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Scientists develop synthetic antibiotics that could save millions of lives

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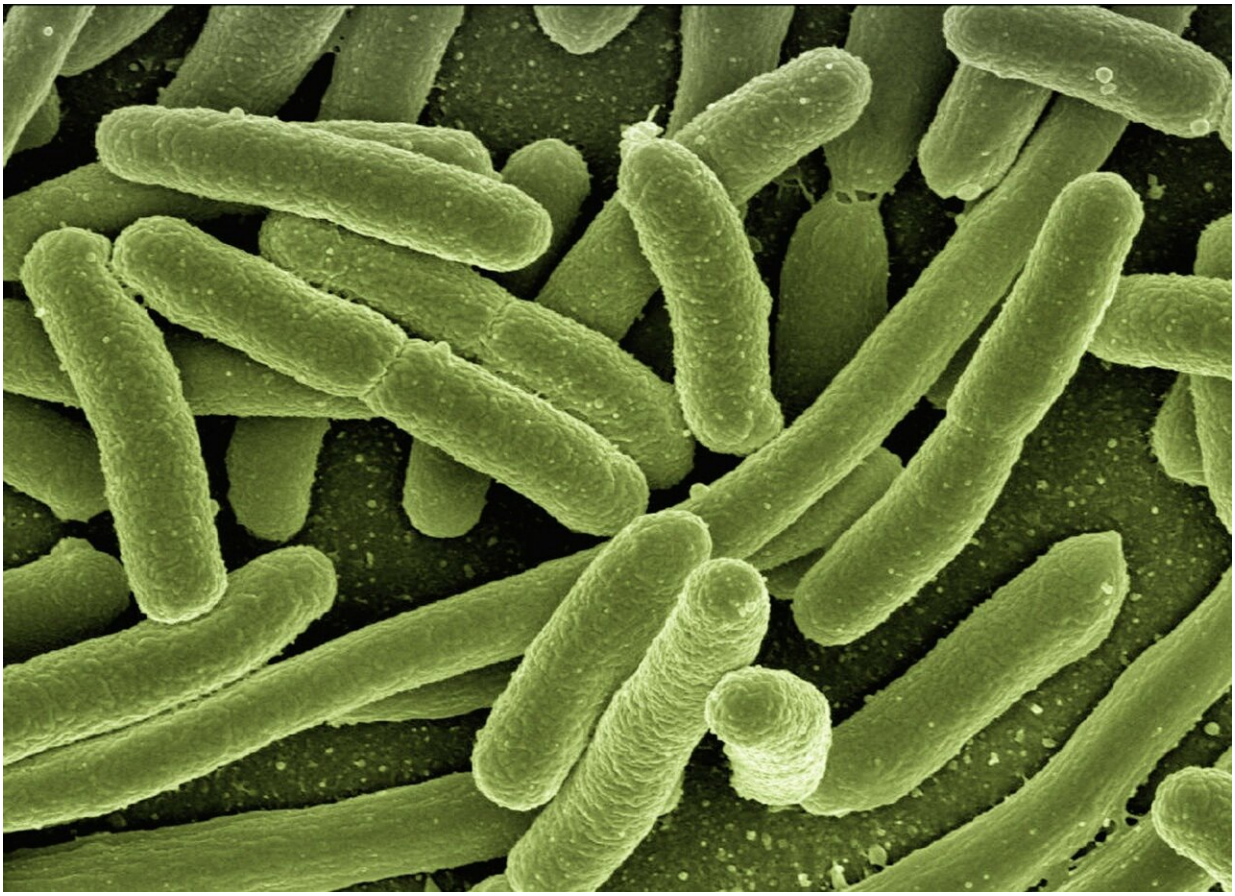

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University of Liverpool scientists have taken a significant step towards unlocking the medical potential of a new class of potent antibiotic

capable of killing "superbugs" including MRSA without detectable resistance.

The researchers have developed simplified synthetic versions of the molecule teixobactin, used by producer bacteria to kill other bacteria in soil.

They have developed and tested a unique library of synthetic versions of the "game changing" antibiotic, optimizing key features of the drug to enhance its efficacy and safety, plus enabling it to be inexpensively produced at scale.

Pioneering research

Lead researcher Dr. Ishwar Singh said: "Introducing synthetic diversity to generate the library of synthetic teixobactins is important to overcome the high failure rates associated with the next stages of drug development."

