Microbiologist explains drug cocktails and how researchers find the right matches to improve outcomes

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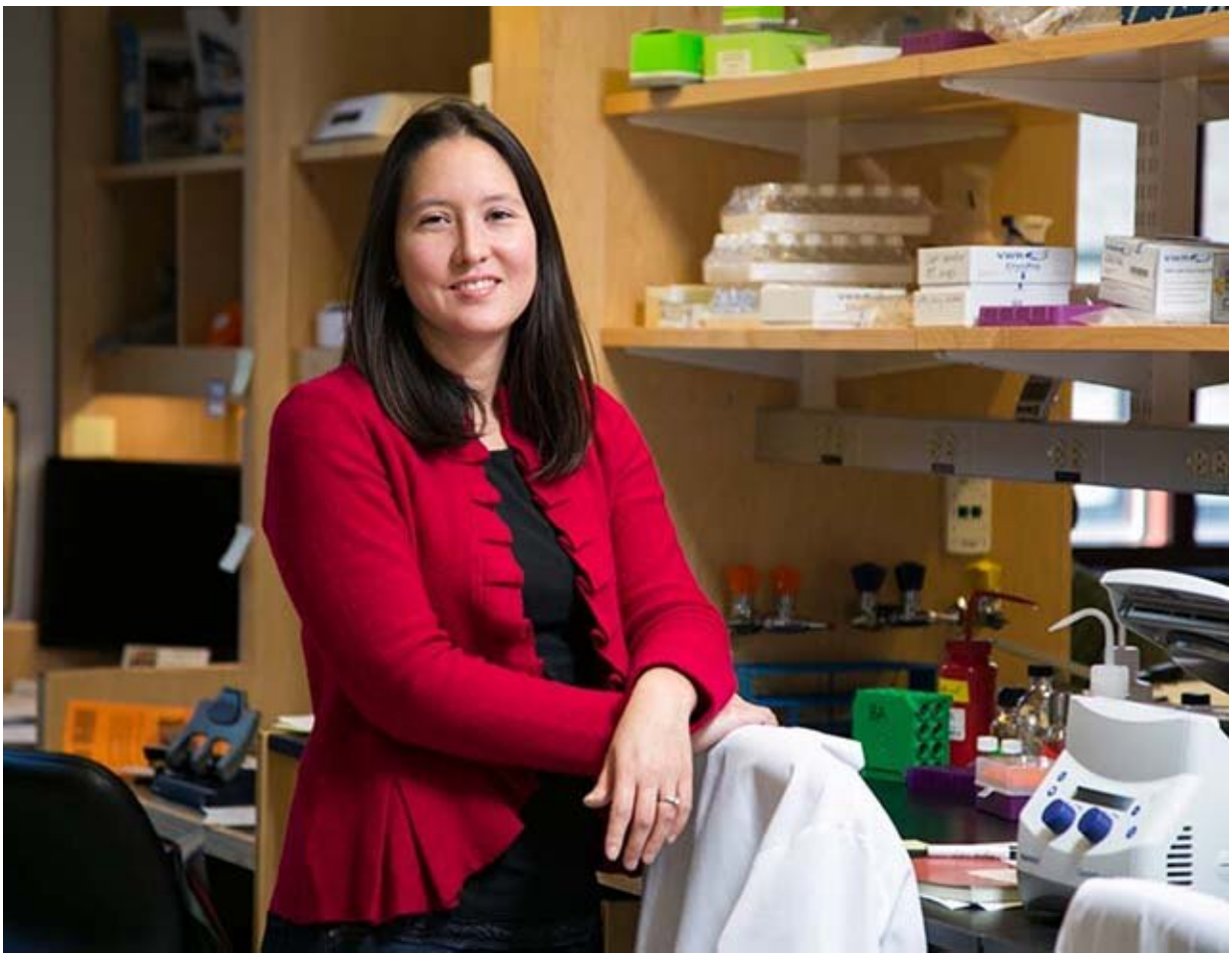

Bree Aldridge is an associate professor of molecular biology and microbiology at Tufts University School of Medicine. Credit: Kelvin Ma

When you open a carton of Neapolitan ice cream, how do you scoop? Maybe you grab some chocolate and strawberry together, or maybe you eat one flavor at a time. The three flavors are in there to satisfy the variation you need for that serving—not unlike combination drug therapy, says Bree Aldridge, an associate professor of molecular biology and microbiology at Tufts University School of Medicine and associate director of the Stuart B. Levy Center for Integrated Management of Antimicrobial Resistance (CIMAR).

