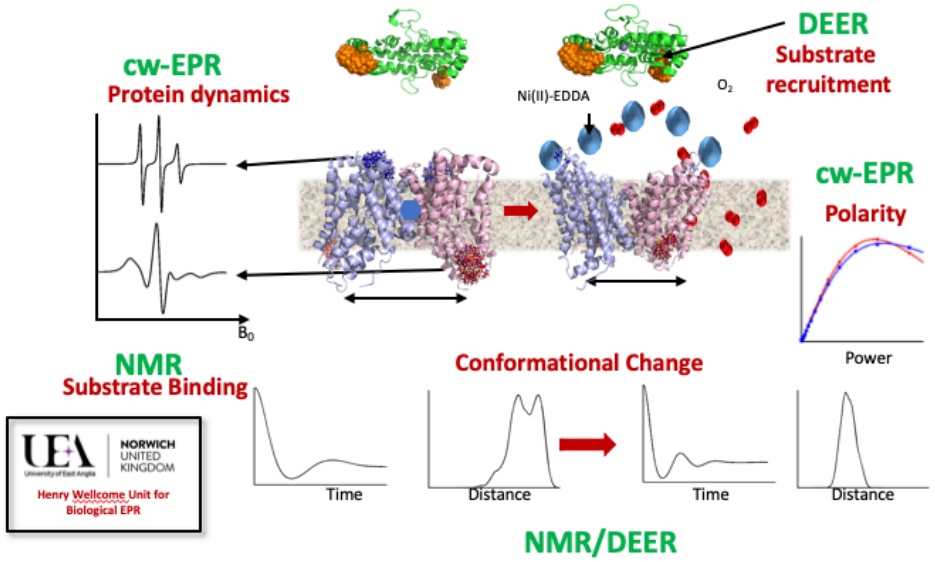
Fully funded PhD Studentship Opportunity for October 2020 start

Application dead-line 25th November 2019

Life's ups and downs: probing the conformational dynamics of DASS transporters, a protein family associated with age-related diseases and lifespan determination

Supervisors: Fraser MacMillan (Univ of East Anglia) and Chris Mulligan (Univ of Kent)

Overview: We study the architecture and functional dynamics of membrane proteins, especially many medically relevant membrane transport systems. There is increasing evidence that membrane proteins do not act alone, but that they are organised as nano-machineries which function through the concerted action of individual components with high precision and specificity observed in both time and space. We are seeking to unravel the principles underlying the architecture and dynamics of these protein nanomachineries as well as their function. Our experimental approach focuses on the use of magnetic resonance techniques specifically Electron Paramagnetic Resonance (EPR) and Nuclear Magnetic Resonance (NMR) spectroscopy in combination with molecular biological, and biochemical approaches.



This project will study a specific divalent anion sodium symporter (DASS) transporter VcINDY. In eukaryotes, reducing cytoplasmic citrate modulates the energy homeostasis of cells and induces caloric restriction-like benefits. Citrate enters the cytoplasm through the DASS transporter family. Disruption of DASS function can increase lifespan, protect against insulin resistance and adiposity, and inhibit cancer cell proliferation. Thus, human DASS transporters are prime drug targets to treat numerous chronic diseases and promote healthy ageing. However, DASS transporters are highly dynamic and the development of DASS inhibitors relies on understanding the distribution of conformational states. Recent structural studies have proposed large scale conformational changes and we aim to probe the functional dynamics of this protein using a combination of state-of-the-art magnetic resonance techniques as well as techniques to purify and stabilise the protein using novel SMA lipid particles.

Informal enquiries can be made to Fraser MacMillan (fraser.macmillan@uea.ac.uk), please include an up to date *curriculum vitae* and letter of motivation

Full application details can be found online (http://www.biodtp.norwichresearchpark.ac.uk/projects)

University of East Anglia
Henry Wellcome Unit for Biological EPR

University of Kent