Ian Collinson
Protein secretory system

At the time of the founding of the Biochemistry department, the translocation of proteins across and into lipid membranes was an almost total mystery. How do antibodies synthesized by our B-cells end up in our blood? How do the cholera and tetanus bacteria secrete their deadly toxins? While many (correctly) reasoned that there must be specialist cellular machinery involved in this complex task, there was opposition who believed it to be a spontaneous process. At the time there was little evidence either way.

A lot of progress has been made since then, with genetic screens and reconstitution of membrane transport in vitro confirming that protein-based machinery is indeed required for translocation. Three membrane-bound proteins were found to comprise the core complex, which are found in almost all cells of all organisms. In E. coli, the most studied system, they are known as SecYEG.

Ian’s work has been centred on SecYEG since his PhD. Using electron microscopy at the Max Planck Institute of Biophysics in Frankfurt and X-ray crystallography at Harvard he was heavily involved with solving the first static structures of SecYEG.

When Ian joined Bristol University in 2004, it was known that SecYEG has a clamshell-like structure, designed to open about a hinge and thereby allow the passage of proteins through the complex. Secretory proteins pass through the channel created by this partitioning on their way to the other side of the membrane. The structure of the complex also explained its capability for membrane protein insertion, through a lateral gate formed between the two halves of the clamshell.

However very little was known about the dynamic mechanism of protein secretion and membrane protein insertion, so when Ian moved to Bristol he decided to play to the Department’s strengths of molecular enzymology and protein dynamics and focus on the interactions and behaviour of SecYEG with its substrate and other proteins which aid translocation.

Structural biology still played a key part of this. In 2012 the Collinson lab solved the structure of SecYEG and the first few amino acids of a protein about to pass through the central pore. This was the first visual representation of the start of translocation and clearly demonstrated some of the structural changes which occur in SecYEG to allow proteins to travel through the pore.

The lab has also sought to understand more about other proteins which assist SecYEG, primarily SecA. This is a motor ATPase which provides the pushing power to get the substrate protein through the central pore of SecYEG. They have made much progress in understanding how SecA is activated by interactions with SecYEG and the membrane, and how it uses the energy from breaking down ATP to force the translocating protein across the membrane. SecA has only been found in bacteria, so this may provide a useful target for future antibiotic development (in collaboration with the Dundee Drug Discovery Unit).

The mechanism of protein translocation is still far from solved, so future work will require the continued deployment of classical biochemical and biophysical, honed in Bristol over 50 years, as well as the development of new methods such as high-resolution electron microscopy and single molecule techniques.