Andreas Marx – "Chemical Biology" of DNA polymerases

Whether inside the cell or in molecular biology laboratories, the synthesis of DNA would not be possible without DNA polymerases. The regulation and application of this versatile enzyme family is the subject of research carried out by Prof. Dr. Andreas Marx at the University of Konstanz in Southern Germany. In addition to basic research into naturally occurring DNA polymerases, Marx deals with the development of novel polymerases that can be used to solve biological issues and also can be used in the molecular diagnosis of diseases.

Prof. Dr. Andreas Marx carries out research in an interdisciplinary field of research between chemistry and biology
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DNA polymerases are enzymes that are involved in all DNA synthesis events, including replication, recombination and DNA repair. They are crucial for maintaining the genetic information encoded in the DNA sequences and therefore for the survival of organisms. DNA polymerases create two identical DNA strands from a single DNA molecule, a process during which the existing DNA strand is used as template to assemble DNA building blocks into a strand that is complementary to the existing one. They need to be very selective in order to ensure that the right nucleotides are joined every time. "One can imagine these enzymes as molecular machines that drive along an existing strand and select a partner that matches the existing strand and undergoes a chemical reaction with it," illustrates Prof. Marx, chair of Organic Chemistry/Cellular Chemistry at the University of Konstanz. Marx has been focused on DNA polymerases since he was a student and is absolutely fascinated by what they can do. The genetic material must be replicated during the process of cell division. Billions of new strands of DNA are therefore synthesised every minute. "It has been estimated that on average 10^{16}, i.e. 10 quadrillion cell divisions take place in the course of a human life," says Prof. Marx.

Enzyme modifications have an effect on the polymerases

Over the last few years, numerous new human DNA polymerases have been discovered. These enzymes have rather different property profiles. Some are very fast as well as highly selective; others are rather slow, make many mistakes, but tolerate damage in the genome. 15 different human DNA polymerases are known, but little is yet known about how they function and how they are regulated. Prof. Marx and his research team are specifically focused on these issues. "We have found that the post-translational modification of replication enzymes has an important regulatory function," says Marx. Modifications such as ubiquitination, i.e. the attachment of ubiquitin to proteins involved in replication, might lead to the recruitment of a DNA polymerase to the replication site. At the same time, another DNA polymerase is displaced.

The understanding of these processes requires an in-depth knowledge of the effect that post-translational modifications have on the polymerases. "Writer" enzymes attach chemical groups, "readers" recognise and are recruited to specific marks and "eraser" enzymes remove the epigenetic mark again. The regulation of these epigenetic processes is, amongst other things, vitally important as an imbalance of these three protein groups might lead to cancer and other diseases. "The elucidation of the dynamics of such post-translational modifications forms the basis of epigenetics and will continue to play an important role in research and may lead to new fundamental findings," says Prof. Marx.

