

## **Important steps towards the development of a human vaccine against malaria based on live, but weakened, parasites**

Every day 2000 children die from malaria in Africa alone. The infection is transmitted from human to human by biting mosquitoes and remains one of the world's most devastating diseases. Despite many years of effort a vaccine is still not available but is urgently needed, if we are to make an impact on this enormous problem.

Continual exposure can generate protection against malaria and can be acquired through an exposure to a high number of infectious mosquito bites. Parasites that are injected by a mosquito first migrate to the liver where they mature and then are released into the blood circulation and it is only here that they cause disease and fatal complications.

A very promising method for vaccination is to sufficiently weaken parasites such that they invade liver cells but then are not able to develop any further. It is, however, required that these attenuated parasites are still able to stimulate a good immune response in the liver. This can be achieved by irradiating the parasites or by genetically inactivating individual parasite genes that are active during the parasites growth in the liver. Researchers from Nijmegen and Leiden have now characterized a large number of parasite proteins ('proteome') that are present only during liver stage development and therefore are potential targets for inactivation (PLoS Pathogen<sup>1</sup>).

The research groups had previously shown that protection in mice can be achieved by vaccinating mice with a rodent malaria which had one of these liver stage genes removed, specifically p36p. Moreover, the protection was long lasting and virtually complete (PNAS<sup>2</sup>). Now, these same researchers from Nijmegen and Leiden have succeeded in making the first critical transition from the rodent system to humans by inactivating the equivalent gene (p52) in the most important human malaria parasite, *P. falciparum* (PLoS ONE<sup>3</sup>). Similar to the results with the rodent parasite, these human parasites are unable to develop in liver cells. This is the first time that genetic modification of a human parasite results in its growth arrest in a liver cell, opening up exciting possibilities for its use as a human vaccine.

These studies form part of a collaborative project with the American company Sanaria ([www.sanaria.com](http://www.sanaria.com)), whose sole purpose is develop a whole organism malaria parasite vaccine for use in humans, and is funded by TI-Pharma. These studies show how results obtained in rodent models of malaria can be pipelined to form the basis for clinical development of anti-malaria vaccines in humans.

Prof. Dr. R. Sauerwein, Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; e-mail: [r.sauerwein@mmb.umcn.nl](mailto:r.sauerwein@mmb.umcn.nl); tel. +31 24-3610577.

Dr. C.J. Janse, Leiden Malaria Research Group, LUMC, Leiden, the Netherlands; e-mail: [c.j.janse@lumc.nl](mailto:c.j.janse@lumc.nl); tel. +31 71-5265062

A. M. Richman, Sanaria Inc. Media contact ; e-mail: [arichman@sanaria.com](mailto:arichman@sanaria.com); tel. +240-403-2726

<sup>1</sup> Edwin Lasonder, Chris J. Janse, Geert-Jan van Gemert, Gunnar R. Mair, Adriaan M. W. Vermunt, Bruno G. Douradinha, Vera van Noort, Martijn A. Huynen, Adrian J.F. Luty, Hans Kroeze, Shahid M. Khan, Robert W. Sauerwein, Andrew P. Waters, Matthias Mann & Hendrik G. Stunnenberg

**Proteomic profiling of *Plasmodium* sporozoite maturation identifies new proteins essential for parasite development and infectivity**

PLoS Pathogen 2008, in press

<sup>2</sup> van Dijk MR, Douradinha B, Franke-Fayard B, Heussler V, van Dooren MW, van Schaijk B, van Gemert GJ, Sauerwein RW, Mota MM, Waters AP, Janse CJ. (2005). **Genetically attenuated, P36p-deficient malarial sporozoites induce protective immunity and apoptosis of infected liver cells.** Proc Natl Acad Sci U S A, 102:12194-9

<sup>3</sup> Ben C.L. van Schaijk, Chris J. Janse, Geert-Jan van Gemert, Melissa R. van Dijk, Audrey Gego Jean-Francois Franetich, Marga van de Vegte-Bolmer, Samir Yalaouic, Olivier Silvie, Stephen L. Hoffman, Andrew P. Waters, Dominique Mazier, Robert W. Sauerwein, Shahid M. Khan

**Gene disruption of *Plasmodium falciparum* p52 results in attenuation of malaria liver stage development in cultured primary human hepatocytes**

PLoS ONE 2008, in press