PhD Student, **Inga Sileikaite**, MSc (Human Biology).

Place of enrolment: University of Copenhagen, Faculty of Health and Medical Sciences

Principal supervisor: Professor **Clare L. Hawkins**, University of Copenhagen, Faculty of Health and Medical Sciences

Title of project: Role of nucleic acid modification in macrophages during the development of inflammatory disease

ABSTRACT

Oxidative stress, through the production of reactive oxygen species (ROS), plays a key role in the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance and type 2 diabetes mellitus (T2D). ROS initiate a chain of reactions that promote both the modification of biological molecules and aberrant signalling to result in cellular dysfunction and death. RNA is prospective target for ROS due to its structure, localization within the cells and lack of RNA repair mechanisms. The nucleobase, guanosine, is highly sensitive to oxidation, which results in the generation of 8-oxoguanosine (8-oxoGuo). The urinary excretion of 8-oxoGuo is strongly associated with T2D morbidity. However, the pathway by which 8-oxoGuo is formed in patients with T2D and whether 8-oxoGuo has a causal role in disease progression and islet dysfunction remains unknown. This is significant as a strategy to decrease RNA oxidation could have strong therapeutic value in the clinic.

The hypothesis for this Ph.D. project is that dyslipidemia in T2DM promotes inflammation and oxidative stress, which drives RNA oxidation to induce β-cell deterioration and the development of diabetes. We will use *in vivo* and *in vitro* approaches to determine 1) the quantitative significance of RNA oxidation in diabetic models including β-islets, 2) the pathways responsible for both the formation and removal of 8-oxoGuo, 3) the role of oxidation in the alteration of β-cell function, and 4) the efficacy of new targeted antioxidant approaches to preserve RNA (and other targets) from oxidative damage to maintain islet function. This project builds on preliminary data showing that 8-oxoGuo and related compounds can alter β-cell function in an *in vitro* β-cell model. Overall, this project will provide novel data regarding the role of oxidation in T2D, which could be important for the design of new therapeutic approaches to reduce diabetic mortality.