Institute of Molecular and Cell Biology

A*STAR

SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by Dr. Adrian Teo:

Date: 19 April 2018, Thursday

Time: 11:00AM – 12:00PM

Venue: Level 3, IMCB Seminar Room 3-46, Proteos, Biopolis

Speaker: Prof. Andrzej Krolewski, Senior Investigator, Section Head, Research Division, Joslin Diabetes Center, Boston, Massachusetts, USA

Title: New Insights into Mechanisms of Diabetic Nephropathy from the -OMICS studies

Despite almost exponential growth of knowledge about the mechanisms of diabetic nephropathy obtained from cellular and animal studies, little progress has been made in our understanding of these mechanisms in humans. To advance this understanding, a new type of clinical research is being developed that uses high through-put data generation methods, so called –omics platforms. The application of this approach to research on the etiology of diabetic nephropathy in humans will be illustrated by our recent proteomics study. Inflammatory processes are involved in the progression of diabetic kidney disease to End Stage Renal Disease (ESRD), but comprehensive studies have not been performed. Here we report a study of baseline plasma specimens, using the SOMASCAN proteomics platform, to find a signature of circulating inflammatory proteins associated with high risk of ESRD in diabetes. Two Joslin cohorts of Caucasians followed for 7-15 years were used. Subjects with T1D (n=219) served as the discovery panel and subjects with T2D (n= 144) served as the validation panel. We identified a **K**idney **R**isk **I**nflammatory **S**ignature (KRIS) comprising 17 proteins, out of 194 examined inflammatory proteins, that were strongly associated with subsequent progression to ESRD. Hazard ratios for ESRD for the KRIS proteins varied between 1.5 and 3.6 per tertile changes (p between $<10^{-4.6}$ and $< 10^{-25}$). The KRIS was enriched for members of TNFR Superfamily (p=0.007) including TNFRSF1A (TNF-R1) TNFRSF1B (TNF-R2), TNFRSF19, TNFRSF19L, TNFRSF21 and TNFRSF27. Other KRIS proteins included IL15RA, IL17F, DAF, CLM6, TNFSF15, CCL14, CCL15, CSF1, TIMD3, IL1R1 and IL18R1. Kidney tissue transcriptomics analysis and urinary proteomics profiling suggested a systemic non-kidney source of KRIS proteins. The majority of the KRIS proteins correlated among each other and pathway analyses pointed to mutual downstream molecules (JAK, SYK, TRAF2, MAPK). Eight out of 17 KRIS proteins (47%) are currently targeted with compounds used for other non-renal, clinical indications. These drugs can be re-purposed and tested for treatment of diabetic nephropathy.

Biography:

Dr. Krolewski heads the Section on Genetics and Epidemiology at the Joslin Diabetes Center and is a Professor of Medicine at Harvard Medical School, Boston, USA. He received his MD and PhD from Warsaw Medical University in Poland. He obtained training in diabetes research at Joslin Diabetes Center in Boston and in

molecular human genetics at Massachusetts Institute of Technology in Cambridge. Drawing upon the large Joslin Clinic patient population, Dr. Krolewski has established a world-renowned multi-disciplinary research laboratory that combines epidemiologic, genetic and proteomic methods to study the causes of kidney complications (diabetic nephropathy) in Type 1 and Type 2 diabetes and how to diagnose and treat them. Following are the major areas of his research.

Development of a new model of early diabetic nephropathy. In large follow-up studies of Joslin Clinic patients, he discovered a new stage of diabetic nephropathy. His discovery changed the established paradigm of early nephropathy, creating a new model that highlights early progressive renal decline, instead of the previously emphasized microalbuminuria, as the primary stage of diabetic nephropathy to be diagnosed and treated to reduce risk of end stage renal disease.

Search for biomarkers of progressive renal decline. Using biobanks of specimens established in his multiple follow-up studies, he examines blood and urinary profiles of proteins, metabolites and microRNAS that are associated with risk of renal decline. This research aims to discover new therapeutic targets to prevent/treat renal decline and find prognostic biomarkers to identify patients at risk of renal function loss. One discovery so far is that high serum uric acid concentration is a determinant of early renal decline. This led to the PERL multi-center clinical trial which tests whether lowering serum uric acid can reduce rate of renal decline. Another discovery is that elevated serum concentrations of TNFR1 is a strong independent predictor of early and late renal decline. The test based on this discovery will soon be available in clinical practice.

Search for susceptibility genes for nephropathy. Dr. Krolewski is the leader in research on genetics of diabetic nephropathy. As one of the PIs of the multi-nation JDRF Collaborative Research Initiative on Genetics of Diabetic Nephropathy, he leads the effort to identify genes that specifically increase risk of progressive renal decline.

ALL ARE WELCOME *(No registration required)*