New surprising finding could alter the face of dengue vaccine development

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As efforts to create a strong and effective vaccine for the dreaded dengue virus continue to hit snags, a new study from researchers at the La Jolla Institute for Allergy & Immunology offers surprising evidence that suggests the need for a revamped approach to dengue vaccine design. The finding runs counter to current scientific understanding of the key cells that need to be induced to develop a successful dengue vaccine.

La Jolla Institute scientist Alessandro Sette, Dr.Biol.Sci., and his team found that T cells, which are key disease-fighting cells of the immune system, play an important protective role in controlling dengue virus infection, rather than creating an aberrant response that can ultimately worsen the disease as is the prevailing belief in the scientific community. "The current thinking in the field is that the goal of a dengue vaccine should be the induction of antibodies and not T cells," says Dr. Sette, an internationally recognized vaccine biologist and director of the Institute's Center for Infectious Disease. "But our results suggest that both cell types are needed to produce a strong immune response against dengue infection."

Scott B. Halstead, M.D., a leading authority on dengue virus and senior scientific advisor to the international Dengue Vaccine Initiative, says the findings provide new insights that should be considered in future dengue vaccine efforts. "Their study of T cell responses in a large group of HLA-defined Sri Lankan adults naturally infected by dengue viruses found that T cell immunity contributed to host protection rather than to

vascular permeability (which occurs in severe cases)," says Dr. Halstead. "This suggests that T cell immunity may be an important element of the strong cross-protection that occurs in humans infected with two or more dengue viruses."

UC Berkeley professor Eva Harris, Ph.D., an internationally recognized dengue expert, praised the study as providing "a refreshing view" of the role of T cells in human dengue infection. "Dr. Sette's work provides important evidence of the protective role of CD8+ T cells through their work with Sri Lankan blood donors," says Dr. Harris, who heads the University's Center for Global Public Health.

Dengue virus causes dengue fever and dengue hemorrhagic fever/dengue shock syndrome, the most significant mosquito-borne viral diseases in the world today in terms of illness, death and economic cost. Dengue exists as four distinct viral strains and infects 50 to 100 million people worldwide each year, predominantly in Southeast Asia and Latin America, but also produced a small outbreak in Florida in 2010. Now categorized by the U.S. Centers for Disease Control as an emerging disease threat, 500,000 cases of dengue's severest form are reported annually worldwide, and it is possible that cases will become even more widespread as a result of climate change.

Dr. Sette said his T cell data may help to explain the results of a dengue vaccine trial announced in September. The trial, conducted by Sanofi-Aventis, was the most highly anticipated vaccine effort in the field, but didn't produce strong protection against all four dengue virus strains as had been hoped. The vaccine candidate, structured to trigger protective antibodies as is typical in vaccine design, was only 30 percent effective overall and provided no protection against DENV2, which was the predominant strain circulating in the trial area.

"Some people have been kind of perplexed by the results," says Dr.

Sette, noting that the vaccine candidate produced antibodies in the trial participants, usually an indicator of a good response. "Despite this, the dengue vaccine did not provide significant protection. We think that the added fire power of the T cells would have been needed to make the vaccine more effective."

Major efforts are underway to create a first-ever vaccine, but have been hampered by the existence of the four different dengue virus strains. People who get the severest forms of the disease are those infected by one dengue strain that later get re-infected by a different strain of the virus. In contrast to most viral infections where T cells are considered a normal part of the body's protective response, many scientists in the dengue field have theorized that T cells raised against an individual's first dengue infection dominate the body's immune reaction upon infection with a second dengue strain and mount an altered immune response. This phenomenon termed "original antigenic sin" was believed to result in the T cells playing a pathogenic role during a subsequent dengue infection, causing some people to get more seriously ill. Dr. Sette says his findings do not support this theory.

The T cell finding was published April 11th in a paper "Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8+ T cells" in the journal *Proceedings of the National Academy of Sciences*. Dr. Sette was senior author on the paper and Daniela Weiskopf, Ph.D., who works with Dr. Sette, was first author. Sujan Shresta, Ph.D., and Bjoern Peters, Ph.D. were significant contributors. They both head research labs at the La Jolla Institute.

In the study, researchers analyzed blood samples from 250 people in Sri Lanka, an island in the Indian Ocean, where dengue virus is endemic, screening the blood for exposure to all four dengue virus serotypes. "We found that the participant's T cells recognized and responded to all dengue virus proteins and we also identified the specific virus pieces that

trigger the strongest T cell attack," says Dr. Weiskopf. "People knew that some of the virus proteins were targeted by T cells, but we have created the most comprehensive picture to date, which could be very useful in creating a vaccine or treatment."

The researchers also showed that genetic differences impact how people will react to dengue infection. "We tested people's HLA molecules, which determine tissue type, and found that certain HLA types produce a strong T cell response that is associated with resistance to the disease, while other genetic variants are associated with a weaker T cell response, which led to poor protection," says Dr. Sette. These findings further confirmed his belief of the T cell's protective role in dengue infection.

La Jolla Institute scientist Sujan Shresta, Ph.D., an international expert on dengue virus infection, notes that the study results confirm in humans what her lab studies found in mice in 2009. "We showed that CD8 positive T cells play a very important role in controlling dengue infection in mouse models," she says. "I am not saying that antibodies are not important, but rather that T cells are also needed to induce strong protection against dengue."

The mouse study was one of several major dengue findings by Dr. Shresta, who is also credited, along with another lab, with proving the controversial theory – first put forth by dengue research leader Scott Halstead, M.D.—that antibodies can, under certain circumstances, enhance rather than protect from dengue infection. Those results, announced in 2009, have figured prominently in the worldwide landscape of dengue vaccine development, and led to the conclusion that any successful vaccine must protect against all four serotypes.

"This latest paper from our research institute provides more vital data that will move the field closer to developing a safe and effective dengue vaccine," adds Dr. Shresta.

Provided by La Jolla Institute for Allergy and Immunology