The mechanistic basis of the 'positive-inside rule' for membrane protein topology

Supervisory team:
Main supervisor: Prof Ian Collinson (University of Bristol)
Second supervisor: Dr Paul Curnow (University of Bristol)
Dr William Allen (University of Bristol)

Collaborators: Dr Robin Corey (University of Oxford (is applying for a Fellowship hosted by Exeter))

Host institution: University of Bristol

Project description:

The topology of trans-membrane alpha-helices of membrane proteins is governed by the distribution of charged amino-acids in the intervening loops: von Heijne's 'positive-inside rule' discovered more than 35 years ago [1]. As the name suggests it describes how positive residues –arginines and lysines– have a strong propensity to be located in the cytosol (inside). This constrain on membrane protein folding has held true in the face of the stream of new membrane protein structures, and for all domains of life. In spite of its simplicity, the underlying mechanistic basis of this seemingly ubiquitous phenomenon is unknown.

The Collinson lab explores the mechanisms of protein-transport during bacterial protein-secretion and membrane protein-insertion and the process of mitochondrial protein-import [2–5]. In the former case, both protein-secretion and insertion proceed through the Sec-machinery. Our analysis of its structure and activity has led to a compelling hypothesis for the explanation of the 'positive-inside rule'. Meanwhile, major differences in the mechanism of protein-transport into and across the mitochondrial inner-membrane suggest that imported membrane proteins may not necessarily conform.

The project will harness complementary bioinformatic and biochemical analyses of the structures and insertion of bacterial, mitochondrial and synthetic membrane proteins, designed to reveal the mechanistic basis of the 'positive-inside rule'. This will provide new insights of a fundamental feature of membrane biogenesis essential for every cell in every organism. Moreover, new basic understanding will be exploitable (by the Curnow lab) for future bioengineering applications –such as manipulating and exploiting membrane processes, enhanced protein production, developing new synthetic tools, and the de novo design or engineering of membrane proteins with novel and valuable activities. See below [2–5] for further subject detail and experimental approaches of interest to the Collinson lab.

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