Using two or more drugs together as treatment is a simple idea with a complicated underpinning. In order to combine drugs to treat complex infections such as tuberculosis, HIV, and most cancers, we have to understand how their mechanisms work together first. One drug may target one pathway, another drug another pathway. If infected cells grow at different rates, some classes of antibiotics kill the fast-growing cells better, while others are better at killing the slow ones. There can be thousands of combinations to measure. If the right combinations are found, such multidrug therapy may increase treatment efficacy and prevent the development of drug resistance, both important long-term goals.

Aldridge's multidisciplinary lab combines quantitative measurement with mathematical modeling to understand survival strategies of Mycobacterium tuberculosis, the bacterium that causes TB, with a goal of shortening treatment time. She also explores how her methods can be applied to other pathogens.

Tufts Now spoke with Aldridge about finding the right drug cocktails, slowing antimicrobial resistance, and the role artificial intelligence can have in both.

Tufts Now: What is combination drug therapy?

Bree Aldridge: Combination drug therapy is simply using drugs together with the purpose of increasing efficacy. There are a lot of diseases treated with combination therapy, including tuberculosis, HIV, and many cancers.

One of the reasons behind this is the idea that infections are heterogeneous, meaning that you're treating more than one type of infection. Sometimes you need more than one drug because the bacteria are in different states. One drug may only target bacteria only in certain states, so you need another drug to clear the others. If you think about why you need long treatment courses, it's because there's a subpopulation of bacteria that weren't successfully treated. We need to learn what those cells are and how they came to be so resilient so we can design therapies to target these so-called persister cells.

This heterogeneity is found in cancer biology as well, in that cells in a tumor can vary and have different responses to each drug. That's why treating cancers can require lengthy combination therapies, just as with treating some infections.

There are a couple other important reasons to use combination therapies for infections. One is to slow the acquisition of drug resistance. If you just use monotherapy, you're going to end up with resistance.

It's worth pointing out that some labs have found that combination therapies can promote acquisition of drug resistance. Bacteria may respond to one drug in a way that helps it deal with another drug better and that can promote resistance. It's a give or take, and really highlights that we need more research in this area.

Second, sometimes drugs enhance the efficacy of each other—this is called synergy. Synergistic combinations may allow you to use lower drug doses—minimizing side effects—or they may clear the infection

more efficiently.

What are some of the challenges with identifying and using combination therapies?

It's hard to know what drugs will work together because drugs in combination don't act together the way you expect them to based on how the drugs perform alone. An analogy is cooking: Sometimes there's a surprising mixture of things that go together that you wouldn't have expected would work based on their individual profile. Why would you put strawberry and goat cheese together? But they taste really good together in a salad.

One of the biggest challenges to finding combinations is the sheer size of the combination space. Say you have 20 available drugs and you're making a three-way combination. That's more than a thousand combinations. How do you survey that without measuring everything?

At the same time, the cells you are targeting for treatment are in different states. This means that we cannot use just one measurement or assessment for each possible drug combination. Instead, we have to measure how effective combinations are when the bacteria are grown in different environments.

How can researchers more efficiently identify synergies between drugs?

Although 1,000 is too many combinations to test in preclinical animal models, we can measure these in the lab with in vitro studies (studying the cells in culture) in multi-well plates, allowing for simultaneous measurement of many drug responses. These quick and economic experiments may be a good enough assessment to learn which

combinations should then be tested in an animal model. This has been one of my lab's goals.

Even the in vitro measurements need to be made more efficient when you go from measuring two drugs in combination to three or more. You need more space and equipment to do these measurements. That's where a method like DiaMOND comes in. With DiaMOND, we measure drug combinations in doses that provide the most information, allowing us to make fewer measurements but still determine the potential of each drug combination. We use artificial intelligence to predict outcomes in animals and in the clinic from data that we can readily measure in the lab.

New antibiotics aren't coming to market quickly, primarily because they're expensive to develop and the anticipated revenue doesn't justify the cost, yet antibiotic resistance remains a growing global health threat. Could new combinations of previously approved drugs provide a potential solution?

New TB drugs are actually on their way, so they are something of a drug development success story. But at the same time, we and other researchers are actively testing new combinations of existing drugs, which should help in the fight against antibiotic resistance.

At CIMAR, we take advantage of collaboration among clinicians and basic scientists to explore how to best utilize in vitro measurements to understand and transform the use of combination therapies in the clinic. Right now, we're working to make sure that the growth models we use in the lab mimic the environments of the infection in the body—these environments may be rich in lipids or have low levels of oxygen. One of the main takeaways from our recent study is that this context in our experimental models really influences how well our data predicts outcomes in preclinical animal models.

I'm really excited about the potential of combination therapies and the approach we are taking in CIMAR to fully utilize data in the lab and in the clinic. Our data-driven approach will help us make the most of the drugs we have, strategize how to use new antibiotics, and learn how to design personalized therapies for bacterial pathogens.

Provided by Tufts University

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