Introducing BMSS 2018 Robinson Lecturer: Professor Kathryn Lilley

Cambridge Centre for Proteomics; Fellow of Jesus College Cambridge; Rosalind Franklin Institute

I am the Professor of Cellular Dynamics in the Department of Biochemistry, University of Cambridge and also the Director of the Cambridge Centre for Proteomics, located in the Systems Biology Centre, Cambridge, UK. I am also the co-theme lead for mass spectrometry at the Rosalind Franklin Institute, a newly forming institute that is being established at the Harwell Research Campus to develop disruptive new technologies designed to tackle major challenges in health and life sciences, a role I share with Perdita Barran of the University of Manchester.

Over the past 15 years my group has developed innovative technologies designed to enable cell biologists to probe dynamic sub-cellular mechanisms using mass spectrometry.

I was born in Mansfield, a former coal mining town in Nottinghamshire. I attended Queen Elizabeth's Girls' School where I was destined to have a career as a musician, having spent my formative years singing as a soloist in a multitude of musical festivals. Having realised that you could be a professional scientist and an amateur musician, but that it would be very difficult the other way around, I chose to study Biochemistry at the University of Sheffield.

As an undergraduate I was not particularly inspired by any of the practical classes we had to take, apart from one involving measuring the kinetic properties of alcohol dehydrogenase in the presence of different substrates. Building on my enthusiasm for enzyme kinetics, I carried out a PhD with Paul Engel at the then Department of Biochemistry at the University of Sheffield, on a project that aimed to characterise the kinetic properties of glutamate dehydrogenase (GDH) with various active site mutations. The project went horribly wrong in its first year as the group trying to clone the enzyme encountered many difficulties. I had to come up with a 'stop-gap' project until the cloning issues were overcome. With the help of Arthur Moir, a senior researcher in the department, I characterised the active site of GDH by chemically labelled peptides using pyridoxal phosphate, sending away my labelled peptides for identification using Edman Degradation. It is sobering to think that I could now have carried out my entire PhD in a few weeks using modern mass spectrometry methods.

One day, whilst I was sat at the HPLC collecting labelled peptides, Bill Shaw, who was then Head of the Biochemistry Department, University of Leicester, saw me in action. He asked if I liked protein sequencing, which I did of course by then, as the method had saved my PhD, and he offered me a job as a laboratory manager to run Leicester's protein sequencing service. From this point onwards, I didn't follow the typical career route of PhD, Post Doc, Fellow etc..... In Leicester, I eventually formed the Protein and Nucleic Acid Chemistry Laboratory, a core facility that operated fee-for-service DNA synthesis and sequencing, protein sequencing and peptide synthesis. For me, at this point, biology came in two flavours, either a tube with some protein in it or a tube with some DNA in it. I lost touch completely with biology and missed all the great biological breakthroughs in the 1990s. On the plus side, I had plenty of time to sing and hone my abilities as an opera singer.

After 10 years in my role in Leicester, several events effectively propelled me into the next stage of my career: I had made enough money to buy a simple mass spectrometer to check the products of my synthetic services; I was very frustrated with the failure rate and lack of sensitivity of protein sequencing using Edman Degradation; even more frustrated with the fact that I couldn't write equipment grants and that no one else seemed as bowled over with LC-MS/MS methods for protein identification and characterisation as I was.

I left Leicester for Cambridge to take up a position in the Biochemistry Department to set up a proteomics core facility. It was a steep learning curve; as a mass spectrometrist, I was largely self-taught and also had to tackle quantitative measurements and the thorny issue of applying statistical tests to data, not a trivial matter, as up until this point anything to do with statistics had brought me out in a cold sweat.

With time and through collaborations with Alfonso Martinez Arias, Paul Dupree, and Tony Jackson, I became increasingly interested in the subcellular location of proteins in cells and their functions at these locations.

Proteins carry out their function in a context specific manner and many diseases are now known to result from either aberrant trafficking of proteins or even mis-localisation of protein translation. The first stage of many proteomics experiments is to take the cells and mash them up, usually adding a healthy dose of detergent along the way, losing all the spatial information about your proteins within a cell. Over the past decade or so, we have developed different methods to capture the subcellular location of proteins using quantitative mass spectrometry methods and biochemical sub-fractionation of cells. Importantly, we have co-developed machine learning tools that allow thorough interrogation of the complex data that results from these methods. Using multiple methods, we have shown, along with Emma Lundberg of the Human Protein Atlas, that up to half of proteins are in more than one location in all eukaryote cell types tested. Some of these mixed localisations are easy to explain using our current perception of how a cell works. Others are not, leading us, and others to suggest that the size of the proteome is expanded simply by context dependent re-purposing of proteins, a cellular gig economy. To shed further light on our theories, and through a Wellcome Trust Investigator Award to myself and Anne Willis of the MRC Toxicology Unit, we are looking at the role that the sites of translation and the RNA binding proteome play in the diversity of protein subcellular locations. We have developed new sets of tools that will not only fulfil our research aims, but will be of

high utility to other researchers interested in the spatial relationship of the transcriptome and proteome, especially with disease mechanisms.

