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Researchers describe strategy to develop first broad-spectrum antiviral drug

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By studying the rare person—about one in a million—who can fight off viral infections more effectively than everyone else, investigators at the Icahn School of Medicine at Mount Sinai have developed a strategy to help the rest of us achieve this enhanced anti-viral state.

Their research, published in *Nature Communications*, provides a path toward creation of the first broad-spectrum antiviral drug. None currently exists.

The international research team demonstrated in human cell and animal studies that switching off a single gene bolsters immunity against seven viruses, including the extremely dangerous Nipah and Rift Valley fever viruses.

"We also have evidence suggesting the strategy protects against Zika infection, and we plan to test Ebola as soon as possible," said the study's lead investigator, Dusan Bogunovic, PhD, Assistant Professor of Microbiology and Pediatrics at the Icahn School of Medicine at Mount Sinai.

"The idea is to develop a pill that people can use to protect against pandemics—or even to help an individual stop an emerging cold sore," he said.

The scientists studied ISG15, a gene whose activity is linked to type 1 interferon, which regulates the immune system's response to viral

infection.

Twenty years ago, scientists demonstrated that mice that do not have the ISG15 gene are more susceptible to viral infections. But in humans, the opposite is true; those rare humans who do not have the gene have an extremely robust response against viral infection, as shown by the Mount Sinai team, which includes collaborating international researchers at the Pasteur Institute in France.

"To our pleasant surprise, what doesn't work in mice works beautifully in humans. If you, as a human, don't have that gene, you may be more able to fight off viral infections than others," said Dr. Bogunovic.

"Additionally, if you do get infected, you control it better. You are basically like a vaccine in yourself," he said. "You don't necessarily experience the same range and degree of symptoms, but you still develop antibodies and T-cells and everything you need to be ready for the next infection."

The researchers found that the normal role of ISG15 in humans is to help turn off the type 1 interferon response to a viral invader once it has been activated and is working. "It fine-tunes the very end of shutting off that inflammation. So when you don't have the gene, your body continues to trickle out type 1 interferon, thus continually priming the body against viral invaders," Dr. Bogunovic said. "So you are persistently ready to take on viruses."

Such long-term antiviral resiliency comes at a price for those lacking the ISG15 gene, he added—many of those individuals developed occasional seizures and detectable auto-antibodies, although none have yet developed autoimmune disorders.

"We believe a drug that turns off ISG15 in humans for a brief amount of

time would help many people facing an emerging viral infection—but of course, all this needs to be tested," Dr. Bogunovic said. He added that his team is now screening millions of small molecules to find a pill that can provide such an antiviral boost.

Provided by The Mount Sinai Hospital