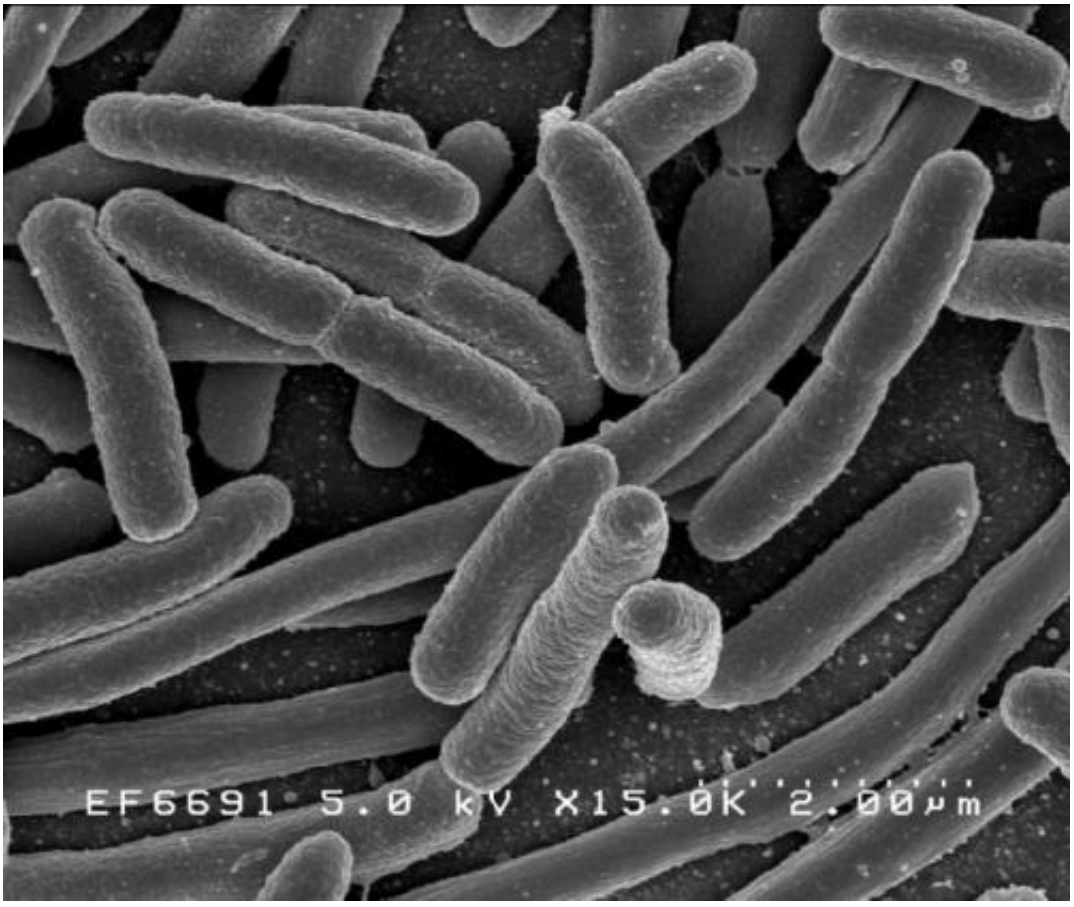
Scientists develop promising vaccine method against recurrent UTI

November 19 2021, by Stephen Fontenot



Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

Researchers at The University of Texas at Dallas are investigating the use of whole-cell vaccines to fight urinary tract infection (UTI), part of an effort to tackle the increasingly serious issue of antibiotic-resistant

bacteria.

Dr. Nicole De Nisco, assistant professor of biological sciences, and Dr. Jeremiah Gassensmith, associate professor of chemistry and biochemistry, recently demonstrated the use of metal-organic frameworks (MOFs) to encapsulate and inactivate whole bacterial cells to create a "depot" that allows the vaccines to last longer in the body.

The resulting study, published online Sept. 21 in the American Chemical Society's journal *ACS Nano*, showed that in mice this method produced substantially enhanced antibody production and significantly higher survival rates compared to standard whole-cell vaccine preparation methods.

