The path to a better tuberculosis vaccine runs through Montana

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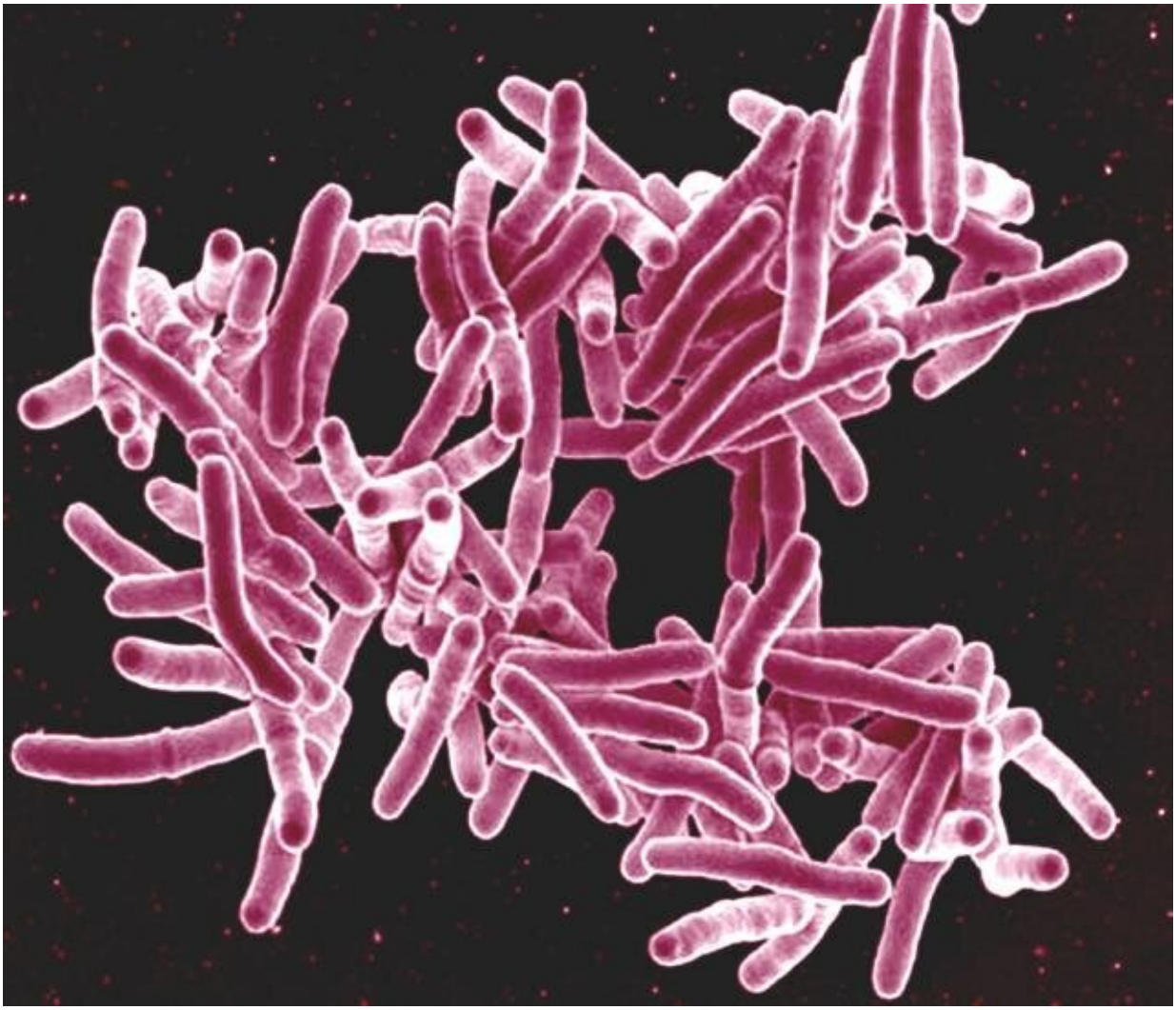

Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause TB. Credit: NIAID

A team of Montana researchers is playing a key role in the development of a more effective vaccine against tuberculosis, an infectious disease that has killed more people than any other.

The BCG (Bacille Calmette-Guérin) vaccine, created in 1921, remains the sole TB vaccine. While it is 40% to 80% effective in young children, its efficacy is very low in adolescents and adults, leading to a worldwide push to create a more powerful vaccine.

One effort is underway at the University of Montana Center for Translational Medicine. The center specializes in improving and creating vaccines by adding what are called novel adjuvants. An adjuvant is a substance included in the vaccine, such as fat molecules or aluminum salts, that enhances the immune response, and novel adjuvants are those that have not yet been used in humans. Scientists are finding that adjuvants make for stronger, more precise, and more durable immunity than antigens, which create antibodies, would alone.