New tools for use in molecular biology and diagnostics

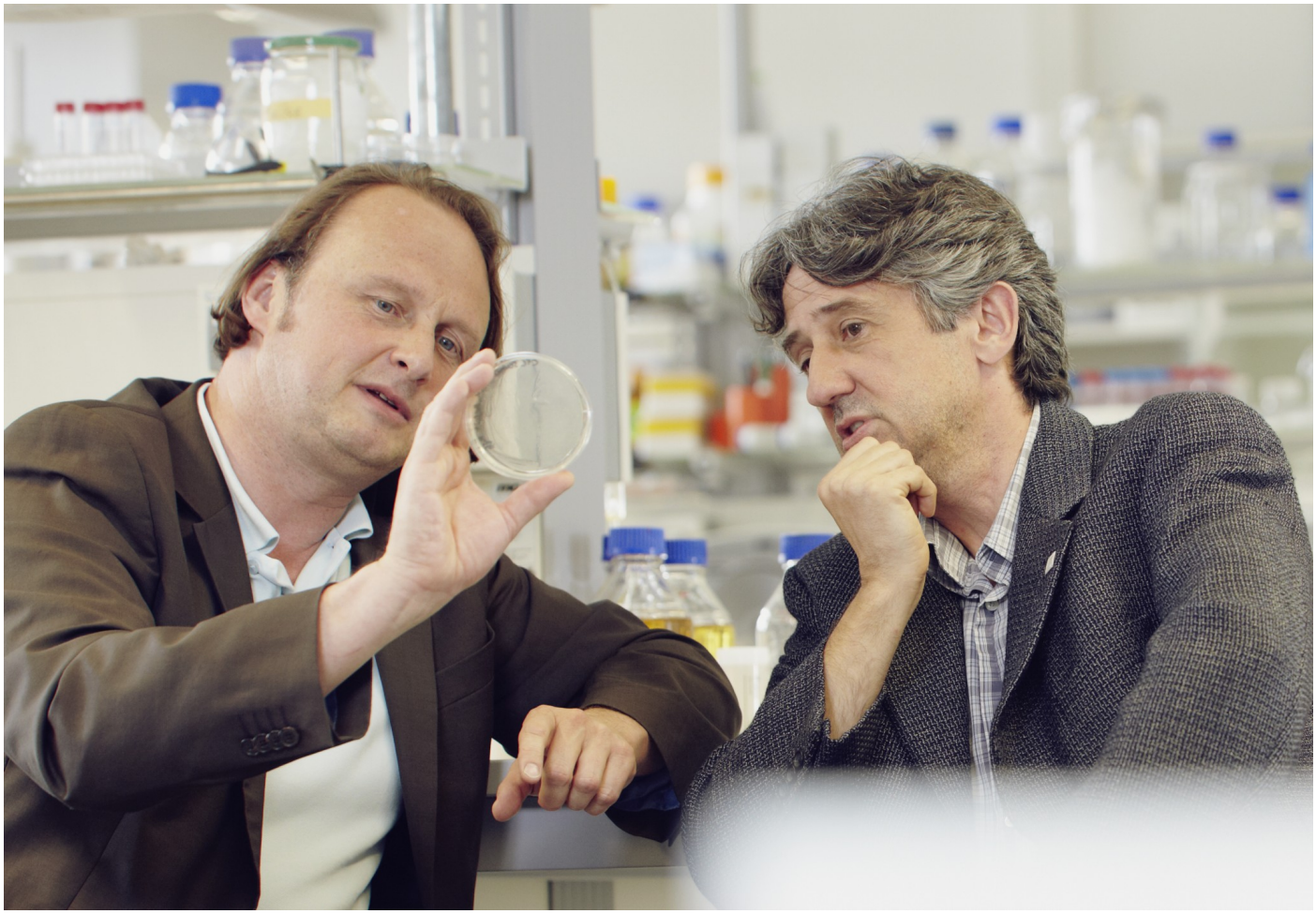
Andreas Marx's interest in DNA polymerases is not only due to their pivotal role in the synthesis of DNA. They also have great practical applications and have become an integral part of molecular biology laboratories. "Polymerases are used in polymerase chain reactions (PCR), a biochemical technology used for cloning procedures and diagnostic applications. Most high-throughput sequencing methods also require the use of DNA polymerases," explains Prof. Marx who has always been interested in combining basic research with practical applications. Another research project therefore focuses on the development of new biotechnological applications. Marx uses combinatorial enzyme design and directed evolution to enable the generation of new enzymes. "Nature has not evolved polymerases for modern applications in molecular diagnostics and other fields, and this is where we want to start our research," says Marx. In many cases, biological issues require the development of suitable chemical agents, and, in this case, of suitable polymerases. Researchers can produce enzymes by carrying

out sequential rounds of random mutagenesis and screening; they can create new polymerases that are better suited for certain applications than existing ones or polymerases that catalyse reactions that cannot be targeted with the standard arsenal of methods.

Made-to-measure polymerases for any application whatsoever

In addition to his research and university work, Andreas Marx has recently entered the world of business. Together with his former PhD student, Marx established the start-up company myPOLS Biotec UG that develops and sells customised enzymes for use in flu diagnosis and the identification of single nucleotide variations (found in mutations, single nucleotide polymorphisms). The company enables Prof. Marx to focus wholeheartedly on the application of polymerases. "To bring an invention to market has always appealed to me. At conferences, many scientists would come up to me and ask whether they could buy our polymerases," explains Marx. The foundation of the company was therefore a logical continuation of his interests. However, he needed the right partner for it to be successful. "I have found a business partner and I look forward to our future cooperation," says Marx who cannot foresee himself pursuing a career solely in industry. "The work of a professor at a university where I can teach and do research suits me perfectly and is also important for me," says Marx.

Talent factory for interdisciplinary research



Prof. Dr. Andreas Marx talking with Prof. Dr. Martin Scheffner (University of Konstanz), a well-known ubiquitin expert.
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Marx is not only active in his own department, but is also the coordinator of the Graduate School Chemical Biology. He knows from his own experience that excellent supervision is important. "My supervisors of my diploma and PhD theses and my postdoctoral and habilitation work sparked my enthusiasm for research and have given me all the freedom I needed to pursue my research interests independently," says Marx who was appointed professor at Konstanz University at a relatively young age.

With the establishment and coordination of the graduate school, Marx, together with colleagues from the departments of biology, chemistry and computer sciences, helps young and motivated scientists to meet in an interdisciplinary environment during their doctorate. "This helps them to understand the research issues and approaches used by their colleagues in other disciplines, something which is crucial for being able to successfully deal with interdisciplinary research topics," concludes Marx.

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