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LJI scientists develop new approach to fighting many viruses at once

New vaccine design pipeline could protect against emerging SARS-CoV-2 variants and more

LA JOLLA, CA — Most vaccines are designed to provide immunity against just one pathogen. Vaccines for chicken pox (caused by varicella-zoster virus) were only developed to fight that one disease, for example.

But in the wake of the COVID-19 pandemic, immune system researchers around the world are working to go beyond traditional single-pathogen vaccines.

"Our pipeline is challenging that approach," says Alba Grifoni, Ph.D., Research Assistant Professor at La Jolla Institute for Immunology (LJI).

As they report in *Cell*, Grifoni and her colleagues have developed a research pipeline to fuel the development of "universal vaccines." These vaccines would address broad viral families and mutated viral variants. If successful, this approach could lead to vaccines with the power to neutralize emerging SARS-CoV-2 variants and many other viruses with pandemic potential.

The science of universal vaccines

Many viruses belong to large viral families, and they share a family resemblance. The virus that causes COVID-19, called SARS-CoV-2, is a type of coronavirus (CoV is short for coronavirus). This means SARS-CoV-2 is closely related to common cold coronaviruses, as well as MERS coronavirus (MERS-CoV) and SARS coronavirus (SARS-CoV).

All of these coronaviruses share certain "conserved" protein sequences that have stayed the same as the viruses have evolved. These closely related viruses share many of the same features and are recognized by some of the same T cells. T cells are white blood cells that can recognize and kill virus-infected cells to stop an infection from spreading.

In previous studies, LJI researchers discovered that some cross-reactive T cells can detect these conserved sites, called epitopes, to target both SARS-CoV-2 and common cold coronaviruses.

Grifoni's laboratory is working to map out these conserved epitope regions. This work is critical for developing a universal coronavirus vaccine. Once the scientists know where T cells should strike, they can develop vaccines that deliver effective T cell immunity against many kinds of coronaviruses—including variants that haven't even emerged yet.

"It is important to induce a neutralizing antibody response," says Grifoni. "But we've shown that T cells are much more stable in the context of viral variants, and that is because T cells look at all the proteins of the virus."

Using data science to fight COVID-19

Researchers are aware of conserved coronavirus T cell epitopes, including some epitopes on the coronavirus "spike" protein. But it is harder to study which of these epitopes sparks the strongest T cell response, and researchers knew there were other promising epitopes hiding in experimental data.

To find these conserved epitope regions, Grifoni and her team extracted and analyzed data from the Immune Epitope Database (IEDB), a public resource designed and led by LJI scientists. The IEDB provided data on more than 200 coronavirus epitopes uncovered by scientists in labs around the world.

Grifoni worked closely with virologists at the J. Craig Venter Institute (JCVI) to compare the similarities between epitopes from different kinds of coronaviruses. The researchers used a combination of bioinformatic tools, including artificial intelligence (AI) approaches, to look for hidden similarities between the coronaviruses.

Once Grifoni and her colleagues had their results, they compared how T cells recognized different coronavirus epitopes, including epitopes on the viral "spike" protein and those outside the spike protein. Uncovering this T cell activity gives researchers an important guide for how to target coronaviruses via a cross-reactive T cell response.

"The idea is that if a new coronavirus emerges, we might not be able to protect from the infection, but we might be able to protect from hospitalization," says Grifoni.

Grifoni is thinking about the bigger picture. She says this coronavirus study shows the accuracy and usefulness of a new research pipeline. Researchers could use this same process to pinpoint conserved T cell epitopes across different respiratory viruses (such as paramyxoviruses, including measles and Nipah virus or enteroviruses, including A71 and D68) and even viral species causing hemorrhagic fevers (such as Lassa virus and Junin virus).

"Our laboratory is collaborating with research groups that are interested in many different viral families," says Grifoni. "We need to fill the knowledge gaps."

Additional authors of the study, "Highly conserved Betacoronavirus sequences are broadly recognized by human T cells," include first author Tertuliano Alves Pereira Neto, Christian Zmaseck, Liliana Avalos, John Sidney, Raphael Trevizani, Elizabeth Phillips, Simon Mallal, April Fraizer, Gene S. Tan, Richard H. Scheuermann, and Alessandro Sette.

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