Platform turbo-boosts development of new antibiotics

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Harmful bacteria react less and less to common antibiotics. The infections they cause are therefore increasingly deadly. World health therefore urgently needs alternative antibacterial agents. "Our VersaTile platform gives the development of new antibiotics a super boost", say researchers at Ghent University and KU Leuven.

The researchers used VersaTile to make a lysin for the dangerous Iraqi bacterium, which was responsible for many wound infections during the war in Iraq. (public domain stock photo of American soldiers in Afghanistan being treated for injuries that typically could lead to infection with Iraqi bacterium)

"Traditionally, we fight superbacteria with antibiotics, small molecules that sabotage the bacterial cell. Unfortunately, antibiotics no longer work well in some cases. The DNA of the bacterium modifies and the cell becomes resistant," says Professor Rob Lavigne of KU Leuven. "Moreover, the search for new molecules to kill bacteria is difficult. Hardly any new drugs make it onto the market. It is crucial that scientists work together in the fight against bacterial infectious diseases. Because it is urgent. Antibiotic resistance is advancing." VersaTile is a platform set up by Professor Yves Briers of Ghent University with his Leuven colleague Rob Lavigne. The shared know-how enables them to develop a new class of antibacterial agents on a large scale.

'Cutting up' superbacteria

An alternative to traditional antibiotics are enzyme-based antibiotics, or enzybiotics for short. These enzybiotics use lysins. "Lysins are proteins that cut up the cell wall of bacteria," says Professor Yves Briers. "It's a totally different way of destroying bacteria. The chance of developing resistance is much smaller. The bacteria don't have time to modify their genetic material because the lysins cut up their surface. A first naturally occurring lysin is in advanced clinical trials. The problem is that this natural lysin can only cut one type of bacteria. While we need to tackle multiple hospital bacteria. Using protein engineering we were already able to develop new lysins for a number of types of superbacteria. It was a slow process that yielded a handful of usable lysins that found their way to the market. But we wanted more! We wanted to make millions of lysins quickly and efficiently to select the strongest shredders. Superbacteria don't wait."

A construction kit of proteins

Ghent University and KU Leuven have now patented VersaTile. In *Science Advances*, the researchers show how they used VersaTile to make a lysin for the dangerous Iraqi bacterium, which was responsible for many wound infections during the war in Iraq. But in the meantime, the superbacteria are also found in hospitals. The VersaTile lysins proved capable of killing the multidrug-resistant Iraqi bacteria in human serum, which is quite a hostile environment for many synthetic proteins. It offers the prospect of intravenous use in patients with infection wounds.

"VersaTile is a construction kit of pieces of protein. Some pieces identify the bacteria, others pierce and cut up the cell wall. It's all about cleverly combining and building," says Hans Gerstmans, who is doing a Ph.D. on VersaTile. "It's like lego. With just a few bricks you can build an enormous number of combinations. Thanks to the VersaTile platform, you can quickly and efficiently click different pieces of

protein together and test them. After the first tests, you choose the best lysin and combine again, each time with that one dangerous super bacterium in mind. VersaTile evaluates and learns, generating a new generation of ultra-powerful lysins".

Focused on the future

The lysins against the Iraqi bacteria were a pilot project of VersaTile. The platform can also produce lysins for other dangerous bacteria, whether it concerns urinary tract infections, lung infections or other conditions. "The next challenge lies with large-scale screenings: Quick and testing as many combinations as possible," says Professor Jeroen Lammertyn of KU Leuven. "It means that we have to rescale the entire platform to nanoscale. The intention is to test candidate proteins by millions at a time in order to be able to build the right lysins". The pharmaceutical industry can use the construction kit to develop antibacterial agents. But proteins are also of great importance outside the medical world. VersaTile has a broad potential for future applications, as the 'construction kit method' can also be used for other types of proteins that are of industrial or medical importance.

More information: H. Gerstmans et al. A VersaTile-driven platform for rapid hit-to-lead development of engineered lysins, *Science Advances* (2020). DOI: 10.1126/sciadv.aaz1136

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