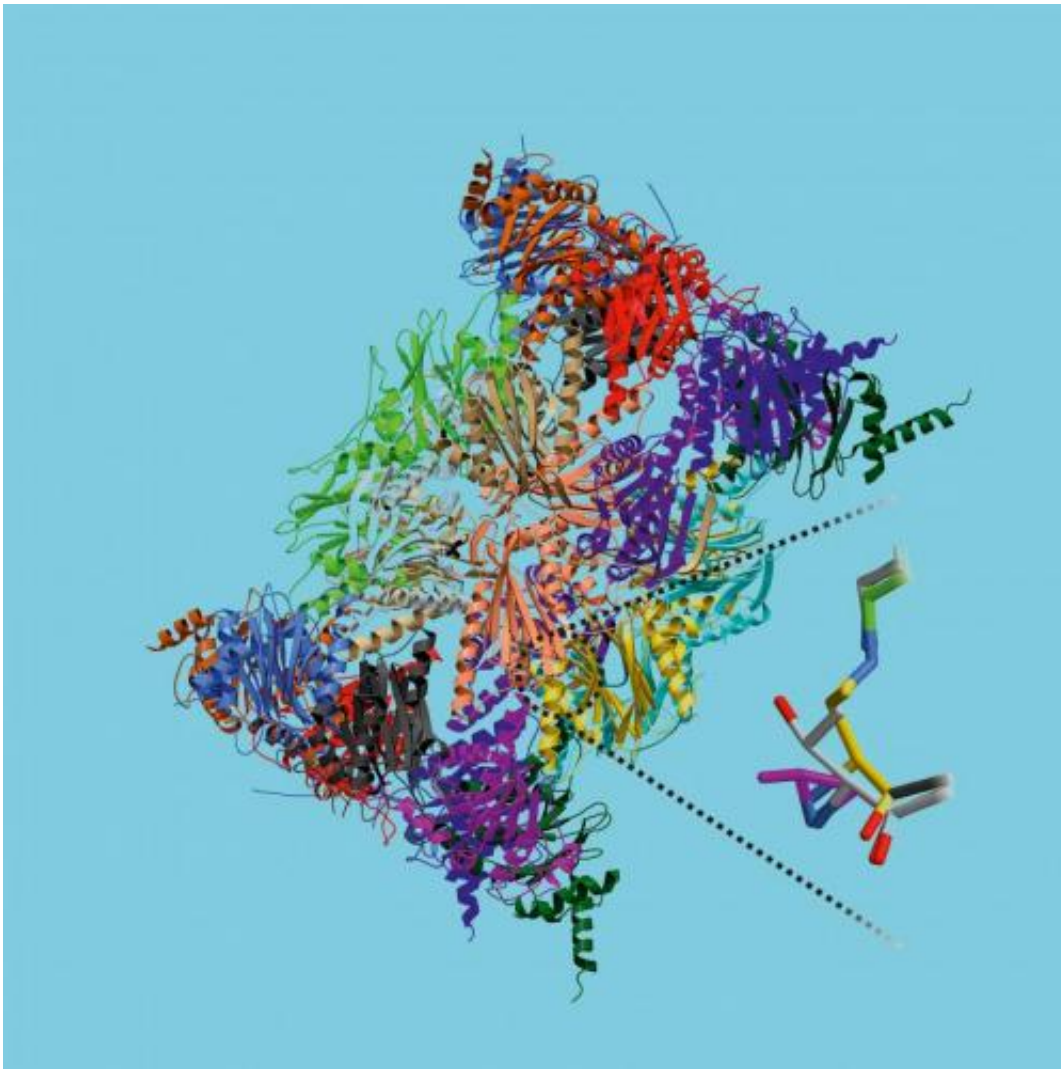


Spot on against autoimmune diseases and chronic inflammations

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Based on structural data of the immunoproteasome researchers at Technische Universität München found an inhibitor, which selectively inactivates the immunoproteasome without influencing the constitutive proteasome. Credit: Prof. Michael Groll / TUM

Multiple sclerosis, type 1 diabetes and lupus are autoimmune diseases in which the immune cells can no longer differentiate between friend and foe and thus attack the body's own tissue. Here, the immunoproteasome, which supplies the immune system with information on processes within the cell, plays a central role. Chemists at Technische Universität München have now discovered a way to inhibit its functionality, thereby laying the foundation for possible optimizations of existing medications.

The [immune system](#) functions as the body's police force, protecting it from intruders like bacteria and viruses. However, in order to ascertain what is happening in the cell it requires information on the foreign invaders. This task is assumed by so-called immunoproteasomes. These are cylindrical protein complexes that break down the protein structures of the intruders into fragments that can be used by the defense system.

"In [autoimmune disorders](#) like rheumatism, [type 1 diabetes](#) or [multiple sclerosis](#) as well as severe inflammations a significantly increased immunoproteasome concentration can be measured in the cells," explains Prof. Michael Groll at the TUM Chair of Biochemistry. "The deactivation of this degradation machinery suppresses the regeneration of immune signaling molecules, which, in turn, prevents an excessive immune reaction."

Subtle but significant differences

For some time now, scientists have been on the lookout for new active substances that block immunoproteasomes in a targeted manner without inhibiting the so-called constitutive proteasomes also present in cells. They break down defective or no longer required proteins and are thus responsible for cellular recycling. Notably cell death occurs, when both the constitutive proteasomes and the immunoproteasomes are

inactivated.

In early 2012 the research team led by Groll fulfilled a prerequisite for designing specific active substances: They solved the crystal structure of the immunoproteasome, allowing them to spot the subtle but significant differences between the otherwise nearly identical structures.

Special mode of action

The potential drug that the researchers developed is based on the epoxyketon ONX 0914, an immunoproteasome inhibitor that is already used in clinical trials. The scientists replaced the epoxyketon with a sulfonylfluoride group and modified its positioning on the inhibitor. The result was a new compound that selectively inhibits the immunoproteasome without influencing the constitutive proteasome.

First author Christian Dubiella explains what makes the discovered mechanism so special: "Normally inhibitors clog up the active center of the enzyme and thereby disable its functionality. The substance synthesized by us, however, attaches to its target, causing the active center to destroy itself, and then gets detached after successful inactivation." Especially the insights into the atomic mechanisms that were uncovered using X-ray structure analysis open the door to the custom-tailored development of immunoproteasome inhibitors. This may pave the road for a future generation of medications.

More information: Selective Inhibition of the Immunoproteasome by Ligand-Induced Crosslinking of the Active Site, Christian Dubiella, Haissi Cui, Malte Gersch, Arwin J. Brouwer, Stephan A. Sieber, Achim Krüger, Rob M. J. Liskamp, Michael Groll, *Angewandte Chemie*, Early view, September 22, 2014 – [DOI: 10.1002/anie.201406964](https://doi.org/10.1002/anie.201406964)

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