ClpX-ClpP protein complex could be starting point for new antibiotics

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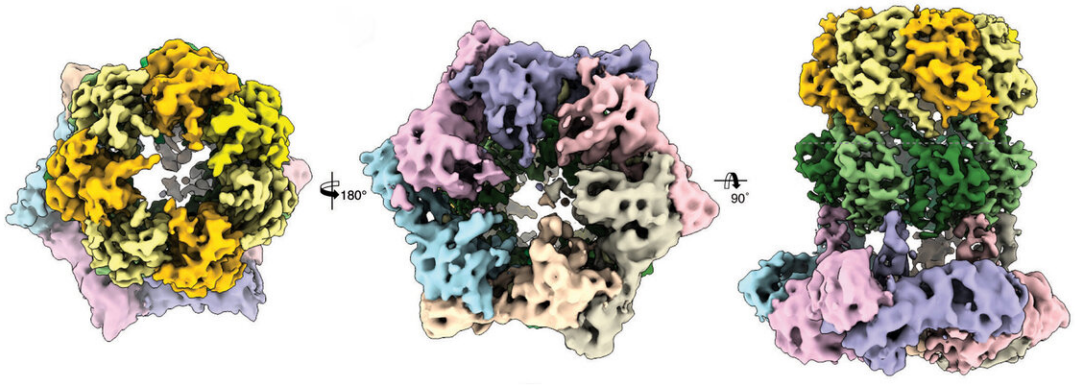


A research team from the Technical University of Munich and the Max Planck Institute of Molecular Physiology has elucidated the structure of the proteolytic complex ClpX-ClpP. This is a key to development of innovative antibiotics which target the degradation process of defective proteins in bacteria. Credit: Dr. Christos Gatsogiannis / MPI of Molecular Physiology

Antibiotics are still the most important weapon for combating bacterial infections. But medical science is running out of ammunition because of more and more frequently occurring resistances. Scientists from the Technical University of Munich and the Max Planck Institute of Molecular Physiology have now elucidated the structure of the proteolytic complex ClpX-ClpP. This is a key to the development of innovative antibiotics that target the degradation process of defective proteins in bacteria.

Almost 700,000 people in Europe suffer from infections of antibiotic-resistant pathogens every year; approximately 33,000 of them die. Despite this globally increasing danger, very few new antibiotics have been developed and approved in the past few decades. It is urgently necessary to find new points of attack in pathogenic bacteria and to develop new antibiotics that exploit these weak spots.

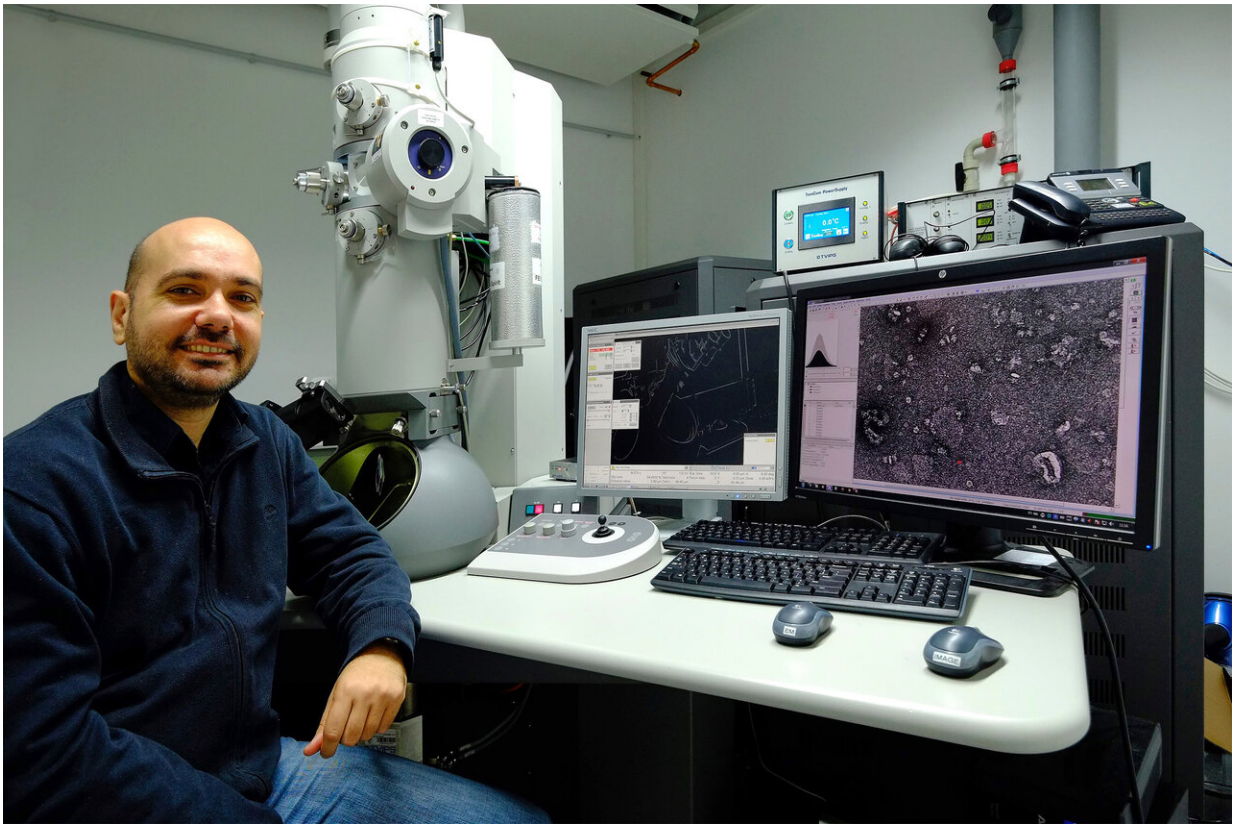
New mechanism of action destroys bacteria

