# Researchers discover path to blocking fatal toxins

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A team of researchers at the Hebrew University of Jerusalem says it has found a way to block a group of fatal bacterial toxins that have to date resisted all attempts to arrest them through the use of conventional drugs.

These toxins, called superantigens, are produced by a group of "violent" staphylococcal and streptococcal bacteria. When these bacteria attack humans, they set off an extreme immune reaction described as an "immune storm," that is, an immune response of a magnitude higher in intensity than during a regular immune reaction. The result is often fatal toxic or septic shock brought on by the excessive immune response.

Working to develop the first effective antidote under funding from the Defense Advanced Research Projects Agency of the US Department of Defense and the US National Institutes of Health, the laboratory headed by Prof. Raymond Kaempfer of the Institute for Medical Research Israel Canada (IMRIC) at the Hebrew University Faculty of Medicine, has studied how superantigen toxins engage the immune system. The researchers discovered that in order to exert its harmful action, a superantigen must first bind to a protein on the surface of the human immune cell, a receptor called CD28.

CD28 has been known for a long time as a key participant in every immune response, but its ability to recognize microbial components -- the superantigens -- came as a complete surprise. The Kaempfer team discovered that superantigens do their lethal work by co-opting CD28 as their receptor, and that binding of a superantigen to CD28 is the key in the pathway to an immune storm.

They mapped the regions where the superantigen and CD28 contact each other and found that to induce an immune storm, superantigens must bind specifically into that part of the CD28 molecule where, normally, it pairs with another CD28 molecule.

Using that insight, they next designed decoys, short protein fragments that mimic the contact domain in the superantigen or in CD28. Such decoys, they could show, act as a monkey wrench that blocks the engagement of CD28 receptor by the superantigen toxin, thereby inhibiting the overly strong immune response and protecting animals from the toxic consequences, including from death.

All the superantigen toxins function via the same CD28 receptor, rendering the decoys broadly effective as protective agents. The decoys proved safe in healthy, normal, laboratory animals.

These findings provide a novel therapeutic approach against toxic shock. The decoys are host-oriented therapeutics, directed at the human immune system itself, rather than at the pathogen. Using a host-oriented therapeutic, resistance cannot arise in the infecting bacteria or in the toxins because the decoy targets a human immune receptor that is constant and will not change.

**More information:** The work of Kaempfer and his team will be published in the *PLoS Biology* journal on Sept. 13.

Provided by Hebrew University of Jerusalem