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# Decoding the structure of the huntingtin protein

**25 years ago, the cause of Huntington's disease was discovered. Mutations on a single gene, the huntingtin gene, lead to an incorrect form of the correspondent protein. With the help of cryo-electron microscopy, the recently awarded Nobel Prize winning method, researchers have now decoded the three-dimensional, molecular structure of the healthy human huntingtin protein. This now enables its functional analysis. An improved understanding of the structure and the function of the huntingtin protein could contribute to the development of new treatment methods in the future. The work of the researchers from the Max Planck Institute of Biochemistry in Martinsried and Ulm University has now been published in the journal *Nature*.**

Huntington's disease often begins with emotional disturbances and is characterized by involuntary muscle movement and loss of mental ability. Until today, the neurological disease is one of the hereditary diseases still incurable and fatal. The protein HTT, also called huntingtin, plays the central role in Huntington's disease. For 25 years it has been known that mutations of the huntingtin gene, which is the blueprint for the same protein, cause Huntington's disease.

Although researchers have worked on it for many years, there are still many hurdles to overcome. Now Rubén Fernández-Busnadiego from the Department of Molecular Structural Biology at the MPI of Biochemistry and Stefan Kochanek, head of the Department of Gene Therapy at the University Hospital Ulm, have succeeded in decoding the molecular, three-dimensional structure of the huntingtin protein.

**Overcome hurdle**

Stefan Kochanek and his team have been working on the production and purification of huntingtin for a long time. What has prevented a detailed analysis of the protein in recent decades? Fernández-Busnadiego, an expert in cryo-electron microscopy, mentions two main factors: "First of all, cryo-electron microscopy has only been optimized in recent years to look at protein structures with almost molecular resolution. The second reason is that the huntingtin protein is very flexible in its structure. Just now, we have found also a solution for this problem." During the analysis, pictures of the protein are being taken from different perspectives under the microscope. The three-

dimensional molecular structure can be computed from the large number of resulting images. For this, the protein must always be in the same conformation. Fernández-Busnadiego explains: "This would be similar to a person being photographed in the dark. If the person does not stand still for a while, the shot will be blurry."

To get a clear picture, the researchers in the Kochanek lab have been looking for other proteins that interact with huntingtin and stabilize it. That worked for the protein HAP40. "Huntingtin in connection with HAP40 is stabilized in a particular conformation. Thus, averaged over many pictures, we were able to derive the three-dimensional structure," said Kochanek. "If we remain in the analogy of the photo in the dark, then the protein acts like a chair for the photographed person. Sitting on it, the person moves much less and the image is much sharper with the same exposure time," adds Fernández-Busnadiego.

**Why is the three-dimensional structure of huntingtin needed?**
"Although we have known for some time that the mutation of the huntingtin gene has severe consequences, we still know relatively little about the function and tasks of the healthy protein," explains Kochanek. Proteins are the molecular machines of the cell. In order to fulfill their versatile tasks, they have a certain three-dimensional structure, similar to a specific component in a machine. "Now that we know the exact structure of huntingtin, we can further study which areas of huntingtin are particularly important and how other proteins cooperate with huntingtin functionally. In this way structures could be deduced to be targeted therapeutically by certain drugs."

Right now, there is a lot going on in Huntington's disease research. Great hope is directed to a method, that mutes the huntingtin gene with so-called Antisense-Oligonukleotiden (ASO) for the treatment of Huntington’s disease. These small molecules reduce the formation of huntingtin proteins in the cells, but the drug cannot differentiate between the normal and the pathologically altered huntingtin protein. Also for this reason, it is important to learn more about the function of the healthy huntingtin protein. Kochanek confidently looks into the future: “The decoded structure will bring us a big step ahead”.
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**Comment from the clinician**
Bernhard Landwehrmeyer is the Director of the Huntington Outpatient Clinic of the Neurology Department at the University Medical Center Ulm and heads the world's largest international cohort study on Huntington's disease (with more than 16,000 participants): "Identifying the structure of huntingtin is a huge step forward for the many families hoping for effective treatment for Huntington's disease. The illness partly arises due to new characteristics of the pathologically changed huntingtin gene products that are the result of the HD mutation, but also in part as a consequence of impaired normal functioning of huntingtin. Now – armed with the knowledge of the architecture of huntingtin – questions about the normal function of huntingtin can be clarified in a