A particularly promising point of attack for antibacterial therapies is the proteolytic enzyme ClpP: on the one hand, it plays an important role in bacterial metabolism, and on the other hand, it ensures the controlled degradation of defective proteins.

But for this purpose, it requires the ClpX protein as a starting aid. In the complex with ClpP, ClpX identifies the proteins that should be degraded, unfurls them, and guides them into its barrel-like degradation chamber.

Scientists in the groups led by Prof. Stephan Sieber, Technical University of Munich (TUM) and Prof. Stefan Raunser, director at the Max Planck Institute of Molecular Physiology in Dortmund, have now elucidated the three-dimensional structure of the ClpX-ClpP proteolytic complex for the first time and have established an important basis for

future pharmacological strategies.



Dr. Christos Gatsogiannis, researcher in the group led by Prof. Stefan Raunser at the MPI of Molecular Physiology, has now elucidated the structure of the ClpX-ClpP complex. The clarification of this mechanism by the research teams from Dortmund and Munich is a milestone on the way to the development of innovative antibiotic substances targeting ClpP. Credit: Christian Luenig / MPI of Molecular Physiology

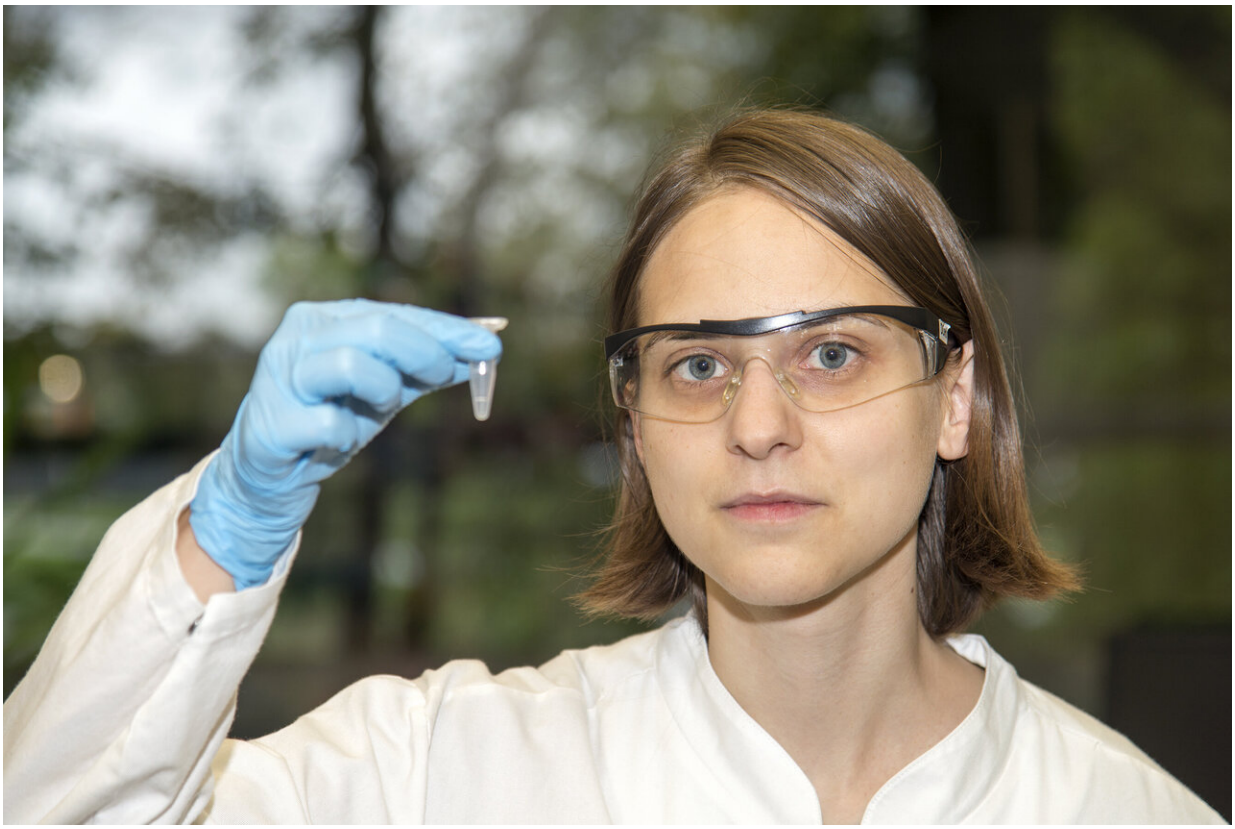
A new class of potential antibiotics—the so-called acyldepsipeptide (ADEP) antibiotics—also brings about an uncontrolled degradation through ClpP without the support of ClpX. As a result, vital proteins are also destroyed, with lethal consequences for the bacteria.

This unique mechanism of action has considerable innovation potential in the fight against pathogenic bacteria. Whereas common antibiotics act through the inhibition of vital processes, in this case, the antibacterial effect is achieved through the activation of a process.

Disarming bacteria

In addition to the degradation of defective proteins, ClpP is also a decisive regulator in the production of an arsenal of bacterial toxins that are primarily responsible for the pathogenic effect of many pathogens.

