Local researchers find key to vaccines

Immune-system map identified

By Keith Darcé

STAFF WRITER
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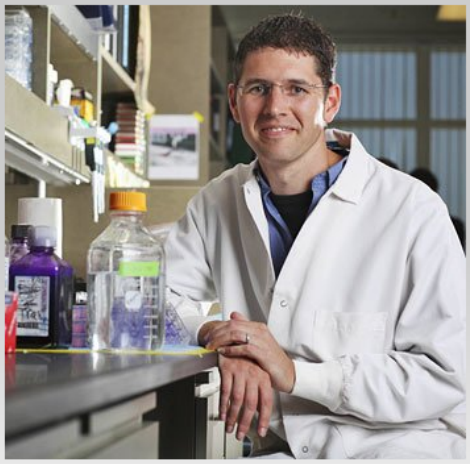
Developing vaccines to prevent diseases has always been a challenge for researchers, mostly because the process is as much trial-and-error as it is a precise science.

But a series of new discoveries made by San Diego biologists could help vaccine makers create more effective formulations faster.

Shane Crotty at the La Jolla Institute for Allergy & Immunology, his colleagues and a team at Yale University have shed light on the core mechanics of immunization, which have largely remained a mystery since an English doctor created a vaccine for smallpox in 1796.

The results of their federally funded work were published yesterday in the online edition of the journal Science.

"A killer for a lot of vaccine designs has been when you try something and it fails, you're basically stuck," Crotty said. "Now, if you try something and it doesn't work, you know what to do to get back in the right direction."



Research led by Shane Crotty, 35, of the La Jolla Institute for Allergy & Immunology, identified cells and genes central to producing virus-fighting antibodies. (Sean M. Haffey / U-T) -

The researchers uncovered an immune-system road map by identifying a type of white blood cell called a T follicular helper. This specialized cell causes another type of white blood cell to produce antibodies, which fight viruses, bacteria and other micro-invaders.

The scientists also showed that a particular gene – Bcl16 – acts as the "on" switch, transforming certain white blood cells into T follicular helpers.

And they proved that another gene – Blimp 1 – turns off the process of making antibodies.

In short, Crotty and his colleagues have charted the path by which successful vaccines unleash the body's defense against pathogens. Their breakthrough could pave the way for vaccines that are stronger and longer-lasting against the flu, polio or other diseases.

It also might help scientists control the inflammation associated with autoimmune conditions, including rheumatoid arthritis and lupus.

The study marks an important step toward cracking the puzzle of how the immune system functions at a molecular level, said Robert Rickert, a specialist in inflammatory diseases at the Burnham Institute of Medical Research in La Jolla.

"This paper really elevates the importance of this subset of T cells" for further examination, he said.

Dr. Pamela Schwartzberg, a senior investigator with the National Human Genome Research Institute, also praised the achievement.

"Nobody had data saying that this (Bcl16) gene was crucial to the function of these T cells. Now we have data saying this is the master regulator," she said.

Her office is part of the National Institutes of Health, which is underwriting Crotty's analysis with a five-year, $1.25 million grant.

Eventually, scientists might use the newly gained information to engineer vaccines that contain chemicals to activate the Bcl16 gene.

It will likely be awhile before they reach that point, Crotty said.

"It took us four years to do these experiments," he said. "I think it will take as long or longer to get to actual medical utility, but we absolutely think that this is a key in the process."

Of the 25 human vaccines that exist worldwide, 23 attack diseases by triggering the production of antibodies.

Attempts to create vaccines for some diseases – including malaria, which infects up to 500 million people annually – have failed because patients receiving the experimental inoculations didn't gain immunological memory. That's the ability to produce the right type of antibodies for long periods of time.

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"We really don't understand enough about how the immune system works to (design vaccines) in a rational, engineered way," said Crotty, 35.

He has devoted much of his young career to exploring immunology.

Crotty earned undergraduate degrees in biology and writing from the Massachusetts Institute of Technology, then a doctorate in biochemistry and molecular biology from the University of California San Francisco. He did postdoctoral work at Emory University before joining the allergy and immunology institute in 2003.

The findings published yesterday involve experiments conducted over four years on mice, which have a widely understood genome and an immune system that resembles the one in people.

Crotty's group in La Jolla inserted the Bcl16 gene – the "on" switch – into the mice. They also inserted the Blimp-1 gene, the "off" switch, to shut down the production of antibodies, and removed Blimp-1 genes to restart production.

At Yale, researchers demonstrated another method for halting antibody production by removing the Bcl16 gene from white blood cells.

This alternate approach could prove useful in treating autoimmune diseases, which cause inflammation and painful joints by turning the body's immune system against its own healthy cells.

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Fascinating article. Especially intriguing is the connection between vaccine mechanism and autoimmune disorders. Something the pro-vaccine camp has continued to deny. Also this quote is particularly telling: "We really don't understand enough about how the immune system works to (design vaccines) in a rational, engineered way," said Crotty, 35.

I'm glad they're on the way to truly understanding how vaccines work (or not).

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