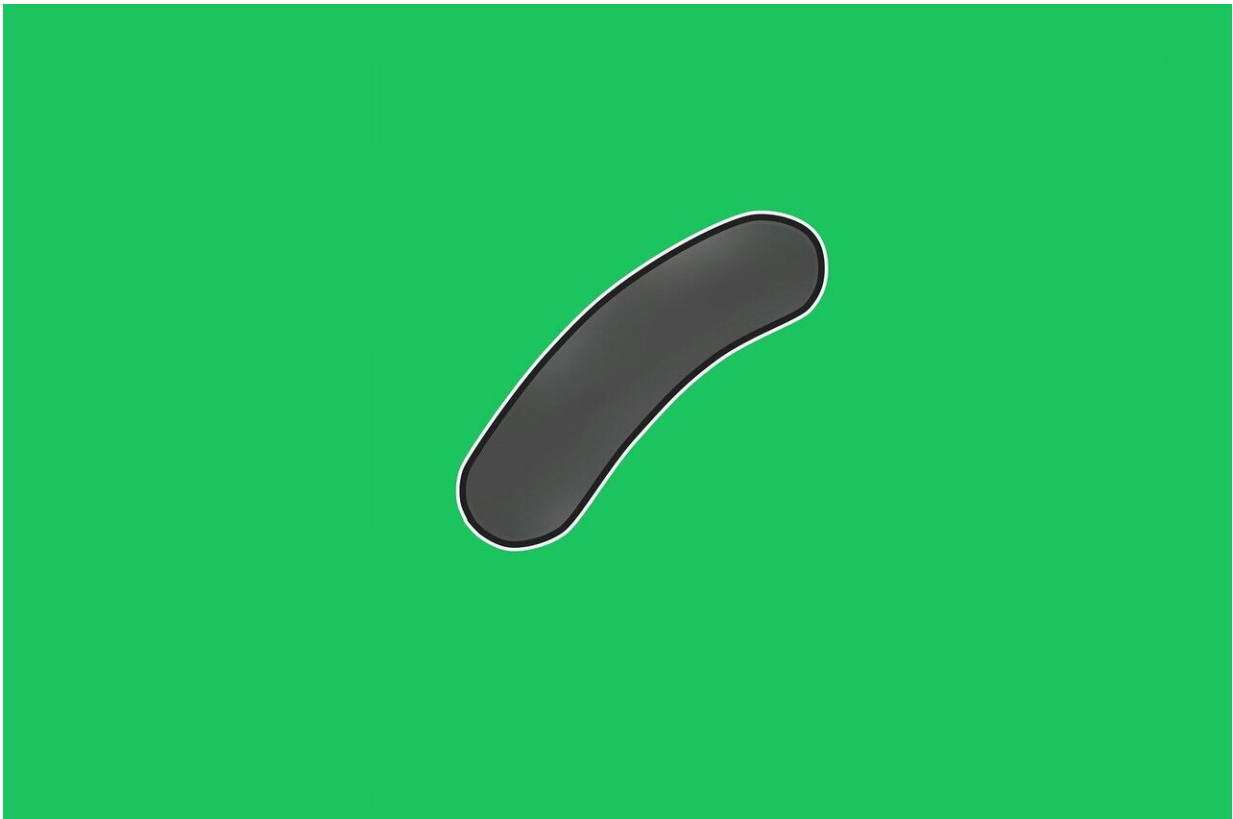


# Study finds potential way to tweak immune system to help it fight tuberculosis

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Tuberculosis is old—ancient even. The infectious bacterial disease that plagued [Old Testament Israelites](#) and [took down pharaohs](#) was eventually stunted by vaccinations, antibiotics, and public health measures like

isolation, but it hasn't been cured yet. More than a million people around the world still die from TB every year.

Now, a Boston University-led research team has found a way to tweak immune cells to better fight the disease and—with the right backing—they say it could be ready for clinical trials as soon as 2024.

In a study published in *Science Advances*, the researchers identified the genetic signatures of TB-susceptible and TB-resistant white [blood cells](#), called macrophages, and then tested the ability of different compounds to transform vulnerable cells into more resilient ones.

"The TB vaccine is not really 100% efficient and [antibiotic resistance](#) is becoming more prevalent," says Igor Kramnik, the study's corresponding author and a BU Chobanian & Avedisian School of Medicine associate professor of medicine. His team's approach could add another weapon to the arsenal that's fighting TB: a host-directed therapy, a way of helping the body better control infection and reduce disease-related inflammation.

"It's a way of treating the host, the patient, rather than focusing on the pathogen." The project mixed lab-based studies at BU's National Emerging Infectious Diseases Laboratories (NEIDL) with a big data audit of potential compounds by scientists at University College Dublin, Ireland.

"Tuberculosis, as one of my colleagues used to say, has studied us much longer than we have studied it," says Kramnik, who's also a NEIDL investigator. "It's a serious and complex disease and our standard interventions are only partially efficient—none of them are sufficient to eradicate the disease."

But the latest work could help change that, according to Shivraj M.

Yabaji, a NEIDL postdoctoral researcher.

