Professor **Sam El-Osta**

Place of employment and host institution: Monash University, Australia

Host principal investigator: Peter Rossing, Steno Diabetes Center Copenhagen

Title of project: Loss of Methylation Predicts Risk of Nephropathy in the Steno PROFIL Diabetes Registry

ABSTRACT

Diabetes is the fastest growing chronic condition in Denmark and Australia, increasing at a faster rate than other chronic diseases such as heart disease and cancer. The prevention and successful management of diabetic complications (DC) are important public health concerns. The major costs of diabetes are due to the progression of DC that include blindness, amputations, coronary heart disease, strokes, kidney failure and premature mortality. Despite the major advances in the detection and management, optimal diabetes control is insufficient to prevent the development and progression of DC, calling for new strategies to cope with the many complications that follow in the wake of the epidemic of diabetes affecting 400 million adults worldwide. The last 20 years has seen the rapid expansion of molecular, genetic and precision approaches used to understand and treat complex human diseases. Increasing attention has been placed on unravelling the genetic architecture of complex - common diseases such as diabetes. Despite the identification of almost 100 genetic variants associated with diabetes through genome wide association studies (GWAS), these account for at less than 10% of disease variance. The results with respect to genetic variants and diabetic kidney disease (DKD) are even more disappointing. Subsequently, there is heightened interest in the field of epigenetics which is the study of DNA modifications without changes in the genetic sequence. It has become increasingly appreciated that genetic heritability cannot fully explain susceptibility to DC and in the context of DKD, epigenetics has been considered a potential explanation for the development and progression of disease. In this proposal we will assess DNA methylation changes as they pertain to DKD using the Steno Diabetes Center Copenhagen (SDCC) PROFIL Diabetes Registry. We hypothesise that epigenetic pathways regulated by DNA methylation determine why some individuals with diabetes (are programmed to) develop complications of their disease, while others do not, despite a similar duration of diabetes, treatment intensity and mean glucose exposure. Given the importance of epigenetic programming in the development and progression of DC we will define for the first time the Danish Methylation Risk Score. Over the last decade we have developed state-of-the-art technologies to characterise DNA methylation in human cohorts. The aim of this proposal is to better understand the burden, natural history and propensity for complication development among Danes with or at risk of diabetes - outlining the clinical, metabolic and epigenetic correlates of disease to ultimately predict, treat, and prevent DKD. The application of contemporary technologies never previously explored in PROFIL in parallel with detailed examination of the clinical patterns and the methylation determinants of DKD, it is anticipated this project will reveal major pathways associated with DKD. Functional network-based analysis of differentially methylated genes may ultimately lead to the development of new therapies, biomarkers and prevention strategies to reduce suffering and deleterious consequences of diabetes on the kidney and possibly other vascular sites. The characterization of mechanisms underlying epigenetic changes using the Steno PROFIL cohort should lead to a better understanding of the susceptibility and progression to diabetic renal disease in the Danish population.