Researchers team up to find new target for dengue virus vaccine

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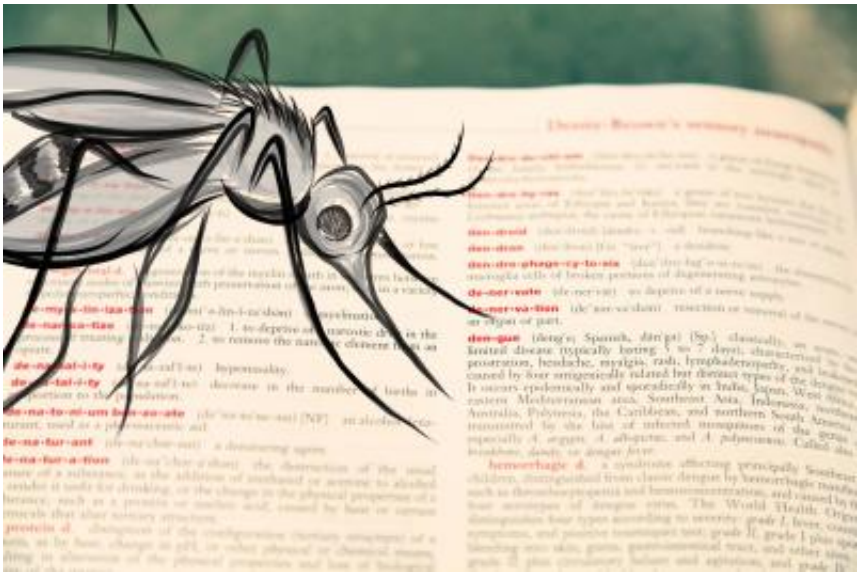

The dengue virus infects approximately 390 million people around the world every year. Credit: Max Englund, UNC Health Care

Creating a vaccine that protects people from all four types of dengue virus has frustrated scientists for decades. But researchers at the University of North Carolina have discovered a new target for human antibodies that could hold the key to a vaccine for the world's most widespread mosquito-borne disease.

Using an experimental technique new to the dengue field, the labs of Ralph Baric, PhD, and Aravinda de Silva, PhD, showed that a molecular

hinge where two regions of a protein connect is where natural human antibodies attach to dengue 3 to disable it. The finding, published in the *Proceedings of the National Academy of Sciences*, shows that after primary infection most human antibodies that neutralize the virus bind to the hinge region.

It's the first study to demonstrate how these binding sites – composed of just 25 amino acids – can be genetically swapped out for amino acids from another dengue type without disrupting the integrity of the virus.

"This gives us a lot of insight into how human antibodies work," said de Silva, a professor of microbiology and immunology in the UNC School of Medicine. "And there could be a lot of translational aspects to this; it could lead to a new way to create vaccines for other diseases."

De Silva and Baric, a professor with a dual appointment in the UNC School of Medicine and the UNC Gillings School of Global Public Health, are now working with vaccine developers at two pharmaceutical companies to test the effectiveness of potential dengue vaccines now in clinical trials. If these vaccines don't bind to their molecular hinge, then the vaccines will likely prove less effective than researchers would like, especially over time.

Dengue, which infects approximately 390 million people each year, is common in tropical and subtropical regions around the world. There were 63 confirmed cases in the Florida Keys in 2010. The virus, widespread in the United States territory of Puerto Rico, has also been confirmed in mainland south Florida and Texas. "The mosquitos that can carry dengue exist throughout the southeastern United States," Baric said. "It's just a matter of time before dengue virus reemerges in the South, making vaccines and therapeutics a critical long-term public health priority."

Making a truly effective dengue vaccine has proven difficult because of a phenomenon called antibody dependent enhancement. People infected with one type of dengue usually develop a natural immune response that rids the body of the virus and prevents a repeat infection of that same virus type. But if those people are infected with a second type of dengue, the virus is enhanced because of that first immune response. The result can be severe dengue hemorrhagic fever, which can be deadly.

Consequently, a vaccine that offers immunity for only one type of dengue would make other types of dengue more virulent and dangerous. The first large clinical trial of a dengue vaccine, conducted in Thailand in 2011, contained a cocktail of all four types of dengue. But for reasons that remain unclear the vaccine was just partially protective. There was no evidence that the vaccine protected people during a dengue 2 outbreak that same year.

To study dengue, de Silva and colleagues have collected samples from infected Sri Lankans and from Americans who had acquired the disease while abroad. Such samples allowed de Silva's team to find that human antibodies are not the same as mouse antibodies, which had served as the basis for vaccine development. De Silva saw that mouse antibodies latched onto a region of a protein that forms an outer shell of the virus. Human antibodies rarely recognize that region; instead human antibodies bind to a different region where two parts of the outer protein connect. De Silva calls this region an epitope hinge. An epitope is any part of a foreign substance that a human antibody binds to.

To prove the importance of the hinge, de Silva recruited Baric, an expert in pioneering novel ways to manipulate genes in viruses using primarily noroviruses and coronaviruses as models. Using de Silva's dengue expertise and the structure of the dengue virus, Baric was able to pinpoint the structurally complex, nonlinear 25-amino-acid hinge domain and remove it from dengue 3 particles. His group, led by

William Messer, PhD, then developed strategies to recover dengue viruses from DNA clones and replace the dengue 3 hinge with a replicated 25-amino-acid chain from dengue 4. Essentially, Baric turned dengue 3 into dengue 4.

The genetically mutated virus survived and grew in cell cultures and in primates. Then the researchers exposed the mutant virus to dengue 3 antibodies, which typically bind to dengue 3. But they had no effect on the genetically modified dengue. They then showed in cell lines that the virus could be neutralized by antibodies directed against dengue 4. In collaboration with researchers at the University of Puerto Rico, de Silva and Baric's team was able to show that the new virus infected primates, which developed antibodies against dengue 4.

"These results amount to a paradigm shift," Baric said. De Silva added, "This told told us that the epitope we thought was important was indeed the main site for antibody binding. If antibodies had been able to bind to other sites on the virus, then we would have seen a small drop in protection against dengue 3." Some antibodies would have bound to those other sites and offered some level of protection. "Instead, we saw a complete loss of protection."

De Silva and Baric are conducting similar experiments with dengue 1 and 3. If they can isolate the major epitopes for each dengue type, then they could potentially genetically modify a virus with all four epitopes. The result could become the basis for a vaccine against all four types.

De Silva and Baric are using their results to study why antibodies bind to a specific epitope but not to other sites. Such information would lend even more insight into how to design effective vaccines.

Also, de Silva and Baric's research could be translated into other fields in need of vaccines. "The general idea is that a complex protein-interaction

site can now be moved from one virus to another," de Silva said. For instance, an epitope from a virus like hepatitis C could be moved onto the live virus used in the measles vaccine. This new chimeric virus would simultaneously offer people protection against hepatitis C and measles.

"We might not even need a virus," de Silva added. "We might just need to create the epitope that we know antibodies can bind to. And that would serve as the vaccine."

De Silva and Baric recently obtained NIH funding to continue their pioneering work to solve the decades-old dengue virus vaccine dilemma.

Provided by University of North Carolina Health Care

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