Description for the General Public

Dr. Sebastian Glatt
Max Planck Research Group Leader
Malopolska Centre of Biotechnology (MCB)
Jagiellonian University Krakow

All living organisms use information coded in their genomic deoxyribonucleic acid (DNA) to produce proteins, so called enzymes, that are responsible for carrying fundamental cellular function to reproduce, stay alive and allow them to sense and react to changing environmental conditions. During a process called "transcription" regions that are the blueprints for specific proteins (genes) are activated and give rise to messenger ribonucleic acid (mRNA) molecules. These mRNA molecules contain copies of the respective DNA sequence and in higher organisms are transported out from the nucleus into the cytoplasm. During a process called "translation", ribosomes and transfer RNA (tRNA) molecules translate sequence information encoded in mRNAs into correctly assembled chains of linked amino acids. These chains fold into specific three dimensional structures and are then called proteins, which have a specific enzymatic activity depending on their intrinsic properties and structural architecture.

Both processes, transcription and translation, are tightly controlled to assure the correct production of the right enzymes at the right time in the right place. In addition, the three dimensional folding of a poly-peptide chain is a very complicated multi-step process that needs tight regulation to produce correctly assembled and functionally active enzymes. Incorrectly folded proteins, inappropriate expression levels or the production of a protein in the wrong cellular context lead to cellular dysfunction and in the worst case promote the development of severe diseases and cancer.

In the outlined research project, we aim to understand cellular mechanisms that are highly conserved from yeast to humans and affect protein synthesis at the level of translation. Cells use a multi-protein machine, called Elongator, to attach small chemical modifications to tRNAs, which should guarantee that proteins are produced with highest precision and at the correct speed. Elongator itself is regulated by different additional factors and we would like to understand how these regulatory networks control the activity of Elongator on the molecular level. We will employ x-ray crystallography and electron microscopy to get snapshots of the involved proteins at atomic resolution and subsequently exploit this structural information to develop working hypotheses, which will be validated using functional assays *in vitro* and *in vivo*.

Strikingly, the Elongator complexes of patients with certain neurodegenerative diseases and cancer are not working properly. Therefore, we initially need to understand how it carries out the modification reaction, how it is regulated by the additional factors and what is going wrong in the affected individuals to develop therapeutic treatment strategies for the benefit of these patients in the future.