Inhibition of meprin β enzyme, linked to the development of Alzheimer's disease, analyzed

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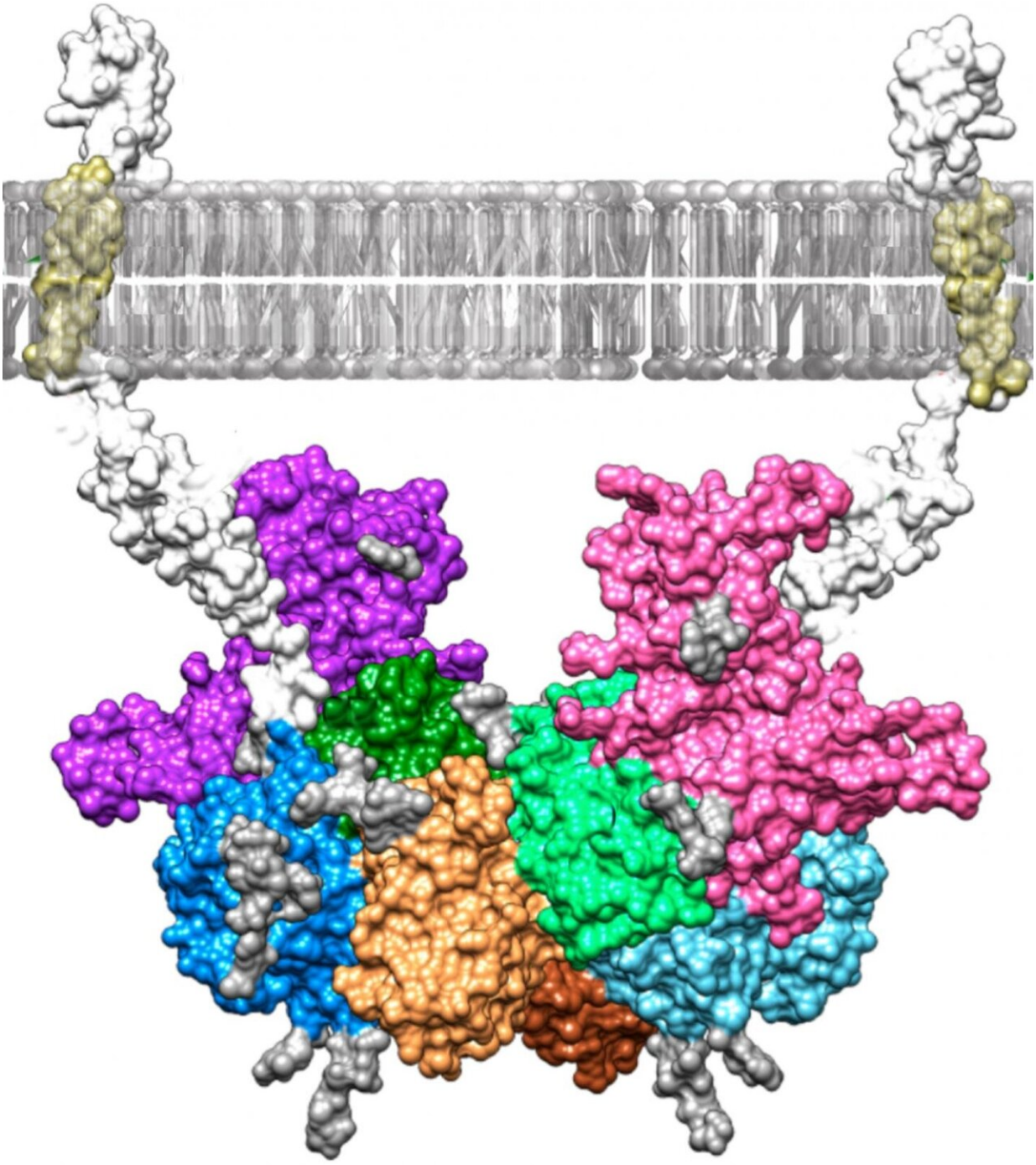

Model of the molecular complex that results when the blood plasma protein fetuin-B (purple and pink) binds with the enzyme meprin β (other colors) Credit: Walter Stöcker

Researchers at Johannes Gutenberg University Mainz (JGU) in Germany and the Institute of Molecular Biology of Barcelona in Spain have discovered how the blood plasma protein fetuin-B binds to the enzyme meprin β and used a computer model to visualize their findings. These results could lead to the development of new drugs to treat serious diseases such as Alzheimer's and cancer. Meprin β releases proteins from cell membranes, thus controlling important physiological functions in the human body. However, a dysregulation of this process can trigger the development of Alzheimer's and cancer. Meprin β is regulated by fetuin-B binding to the enzyme when required, thereby preventing the release of other proteins. Presenting their findings in the journal *Proceedings of the National Academy of Sciences*, the researchers are now the first to describe this binding in detail.

The team at Mainz University produced both meprin β and fetuin-B in insect cells and then allowed them to react with one other in a test tube. By means of measurement of enzyme kinetics and biophysical analyses, the researchers determined that this reaction resulted in an exceptionally stable, high-molecular-mass complex. Their colleagues in Barcelona subsequently managed to crystallize the complex and determine its three-dimensional structure using X-ray crystallography. This involved X-rays being fired at the protein crystals, which allowed the atomic structure of the crystals to be calculated from the diffraction of the X-rays. A computer model of the structure was then generated.

"Thanks to the model, we can now see exactly how meprin β and fetuin-B bind together," said Professor Walter Stöcker, who conducted the research at JGU together with Dr. Hagen Körschgen and Nele von Wiegen. "This research represents an excellent starting point for gaining a better understanding of diseases such as Alzheimer's and for developing the drugs to combat them." Meprin β is already known to be involved in the formation of so-called beta-amyloid plaques, which are a characteristic feature of the condition. Moreover, people with

Alzheimer's disease have relatively little fetuin-B in their blood, which in turn may lead to a lack of regulation of meprin β. "If it is possible to develop a drug that binds to the enzyme and inhibits it in a similar way to fetuin-B, this could be a new way of treating Alzheimer's," concluded Stöcker.

More information: Ulrich Eckhard et al, The crystal structure of a 250-kDa heterotetrameric particle explains inhibition of sheddase meprin β by endogenous fetuin-B, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2023839118

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