New approach for making vaccines for deadly diseases

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Credit: National Cancer Institute

Researchers at the Perelman School of Medicine at the University of Pennsylvania have devised an entirely new approach to vaccines - creating immunity without vaccination.

The study, published in *Scientific Reports*, demonstrated that animals injected with synthetic DNA engineered to encode a specific

neutralizing antibody against the dengue virus were capable of producing the exact antibodies necessary to protect against disease, without the need for standard antigen-based vaccination. Importantly, this approach, termed DMAb, was rapid, protecting animals within a week of administration.

Dengue virus is one of the most important mosquito-borne viral infections in humans. Nearly 400 million dengue infections occur each year, and cases of dengue fever and the potentially fatal Dengue hemorrhagic fever/dengue shock syndrome have grown in recent decades. The geographical reach of dengue has expanded to include over 100 countries, resulting in a significant health and economic burden worldwide.

Although vaccines are being developed to fight dengue virus, none are currently available that provide balanced protection against all four dengue viral strains, or serotypes. Patients who are infected with one serotype develop protective immunity against that serotype alone - however, this immunity oddly leaves patients vulnerable for severe disease if future infections are caused by a different serotype.

Paradoxical Reaction

One strong theory for this paradoxical reaction to new dengue infections involves the antibodies the body makes in response to infection. Antibodies have two important regions that give them their power: one end, known as the variable region, recognizes target proteins, such as those on the surface of a dengue virus particle. The other end, known as the constant region, binds to receptors on the surface of cells that can direct the immune system to respond in a variety of ways, all in the hopes of eliminating the target on the variable end of the antibody.

However, the dengue virus uses this natural process to its advantage: the

cells that recognize the constant region of an antibody are the exact cells dengue virus prefers to infect. When low levels of antibodies from a previous dengue infection sense a new serotype is around, they weakly bind to the different serotype, lead it to cells with receptors for their constant regions, and the new serotype ultimately enters those cells. The Dengue virus can then infect these cells, leading to greater levels of virus production and enhanced, sometimes lethal, disease. Many researchers have explored ways to eliminate cell receptors from recognizing the constant region of dengue antibodies; however, traditional immunization techniques are generally incapable of creating antibodies that cannot bind to these receptors.

In the current study, the DNA used to encode the neutralizing antibodies against dengue virus was altered to produce a neutralizing antibody that does not bind to cell receptors, effectively eliminating the chance for dengue infection to lead to enhanced, lethal disease.

"Engineering novel methods of delivering monoclonal antibodies could be an important approach in the fight against infection and in unique treatment situations," said senior author David B. Weiner, PhD, a professor of Pathology and Laboratory Medicine and chair of the Gene Therapy and Vaccine Program. "We can produce a synthetic immune response by encoding an antibody and delivering it as a non-live, non-viral, non-permanent antibody."

Technology Shift

Over the last few decades, monoclonal antibodies (mAbs) have become one of the most important approaches to treating a variety of diseases, including cancers, autoimmune disorders, and, to a smaller degree, infectious diseases. However, they remain expensive and require time-consuming processes to produce and study.

Traditionally, mAbs are manufactured outside of the body, in costly, large-scale cell culture laboratory. Since antibodies eventually break down over time, mAbs in the clinic require frequent repeat administrations, further increasing costs. DMAbs, which are produced in the body, have the potential to overcome many of these limitations, reducing cost barriers that would allow such technologically advanced therapies to reach more populations around the globe.

The study's lead author, Seleeke Flingai, a doctoral candidate in the Weiner lab, said the rapidity of protection, along with the ability to tailor the exact features of a protective antibody - including those that cannot be created by a traditional vaccination response - give the DMAb platform great versatility.

In the study, mice given a lethal dose of dengue virus less than a week after receiving the protective DMAb were completely protected from lethal disease - significantly more rapid than vaccine-driven protection, which can take weeks to months to reach peak efficacy levels.

"One intramuscular injection of our DMAb was able to protect these animals from severe disease and death," Flingai said.

"The rapid induction of immunity may be advantageous to unique populations, including travelers, as well as the elderly or other populations who respond poorly to vaccines," Weiner noted. "Travelers to endemic regions frequently receive a number of intramuscular vaccinations prior to travel. We can envision this approach being included alongside normal travel immunization regimens."

The next step will be to demonstrate efficacy in larger animal models, as well as test whether this approach can be used to protect against or treat other diseases.

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