Laudation for Dr. Thi Hoang Duong Nguyen

Group Leader
MRC Laboratory of Molecular Biology, Cambridge, UK

Winner of the Eppendorf Award for Young European Investigators 2022

by Prof. Laura Machesky, Beatson Institute for Cancer Research, Glasgow, UK
Member of the independent Eppendorf Award Jury

Winner of the 2022 Eppendorf Young Investigator Award, Thi Hoang Duong Nguyen (Kelly), grew up in rural Vietnam, surrounded by the beautiful countryside. Kelly's mother was a mathematics teacher, stimulating her early affinity for numbers. A life changing event proved to be Kelly's winning a mathematics Olympiad aged 15 and thus gaining an opportunity to finish high school in New Zealand at 16. This sparked the beginning of Kelly's world travels and passion for mathematical and scientific pursuits. She went on to study at Wellington Girls College in Wellington NZ, where she was inspired by a fantastic chemistry teacher, Mr Brian Sturman, who recognised her talents and drive and provided extra mentoring. Motivated by her now dual love for both chemistry and mathematics, Kelly went on to pursue a joint undergraduate degree at the Australian National University of Canberra (ANU). There, she benefitted from the unusual opportunity offered by ANU to spend a full 25% of her time doing research in the lab during her undergraduate degree and additional summer research. She was able to sample chemistry, mathematics and structural biology research during this time and gain a true multidisciplinary basis for her future career. What a remarkable opportunity for undertaking cross disciplinary studies from the beginning of one's career. Could this be a possible solution to the increasing need for multidisciplinarity to solve the complex problems facing modern society?

During the 3rd year of Kelly's studies, she was greatly inspired by a talk from the visiting speaker Thomas Steitz, recipient of the 2009 Nobel Prize in Chemistry for his ground-breaking structural work that gave atomic level resolution into the ribosome, the major protein assembly machine of the cell. Steitz used X-ray crystallography to piece together the machinery of ribosomes and to reveal that the catalytic heart of the ribosome was made of RNA. He eloquently pointed out that while it was possible to piece together much of the mechanism of protein synthesis from the available crystal structures, there were many unanswered questions that would require tackling the atomic-resolution structure of the large 70S subunit of the ribosome with substrates bound to both of its major catalytic sites. In effect, to capture peptide elongation in the process of happening. Challenges like this sparked Kelly to decide that structural biology made excellent use of her skills and passion for mathematics and chemistry and offered exciting chances to discover how nature works. But Kelly realised that she needed to gain extra training in biology, so spent her Honours year and an additional 9 months at ANU working with the then recently recruited Prof. Gottfried Otting, an NMR structural biologist. There, she gained experience in a number of molecular and biophysical methods before travelling to the UK to undertake a PhD with Dr. Kyoshi Nagai at the Medical Research Council Laboratory for Molecular Biology (LMB) in Cambridge.

Landing at the LMB in Cambridge put Kelly into one of the best environments in the world for structural biology. Kelly describes the early years of her PhD as a discovery that doing crystallography can be very hard. She had decided to tackle the structure of the spliceosome, a large macromolecular complex comprising proteins and RNA that mediates exon splicing. She spent two years with what felt like little return in the way of results for her hard work. But at the same time, this huge challenge excited her and she appreciated the great learning opportunities afforded by undertaking a really challenging project. In Kelly's 3rd year of her PhD, she was inspired by breakthroughs in the Cryo-electron microscopy (Cryo-EM) field allowing the structure of the ribosome to be solved to 4 angstroms, providing insights to answer many of Steitz's earlier questions about protein synthesis. Cryo-EM was a method developed by many groups around the world that came into maturity in large part due to the seminal contributions of Richard Henderson at the LMB, where Kelly was a student. She was at one of the key world epicentres for development of this tool- working alongside Sjors Scheres, who develops methods for computational analysis of images and Venke Ramakrishnan, who is world renowned for his cryo-EM structural studies of the ribosome. Advances in the field around this time meant that larger and more complex macromolecular assemblies were suddenly more accessible for analysis by cryo-EM. Importantly, samples could be frozen in water-based buffers and with membrane attachments intact, allowing a more physiological setting than was previously possible. Kelly had also become inspired by the work of Eva Nogales, a structural biologist at the University of California Berkeley and a pioneer of Cryo-EM structural discovery work. They eventually met and formed a lasting collaboration.

Kelly's decision to use Cryo-EM proved to be a breakthrough for her ambitions to tackle large complex structures such as the spliceosome. Her PhD work took off and, in her words, she was so excited by the pace of discovery and progress that sometimes she could hardly wait to wake up in the morning and go into the lab! Even though this project was still extremely challenging, as the spliceosome comprises multiple RNAs and more than 30 proteins, Kelly could sense that the breakthrough was in sight. She had to finish her PhD before the structure was complete, but was able to gain an extension from her supervisor to finish her project. It all paid off, as in 2015 she published her first completed Cryo-EM structure of the *S. cerevisiae* tri-snRNP spliceosomal complex at 5.9 angstrom resolution and in 2016 a higher resolution structure with additional mechanistic insights into the splicing reaction. These amazing structures and the molecular and atomic level insights provided revealed how introns were spliced from pre-mRNAs, uncovering a fundamental aspect of gene expression.

This discovery launched Kelly's career as an emerging leader in the Cryo-EM structural field with a deep interest in nucleic acid-protein assemblies.

She has continued to pursue mechanistic studies of nucleotide-protein complexes, tackling the structure of the telomere- telomerase complex first as a joint postdoc with Prof Kathleen Collins, a pioneer in telomerase biochemistry, and Prof. Eva Nogales at UC Berkeley and later in her independent laboratory at the MRC-LMB in Cambridge. Telomeres maintain the ends of chromosomes to protect against damage caused by mistakes in replication- somewhat analogous to the plastic protector on the end of a shoe lace that keeps it from fraying. Telomerase is a large multiprotein and RNA-containing complex that adds DNA sequence repeats onto the end of the chromosome to form this cap. As a postdoc at UC Berkeley, Kelly developed the purification of active telomerase in sufficient quantity and quality for structural determination by cryo-EM at 8 Å resolution. Recently, Kelly's group solved the structure at high enough resolution to decipher the mechanisms by which this large enzyme complex maintains the DNA ends of chromosomes. They proposed a new model based on this high-resolution structure that today defines how we understand this important complex. They went on to additionally solve the structure of telomerase bound to part of the six-membered shelterin complex, which recruits telomerase to chromosome ends and which is important for mediating the addition of multiple telomeric repeats in a processive way to the chromosome end. These two studies have placed Kelly as a leader in the field, causing a rethink of how telomerase functions to maintain chromosomes.

This work has broad implications for our basic understanding of how cells maintain the genetic information. It also has impacts in ageing and disease, where telomere regulation can be a crucial determinant of life or death. Various telomere-based therapies have been attempted and trialled, but so far targeting this large enzymatic complex has proven elusive. Perhaps now, though, Kelly's breakthrough discoveries will pave the way to greater progress toward new tools against diseases such as cancer and even toward healthy ageing.