This work builds upon pioneering research by Dr. Singh, an expert in antimicrobial drug discovery and development and medicinal chemistry at Liverpool's Centre of Excellence in Infectious Diseases Research (CEIDR). The latest results were achieved as part of a Small Business Research Initiative (SBRI) project, funded by the Department of Health and Social Care. This program was delivered by Innovate UK on behalf of DHSC, with a goal of creating five lead compounds for future use in the battle against antimicrobial resistance (AMR).

The research has proved that simplified synthetic teixobactins kill a wide range of bacteria taken from human patients, where current antibiotics fail. They also successfully eradicated MRSA in mice and were found to accumulate at sites of infection for up to 24 hours in amounts greater than that required to kill superbugs.

This suggests that in future, patients may be treated with just one dose of teixobactin per day for systemic life-threatening resistant bacterial infections. The synthetic teixobactins have been found to be robust and stable at room temperature for years thus do not need a cold chain for distribution and storage, thus have potential to tackle resistant bacterial infections in different clinical settings globally.

Improving efficacy and safety

Dr. Singh has also identified designs and method for cheaply "scaling up" viable antibiotics based on natural teixobactin—previously prohibitively expensive. By swapping out certain amino acids on the molecule for low cost, commercially available alternatives, the cost of materials has been reduced by over 2,000 times, while improving efficacy and safety. The researchers developed highly efficient solid phase synthesis using automation, speeding up a single coupling step from 30 hours to just 10 minutes in high yields.

Furthermore, the team have optimized preparation to scale up yield from 30mg to 1g scale and beyond. The process can now be adapted for application up to 1kg scale or higher, simply by increasing the scale and size of the reactor. Scalability is an important key building block for commercial production to realize the therapeutic potential of synthetic teixobactins.

'Last line of defense' against superbugs

Dr. Singh said: "Our motivation is to adapt the natural teixobactin molecule and make it suitable for human use. This is a journey. Through this project we have demonstrated that we can make synthetic molecules at low cost and with high safety, which potently kills the resistant bacteria in mice. The advantage of synthetic diversity is that we can

select or deselect properties and modify molecules to impact potency and other desirable drug-like qualities. Our ultimate goal is to have a number of viable drugs from our modular synthetic teixobactin platform which can be used as a 'last line of defense' against superbugs to save lives currently lost due to AMR.

"Our next steps will be to focus upon the central benefit of synthetic teixobactin to overcome multi-drug resistant bacteria in different disease models, scale up process, followed by safety testing, which if successful, could potentially be used in hospitals as an investigational new medicine and be turned into a drug fit for treating resistant bacterial infections in humans globally. We will work with colleagues from CEIDR which have expertise in antimicrobials from drug discovery to clinic, to develop synthetic teixobactins into viable drugs."

Professor William Hope, director of CEIDR, said: "New antibiotics are urgently needed to address unmet medical needs related to multiple and extremely drug resistant bacteria. Infections due to these superbugs compromise the treatment outcomes for many patients. The teixobactins have the potential to provide valuable new therapeutic options for patients throughout the UK and globally."

Forefront of scientific advancements

Health and Social Care Secretary Sajid Javid said: "It is fantastic to see such innovative work like this happening in the UK—another clear example of this country being at the forefront of scientific advancements which can benefit people across the world.

"The rising tide of antimicrobial resistance is threatening the future of modern medicine, with currently treatable infections becoming untreatable and routine medical procedures such as cesarean sections becoming far less safe.

"Continuing to develop new drugs is critical in ensuring this risk does not become reality and that is why these results are so encouraging."

'Delighted' with results

Dr. Phil Packer, Innovation lead for AMR and vaccines at Innovate UK said: "This has been an excellent project and we sincerely hope this work will continue and go much further. There is lots of development going on in the AMR space, however much of it is focused on modifying existing classes of molecules. This is useful in the short term, but these scaffold molecules are already familiar to bacteria, making resistance development against these molecules more likely. There is a lack in the AMR pipeline for new classes of antibiotics, which is where this project fits in.

"We are delighted with results, which have validated synthetic teixobactin's promise to tackle resistant bacterial infections when currently used antibiotics fails. We look forward to following this journey closely in future."

An AMR review commissioned by the UK government has predicted that by 2050 an additional 10 million people will succumb to drug resistant infections each year. Furthermore, COVID-19 is thought to be accelerating the global threat of antimicrobial resistance as many infected patients admitted to hospital receive antibiotics to keep secondary bacterial infections in check. Greater use of antibiotics leads to increase in bacterial resistance. The development of new antibiotics which can be used as a last resort when other drugs are ineffective is therefore a crucial area of study for healthcare researchers around the world.

Provided by University of Liverpool