Laudation for Dr. Clemens Plaschka

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Winner of the Eppendorf Award for Young European Investigators 2024

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Expression of genes to make RNA and proteins is perhaps one of the most fundamental aspects of how organisms function and maintain their distinct identities. When we think about gene expression and how DNA is transcribed into messenger RNA and then translated into protein, we may picture a cartoon from the various textbooks that we have read during our undergraduate training. While having these cartoons is helpful to visualize the key concepts in gene expression or other processes, they might also give us a false sense of the simplicity of a process. In recent years, we have come to learn that key machinery such as RNA polymerase and the RNA spliceosome are far from amorphous blobs as they are drawn in textbooks. They are among several the exquisitely beautiful macromolecular machines, which synthesise, process, package and transport RNA through intricate mechanisms. Clemens Plaschka elucidated key structural aspects of these machines, while he followed his curiosity about how genes instruct the production of mRNAs and proteins. For these exciting and fundamental contributions to knowledge, he is being awarded the Eppendorf Young European Investigator Award 2024.

It was during his time at university that Clemens Plaschka became fascinated by gene expression and began to think about the molecular processes that were represented by such biological drawings as we find in textbooks and research articles. At the same time, he was struck by the power of structural biology, which is used to investigate the three-dimensional organization and mechanisms of macromolecular machines.

A summer internship with Professor Xiaodong Zhang at Imperial College London, further gave him a taste of the precision and systematic nature of structural biology. He therefore set out to investigate how our genome codes for and organizes the production of the approximately 100,000 proteins that our cells express. A guiding fascination for him has been to understand how the vast diversity of genes and mRNA species is acted upon by a small number of extremely precise but quite complex molecular assemblies.

His curiosity motivated him to choose a PhD with Patrick Cramer at the Gene Centre in Munich and the Max Planck Institute for Multidisciplinary Sciences in Goettingen, where he used structural methods to study how RNA polymerase II and its cofactors homed to the correct location on the DNA to transcribe mRNA.

Together with his then supervisor, Patrick Cramer, Clemens focused his studies on transcription initiation, which included RNA polymerase-II and the multi-subunit Mediator complex. While they made good progress using X-ray crystallography with a partial Mediator structure in 2012, it also became apparent that current technology was limiting for such large and dynamic complexes. Fortunately, at the same time, breakthroughs in the hardware and software used for cryo-electron microscopy - the so-called resolution revolution - meant that structural studies of complex machines were now becoming possible. Clemens was eager to try this new technique in collaboration with Wolfgang Baumeister's lab at the Max Planch for Biochemistry in Munich. After the heroic feat of assembling a 15-subunit active core mediator, Clemens and his colleagues solved the structure of this complex bound to a RNA polymerase II transcription initiation complex. This structure, published in 2015, revealed how the evolutionarily conserved eukaryotic core transcription initiation complex interacts with transcription factors and stabilizes the RNA Pol II complex on DNA and stimulates its activity. This experience also cemented with Clemens the idea that extremely challenging projects in science are often best tackled in teams, a principle he promotes in his own lab.

From transcription initiation, Clemens thought about the other fundamental machineries that facilitate gene expression and noted that RNA-splicing was another area where a large molecular machine was doing an atomic-level precision job by a poorly understood mechanism. This led to his postdoctoral work with Kiyoshi Nagai at the MRC Laboratory for Molecular Biology in Cambridge, where he and his colleagues solved the structures of pre-catalytic spliceosomes in 2017 and 2018. This work helped to elucidate the mechanisms for how introns are chosen for splicing from pre-mRNA prior to its translation into protein.

Now, a group leader at the IMP in Vienna since 2018, Clemens has been inspired to ask the question of how mRNA is packaged and exported from the nucleus. This is a precise process, requiring that maturity of the mRNA is recognized and that each of the many diverse mRNA species is recognized and carefully packaged to aid its journey through the nuclear pores. To understand this process, Clemens' lab at the IMP have been tackling the massive 2M-Dalton human transcription export complex, appropriately named TREX (for TRanscription EXport). Their two key studies on this complex have revealed a previously unknown 3D packaging structure for newly matured mRNAs that suggest revision of the textbook cartoons showing long strings of mRNA being exported from the nucleus. This new work changes our view of how gene expression takes place and future studies might include how mRNA gets unpackaged, perhaps with the help of the translation machinery, as it is translated into protein.