Fact Sheet: Top Australian Scientists Collaborate to Develop Blood-Stage Antigens for Malaria Vaccines

The Project: Exploring the Potential of Five Blood-Stage Antigens

In 2001, the PATH Malaria Vaccine Initiative (MVI) entered into three collaborative partnerships in Australia to develop five blood-stage antigens (proteins from the parasite) into potential malaria vaccines. The projects' current scope is to produce vaccines under current good manufacturing practice (cGMP) requirements for use in clinical trials. The long-term goal is to create vaccines that will prevent death and severe disease in children in the developing world.

Merozoite Surface Protein 2 (MSP-2)

MSP-2 is a blood-stage antigen that appears essential for the *Plasmodium falciparum*, the most deadly malaria parasite, to function. Most people living in areas with intense transmission of *P. falciparum* develop an immune response to MSP-2 by age five. GroPep Ltd. and researchers at La Trobe University have developed the production process for two forms of MSP-2 (3D7 and FC27). GroPep will manufacture the antigens for use in clinical trials. CSL Limited will formulate the vaccine using a number of promising adjuvant technologies intended to enhance the body's immune response. LaTrobe will conduct immunogenicity studies, and then CSL Limited will manufacture the vaccines for clinical trials. The 3D7 form of MSP-2 was part of a previous vaccine candidate that appeared to reduce the number of parasites in the blood when evaluated in malaria-infected children in Papua New Guinea. Decreasing the number of parasites could reduce the severity of disease in someone infected with malaria. If the vaccines perform as hoped in initial clinical trials, field trials would be envisioned.

Merozoite Surface Proteins 4 and 5 (MSP-4 and MSP-5)

MSP-4 and MSP-5 are blood-stage antigens with the potential to induce an immune response before the parasite has a chance to cause illness. This project links public-sector scientists at Monash University with the biopharmaceutical company, CSL Limited, in order to complete development of laboratory and industrial scale production processes, formulation, pre-clinical testing, cGMP manufacture, and regulatory documentation for MSP-4 and -5. If all pre-clinical milestones are met, the intent is to drive the two vaccine candidates into clinical trials under a new agreement.

Rhoptry Associated Protein 2 (RAP-2)

It is possible that RAP-2 could decrease parasite growth rates during the blood stage and inhibit the parasite from invading red blood cells. This project, based on early development work by the Cooperative Research Centre for Vaccine Technology at Queensland Institute of Medical Research (QIMR), partners QIMR with the Commonwealth Scientific & Industrial Research Organisation (CSIRO) to develop a cGMP production process and optimize the formulation for pre-clinical safety testing. RAP-2 is difficult to isolate and purify, so development of an industrial-scale production process adds technical risk to the project. If all the pre-clinical development milestones are achieved, the partnership would seek approval to begin clinical trials.

The Potential: Mimicking natural immunity to prevent severe illness in children

The malaria parasite passes through several stages once inside the body, changing form at each stage. After the mosquito injects sporozoites into the body, they enter the liver within minutes and develop into merozoites over seven to ten days. Exiting the liver, tens of thousands of merozoites invade red blood cells, multiply rapidly, and cause the cells to burst. It is at this stage, the blood stage, that the infected person becomes sick. Some merozoites mature into forms that are taken up by other mosquitoes when they feed on infected people. The parasite is poised to begin its cycle again when new sporozoites form in the infected mosquito.

The Australian projects focus on blood-stage antigens that were discovered by public-sector scientists and have the potential to prevent the malaria parasite from causing severe disease and death. Many adults that carry the parasite do not get sick because they have developed partial immunity to the parasite in the blood stage of its life cycle. A vaccine that could prompt such immunity in children would be a considerable achievement.

The Partners:

Australia possesses an exceptional wealth of knowledge about the basic behavior of the malaria parasite. Scientists in Australia, however, have lacked the resources required to drive their vaccine candidates from the laboratory into cGMP manufacture for clinical trials.

