SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
Joint Office of Research
Research e-Bulletin
A weekly e-newsletter for the research community

A Promising Future for Cellular Replacement Therapies in Neurodegenerative Diseases

In the third session of Research Grand Round, 1st prize winners of the *SingHealth Duke-NUS Research Team Award*, Professor Tan Eng King, Senior Consultant Neurologist and Research Director, National Neuroscience Institute, Singapore General Hospital (SGH) and Assistant Professor Je Hyunsoo, Shawn, Neuroscience and Behavioural Disorders (NDB) Programme, Duke-NUS Medical School, shed some insights and discoveries on the science of neuronal characteristics and the latest developments in Parkinson's Disease (PD) and autism research. The session, attended by over seventy clinician scientists, researchers and medical professionals, highlighted some of the challenges and limitations in seeking optimal replacement therapies for patients with neurodegenerative disorders. Presenting both laboratory and clinical research findings, Prof Tan and Asst Prof Shawn discussed their ongoing work and how they have looked at various ways of overcoming these challenges and limitations.

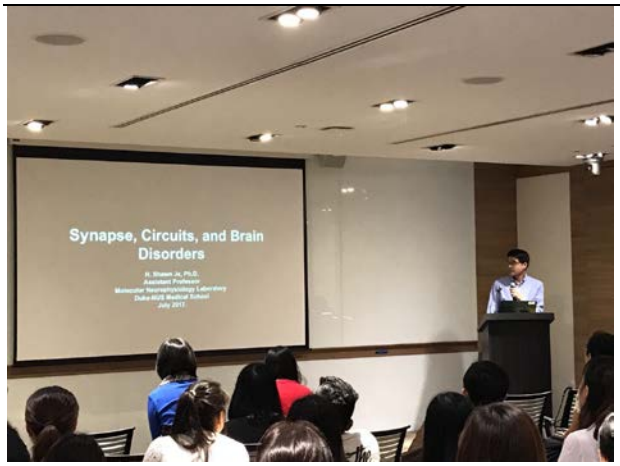
Prof Tan opened the session with a brief introduction on the milestones in research on PD. He highlighted some of the major discoveries made, with emphasis on the last ten years on the generation and transplantation of alternative cells that can produce dopamine. Prof Tan commented that the neuropathology of Parkinson's Disease is unique among the many neurodegenerative disorders as the pathology in the predominant stages is restricted to the

substantia nigra (a basal ganglia structure located in the midbrain that plays an important role in reward and movement) where there is a loss of dopamine producing neurons.

Through the use of patient videos, he highlighted the effects of the first PD drug that was hailed as a “miracle” drug back in the 1960s before it was discovered that the subsequent plethora of dopamine treatment drugs come with a lot of complications such as gambling addictions, varying responses to therapies and so forth. Moving into the main focus of the session’s presentation, Prof Tan explained how although the condition of PD may be homogenous, there are significant clinical heterogeneity that highlights both the importance and difficulty of treating PD. He stressed that PD is not a monosymptomatic problem. Using data and statistics, he shed light on the important considerations in developing dopamine replacement therapies, with one main consideration being how in a degenerative brain, the patients’ neurons are dying as they are trying to be replaced.

With this in mind, Prof Tan presented the *in vivo* laboratory research findings on brain transplants, the key features of cellular replacement therapies for PD and what are some of the lessons learnt. Transplantation using human fetal mesencephalic tissue, an area Prof Tan has been actively involved in since its discovery, and experimental transplantation using stem cells have shown great clinical benefits.

Prof Tan also shared on the nationally funded Translational Clinical Research Program in Parkinson's Disease which he is an active member of. This is a collaboration with A*STAR's Bioprocessing Technology Institute (BTI), where the main research focus is on the clinical implications of using microcarriers (MC) to address the debate on preparation of tissue in transplantation in PD patients. He concluded his presentation with a brief look into future work in PD research and some take home messages on how the team looks forward to new clinical trials that will expand the field.



Asst Prof Shawn then took over to address the fundamental question on how changes in synapse activity or dysfunction of synapses can alter the behaviour of patients. He presented on studies on cellular and molecular mechanisms underlying synapse developments using various model systems and how they affect neuron circuits.

To study human brain in schizophrenia and autism disorder, Asst Prof Shawn showcased laboratory research findings, on growing human neurons from patient-derived induced stem cells, to demonstrate that the efficiency of *in vitro* models of human neural cells is very low. He shared that what is unique about a neuron is that they are electrically excitable cells which make synaptic connections and networks. He also highlighted various biological techniques that are used in the laboratory to identify neuronal activity.

Moving into his main research focus and interest on autism, Asst Prof Shawn presented the findings of a large scale genomic study conducted that identified gene mutations to study Autism Spectrum Disorder (ASD), a neurodevelopmental disorder prevalent in Singapore. The study involved over 500 patients which involved complexity of genetics and multiple risk factors. Considerable efforts have been put forth to study molecularly defined syndromes in which ASD was observed at higher than expected frequency, in particular Angelman syndrome (AS), which is characterized by severe intellectual and development disability, sleep disturbance, seizures, frequent laughter or smiling. The study deviated from

conventional methods in developing neurons for which findings yielded higher efficiency rates.

Asst Prof Shawn concluded his presentation with a sharing on their award-winning development of living 3-dimensional (3D) grown *in vitro* “mini-brain” organoids. The findings of the study successfully remodelled PD through the artificial creation of the Lewy body, a common pathophysiological signature of PD, in the organoid system. As the “mini-brain” produced dopaminergic neurons showcasing similar neuronal activity, the study is still ongoing with the characterisation of the different sub-types of PD with a promising outlook for better clinical implications.

About Research Grand Rounds (RGR)

Held every alternate month on Wednesdays at lunch-time, RGR showcases the achievements of researchers from the AMC, serving as a knowledge exchange and community engagement platform. For more information, please visit http://research.singhealth.com.sg.

About Joint Office of Research

With its key objective being to accelerate the discovery and development of diagnostic tools, drugs and therapies that would translate into better prevention, diagnosis and treatment of diseases, the Joint Office of Research works seamlessly to identify and harness talent, support projects with state-of-the-art resources and synergise expertise across the SingHealth Duke-NUS Academic Medical Centre.