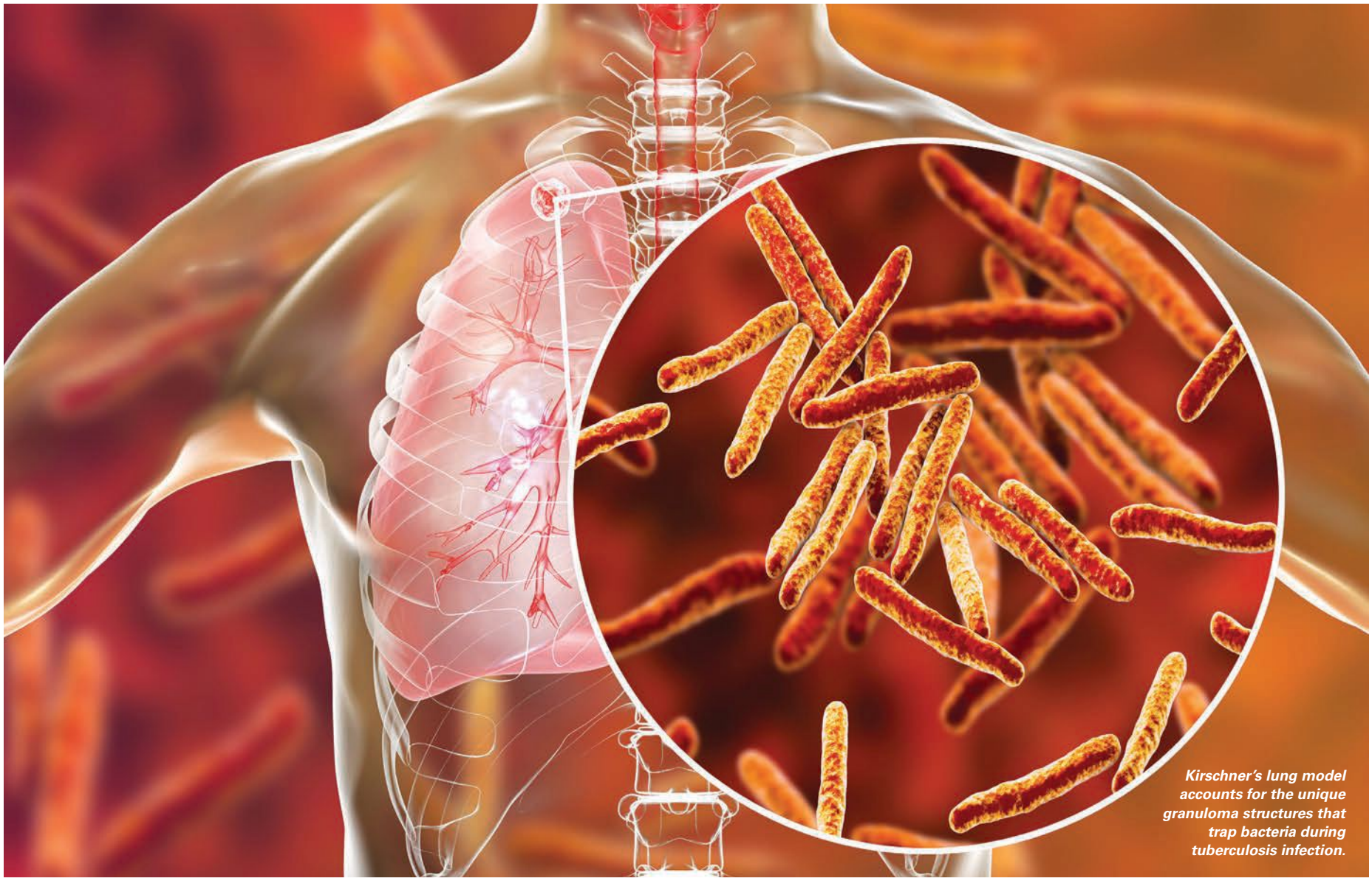
Calculating Better Tuberculosis Treatments

Denise Kirschner developed an equation-based lung model of a fatal but forgotten infectious disease, revealing an unexpected role for math in drug discovery.



Kirschner's lung model accounts for the unique granuloma structures that trap bacteria during tuberculosis infection.

INTERVIEWED BY SARAH ANDERSON, PHD

DENISE KIRSCHNER thought she needed to become a doctor to help sick people. But as she discovered an aptitude for mathematics throughout high school and college, she wondered whether math might provide an underexplored route toward treating disease. She found her answer during a summer research program at Los Alamos National Laboratory where she used mathematical modeling to study the dynamic interactions of the HIV virus within the body. "I was hooked," Kirschner said. "I thought, this is what I'm supposed to do because I'm really good at math, but I love biology. So, it's a perfect marriage for me."

Now the director of the Computational Immunobiology of Tuberculosis Lab at the University of Michigan, Kirschner continues to take the road less traveled, focusing on an overlooked bacterial disease. "If you ask anybody in the street about tuberculosis, they'll say, 'Oh, that was in the 1800s, right?'" she said. In reality, tuberculosis currently infects almost two billion people — one fourth of the world's population — with more than 80 percent of cases and deaths concentrated in low and middle income countries (1,2).

