

Two Rare Antibodies, One Drug, Four Viruses

Researchers discover antibodies to block common respiratory viruses that put bone marrow and stem cell transplant patients at risk.

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There are few complications of bone marrow transplantation more dangerous than a viral infection that heads for the lungs.

[Jim Boonyaratanakornkit, MD, PhD](#), aims to do something about it.

With a team of researchers at Fred Hutchinson Cancer Center, he is reporting progress on the development of an experimental drug combination to prevent infection by four common respiratory viruses. Before the emergence of COVID-19, these four have been blamed for [more than half](#) of serious lung infections in patients with compromised immune systems, such as those recovering from transplants.

In experiments described in the journal [Nature Communications](#), the team reports how they discovered two rare antibodies that, if combined into a “cocktail,” can block infection by all four of those viruses: respiratory syncytial virus, or RSV; human metapneumovirus, or HMPV; and two types of human parainfluenza viruses, HPIV1 and HPIV3.

Respiratory viruses of all kinds are a serious threat for patients recovering from transplants of bone marrow or blood stem cells, while their new immune systems are gaining strength. Boonyaratanakornkit said one third of those patients acquire a respiratory viral infection within six months; and in a third of those, the virus progresses to the lower respiratory tract.

“Once the virus gains a foothold in the lower tract, little can be done,” he said. “As a result, up to 40% of patients with lower tract disease die within three months.”

RSV has been in the news lately because of a [U.S. outbreak last fall](#) that led to a spike in hospitalizations of children in respiratory distress. In addition, [a first ever vaccine](#) for RSV is nearing U.S. Food and Drug Administration approval for adults over 60. A [new drug](#) to prevent RSV in infants and children up to 24 months old is also under FDA review. It could be an improvement over an old standby, palivizumab, in use since 1998.

While these advances may be good news for young children, Fred Hutch's Boonyaratanakornkit said that cancer patients facing transplant have more complex needs because of the threats from multiple viruses.

"The new drugs and vaccines don't translate well into the immune compromised population," he said. "You really need to cover much more ground to make an impact on these patients. The key point of our work is that we wanted to go broad."

His team's answer is to produce a single drug, an infusion of immune-proteins called antibodies, that can block RSV and the other three viral threats at once. Their new paper describes how they came up with it, and although it has been tested only in hamsters so far, it has shown it can block infections by all four viruses.

Years more work is needed before a candidate drug can be readied for human clinical trials, and the Fred Hutch team is continuing to study [ways to improve](#) on antibodies they discovered and describe in their new paper.

It took some nifty lab detective work to find the two rare antibodies used in their formulation.

The ability to block two different viruses with one antibody is known as "cross-reactivity," a feature that is critical for giving one drug the capability to deal with multiple viruses.

One antibody, dubbed 3 x 1, is capable of blocking two different parainfluenza viruses. A second antibody, which they call MxR, cross-reacts to both respiratory syncytial virus and human metapneumovirus (yes, they are a mouthful).

Boonyaratanakornkit's work on this project took off when he and Fred Hutch immunologist [Justin Taylor, PhD](#), began tracking down [antibodies that can block parainfluenza](#).

Despite the name, parainfluenza has nothing to do with the flu. Influenza and parainfluenza viruses may look similar under a microscope, but they are from entirely different viral families. Instead of causing respiratory illness in winter like influenza, parainfluenza causes disease in the other nine months of the year.

Boonyaratanakornkit and Taylor's first success was with HPIV3. Their research focused on finding white blood cells, components of the immune system known as B cells, that produced antibodies that could block that virus. They came up with one that did.

To find an HPIV3 antibody that would also block HPIV1, they started with a pool of 200 million cells from human spleens, which are rich in B cells. They used a high speed cell-sorting method to isolate only those B cells that could make HPIV3 antibodies — and narrowed the pool to 900 cells.

Next, in the lab they created small pools containing those 900 B cells and exposed them to live HPIV1 virions. That narrowed the group to just two B cells — which already produced HPIV3 antibodies — that also produced antibodies to HPIV1.

In other words, out of 200 million B-cell rich spleen cells, they fished out two rare B cells that were naturally cross reactive. Using laboratory techniques, they were able to generate multiple copies of just one of them.

Voila! They now could grow a single antibody that could knock down both parainfluenza viruses. They named it 3 x 1.

“We didn’t know that a cross-reactive antibody for these existed, but we found one we could use. It was just luck,” Boonyaratanakornkit said.

With a somewhat similar screening process, they used bits of RSV and HMPV as bait in a pool of 200 million blood cells taken in blood draws. Out of that large pool, they were able to fish out B cells that made an antibody that would cross-react, or bind, to either of those viruses.

Voila! They had MxR.

When these rare immune proteins are produced in large numbers through a laboratory process, they are called monoclonal antibodies.

The researchers then made batches of 3 x 1 and MxR monoclonal antibodies and mixed them into a “cocktail.” It is a single drug meant to be injected, designed to prevent infection by any of the four viruses. In tests with hamsters, the experimental drug bound to the viruses and prevented infection.

Boonyaratanakornkit said that a drug containing separate antibodies against each of the four viruses would, in theory, be just as effective. But he noted that pharmacologists set strict limits on how much antibody can be infused into a patient. That limit could be surpassed quickly with four infusions. With cross-reactive MxR and 3 x 1, those same viruses could be blocked with roughly half the amount of antibodies, since each antibody in the mix knocks two different viruses for the price of one.

During the pandemic, the idea of using a monoclonal antibody cocktail to protect people from a single virus was tested [with a number of new combination drugs](#) to block SARS-CoV-2, the virus that causes COVID-19. One drug in particular, Evusheld, consisting of two injection of different antibodies (tixagevimab and cilgavimab), was aimed at protecting people with weakened immune systems. However, in the past year, the swiftly mutating virus developed variants that rendered Evusheld and the other monoclonal antibodies ineffective.

The Fred Hutch team, by contrast, is attempting to target four different viruses with their two-antibody cocktail, delivered in a single injection. Boonyaratanakorkit said the four drugs they are targeting do not have a history of rapid genetic mutation, like influenza and SARS-CoV-2.

In future research, Boonyaratanakornkit and colleagues are hoping to genetically engineer their experimental drug so it will last longer in the body. Antibodies lose their potency over time, and longer-lasting versions of these two cross-reactive antibodies would hold an advantage.

Eventually, they hope to engineer a so-called “bi-specific” antibody, which on a single Y-shaped protein would contain, on the respective left and right arms of the protein, the separate binding sites for MxR and 3 x 1. This is a dream drug — an infusion containing millions of antibodies of a single design that can efficiently knock out four dangerous respiratory viruses.

“We’re working on that,” Boonyaratanakornkit said.

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<http://beta.docker.tusaludmag.com/article/two-rare-antibodies-one-drug-four-viruses-rsv-bone-marrow-stem-cell-transplant>