I've been very lucky since joining the University of Cambridge. My department has been very supportive and despite never having been a traditional post-doc., I've been encouraged to follow my research dreams, and become a research group head. I have worked with some fabulous co-workers, too many to single out by name here.

The only down-side is that I have less time to sing, so perhaps I was wrong all those years ago – the life of a research group head doesn't leave much time for amateur endeavours.

Interested in finding out more about your scientific heroes?

See their interviews on the Science History Institute website https://oh.sciencehistory.org/oral-histories

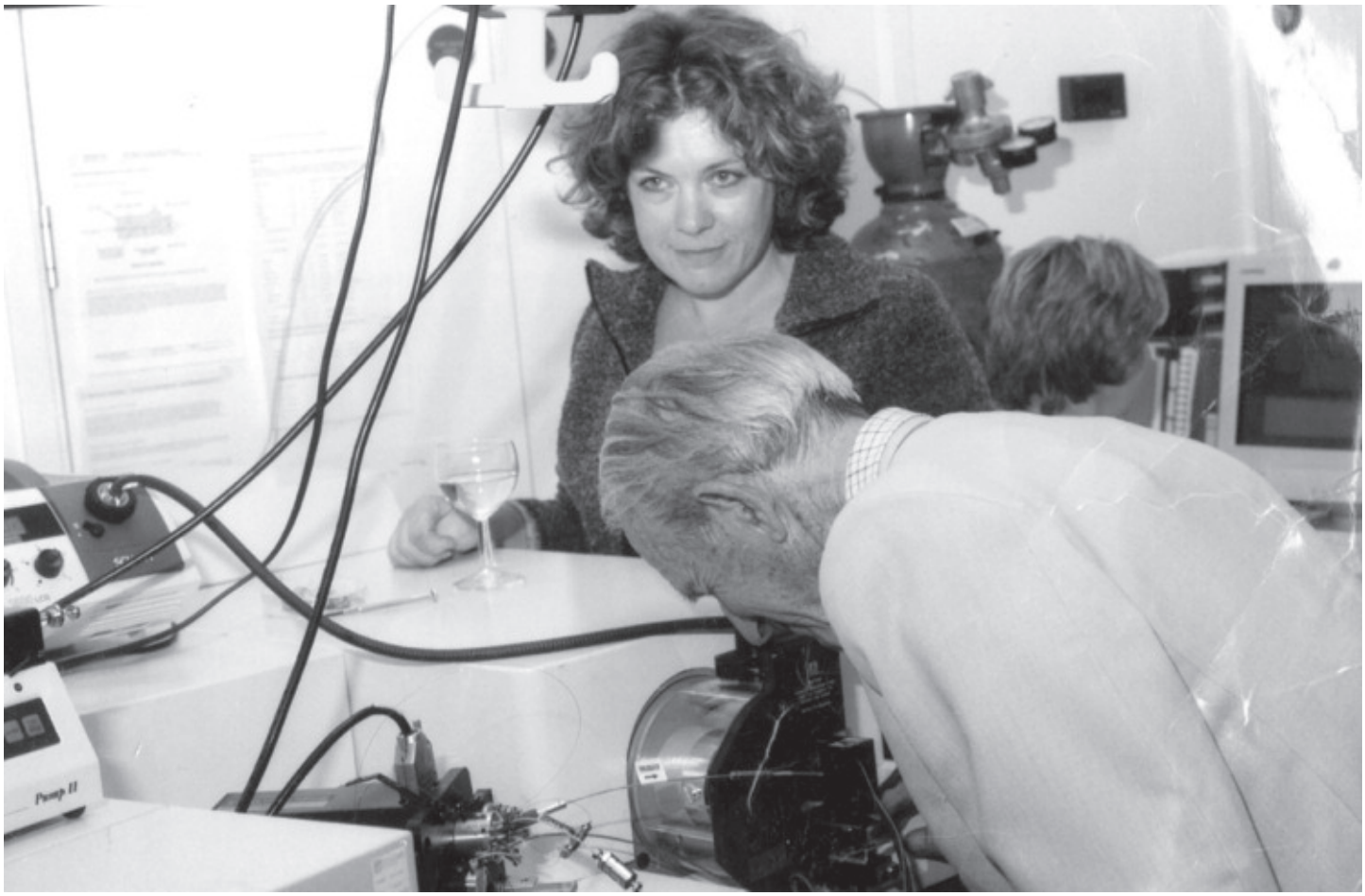

Photo: Professor Kathryn Lilley with Fred Sanger, the double Nobel Prize winner, at a laboratory opening.