New hope in the fight against tuberculosis

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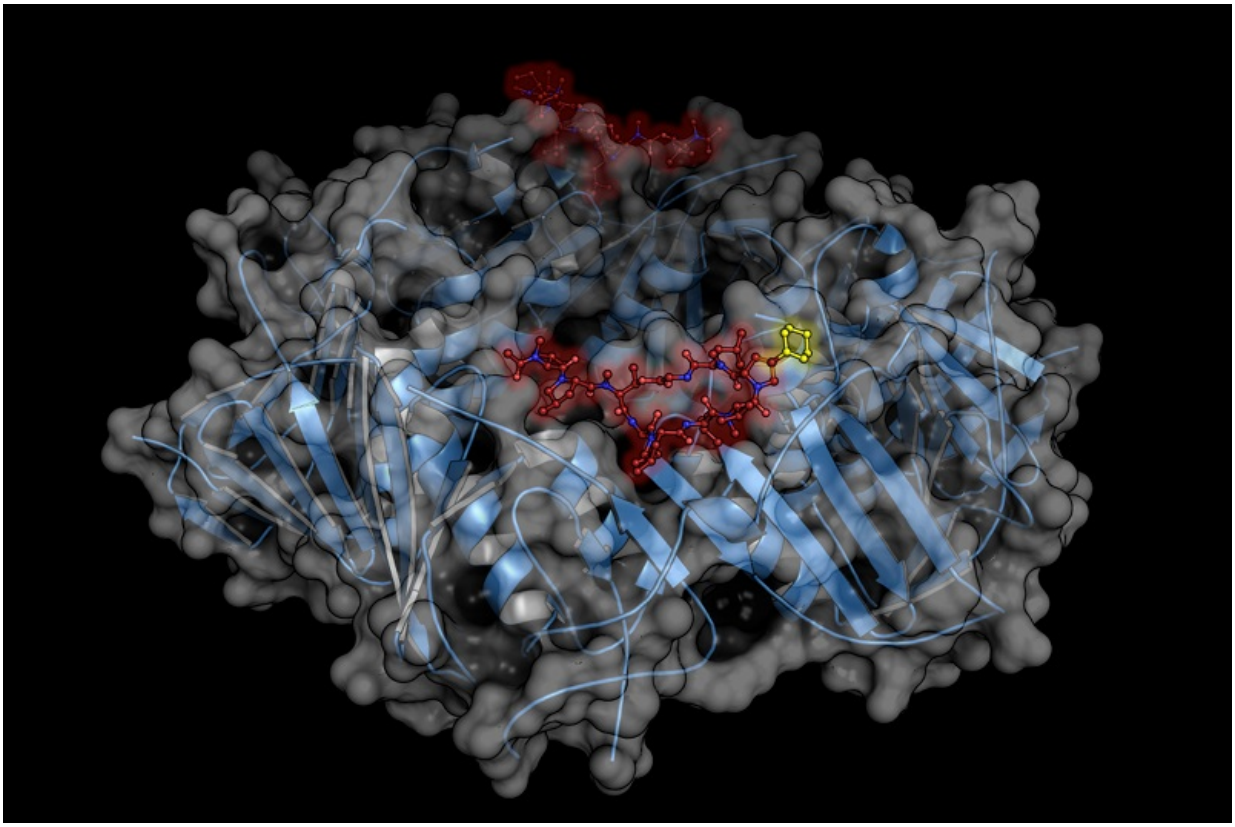

The protein forms a homodimeric ring (shown as blue cartoon & surface representation). Each polypetide chain binds one molecule of griselimycin (red). The optimized compound cyclohexylgriselimycin contains an additional cyclohexane moiety (yellow, shown only for the ligand in the foreground). Credit: HZI/Lukat

According to figures of the World Health Organization, some 8.7 million

people contracted tuberculosis in 2012 and this disease is fatal for approximately 1.3 million people throughout the world each year. One of the main problems is that the tuberculosis pathogens have become resistant to the antibiotics used to fight them. Scientists from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken, the Helmholtz Centre for Infection Research (HZI) in Braunschweig and the German Center for Infection Research (DZIF) joined forces with scientists from Sanofi, a global health care company, and identified a new agent, which might potentially remedy these problems.