Each of the partnerships links academic investigators and commercial biotechnology firms to translate laboratory discoveries into vaccines suitable for clinical evaluation. This academia-industry collaboration is critical in building the necessary bridge between excellent research (the domain of universities and research institutions) and product development (a core strength of industry).

Because of the complexity of the malaria parasite and its interaction with its human host, many scientists hypothesize that a vaccine combining two or more antigens has a better chance of offering maximum protection against the disease. The three MVI-supported projects in Australia are developing their vaccine candidates in a way that will allow them to be combined with other antigens, potentially increasing the chances of successfully protecting against malaria disease.

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The **Australian Cooperative Research Centre for Vaccine Technology (CRC-VT)** is an unincorporated research joint venture comprising three universities, two medical research institutes, Australia's premier government research organisation, CSIRO, and two industry users. The CRC-VT's research is focused on human and veterinary vaccines, which are developed by the CRC-VT parties to proof-of-principle and in some cases, into Phase 1 clinical trials. For more information, visit www.crc-vt.qimr.edu.au.

Commonwealth Science and Industrial Research Organisation (CSIRO) is one of the world's largest and most diverse scientific global research organisations. CSIRO focuses on providing new ways to improve quality of life, as well as the economic and social performance of a number of industry sectors through research and development. For more information, visit http://www.csiro.au.

GroPep is a biopharmaceutical company that develops, manufactures, and commercializes products that bring significant benefit to human health. GroPep develops biopharmaceuticals from preclinical proof-of-concept through clinical trials. Late stage clinical development and marketing of successful products is licensed to major pharmaceutical companies. GroPep develops, manufactures, and markets products used in the discovery, development, and manufacture of new pharmaceuticals. For more information, visit www.gropep.com.au.

CSL Limited is the parent company of the CSL Group. Business operations are carried out through CSL's Bioplasma, Pharmaceutical and Biosciences. CSL's Pharmaceutical Group develops, manufactures, and markets biological products for human use and markets vaccines and other prescription pharmaceuticals in Australia and New Zealand for international partners. CSL's research and development team works in late stage research, early stage development, clinical trials, product registration, and market entry. Based in Melbourne, Australia, the CSL Group has subsidiaries in New Zealand, the United States, and Europe. For more information, visit http://www.csl.com.au.

La Trobe University is acknowledged as one of the finest research universities in Australia, with many researchers and scholars who are recognized worldwide for their outstanding contributions. For more information, visit www.latrobe.edu.au.

Monash University is Australia's most internationalized university, with eight campuses including one in Malaysia, one in South Africa, and centers in London, United Kingdom and Prato, Italy. The university's Department of Microbiology is home to a specialist repository of information of use to malaria researchers. For more information, visit www.med.monash.edu.au/microbiology.

The **Queensland Institute of Medical Research (QIMR)** is one of the largest medical research institutes in the southern hemisphere, and is recognized worldwide for the quality of its research. Originally established to further the study of tropical diseases in North Queensland, QIMR has over its 60 years' history, broadened its scope to include the immunological, biological, and molecular basis of a wide range of infectious diseases, cancers, and other disorders. QIMR has also built a strong research stream in epidemiology, the study of the environmental, lifestyle, and genetic factors that contribute to disease incidence among populations. For more information, visit www.qimr.edu.au.

PATH is an international, non-profit organization that creates sustainable, culturally relevant solutions enabling communities worldwide to break longstanding cycles of poor health. For more information, please visit www.path.org. The **PATH Malaria Vaccine Initiative (MVI)** is a global program established through an initial grant of $50 million from the Bill & Melinda Gates Foundation, which has since invested an additional $207.6 million in the program. This funding is a crucial part of the support needed. MVI's mission is to accelerate the development of promising malaria vaccines and ensure their availability and accessibility in the developing world. For information, visit www.malariavaccine.org.