"We hope that our research will contribute to the development of more effective treatments for TB by better understanding how to fine tune the activation states of [immune cells](#)," says Yabaji, the paper's lead author. "This could potentially lead to therapies that target host immunity to tuberculosis."

## **Weak TB vaccine, rising antimicrobial resistance**

The cause of tuberculosis is a bacteria called Mycobacterium tuberculosis—a tiny rod-shaped germ less than 0.5 micrometers in diameter. Spread by a cough, sneeze, or even just a conversation, it can cause symptoms like fever, weight loss, and chest pain. In 2021—the most recent numbers available—more than [10 million people worldwide fell ill with TB](#), with the disease typically concentrating its attacks on their lungs.

For 100 years, a vaccine—bacille Calmette-Guérin (BCG)—has been the first line of defense against TB, albeit a somewhat ramshackle one.

A recent study from Boston University showed that BCG has limited impact: [researchers found it was only about 37 percent](#) effective in children under five years of age and offered no protection for adolescents and adults. And antibiotics, the fallback for those who do become infected, are losing their power.

[According to the World Health Organization](#), "drug-resistant tuberculosis is a major contributor to antimicrobial resistance worldwide and continues to be a public health threat;" it reports that around 500,000 people die annually from drug-resistant TB.

Kramnik has been studying TB for 30 years, though he'd initially

expected to only spend a few years scrutinizing it before turning his focus to tumor biology.

"I thought that tuberculosis would be a nice stepping stone, but I'm still here, trying to understand it," he says. "It's a disease that's very different from others. Thinking about tuberculosis as a battle between a pathogen and a host isn't really productive. What we're probably dealing with is an evolutionarily refined coexistence of a pathogen and a host that eventually leads to incurable disease at its terminal stage."

## **A new treatment to enhance natural defenses against TB**

One of TB's biggest mysteries is why some people get sick when most others don't; in particular, why so many patients initially ward off infection, then eventually succumb to it. Kramnik is also interested in why the bacteria is so intent on destroying the lung, which enables its transmission by infectious aerosols.

In recent studies, his lab has used experimental mouse models, which mimic what happens to humans when they contract TB, to try to provide some answers.

"It all led us to identify the importance of macrophage cells as major determinants, and regulators and controllers, of local immune response in the lung," he says, "and a major cell that affects susceptibility in cases of growing infection."

Macrophages typically have two disease fighting states, says Kramnik: an active one that takes on and eliminates pathogenic intruders, and a regenerative one that helps rebuild tissue after infection. He discovered that in the case of TB, the cells can get stuck in a hyperactive, but

ineffective, fight mode: a persistent and damaging inflammatory response that hurts the body, but doesn't take down the pathogen.

In the latest study, Kramnik, Yabaji, and their colleagues used the mouse models to look for ways to shut this response off and help the macrophages work more effectively.

To start, they used RNA sequencing—a method for pinpointing which genes are expressed, or turned on—hoping it would help them zero in on the "genetic signature that differentiates the normal/resistant and aberrant/susceptible activation states," says Kramnik.

Using a test developed in collaboration with study co-author Alexander A. Gimelbrant, an investigator at the Seattle-based Altius Institute for Biomedical Sciences, the team simultaneously measured the expression of 46 different genes that represented this signature.

"This allowed us to look at gene expression patterns rather than individual genes to characterize the cell states and their changes in response to treatments." They then tested a range of drugs to see if any would perturb, or change, the expression of the genes.

Some molecules worked better than others, but no single one could shift a macrophage from a TB-vulnerable to a TB-resistant state. To uncover a potential combination that would work in synergy, the lab-based team sent all of their data to researchers at University College Dublin, Ireland, who had developed a machine learning algorithm they could use to predict whether particular combinations of drugs would be more effective. "We then went back to the bench and tested those predictions," says Kramnik.

They found two molecules that have shown promise as cancer treatments—Rocaglamide A (RocA) and a c-Jun N-terminal kinase

(JNK) inhibitor—formed an especially good partnership. Together, they helped hinder cell signals related to inflammation and stress, while also boosting the pathways that carry stress resistance signals. "They would be good candidates for clinical trials, so it could change the medical treatment of tuberculosis," says Kramnik.

The researchers also discovered that using the two together allowed them to dial back on the effective dose of RocA, which can be potentially toxic at higher levels. Kramnik says their results show how to increase "therapeutic efficacy at lower drug doses and decrease toxic side effects. This is particularly important for chronic diseases that require long course treatments, such as tuberculosis."

Although the team is ready to move the research forward, bringing any therapy to trial would require fresh backing, whether from a pharmaceutical company or other institution. "We will be in position," says Kramnik, "to partner with people who can bring it to the clinic. This is our goal."

**More information:** Shivraj M. Yabaji et al, Cell state transition analysis identifies interventions that improve control of *M. tuberculosis* infection by susceptible macrophages, *Science Advances* (2023). DOI: [10.1126/sciadv.adh4119](https://doi.org/10.1126/sciadv.adh4119). [www.science.org/doi/10.1126/sciadv.adh4119](https://www.science.org/doi/10.1126/sciadv.adh4119)

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