The scientists just described this agent and its unique mechanism of action in the highly renowned scientific journal *Science*.

Mycobacterium tuberculosis is the main cause of tuberculosis. The treatment for drug-susceptible tuberculosis consists of the daily administration of multiple drugs for a minimum of six months. Lack of adherence to this regimen can result in treatment failure and the emergence of drug resistance. "Complexity and duration of the treatment are true issues and the main reasons for the development of resistant pathogens," says Prof Rolf Müller, who is the Executive Director and head of the Microbial Natural Substances department of the HIPS, an institution jointly sponsored by the HZI and Saarland University.

Consequently, there is an urgent need for new medications and therapeutic approaches to both fight the resistant pathogens, as well as to shorten the duration for the treatment of drug-susceptible organisms. Based on earlier reports, Müller, in collaboration with Prof Jacques Grosset from the Johns Hopkins University School of Medicine in Baltimore, and his colleagues from the HZI and Sanofi scientists, initially focused on the natural substance called griselimycin. The potential of this natural substance, was discovered in the 1960s. However, due to the success of other tuberculosis medications and its

low efficacy in an infection model, the substance was not developed any further at the time.

"We resumed the work on this agent and optimised it such that it shows excellent activity in the infection model - even against multi-resistant tuberculosis pathogens," says Müller. In the course of their work, the scientists discovered that cyclohexylgriselimycin, a variant of griselimycin, is particularly effective against Mycobacterium tuberculosis, both in cells and in the animal model. Importantly, cyclohexylgriselimycin was effective when administered orally, which is key in tuberculosis treatment, non-orally available drugs are extremely burdensome to administer daily during the many months of treatment. Moreover, combining this substance with current TB antibiotics increases the efficacy compared to the antibiotic cocktail that is usually administered.

The scientists were not only able to demonstrate the efficacy of cyclohexylgriselimycin against tuberculosis, but they also elucidated the underlying mechanism of action. "In the tuberculosis pathogen, the substance binds to the so-called DNA clamp and thus suppresses the activity of the DNA polymerase enzyme, which multiplies the genetic information inside the cell," says Müller. Neither DNA replication nor efficient DNA repair can proceed in the absence of the DNA clamp, which means that the bacterial pathogens are prevented from proliferating in the body. Structural biologists at the HZI successfully elucidated the detailed structure of the DNA clamp in a complex with cyclohexylgriselimycin bound to it. "This allowed us to elucidate the special mode of action of the new antibiotic at high resolution," says Prof Dirk Heinz, Scientific Director of the HZI, who was also involved in the study.

Since this mechanism is different from the mechanism of action of the antibiotics used previously against tuberculosis and all other bacterial

pathogens, the risk of resistance developing is low for now. In addition, the scientists were able to show that the development of resistance in mycobacteria, which include the tuberculosis pathogen, albeit possible, is associated with a drastic decrease in the growth of the pathogens such that the potential of the development of resistance is estimated to be low. "We hope that cyclohexylgriselimycin will become an agent that can even be used against resistant tuberculosis pathogens in the future and contributes to a more successful fight against this dreadful disease," says Müller.

"There is an urgent need for new medicines to fight drug-resistant microbes," says Gary Nabel, Sanofi's Chief Scientific Officer. "This elegant study identifies a potential new therapy for tuberculosis and defines its mechanism of action, importantly targeting a genetic synthesis and repair pathway that supports the development of drug resistance. We are pleased to work with our valued academic partners in Germany and the US to harness the collective expertise of academia and industry for the benefit of patients."

More information: Targeting DnaN for tuberculosis therapy using novel griselimycins, *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.aaa4690

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