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New agent inhibits *Staphylococcus aureus* toxin – hope for pneumonia patients

Helmholtz Centre for Infection Research develops innovative class of agents to inhibit hospital germs

An international research group led by the Helmholtz Centre for Infection Research (HZI) has discovered a promising new drug candidate against severe lung infections caused by the hospital germ *Staphylococcus aureus*. The study, which has just been published in *Cell Host & Microbe*, describes for the first time how small molecules from the quinoxalinedione class specifically block the bacterial toxin α -hemolysin – a key trigger of tissue damage and inflammation.

Pneumonia caused by the bacterium *Staphylococcus aureus* is one of the most dangerous infections that can occur in hospital. Particularly worrying are multi-resistant strains, against which many antibiotics are no longer effective. These pathogens are widespread worldwide and pose a major challenge even for modern healthcare systems. Despite intensive therapy, mortality among affected patients is over 20 percent.

“Even with effective antibiotics, infections with *Staphylococcus aureus* are often difficult to treat,” says Prof. Mark Brönstrup, senior author of the study and head of the “Chemical Biology” department at the HZI. “Our novel strategy therefore does not attack the bacterium itself, but specifically neutralizes a toxin it produces. This opens up a new therapeutic perspective – especially for critically ill people at high risk.”

The new research approach is aimed at the targeted inhibition of the key virulence factor α -hemolysin. Hemolysin is a protein that forms pores in cell membranes in the lungs, leading to the destruction of lung tissue and immune cells, inflammation and ultimately to a worsening of the disease. The researchers developed a miniaturized test system that allowed them to screen over 180,000 compounds for their ability to block the effect of α -hemolysin. Drug candidates from the quinoxalinedione class, in particular the compound Ho52, proved to be highly effective, both in cell culture and in animal models.

“Our goal was to develop a small molecule that neutralizes the toxin before it causes damage – and that is exactly what the quinoxalindiones do,” says Dr. Aditya Shekhar, first author of the study. “It was particularly impressive that we were not only able to protect cells, but also significantly improve survival in infected mice.”

In the mouse model, the active substance was able to increase the survival rate in the case of an acute lung infection with the highly virulent *S. aureus* USA300 strain, both when administered preventively or therapeutically. At the same time, inflammatory markers and the bacterial load in the lungs of immunocompetent mice were reduced. The combination of Ho52 with the antibiotic linezolid was also effective.

New approaches in the fight against antibiotic resistance

The concept of so-called “pathoblockers”, i.e. agents that target bacterial virulence mechanisms rather than the bacterium itself, is considered a promising approach. Since no selective pressure is exerted on the bacterium, the risk of development of resistance is significantly lower.

“Our results show that even large bacterial toxins can be specifically inhibited by small molecules – this opens doors for a completely new class of anti-infectives,” adds Shekhar. Thanks to good manufacturing options and tolerability, the drug candidate Ho52 could be used in particular as an infusion preparation in hospitals – for example to prevent severe pneumonia in high-risk patients.

The research was carried out mainly at the HZI in Braunschweig and as part of the German Center for Infection Research (DZIF) in close partnership with the Lead Discovery Center (LDC) in Dortmund. The research team received milestone-dependent funding of 4.9 million US dollars to date from the non-profit organization Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X); CARB-X has indicated that further funding may be provided through the end of Phase 1 of the clinical trial based on project progress.

Background: Responsible approach to animal testing

The animal experiments with mice used in this study were carried out in strict compliance with the applicable legal requirements and ethical standards. The aim was to generate meaningful data with as few animals as possible that could contribute to the development of new therapeutic options for seriously ill patients. The insights gained represent an important step towards developing animal-free models and clinical applications in the long term.

About CARB-X:

The “Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator” (CARB-X) is a global, non-profit funding initiative of Boston University that aims to accelerate the development of innovative antibiotics and develop novel therapeutics, vaccines and diagnostics to combat drug-resistant bacterial infections. It supports companies and research institutions that are developing such products in the early phases up to clinical phase I. CARB-X focuses on the dangerous bacteria listed in the priority lists of the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC). Germany, represented by the Federal Ministry of Education and Research (BMBF), has been funding CARB-X since the beginning of 2019 and will continue to support the partnership with a further 40 million euros in the second funding phase starting in 2023. In total, CARB-X has invested approximately 400 million US dollars in 92 projects worldwide since its inception, supporting the largest and most innovative pipeline of preclinical and early-stage products against antibiotic-resistant infections in the world. The work of CARB-X and the portfolio companies it supports is supported by local accelerators. The German Center for Infection Research (DZIF) and its partners, the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI), have established themselves as a CARB-X accelerator within the CARB-X Global Accelerator Network (CARB-X GAN). <https://carb-x.org/>

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This press release and an image is also available on our website: <https://www.helmholtz-hzi.de/en/media-center/news-room/news-detail/new-agent-inhibits-staphylococcus-aureus-toxin-hope-for-pneumonia-patients>.

