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Combating antiviral drug resistance with dynamic therapeutics

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Antiviral drug resistance has long been a problem in modern society. As viruses evolve, they develop resistance to antiviral drugs, which become less effective at treating diseases such as influenza.

Now, a group of researchers is approaching this problem with a new idea: what if antiviral drugs could evolve along with viruses to stop this resistance?

Christopher Brooke, assistant professor of microbiology at the University of Illinois and member of the Infection Genomics for One Health (IGOH) research theme at the Carl R. Woese Institute for Genomic Biology is part of a DARPA-funded program called INTERfering and Co-Evolving Prevention (INTERCEPT) that hopes to achieve this.

The program's goal is to develop a new class of biological therapeutics that can coevolve with viruses. That way, as the virus develops resistance to the therapeutic, the therapeutic would evolve and develop anti-resistance.

"It would be as dynamic as the pathogen, and so that would, ideally, eliminate or at least blunt the problem of evolved resistance," Brooke said.

Nine teams in the program are targeting other viruses such as HIV and Zika virus, but Brooke's team of five researchers will work on

developing a therapeutic specifically for influenza.

They hope to do this by creating therapeutics with a design based on viruses themselves. This idea is based on a natural phenomenon known as defective interference.

Under certain conditions, many viruses spontaneously produce virus mutants that are missing parts of their genome. These mutants, called defective interfering particles, compete with the virus and inhibit its ability to replicate.

Influenza produces these defective interfering particles regularly, and it has generally been believed that they're detrimental to the virus.

"We're not totally convinced that's the case," Brooke said.

He and his colleagues will instead use the particles as a starting point. They plan to make changes to the particles and see if they have a detrimental effect on the viral population.

"This program is basically trying to see if we can take that idea . . . and engineer versions of these that can act as therapeutics," Brooke said.

A major part of this research will involve the creation of mathematical models that will help them better understand influenza infection.

Mathematical modeling, which involves using mathematical concepts to describe real world situations, can help the researchers make useful predictions. Two mathematicians on Brooke's team will work with experimenters to try and predict what a defective interfering particle that could serve as an efficacious therapeutic might look like.

Mathematical modeling is common in biology research, but there is

typically a communication gap between those doing the modeling and those doing experimental work.

"There's not a huge amount of crosstalk," Brooke said. "But this program is bridging that to some extent."

Each side brings a level of expertise that can help the other—for example, experimental researchers don't always have precise control over what they're testing.

"Say we add a virus to a well of cells. We can't dictate exactly how many virus particles go into every cell . . . We just can't do that," Brooke said. "But in a mathematical model, you can do whatever you want."

Using the advantages of mathematical modeling, they can decide which particles they want to test in the lab.

"What I really like about the mathematical modeling is that it allows us to test hypotheses that we may have . . . in a much more quantitatively rigorous way than we can through experimentation," Brooke said. "It also allows us to test things that we can't really test experimentally."

Brooke explained that having input from the theoretical side of biology will give the project greater insight.

"The more times you bring more perspectives to one problem, the greater your chances are of finding some sort of insight . . . it's one of the things I'm most excited about."

With mathematicians and experimenters working side by side and having access to higher quality data, Brooke predicts the resulting models will be more accurate.

For now, Brooke and his team are working on identifying and characterizing every possible defective interfering particle that can be generated by influenza virus.

"We're going to try and capture different ones that we think will behave differently," he said. "We have no idea what to expect and we can't necessarily predict or judge who would be more likely to be efficacious, so we're just going to test everything."

They will analyze how the particles affect viral replication and transmission, how they affect the host cell, and more.

Their end goal is to identify a particle known as a therapeutic interfering particle that could be introduced to an individual infected with influenza.

"It will dramatically decrease disease severity and forward transmission of the virus," Brooke said. "It would do so without the virus being able to evolve resistance to it."

Regardless of whether this research will have impact on driving influenza virus to extinction, the researchers expect to gain valuable information on how virus populations evolve, which is an area Brooke and his lab have already been exploring.

In the 20th century, vaccines were introduced against diseases such as poliovirus, measles virus, and influenza virus, which all have similar mutation rates. Poliovirus and measles were controlled by vaccines, but influenza was not. It has remained a public health issue despite the fact that most people are immune to some influenza virus strains.

This leaves many large-scale questions that Brooke and his lab hope to answer: Why is influenza so good at outrunning host immunity? Why are other viruses not? How does influenza's genome affect how it evolves?

Through this research, parts of these questions could be answered.

"We're going to learn a huge amount about how influenza virus populations behave and evolve," Brooke said. "That's going to be useful for the development of this class of therapeutics, but also just more generally in terms of improving vaccines."

For Brooke, this research is a chance for him to continue studying viruses, which consistently fascinate him.

"They're super weird and they're really interesting," he said. "They're always surprising us in terms of what we find them doing and how they work."

Provided by University of Illinois at Urbana-Champaign

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