Innovations in Cell & Gene Therapy, 3rd Medicine by Design Symposium

Isis So[1], Kawther Nemrish[1], Clarke Blair[1], Chengyin Li[1], Olga Sirbu[1], Zonelle Wijesinha[1] & Paxton Wong[1]

[1]University of Toronto, Canada

Medicine by Design, a group of regenerative medicine and cell therapy researchers at the University of Toronto (U of T), hosted its 3rd annual symposium at the MaRS Discovery District Auditorium on December 4th, 2018. Twelve researchers from local and international institutions presented their research on muscle, gene, neural, and immune engineering.

Commencing the session on muscle engineering, Dr. Bénédicte Chazaud (Université Claude Bernard Lyon) discussed the role of macrophages in skeletal muscle repair and disease. Macrophages are most notably involved in destroying pathogens, but are also crucial in regeneration, stimulating muscle stem cell proliferation and differentiation. Dr. Chauzaud highlighted recent work on Duchenne muscular dystrophy (DMD) drug treatments, where macrophage behaviour was manipulated to prevent fibrosis and improve muscle function in DMD models. Regarding heart function, Dr. Stephanie Protze (University Health Network – UHN) introduced the use of human pluripotent stem cells (hPSC) to generate sinoatrial node pacemaker cells for patients with abnormal heart rhythms. This technique exposes hPSC-derived cardiomyocytes to specific signaling molecules, triggering their differentiation to sinoatrial node pacemaker cells. If clinical trials are successful, this personalized approach may evade complications of electronic pacemaker implantation. For patients experiencing heart failure, Dr. Michael Laflamme (UHN) presented his work on myocardial regeneration. When a heart attack occurs, healthy myocardium is replaced with non-contractile scar tissue, limiting the heart's contractility and leading to eventual failure. Dr. Laflamme's research explores two therapeutic possibilities: synthesizing new myocardium from pluripotent stem cells and converting scar tissue into healthy myocardium. Both options aim to improve heart function after a heart attack without the need for a transplant.

Transitioning into gene engineering, Dr. Rudolf Jaenisch (Massachusetts Institute of Technology) discussed epigenetic regulation in development, aging and disease. Since epigenetics affect gene expression through covalent modification of DNA or its histones, Dr. Jaenisch examined the need for a dynamic reporter to track individual cells' DNA methylation status. He additionally presented his work employing a modified CRISPR/Cas9 system to treat epigenetic disorders like Fragile X Syndrome. Dr. Laura Prochazka (U of T) presented work

on the development of synthetic gene circuits to direct hPSC differentiation. She utilizes miRNA-based gene circuits which combine sensory input, computational processing, and physiological output to alter gene expression. Compared to traditional approaches, gene circuits are inexpensive and provide an internal control system that is less dependent on the environment. Dr. Prochazka is currently working on implementing multi-inputs/outputs circuits to optimize the efficiency of induced stem cell differentiation. Closing the session, Dr. Jennifer Mitchell (U of T) discussed her research examining stem cell gene regulation by identifying transcription enhancers. Her work is focused on *Sox2*, a gene known to regulate neural stem cell differentiation and maintenance. *Sox2* was recently found to be regulated by the *Sox2* Control Region (SCR) enhancer, where mutations in the SCR impair neuronal differentiation. Her research may elucidate stem cell manipulations for medical applications.

Following a break, Dr. Lorenz Studer (Memorial Sloan Kettering Cancer Centre) introduced the theme of neural engineering, presenting his studies on neural crest development and hPSC therapy for treating nervous system diseases. He explained how genetically-manipulated cells derived from stem cell precursors can be used to treat Hirschsprung's disease, which causes impaired neural cell migration. Dr. Studer demonstrated the efficacy of this therapy in chick and mouse

models, where migratory behaviour was restored with direct cell injections. Dr. Yun Li (SickKids Hospital) discussed brain organoids (3D cell cultures) as a model for in vivo human-specific cortical development. Using organoids, her studies of ventricular formation and neuronal emergence involve genetic manipulation to enhance cortical growth and folding. For example, Dr. Li demonstrated Zika virus infections result in microcephaly and prevent normal cortical development. To conclude the session, Dr. Alain Dabdoub (Sunnybrook Research Institute) addressed auditory neuron regeneration. Currently, auditory neuron damage leads to permanent hearing loss. However, cochlear cells can be endogenously reprogrammed with transcriptional activators that turn on genes expressed in auditory neurons. *In vivo*, adenoviruses were applied to mouse models to introduce neuronal differentiation genes. Ultimately, Dr. Dabdoub aims to apply these techniques to human models.

As an interlude, Dr. Alán Aspuru-Guzik (U of T) highlighted the use of artificial intelligence and automation in current science. He discussed two major developments from his lab: 1) machine learning algorithms that can accelerate the process of drug candidate generation; and 2) a software, ChemOS, that can be combined with robotic platforms to create self-driven laboratories. Overall, Dr. Aspuru-Guzik hinted that these technologies can revolutionize the technique and efficiency of scientific discovery.

Opening the final session on immune engineering, Dr. Yvonne Chen (University of California, Los Angeles) presented her work on immune cell therapy for cancer treatment. This involves manipulating existing immune cell receptors and engineering new ones to improve tumour targeting. Although this technique allows for personalized treatments, it may miss some tumour cells or target healthy cells. To prevent the former, Dr. Chen described a specifically engineered immune receptor that recognizes a wider range of tumour cells. To address the latter, Dr. Chen described another engineered receptor which activates only under specific multi-component target recognition. Dr. Sarah Crome (UHN) concluded the conference with a discussion on characterizing novel innate immune cells for immunotherapy. In tumours, these cells negatively impact immune response and shorten relapse time. As demonstrated in mouse models for autoimmune disease, these cells can control harmful inflammation and may stimulate tissue regeneration. Dr. Crome highlighted the importance of cell characterizations for future clinical applications, such as targeting immune cells to enhance immune tolerance, which could reduce transplant rejection and autoimmune disease risks.

In all, the 3rd Medicine by Design Symposium on cell and gene therapy served as a platform to share innovative ideas among the regenerative medicine community and to inspire the next generation of scientists. Congratulations to all the speakers for presenting their exciting findings, and to Medicine by Design for the hosting of a successful conference.

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