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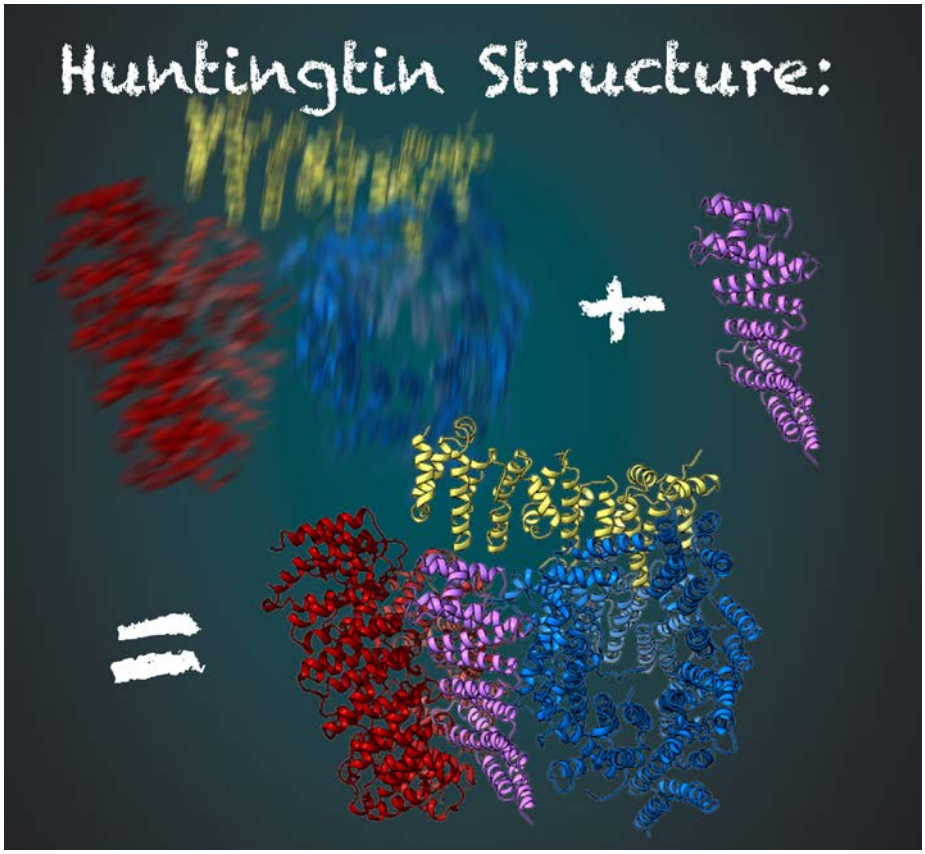
much quicker and more tightly focused way, and tailored drugs can be developed that promote normal function."

“The antisense oligonucleotide (ASO) treatment trials are presently only conducted at very few clinics; the Neurological University Clinic Ulm leads the drug testing for Germany. Some of the currently reviewed ASOs reduce both the formation of the normal and the mutant huntingtin protein, while other ASOs predominantly seek to lower the altered huntingtin. It is currently unclear whether a partial inhibition of the formation of normal huntingtin protein has disadvantages and is tolerated without undesirable side effects. This is yet another reason why it is important to learn more about the normal function of the huntingtin protein. To this end, the study published in the journal *Nature* will make an important contribution."




**Caption**

The protein huntingtin consists of three flexible regions, shown in red, yellow and blue. Together with its interaction partner HAP40, shown in purple, huntingtin is more stable. This enabled the scientists to deduce their three-dimensional structure using cryo-electron microscopy.

