Professor **Nicholas Michael Morton**

**Place of employment and host institution:** University of Edinburgh, United Kingdom

**Host principal investigator:** Kei Sakamoto, University of Copenhagen, NNF Center for Basic Metabolic Research

**Title of project:** Determining the molecular mechanism of sulfide–mediated regulation of AMPK kinase activity and its relevance to type 2 diabetes; a platform for knowledge exchange between the Edinburgh and Copenhagen diabetes research networks


**ABSTRACT**

Sulfide is a biologically active gas produced principally from the metabolism of the dietary amino acid cysteine. Physiological or pharmacological elevation of sulfide has emerged as a potential therapeutic strategy for cardiometabolic diseases including type 2 diabetes. However, sulfide is a respiratory toxin if it reaches supra-physiological levels and a series of enzymes present in the mitochondrion exist to oxidise sulfide and maintain it within safe levels. This sulfide oxidation pathway has been overlooked in terms of its therapeutic potential because mutations in one of the key enzymes, ETHE1 leads to fatal sulfide toxicity. The Morton lab discovered that elevated adipose tissue levels of another SOP enzyme, thiosulfate sulfur transferase (TST), was a causal genetic driver of healthy leanness in mice and, potentially, humans. We showed that treatment of mice with a TST substrate activator ameliorated diabetes in mice. In contrast, mice lacking TST (*Tst*–/– mice) had impaired glucose tolerance and markedly elevated circulating sulfide levels. New work shows that sulfide elevation in *Tst*–/– mice has complex tissue–specific effects on metabolism, driving increased hepatic glucose production but increasing insulin sensitivity in muscle and protecting mice from atherosclerosis. The scientific work proposed for the visiting professorship aims to delineate a novel mechanism of action whereby sulfide elevation mediates its metabolic effects through post–translational "persulfidation" of a key cysteine residue (Cys174) on the catalytic a-subunit of the AMP-activated protein kinase (AMPK) – a master regulator of cellular energetics and promising target for metabolic disorders. We will determine whether persulfidation of Cys174 modulates AMPK activity in cells *in vitro* and profile the persulfidation status of AMPK in liver and skeletal muscle in mouse and human metabolic disease (NAFLD and Type2 diabetes). This project is designed to synergise the scientific strengths of the Morton and Sakamoto labs but crucially and more broadly, it seeks to build a new bridge between the Edinburgh Diabetes Network newly formed by Morton and the world–leading metabolic/diabetes research conducted by Professor Sakamoto and the numerous leading researchers at the Novo Nordisk Foundation Center for Basic Metabolic Research (NNF CBMR), University of Copenhagen and across Denmark. The knowledge exchange aspect will involve development of a graduate student exchange programme supported by a recent successful British Heart Foundation 4Y PhD Programme award led by Morton (2021-24).