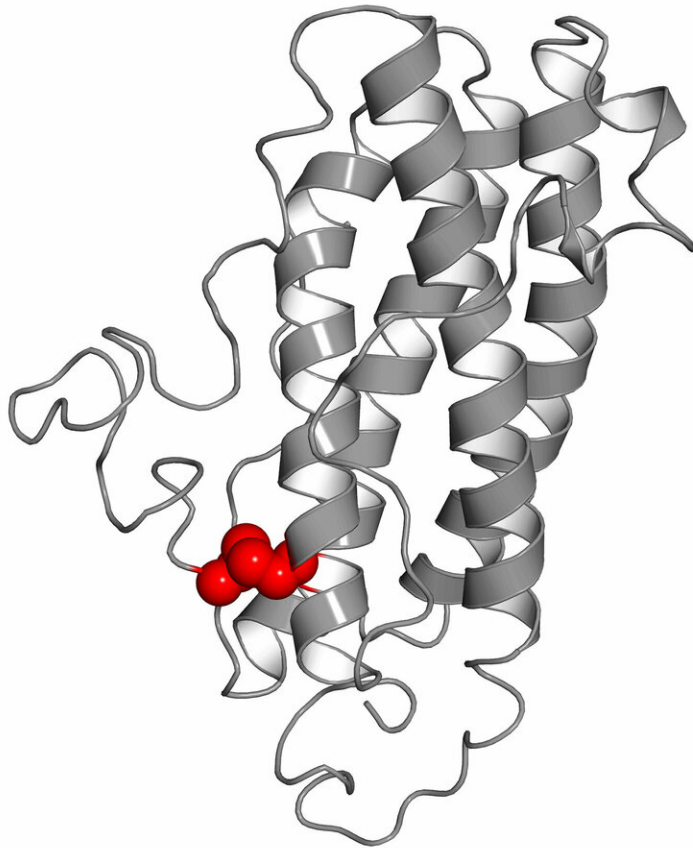


Evolution of signaling molecules opens door to new sepsis therapy approaches

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This the modified human interleukin-27-alpha. Inspired by the murine interleukin-27-alpha, one amino acid has been exchanged, enabling the formation of a disulfide-bridge (marked in red). Credit: Matthias Feige / TUM

Minor infections can become fatal: Millions of people die each year from sepsis, an overreaction of the immune system. A new immune signaling molecule designed by a research team from the Technical University of Munich (TUM) now provides the basis for potential new approaches in sepsis therapy.

According to estimates by the World Health Organization (WHO), around 6 million people die every year from sepsis. The disease, sometimes called "[blood poisoning](#)," normally starts with a harmless infection; it then triggers an excessive reaction of the immune system, damaging the body's own tissue. The overreaction eventually leads to a life-threatening collapse of immune defenses. In Germany alone, more people die of sepsis than of AIDS, colon cancer and breast cancer combined.

An interdisciplinary team from the fields of structural biology, immunology and [cell biology](#) has now successfully produced a protein that could balance the overshooting immune response.

The language of immune cells

In their work, the scientists were inspired by evolution. They noted that mice are well protected from sepsis by their immune systems. Here, interleukins, messengers that mediate communication between the cells of the immune system, play a key role.

"Interleukins are the vocabulary with which [immune cells](#) communicate," explains Matthias Feige, professor of cellular protein biochemistry at the Technical University of Munich. The cells form these messenger molecules according to a very specific blueprint of individual amino acids. Their arrangement determines which three-dimensional structure an [interleukin](#) adopts, and consequently, which information it transmits.

Humans and mice have similar, yet different interleukins. The researchers discovered one striking difference in interleukin-27-alpha. This molecule is released by cells of the mouse immune system, but not by human cells, and regulates immune cell function. "Using computer models and cell biological experiments, we discovered that a single structurally important amino acid defines whether interleukin-27-alpha is released by cells of the immune system," explains Stephanie Müller, the first author of the study. "That gave us an idea about how we can engineer novel human interleukin proteins that are released by cells so that we can produce them biotechnologically."



Stephanie Müller and professor Feige in the Laboratory for Cellular Protein Biochemistry at the Technical University of Munich produced a protein, that

might be the basis for potential new approaches in sepsis therapy. Credit: Andreas Battenberg / TUM

Proteins with new functions from the laboratory

The team then prepared the modified interleukin in the laboratory and tested its biological functions with very encouraging results: The engineered messenger molecule was recognized by [human cells](#). First analyses suggest that it can, indeed, balance an overreaction of the [immune system](#), making it a promising candidate for [sepsis](#) therapy.

"Our approach allowed us to rationally extend the language of immune cells by engineering a key signaling molecule. This provides us with an opportunity to modulate the reaction of immune [cells](#) in a targeted manner. Such a finding was only possible thanks to the close collaboration with immunologists and clinicians from TUM, the Université Sorbonne in Paris and the Helmholtz Zentrum München," says Feige. A patent for the new protein is already pending.

More information: Stephanie I. Müller et al, A folding switch regulates interleukin 27 biogenesis and secretion of its α -subunit as a cytokine, *Proceedings of the National Academy of Sciences* (2019). [DOI: 10.1073/pnas.1816698116](https://doi.org/10.1073/pnas.1816698116)

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