunohistochemical method, and the small arteries in the skeletal muscle were labeled with alpha-SMA immunohistochemical staining method, the density of small arteries (number of arterioles/number of muscle fibers) and the number of the blood vessel with VEGF positive expression were calculated. The serum levels of VEGF and nitric oxide (NO) were detected. RESULTS: Compared with the model group, the expression of VEGF and TGF-beta1, and the density of small arteries and the number of VEGF-positive blood vessels in the AI group and the MI group significantly increased (both $P < 0.01$). Compared with the MI group, the density of small arteries and the number of VEGF-positive blood vessels in the AI group significantly increased (both $P < 0.01$); Compared with the model group and the normal control group, the serum expression quantity of NO and VEGF in the AI group and the MI group were significantly increased ($P < 0.01$). CONCLUSIONS: Acuppoint injection of BM-MSCs secrets more VEGF, TGF-beta1 and NO to increase angiogenesis and arteriogenesis, so as to improve blood flow of the rats of hind limb ischemic.

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