60 years of the Colworth Medal

Lucy Ollett (Biochemical Society, UK)

The Colworth Medal is an esteemed annual award for outstanding research by a young biochemist of any nationality who has carried out the majority of their work in the UK or Republic of Ireland. Donated in 1963 by Unilever Research Colworth Laboratory, the award is made to an early-career scientist who is within 10 years of receiving their highest qualification. Interviews with past winners from 1963 to 2013 were previously published throughout 2013. To celebrate the 60th anniversary of the Colworth Medal, interviews with our latest winners will appear in *The Biochemist* throughout 2023. In this issue, we will hear from Dr M. Madan Babu (2014) and Professor Helen Walden (2015).

Dr M. Madan Babu (2014)

Photo credit: St. Jude Children's Research Hospital

What led you to a career in the molecular biosciences?
Growing up in India, I had a natural affinity for various scientific subjects, especially computer science. In high school, I had a fantastic biology teacher who inspired me to explore the world of molecular biology. Another key moment for me was the opportunity that I had to work as an undergraduate research intern at the Indian Institute of Science. For the first time, I experienced how to define a scientific problem, develop methods to solve it, write up and defend the findings for publication. Looking back, I was particularly excited about the genomic revolution and explosion in structural data that had enormous potential to reveal how organisms function at the molecular level. It occurred to me that a career in science would never be boring as it always presents opportunities to learn something new. It became clear to me that pursuing research that combines computer science and biology would present enormous opportunities to push the boundaries of our understanding of the molecular basis of life.

The Colworth Medal is presented for outstanding research. Can you tell us about your work?
A fundamental question in biology is how protein sequences determine cellular function. My group investigates the sequence–function relationship by examining (a) how structured protein regions contribute to function through studying G-protein-coupled receptors (GPCRs) and (b) how intrinsically disordered protein regions (IDRs) contribute to biology and disease.

GPCRs: GPCRs are attractive drug targets, with over 30% of all approved drugs acting on proteins from these families. We used integrative computational approaches to derive mechanistic insights in the GPCR signalling pathway. Specifically, we revealed principles of ligand binding to GPCRs (*Nature* 2013), mechanism of receptor activation (*Nature* 2016), molecular determinants of selectivity in G-protein binding (*Nature* 2017) and the allosteric mechanism of G-protein activation (*Nature* 2015). Our work revealed that the GPCR drug targets are polymorphic in the human population (*Cell* 2018) and undergo extensive splicing in different tissues (*Nature* 2020) – discoveries that have implications for personalized medicine and for developing targeted therapeutics with minimal side effects.

IDRs: Although intrinsically disordered protein regions (IDP/Rs) are prevalent in nature (~40% of human proteins have IDRs), it remained unclear how they contribute to function and disease. Through a

combination of computational studies, high-throughput approaches, large-scale data analysis and experimental validation, our work revealed that specific regions within IDRs and variation within them drive disease states as well as evolution of organismal complexity through the creation of novel networks of interactions (*Science* 2008, 2012; *Mol Cell* 2012, 2014, 2016; *NSMB* 2014, 2017; *Mol Sys Biol* 2018). Our work helped establish IDPs from a niche field to an established area of broad significance in biology and disease.

What are you doing now?

In 2020, I moved from the MRC Laboratory of Molecular Biology in Cambridge, UK, to St. Jude Children's Research Hospital, USA, as an Endowed Chair in Biological Data Science and Director of the Centre of Excellence for Data Driven Discovery in the Department of Structural Biology. The mission of the centre is to pioneer data science approaches to discover new biology and reveal fundamental principles of biological systems. We employ and develop computational and experimental methods to study biological systems at different scales of complexity: from systems at the atomic level (e.g., structures) to the network of interactions between molecules (e.g., protein interaction networks) and those pertaining to the level of an entire population (e.g., variation in the human population and cancer genomes). We envision that our findings will help to better understand how mutations cause diseases such as cancer and that the knowledge can be used in biotechnology, drug discovery and personalized medicine.

How did receiving the Colworth Medal impact your career?