At the TUM, the group led by Prof. Stephan Sieber has been researching the ClpP protease for years, and has already developed a large number of potent inhibitors against ClpP and ClpX that stop the production of bacterial toxins and can therefore more or less disarm them. Dóra Balogh has now managed to produce and stabilize the ClpX-ClpP complex.



The proteolytic enzyme ClpP plays an important role in bacterial metabolism and ensures the controlled degradation of defective proteins. It is therefore a particularly promising point of attack for future antibacterial therapies. Dora Balogh, member of the research group of Prof. Dr. Stephan Sieber at the Technical University of Munich, managed to produce and stabilize the ClpX-ClpP complex for the first time. Credit: Andreas Battenberg / TUM

But until recently, the structure of the ClpX-ClpP complex could not be elucidated in detail. Dr. Christos Gatsogiannis, researcher in the group led by Prof. Stefan Raunser at the MPI of Molecular Physiology, has now managed this by means of cryogenic electron microscopy.

With this technology, they were able to demonstrate that ADEP and ClpX dock onto ClpP at the same spot, but control the process of protein

degradation in a different way: Whereas ClpX does not lead to an alteration in the structure of ClpP, ADEP brings about an unintended opening of the complex. As a result, intact proteins are also degraded in an uncontrolled manner and without the support of ClpX.

The clarification of this mechanism by the research teams from Dortmund and Munich is a milestone on the way to the development of innovative antibiotic substances targeting ClpP.

More information: Christos Gatsogiannis et al, Cryo-EM structure of the ClpXP protein degradation machinery, *Nature Structural & Molecular Biology* (2019). DOI: 10.1038/s41594-019-0304-0

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