PRESS RELEASE

Designer organelles in cells produce synthetic proteins

Mainz, 29 March 2019. *A research team led by biophysical chemist Professor Edward Lemke has engineered a designer organelle in a living mammalian cell in a new complex biological translation process. The created membraneless organelle can build proteins from natural and synthetic amino acids carrying new functionalities. For example, scientists might incorporate fluorescent building blocks into proteins via the organelle that allow a glimpse inside the cell using imaging methods. The research work now published in* Science *was a collaboration of Johannes Gutenberg University Mainz (JGU), the Institute of Molecular Biology (IMB) and the European Molecular Biology Laboratory (EMBL).*

Organelles are compartments in cells that, like the nucleus or the mitochondria, perform specific functions. The Lemke group has now created a new compartment in which special proteins can be synthesised. "Figuratively speaking, we look for a corner in the cell where we build our house and then bring in some of the ribosomes that are present in the cell," explained Professor Edward Lemke. The biosynthesis of proteins takes place at the ribosomes. Using the genetic code, the messenger RNA (mRNA) is translated into the sequence of amino acids for the protein to be newly formed.

Translation is a very complex process that cannot easily be contained in an organelle surrounded by a membrane. Therefore, Lemke's team drew inspiration for creating the designer organelle from phase separation, i.e., the process responsible for the formation of membraneless organelles *in vivo*, such as nucleoli or stress granules. Cells use phase separation to concentrate specific proteins and RNAs locally as well as to build new membraneless compartments. "Our membraneless organelle is virtually an open reaction centre," said Lemke.

This allows protein biosynthesis to occur in a well-defined place, which is important for working with synthetic amino acids. Researchers have already been able to create a new protein with the help of a synthetic, non-natural amino acid. However, incorporating the protein nonspecifically throughout the cell causes high cellular stress and the cell may be severely affected. The new orthogonal translation method avoids this problem.

"Our organelle can make proteins by using synthetic non-canonical amino acids. Currently, we know of more than 300 different non-canonical amino acids – compared to 20 naturally occurring. This means that we are no longer restricted to the latter ones," said Gemma Estrada Girona, who together with Christopher Reinkemeier is the first author of the *Science* paper. Human proteins consist of the 20 naturally occurring, so-called canonical amino acids. In addition, there are a number of non-canonical amino acids, which are not found in regular human proteins. However, the extension of the genetic code allows the incorporation of these non-canonical amino acids and the new designer organelle is able to expand the genetic code selectively. This translates the RNA differently within the organelle than in the rest of the cell. "We have taken nature as our model, especially the membraneless nucleolus, which is involved in the synthesis of RNA in the nucleus," explained Lemke. "We were surprised that we can actually build such a complicated structure and function with just a few steps."

The new concept may serve as a platform for the design of other organelles and the building of semisynthetic cells and organisms. "Our tool can be used to engineer translation and maybe other cellular processes like transcription and post-translational modifications, too. This might even allow us to engineer new types of organelles that extend the functional repertoire of natural complex living systems," said Christopher Reinkemeier.

Designer organelles combine the fields of biology and chemistry to achieve a completely new functionality. One field of application is the aforementioned fluorescence method in imaging, another could be in the production of antibodies for therapeutic purposes. First of all, Lemke and his group aim to engineer minimal designer organelles to minimize the impact on the physiology of the healthy organism.

Edward Lemke is Visiting Group Leader at the European Molecular Biology Laboratory, Professor of Synthetic Biophysics at Johannes Gutenberg University Mainz, and Adjunct Director at the Institute of Molecular Biology. He also coordinates the new Priority Program "Molecular Mechanisms of Functional Phase Separation" (SPP 2191), funded by the German Research Foundation.

Further details
Edward Lemke is an Adjunct Director at IMB and Professor of synthetic biophysics at Johannes Gutenberg University Mainz. Further information about research in the Lemke lab can be found at www.imb.de/research/Lemke. The paper mentioned in this work can be found at https://science.sciencemag.org/content/363/6434/eaaw2644. The original press release by JGU can be found here www.uni-mainz.de/presse/aktuell/7942_ENG_HTML.php.

About the Institute of Molecular Biology gGmbH
The Institute of Molecular Biology gGmbH (IMB) is a centre of excellence in the life sciences that was established in 2011 on the campus of Johannes Gutenberg University Mainz (JGU). Research at IMB focuses on three cutting-edge areas: epigenetics, developmental biology, and genome stability. The Institute is a prime example of successful collaboration between a private foundation and government: The Boehringer Ingelheim Foundation has committed 154 million euros to be disbursed from 2009 until 2027 to cover the operating costs of research at IMB. The State of Rhineland-Palatinate has provided approximately 50 million euros for the construction of a state-of-the-art building and will give further 52 million in core funding from 2020 until 2027. For more information about IMB, please visit: www.imb.de.

About Johannes Gutenberg University Mainz
Johannes Gutenberg University Mainz (JGU) is a globally recognized research-driven university with around 31,500 students. Its main core research areas are in particle and hadron physics, the materials sciences, and translational medicine, while its most outstanding research achievements in the humanities have been attained in the fields of American Studies and Historical Cultural Studies. JGU's academic excellence is reflected in its success in the Excellence Initiative of the German federal and state governments: In 2012, the university's Precision Physics, Fundamental Interactions and Structure of Matter (PRISMA) Cluster of Excellence was approved and the funding of its Materials Science in Mainz (MAINZ) Graduate School of Excellence was extended. Moreover, excellent placings in national and international rankings, as well as numerous other honors and awards, demonstrate just how successful Mainz-based researchers and academics are. Further information at www.uni-mainz.de/eng.

Boehringer Ingelheim Foundation
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