The World Health Organization and United Nations declared March 24 World Tuberculosis Day, marking the date in 1882 on which microbiologist Robert Koch discovered the *Mycobacterium tuberculosis* pathogen, aiming to raise public awareness and drive research efforts to eradicate the disease.

Kirschner has the same goal. By creating mathematical equations that represent the biological processes at play during pulmonary tuberculosis infection, she developed a novel computational lung model of the disease to expedite the search for new treatments. Kirschner can use her virtual lung to screen antibiotic and vaccine regimens and predict the most promising ones, providing a valuable complement to gold standard large animal models of tuberculosis. What's more, her simulated lung is part of a larger body of computational organ models that together could revolutionize early-stage drug development.

What are the limitations of existing tuberculosis treatments?

The tuberculosis pathogen has existed since the time of the Egyptian mummies, and yet we still don't know how to effectively combat it. The current vaccine for tuberculosis consists of a live bacteria that is a weaker cousin of the tuberculosis pathogen that is intended to train the immune response to infection. However, this vaccine was developed about 100 years ago, and its efficacy falls somewhere between zero and 80 percent.

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The vaccine is generally not administered in the United States and United Kingdom because the efficacy is so low and because it interferes with the skin test for tuberculosis. There is a drug regimen that can squelch the disease, but it requires people to take four antibiotics that can cause side effects such as vomiting and diarrhea for six to nine months. Most people don't even finish a 10-day course of a single antibiotic. Getting people to comply with this treatment is a major challenge, and if they don't, drug resistance develops rapidly.

How can computational models help develop better drugs for tuberculosis?

The hallmark of tuberculosis is lung granulomas, which are dense structures similar to tumors. They are made up of the bacteria and various immune cells. Drugs need to reach the granuloma, penetrate it, and find the bacteria, many of which are trapped in necrotic areas deep in the granuloma core. There isn't a good small animal model for this system; mice don't get granulomas in their lungs. Rabbits do, but no immunoreagents to study rabbit granulomas have been developed. Researchers use nonhuman primates as tuberculosis models, but they are very expensive to acquire and maintain. It's virtually impossible to get 50 monkeys for a study.

What computational modeling brings to the table is the ability to narrow the design space. Just 10 drug candidates in different combinations, doses, and time courses can yield 10^{17} possible regimens, which is too many even for a computer to handle, so we still need to optimize the regimen design parameters up front. But essentially, we can say that these are the most promising drug regimens within that giant space, so here's where the experimentalists should focus.

How did you develop your computational lung model of tuberculosis?

We wanted to model the immune response to understand how a drug affects the dynamics between all of the relevant cells and not only the bacteria. We studied the literature and worked with collaborators to gather everything known about the immune response to tuberculosis. We wrote it all down in equations that track the physical and chemical interactions between various components over time and space. This method examines the average behavior of the entire population of T cells, macrophages, bacteria, and so on. We then moved from equation-based modeling to computer algorithm-based modeling, in which we translate those equations into computer code, such as "if-then" statements, for each individual species. For example, if a T cell meets a macrophage, then it can secrete a cytokine that activates that macrophage to kill bacteria.

To develop a whole lung model for pulmonary tuberculosis, we expanded this approach to include the lungs, which serve as the site of the disease, the lymph nodes, which produce immune cells, and the blood, which carries immune cells back and forth from the lymph nodes to the lungs (3). We developed a system of equations representing the processes occurring within the lung granulomas, the lymph nodes, and the blood as well as the dynamics as immune cells move between them.

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Denise Kirschner developed a mathematical model of pulmonary tuberculosis to improve the efficiency of drug discovery.

How can you use this model to screen drug regimens for tuberculosis?

Our collaborators evaluate tuberculosis drugs in nonhuman primate and rabbit models and provide data on the drug's pharmacokinetic and pharmacodynamic properties and, for the primates, its effect on the granulomas. We use some of those datasets to calibrate the model and then test it against separate datasets to confirm that when we input information about a drug's mechanism, the model gives the correct output in terms of the host response.

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Once we've validated the model in this way, we can use it to explore many questions about drug regimens. For example, we recently used the model to screen different regimens of standard and new tuberculosis antibiotics and identified those that eliminated the bacteria the fastest, which we predicted to be the most effective. Our collaborator then tested the drugs in nonhuman primates and observed that we had successfully predicted the regimens that performed the best *in vivo*.

How adaptable is your model to other organs?

It is lung specific, but we could adapt it to study other respiratory diseases such as lung cancer, chronic obstructive pulmonary disease, and COVID-19. I want to be the lung person and work with other researchers who are the kidney or heart or brain people. There are about 20 of us in the computational world who have built these types of models in various organs, and our goal is to sew them all together to build a digital human twin. When Ford built the first car, it was a clunker, but it drove, and now we have the Mercedes-Benz. Similarly, we'll start with a Model T and build our way up. We could link the different components together with some nuts and bolts, and over time, turn our digital twin into a Mercedes. ■

This interview has been condensed and edited for clarity.

REFERENCES

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