Receiving the Colworth Medal gave me a platform to present my research and highlight the power of using data science in biology to a broad audience of scientists. It also expanded my horizons by providing the opportunity to meet scientists in the Unilever Research Labs and through events organized by the Biochemical Society. This allowed me to expand my scientific network, allowing me to pursue impactful, inter-disciplinary studies through new scientific collaborations.

What advice would you give to a future molecular bioscientist?

I would say three things.

First is go deep, but also be interested broadly. Having breadth and depth of knowledge allow you to integrate knowledge from various disciplines such as biology, statistics, computer science, mathematics, physics and chemistry in a principled manner. It also provides the opportunity to interpret the same findings in different contexts, which is often key to succeed in inter-disciplinary research.

Second, while it can be exciting to make a discovery, the scientific process can be slow and tedious with lots of uncertainties. It's important to take risks, enjoy the process of discovery and persevere in the face of failures.

And finally, it's important to have confidence in what you know and what you can do but it is equally important to stay open-minded and embrace new ideas to be able to push the boundaries of knowledge and challenge conventional wisdom.

Professor Helen Walden (2015)

Photo credit: University of Glasgow

What led you to a career in the molecular biosciences?

I did my undergraduate degree in Biochemistry at the University of Bath, starting in 1994. At the time, that BSc course had two 6-month research placements as part of the second and third years. I had the opportunity to go to the Weizmann Institute in Israel in my third year and absolutely loved the experience. It made me realize research in the molecular biosciences was what I wanted to do.

The Colworth Medal is presented for outstanding research. Can you tell us about your work?

My lab is focussed on understanding how ubiquitin signals, which control many aspects of cellular function, regulate different cellular processes. At the time the Colworth Medal was awarded, my lab's research focussed on the E3 ligase parkin, a very important protein that is mutated in heritable forms of Parkinson's disease. Parkin was thought to be constitutively active for over a decade and many drug companies had programmes designed to find inhibitors of activity. We found, through some pretty challenging work, that parkin was auto-inhibited by its

N-terminal domain, and that pathogenic mutations in that domain made it active. These findings met with considerable resistance but are now widely accepted. In recent years, we have worked out how it is activated, and are still trying to understand fully how it works and the roles it plays in the development of disease. We also work on DNA repair pathways that are regulated by specific ubiquitin signals, primarily in the childhood disease, Fanconi anaemia. Our most recent findings include understanding how such signals are generated, how they are removed and what they actually do to their targets.

What are you doing now?

I'm currently the Head of the School of Molecular Biosciences at the University of Glasgow. In 2022, I was fortunate enough to be named as a Fellow of the Royal Society of Edinburgh and elected as an EMBO member.

How did receiving the Colworth Medal impact your career?

Being honoured with such an award definitely raised my research profile, and is a marker of esteem, which helps to open other doors. I remember a grant reviewer writing that all previous winners of the Colworth Medal were leaders in their field, without exception. I think it was a powerful comment, and I did indeed get that grant (an ERC Consolidator award), which funded my lab for the next 6 years and has supported much of the recent success in my lab. I just remember being so grateful that there was something tangible to help me stand out from the many, many talented and creative scientists applying for funding.

What advice would you give to a future molecular bioscientist?

Over the years I've learned a lot more about survivorship bias, so I am quite mindful of offering advice. However, in my own case, learning to take the knockbacks without letting them affect my self-esteem and my confidence was key. If there is one thing I wish I had understood about science when I was younger, it is that ultimately you have to do what interests YOU. Science is about criticism and evaluation, and these things are subjective. One day you fail to get a grant, the next day you win a lovely medal! But the only thing that really keeps you going through the dark days is the desire to know, to find out. Doing what someone else wants you to do or what you think others want you to do is sometimes necessary, but shouldn't be the driving force. Beyond the philosophical, networking is very important. Go to meetings and introduce yourself to PIs, ask about opportunities at their institutions. And always ask the people in the place or position you want to be what the best and worst things are about their current role. The answers can be very revealing. ■