Helmholtz Centre for Infection Research:

Scientists at the Helmholtz Centre for Infection Research (HZI) in Braunschweig and its other sites in Germany are engaged in the study of bacterial and viral infections and the body's defence mechanisms. They have a profound expertise in natural compound research and its exploitation as a valuable source for novel anti-infectives. As member of

the Helmholtz Association and the German Center for Infection Research (DZIF) the HZI performs translational research laying the ground for the development of new treatments and vaccines against infectious diseases.
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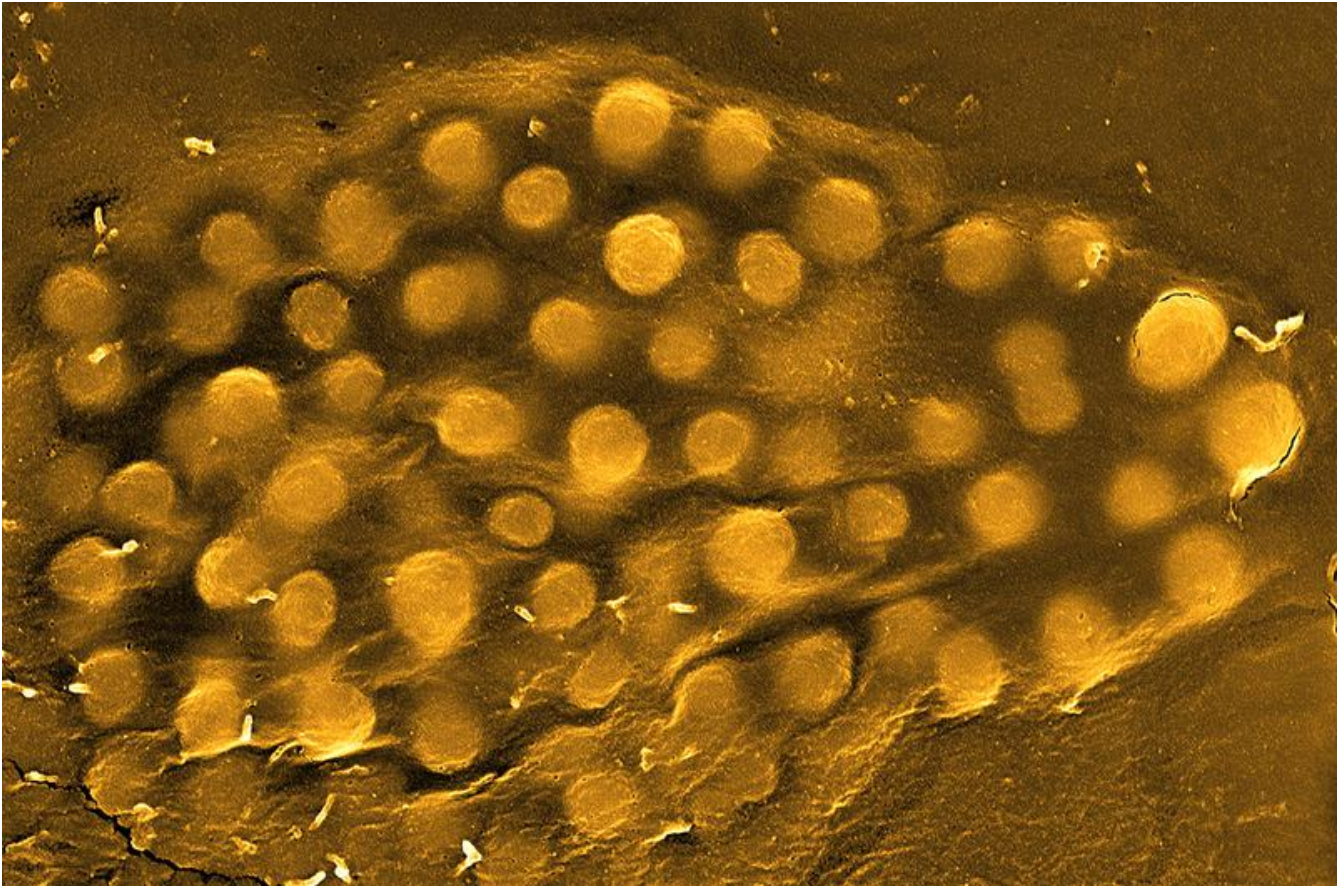
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Invasion of staphylococci into a host cell
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