NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

SEMINAR

Mon, 23 May 2016 | 4pm | S1A – 02-17

Hosted by A/P Ganesh Anand

Stable Isotope Approaches for Interrogating Triglyceride Metabolism: A Case Study Evaluating DGAT1 and MGAT2 as Putative Targets for Treatment of Type 2 Diabetes



By **David McLaren**

Merck Sharp and Dohme, NJ

Disorders of lipid metabolism are contributing causes or comorbidities in a variety of diseases including hyperlipidemia, pancreatitis, type 2 diabetes and atherosclerosis. Discovery and development of novel therapies to treat these disorders depends on reliable methods to measure effects on lipid homeostasis in vivo. We have developed fit-for-purpose general protocols for studying modulation of lipid metabolizing enzymes in preclinical species specifically to enable rapid evaluation of pharmacodynamic effects. This presentation will describe strategies for identifying potential biomarkers and the application of stable isotope tracer methodologies with mass spectrometry analysis for evaluating lipid flux. The core experimental design, important considerations for accurate quantitation and proper interpretation of the tracer data will be discussed and the key considerations employed to develop these protocols – and to harmonize them with clinically relevant approaches - will be highlighted. Finally, specific examples on measuring lipid synthesis following inhibition of selected acyltransferase enzymes – diacylglycerol acyltransferases (DGAT1 and DGAT2), glycerol-3-phosphate acyltransferase-1 (GPAT1) and monoacylglycerol acyltransferase-2 (MGAT2) - in mouse and non-human primate models will be offered. .

David earned his B.Sc. in Chemistry from the University of Manitoba and his Ph.D. in Analytical Chemistry from the University of British Columbia under the direction of Professor David Chen. His Doctoral studies were focused on the development of ultra-high resolution separation techniques which he applied to the study of metabolite profiles in patients with inborn errors of metabolism.

Upon completion of his graduate studies David joined Xenon Pharmaceuticals in Vancouver, Canada as a Scientist in the bioanalytical group. While there, he led a team of analytical chemists and was responsible for a variety of activities including small molecule ADME, preclinical DMPK and the development of exploratory & translational biomarkers to support Xenon's Cardiometabolic and Pain research programs.

David joined Merck, Sharp and Dohme in 2009 and has held positions in a variety of departments, including the Atherosclerosis disease area, In Vivo Pharmacology and Molecular Biomarkers. He currently holds the position of Principal Scientist and Team Leader in in vitro Pharmacology where his work focuses on the application of mass spectrometry for high-throughput screening, biophysics and pharmacological characterization of target:ligand interactions.

Artwork by Ann Nee, DBS, NUS