Eliciting specific responses from the immune system and deepening and broadening the response with adjuvants is known as precision vaccination. "It's not one-size-fits-all," said Ofer Levy, a professor of pediatrics at Harvard University and the head of the Precision Vaccines Program at Boston Children's Hospital. "A vaccine might work differently in a newborn versus an older adult and a middle-aged person."

The ultimate precision vaccine, said Levy, would be lifelong protection from a disease with one jab. "A single-shot protection against influenza or a single-shot protection against COVID, that would be the holy grail," Levy said.

Jay Evans, the director of the University of Montana center and the chief scientific and strategy officer and a co-founder of Inimmune, a privately

held biotechnology company in Missoula, said his team has been working on a TB vaccine for 15 years. The private-public partnership is developing vaccines and trying to improve existing vaccines, and he said it's still five years off before the TB vaccine might be distributed widely.

It has not gone unnoticed at the center that this state-of-the-art vaccine research and production is located in a state that passed one of the nation's most extreme anti-vaccination laws during the pandemic in 2021. The law prohibits businesses and governments from discriminating against people who aren't vaccinated against COVID-19 or other diseases, effectively banning both public and private employers from requiring workers to get vaccinated against COVID or any other disease. A federal judge later ruled that the law cannot be enforced in health care settings, such as hospitals and doctors' offices.

In mid-March, the Bill & Melinda Gates Medical Research Institute announced it had begun the third and final phase of clinical trials for the new vaccine in seven countries. The trials should take about five years to complete. Research and production are being done in several places, including at a manufacturing facility in Hamilton owned by GSK..

Known as the forgotten pandemic, TB kills up to 1.6 million people a year, mostly in impoverished areas in Asia and Africa, despite its being both preventable and treatable. The U.S. has seen an increase in tuberculosis over the past decade, especially with the influx of migrants, and the number of cases rose by 16% from 2022 to 2023. Tuberculosis is the leading cause of death among people living with HIV, whose risk of contracting a TB infection is 20 times as great as people without HIV.

"TB is a complex pathogen that has been with human beings for ages," said Alemnew Dagnew, who heads the program for the new vaccine for the Gates Medical Research Institute. "Because it has been with human beings for many years, it has evolved and has a mechanism to escape the

immune system. And the immunology of TB is not fully understood."

The University of Montana Center for Translational Medicine and Inimmune together have 80 employees who specialize in researching a range of adjuvants to understand the specifics of immune responses to different substances. "You have to tailor it like tools in a toolbox towards the pathogen you are vaccinating against," Evans said. "We have a whole library of adjuvant molecules and formulations."

Vaccines are made more precise largely by using adjuvants. There are three basic types of natural adjuvants: aluminum salts; squalene, which is made from shark liver; and some kinds of saponins, which are fat molecules. It's not fully understood how they stimulate the immune system. The center in Missoula has also created and patented a synthetic adjuvant, UM-1098, that drives a specific type of immune response and will be added to new vaccines.

One of the most promising molecules being used to juice up the immune system response to vaccines is a saponin molecule from the bark of the quillay tree, gathered in Chile from trees at least 10 years old. Such molecules were used by Novavax in its COVID vaccine and by GSK in its widely used shingles vaccine, Shingrix. These molecules are also a key component in the new tuberculosis vaccine, known as the M72 vaccine.

But there is room for improvement.

"The vaccine shows 50% efficacy, which doesn't sound like much, but basically there is no effective vaccine currently, so 50% is better than what's out there," Evans said. "We're looking to take what we learned from that vaccine development with additional adjuvants to try and make it even better and move 50% to 80% or more."

By contrast, measles vaccines are 95% effective.

According to Medscape, around 15 vaccine candidates are being developed to replace the BCG vaccine, and three of them are in Phase III clinical trials.

One approach Evans' center is researching to improve the new vaccine's efficacy is taking a piece of the bacterium that causes TB, synthesizing it, and combining it with the adjuvant QS-21, made from the quillay tree. "It stimulates the immune system in a way that is specific to TB and it drives an immune response that is even closer to what we get from natural infections," Evans said.

The University of Montana center is researching the treatment of several problems not commonly thought of as treatable with vaccines. They are entering the first phase of clinical trials for a vaccine for allergies, for instance, and first-phase trials for a cancer vaccine. And later this year, clinical trials will begin for vaccines to block the effects of opioids like heroin and fentanyl.

The University of Montana received the largest grant in its history for anti-opioid vaccine research. It works by creating an antibody that binds with the drug in the bloodstream, which keeps it from entering the brain and creating the high.

For now, though, the eyes of health care experts around the world are on the trials for the new TB vaccines, which, if they are successful, could help save countless lives in the world's poorest places.

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