New tobacco plant produced therapeutics effective against West Nile virus, even days after infection

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An international research group led by Arizona State University professor Qiang "Shawn" Chen has developed a new generation of potentially safer and more cost-effective therapeutics against West Nile virus, and other pathogens.

The therapeutics, known as monoclonal antibodies (MAbs) and their derivatives, were shown to neutralize and protect mice against a lethal dose challenge of West Nile virus—-even as late as 4 days after the initial infection.

"The overarching goal of our research is to create an innovative, yet sustainable and accessible, low cost solution to combat the global threat of West Nile virus," said Chen, a researcher at Arizona State University's Biodesign Institute and professor in the Department of TEIM.

West Nile virus is spread by infected mosquitoes, and targets the central nervous system. It can be a serious, life-altering and even fatal disease and currently, there is no cure or drug treatment against West Nile virus, which has been widely spread across the U.S., Canada, Latin America and the Caribbean.

"The goal of this latest research was twofold," said Chen. "First, we wanted to show proof-of-concept, demonstrating that tobacco plants can be used to manufacture large and complex MAb-based therapeutics. Secondly, we've wanted to improve the delivery of the therapeutic into the brain to combat West Nile virus at the place where it does the greatest harm."

The study appears in the March 27 online edition of *PLOS ONE*. Along with Chen, the research team included Junyun He, Huafang "Lily" Lai, Michael Engle, Sergey Gorlatov, Clemens Gruber, Herta Steinkellner and long-time Washington University collaborator Michael S. Diamond.

Chen's group has been a pioneer in producing MAbs as therapeutic candidates in plants, including tobacco and lettuce plants. A couple of years ago, his team demonstrated that their first candidate, pHu-E16, could neutralize West Nile infection and protect mice from exposure. MAbs target proteins found on the surface of West Nile virus.

However, this antibody was not to be able to accumulate at high levels in the brain.

One approach to tackle this challenge is to program into the therapeutic antibodies the capability of binding to receptors that can help the MAbs to cross into the brain. Chen wanted to use this strategy to produce a more effective way to combat West Nile virus.

In the new study, they improved upon their pHu-E16 design, making half a dozen new variants that could, for the first time, lead to the development of MAbs that effectively target the brain and neutralize West Nile virus.

Mice were infected with a lethal dose of West Nile virus, and increasing amounts of a MAb therapeutic were delivered as a single dose the same day of infection. In another experiment, Chen's team tested whether the therapeutic, called Tetra pHu-E16, could be effective after infection. In this case, the therapeutic was administered 4 days after West Nile virus infection, when the virus has already spread to the brain. In each case, they protected up to 90 percent of the mice from lethal infection.

This is the first instance of such an effect and makes possible neutralizing West Nile virus even after infection by a tetravalent MAb. The tetravalent MAbs design will offer the researchers greater

flexibility toward selection of disease, tissue and antigen targets.

For Chen, this also gives promise to his team developing a plant-based system to dramatically reduce the costs of commercial manufacturing of MAbs.

"This study is a major step forward for plant-based MAbs, and also demonstrates for the first time the capacity of plants to express and assemble large, complex and functional tetravalent MAb complexes," said Chen.

MAbs are a hot and highly competitive research field, having been shown to effectively target cancer, autoimmune and inflammatory diseases. Now a $60 billion market for the biotechnology and pharmaceutical sectors, growth of the market has been hampered by high development costs of producing these in animal cell systems, which when factoring in a long period for manufacturing, R&D and clinical trials, may reach around $1 billion per each therapeutic candidate.

Therapeutic MAbs are typically made in animal host cells and assembled into Y-shaped complexes. Until now, tetravalent MAbs had never been made in a plant system before. To make the potential therapeutics, the group is able to use young tobacco plants and a protein expression system to make and harvest the proteins in the leaves.

For the study, MAbs were rapidly produced in tobacco plants in as little as ten days, giving promise to change the image of scourged product that causes lung cancer into a manufacturing system for societal benefits against infectious diseases.

"It is our hope that these results may usher in new age of cost-effective, MAbs therapeutics against WNV and other neurological diseases," said Chen. "Our next step is to move this forward with the development of bifunctional MAbs that can target to the brain with the ultimate goal of entering human clinical trials."

Provided by Arizona State University