Treating tuberculosis when antibiotics no longer work

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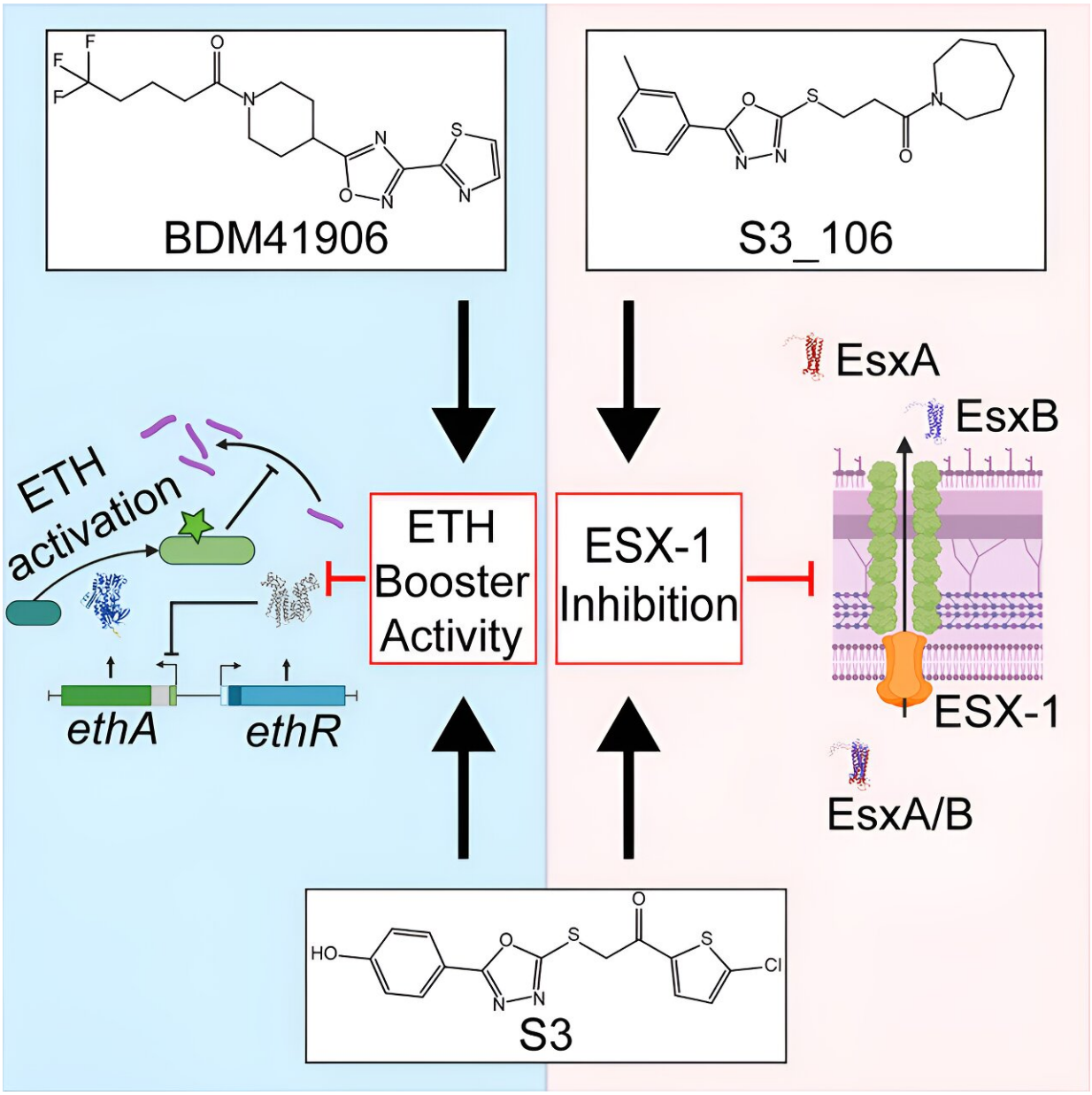

Credit: *Cell Chemical Biology* (2024). DOI: 10.1016/j.chembiol.2023.12.007

Researchers have identified new antibiotic molecules that target Mycobacterium tuberculosis and make it less pathogenic for humans. In addition, some of the discovered substances may allow for a renewed treatment of tuberculosis with available medications—including strains of the bacterium that have already developed drug resistance.

The research is published in an article titled "Discovery of dual-active ethionamide boosters inhibiting the Mycobacterium tuberculosis ESX-1 secretion system" in *Cell Chemical Biology*.

Tuberculosis (TB)—or "consumption," as it used to be called—mainly affects the lungs, but can also damage other organs. If diagnosed early and treated with antibiotics, it is curable. Although the disease is relatively rare in most western European countries, it still ranks among the infectious diseases that claim the most lives worldwide.

According to the World Health Organization (WHO), only COVID-19 was deadlier than TB in 2022. The disease also caused almost twice as many deaths as HIV/AIDS. More than 10 million people continue to contract TB every year. This is mainly due to insufficient access to medical treatment in many countries.

Limited targets

Multidrug-resistant tuberculosis is emerging especially in eastern Europe and Asia. That is of particular concern to researchers because like all bacteria that infect humans, Mycobacterium tuberculosis possesses only a limited number of targets for conventional antibiotics. That makes it increasingly difficult to discover new antibiotic substances in research

laboratories.

Working together with colleagues from the Institute Pasteur in Lille, France, and the German Center for Infection Research (DZIF), the researchers at University Hospital Cologne have now identified an alternative treatment strategy for the bacterium. The team utilized host-cell-based high-throughput methods to test the ability of molecules to stem the multiplication of bacteria in human immune cells: From a total of 10,000 molecules, this procedure allowed them to isolate a handful whose properties they scrutinized more closely in the course of the study.

Double attack

Ultimately, the researchers identified virulence blockers that utilize target structures that are fundamentally distinct from those targeted by classical antibiotics.

"These molecules probably lead to significantly less selective pressure on the bacterium, and thus to less resistance," said Jan Rybniker, who heads the Translational Research Unit for Infectious Diseases at the Center for Molecular Medicine Cologne (CMMC) and initiated the study.

In deciphering the exact mechanism of action, the researchers also discovered that some of the newly identified chemical substances are dual-active molecules. Thus, they not only attack the pathogen's virulence factors, but also enhance the activity of monooxygenases—enzymes required for the activation of the conventional antibiotic ethionamide.

Ethionamide is a drug that has been used for many decades to treat TB. It is a so-called prodrug, a substance that needs to be enzymatically activated in the bacterium to kill it. Therefore, the discovered molecules

act as prodrug boosters, providing another alternative approach to the development of conventional antibiotics.

In cooperation with the research team led by Professor Alain Baulard at Lille, the precise molecular mechanism of this booster effect was deciphered. Thus, in combination with these new active substances, drugs that are already in use against tuberculosis might continue to be employed effectively in the future.

The discovery offers several attractive starting points for the development of novel and urgently needed agents against tuberculosis.

"Moreover, our work is an interesting example of the diversity of pharmacologically active substances. The activity spectrum of these molecules can be modified by the smallest chemical modifications," Rybniker added. However, according to the scientists, it is still a long way to the application of the findings in humans, requiring numerous adjustments of the substances in the laboratory.

More information: Raphael Gries et al, Discovery of dual-active ethionamide boosters inhibiting the Mycobacterium tuberculosis ESX-1 secretion system, *Cell Chemical Biology* (2024). DOI: 10.1016/j.chembiol.2023.12.007

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