Illustration: Gabriele Stautner, ARTIFOX © Max Planck Institute of Biochemistry

**Original publication:**

Q. Guo, B. Huang, J. Cheng, M. Seefelder, T. Engler, G. Pfeifer, P. Oeckl, M. Otto, F. Moser, M. Maurer, A. Pautsch, W. Baumeister, R Fernández-Busnadiego and S. Kochanek: The cryo-EM structure of huntingtin, Nature, February 2018
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**About Rubén Fernández-Busnadiego**

Rubén Fernández-Busnadiego studied physics at the Universidad Complutense de Madrid in Spain. In 2010, he earned a PhD in Chemistry at the Technical University of Munich. Fernández-Busnadiego spent two years as a postdoctoral fellow at Yale University School of Medicine in New Haven, CT, USA. Since 2013, he is project group leader in the Department of Molecular Structural Biology of Wolfgang Baumeister. Fernández-Busnadiego and his team investigate the structural basis of toxic protein aggregation in neurodegenerative diseases at unprecedented resolution using novel microscopy techniques. For his work, he was awarded the FEBS Anniversary Prize in 2017.

**About Stefan Kochanek**

Stefan Kochanek studied medicine at the University of Cologne, followed by a three and a half year clinical work in internal medicine. After completing a scientific education at the Institute for Genetics of the University of Cologne with studies on the importance of DNA methylation, he worked for four years at the Institute for Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, clinically in the field of human genetics and scientifically in the field of gene therapy. Afterwards, he worked as group leader at the Center for Molecular Medicine (ZMMK) of the University of Ulm. Since 2003 he is head of the gene therapy department of the University of Ulm. His main research interests include gene therapy of congenital and acquired diseases and fundamental research of various neurodegenerative diseases, including Huntington's disease.
(https://www.uniklinik-ulm.de/abteilung-gentherapie.html)

**ToPAG**

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's are characterized by toxic protein deposits in particular regions of the brain. How exactly these aggregates damage nerve cells and lead to their death is the main focus of the ToPAG (Toxic Protein AGgregation in neurodegeneration) consortium, an association of scientists from the Max Planck Institutes in Martinsried outside Munich. This interdisciplinary research project is led by the departments of Ulrich Hartl, Wolfgang Baumeister and Matthias Mann at the MPI of Biochemistry and Rüdiger Klein at the MPI of Neurobiology. They combine biochemical, cell biological, systems biology and structural approaches to obtain a comprehensive understanding of the basic cellular mechanisms by which protein aggregation causes cellular toxicity and disease.ToPAG is supported by the European Research Council (ERC). (http://www.topag.mpg.de)

**The Max Planck Institute of Biochemistry**

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top-level basic research. As one of the largest Institutes of the Max Planck Society, about 800 employees from 45 nations work here in the field of life sciences. In currently about 35 departments and research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus in close



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proximity to the Max Planck Institute of Neurobiology, a Helmholtz Center, the Gene-Center, several bio-medical faculties of the Ludwig-Maximilians-Universität München and the Innovation and Founding Center Biotechnology (IZB). (http://biochem.mpg.de)

**About the University of Ulm**

The University of Ulm, the youngest in Baden-Württemberg, was founded in 1967 as a medical and natural science university. Since then, the range of subjects has been significantly expanded. The presently around 10,000 students are spread across four faculties ("Medicine", "Natural Sciences", "Mathematics and Economics" and "Engineering, Computer Science and Psychology"). The University of Ulm is the engine and center of the Science City, in which a diverse research environment of clinics, technology companies and other institutions have developed. The research focuses of the university are life sciences and medicine, biotechnology, nano- and energy materials, financial services and their mathematical methods, as well as information, communication and quantum technologies. In the Times Higher Education Young University ranking, the University of Ulm 2017/18 is the best German university under 50 years and among the top 10 worldwide.