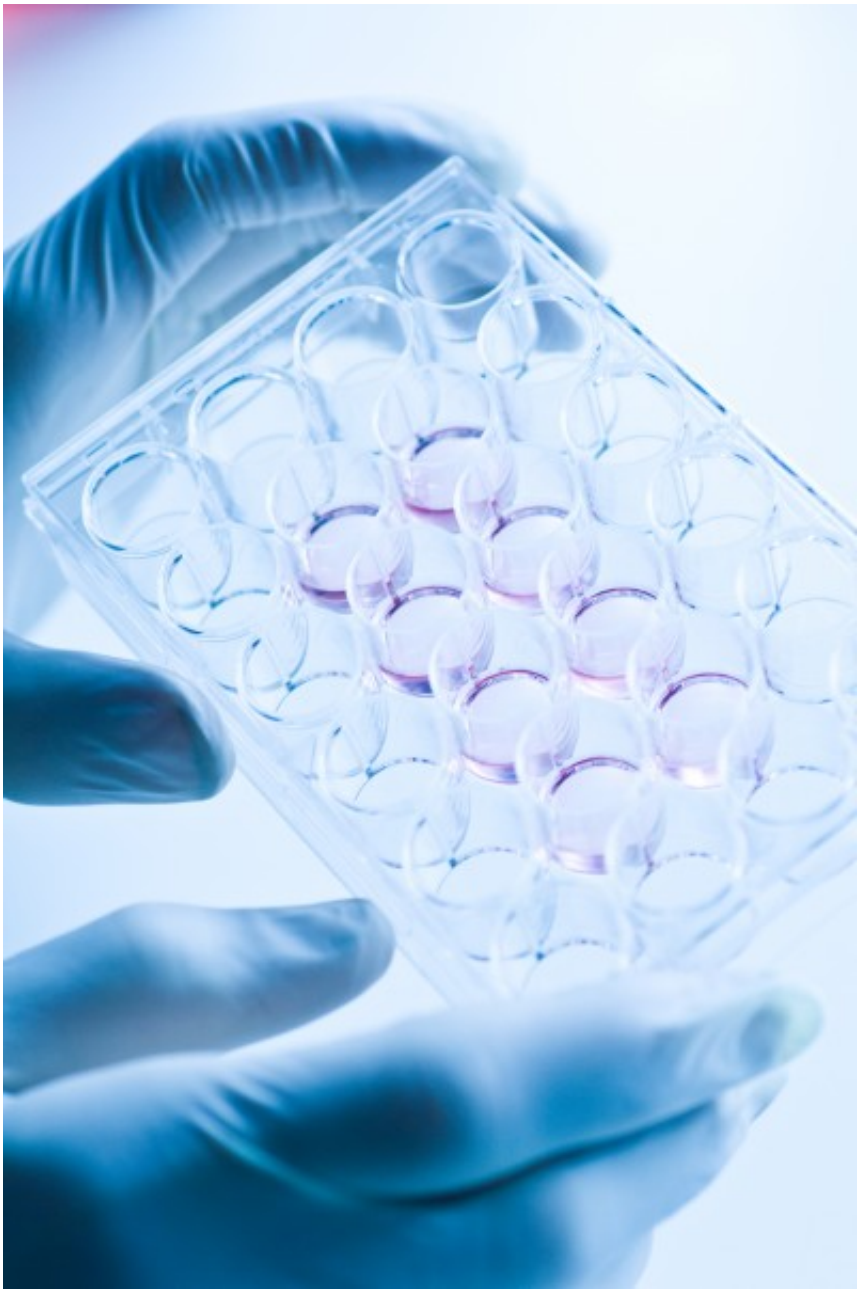
Protein discovery fuels re-design of mosquito-based malaria vaccine

June 16 2015



A promising type of vaccine designed to eradicate malaria by blocking parasite transmission could be a step closer, as a result of experts uncovering new information about the targeted protein.

The international team of researchers co-led by Dr Natalie Borg from the Department of Biochemistry and Molecular Biology at Monash University, and Dr Rhoel Dinglasan from the Malaria Research Institute at the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA, focused on a protein in the Anopheles mosquito midgut called AnAPN1.

The research, published in the journal *Nature Structural & Molecular Biology*, provides for the first time, detailed information on the shape of AnAPN1 and where antibodies against AnAPN1 that can and can't block parasite development, bind to the protein.

Malaria is transmitted to humans by the bite of a mosquito infected with the Plasmodium parasite. Malaria transmission-blocking vaccines are designed to prevent the spread of malaria by interrupting parasite transmission.

Vaccinated individuals in malaria-endemic countries produce antibodies to AnAPN1. During routine disease transmission, when these same immunised individuals become infected with malaria parasites, both antibodies and parasites are ingested by a mosquito during blood feeding. The antibodies block parasite development in the mosquito, breaking the cycle of transmission.

The AnAPN1 protein is a leading candidate for a mosquito-based

malaria transmission-blocking vaccine that is being developed by Dr Dinglasan.

"This type of vaccine won't boost people's immunity to malaria, but instead it will provide a delayed benefit to the individual by protecting the entire community from parasite transmission," Dr Dinglasan said.

"Ultimately it could lead to a reduced number of infected mosquitoes and the eventual elimination and eradication of the disease," he said.

AnAPN1 is found on the mosquito gut and is potentially a receptor for the parasite. Dr Dinglasan said as a vaccine antigen, AnAPN1 prompts people to make antibodies; however only some of these antibodies block parasite transmission, while others do not.

"This dilution of the overall antibody response to AnAPN1 is problematic. To further improve vaccine immunogenicity at the preclinical stage, we need to immuno-focus the antibody response to only the critical, 'transmission-blocking' regions of the protein," he said.

An understanding of how AnAPN1 antibodies that are generated can block parasite transmission to mosquitoes and their binding region on AnAPN1 has remained elusive until now. Using the Australian Synchrotron, Dr Borg's team at Monash University were able to visualise the crystal structure of the AnAPN1 protein for the first time, providing valuable insights. Dr Dinglasan's team then provided the critical functional data to support the hypotheses generated by the AnAPN1 structure.

"The Australian Synchrotron was critical in providing detailed imaging of the structure of AnAPN1. In combination with other experimental data, the structure enabled us to pinpoint the binding site of AnAPN1 antibodies that can and can't block parasite development," Dr Borg said.

"We now know much more about which parts of the AnAPN1 protein are involved in generating transmission-blocking antibodies and have a new hypothesis as to how they might work," she said.

This discovery will fuel further work to understand what critical interaction the AnAPN1 transmission-blocking antibodies are blocking. It will also prompt the redesign of the AnAPN1 antigen to make it more effective.

More information: The Anopheles-midgut APN1 structure reveals a new malaria transmission–blocking vaccine epitope, DOI: 10.1038/nsmb.3048

Provided by Monash University