"Vaccination as a therapeutic route for recurrent UTIs is being explored because antibiotics aren't working anymore," De Nisco said. "Patients are losing their bladders to save their lives because the bacteria cannot be killed by antibiotics or because of an extreme allergy to antibiotics, which is more common in the older population than people may realize."

The American Urological Association estimates that 150 million UTIs occur yearly worldwide, accounting for $6 billion in medical expenditures. If not successfully treated, a UTI can lead to sepsis, which can be fatal.

Recurrent UTI, De Nisco said, is primarily regarded as a women's health issue, and although it's common—especially in postmenopausal women—it's something many women don't talk about a lot.

"Every subsequent infection becomes more difficult to treat," De Nisco said. "Even if you clear the bacteria from the bladder, populations persist elsewhere and usually become resistant to the antibiotic used. When patients accumulate antibiotic resistances, they're eventually going to run

out of options."

De Nisco's continuing exploration of how UTIs progress and recur in older women is funded by a recent five-year, $1.3 million grant from the National Institutes of Health.

De Nisco's collaboration with Gassensmith began in late 2018 after she gave a presentation on the microbiology of UTI to a campus safety protocol committee.

"Afterward, we talked about my research group's idea of creating better whole-cell vaccines by preserving antigens in this slow-release depot," Gassensmith said. "At the time, we had no real models to test it with, and I thought UTI presented a very good opportunity."

Vaccines work by introducing a small amount of killed or weakened disease-causing germs, or some of their components, to the body. These antigens prompt the immune system to produce antibodies against a particular disease. Building vaccines against pathogenic bacteria is inherently difficult because bacteria are significantly larger and more complex than viruses. Selecting which biological components to use to create antigens has been a major challenge.

Consequently, using the entire cell is preferable to choosing just a piece of a bacterium, Gassensmith said.

"We throw the whole kitchen sink at them because that's what your body normally sees when it becomes infected," he said.

The whole-cell approach has its own issues, however.

"Vaccines using whole-cell dead bacteria haven't succeeded because the cells typically don't last long enough in the body to produce long-term,

durable immune responses," Gassensmith said. "That's the reason for our MOF antigen depot: It allows an intact, dead pathogen to exist in tissue longer, as if it were an infection, in order to trigger a full-scale immune system response."

The metal-organic framework Gassensmith's team developed encapsulates and immobilizes an individual bacterium cell in a crystalline polymeric matrix that not only kills the bacterium but also preserves and stabilizes the dead cell against high temperature, moisture and organic solvents.

In their experiments, the researchers used a strain of *Escherichia coli*. There are no vaccines against any pathogenic strain of this bacterium. Uropathogenic *E. coli* causes about 80% of all community-acquired UTIs.

"When we challenged these mice with a lethal injection of bacteria, after they were vaccinated, almost all of our animals survived, which is a much better performance than with traditional vaccine approaches," Gassensmith said. "This result was repeated multiple times, and we're quite impressed with how reliable it is."

Although the method has not yet been tested in humans, De Nisco said it has the potential to help millions of patients.

"This study on UTI was a proof of concept that whole-cell vaccines are more effective in this extreme, lethal-sepsis model," De Nisco said. "Showing that this works against recurrent UTI would be a significant breakthrough."

Beyond recurrent UTI or urosepsis, researchers believe the antigen depot method could be applied broadly to bacterial infections, including endocarditis and tuberculosis.

"We're working on translating this approach to TB, which is a very different organism, but like uropathogenic *E. coli*, when it enters the tissue, it stays, and it recurs," Gassensmith said. "It requires a new way of thinking about how vaccines should work.

"Vaccine technology is about two centuries old, and it has evolved amazingly little. We hope our platform can open up using existing, well-studied pathogens to create more directed and engineered immune responses."

More information: Michael A. Luzuriaga et al, Metal–Organic Framework Encapsulated Whole-Cell Vaccines Enhance Humoral Immunity against Bacterial Infection, *ACS Nano* (2021). DOI: 10.1021/acsnano.1c03092

Provided by University of Texas at Dallas