Healthcare industry BW

Campaign to eradicate malaria

After many decades, efforts to develop an effective vaccine against malaria have finally brought researchers closer to their goal. However, the goal of eradicating malaria completely can only be reached through a complex strategy, to which researchers from Heidelberg are making intensive contributions.

Anopheles mosquito
© TLB

The most devastating plague is not AIDS but malaria, an infectious disease caused by a eukaryotic parasite of the genus Plasmodium transmitted by Anopheles mosquitoes. Every year, there are around 300 million cases of malaria, killing between one and three million people. Children under five are the most severely affected. In some areas of Africa, one in four children dies from primary Plasmodium falciparum infections. P. falciparum causes malaria tropica, one of the most severe forms of malaria.

Changing parasites make the eradication of malaria difficult

Despite many decades of intensive research, an effective malaria vaccine is not yet available. Many sound research approaches have unfortunately not yet had the desired effect. The major problem is the very complex life cycle of parasites. In humans, plasmodia change their form and go through several intracellular stages in the liver and red blood cells. This makes the search for antigens, which would enable the human immune system to recognise and combat the parasites, very difficult. An effective malaria vaccine needs to induce an antibody reaction as well as a T-cell response in order to prevent the plasmodia from infesting cells at the same time as enabling the destruction of already infected cells.

Vaccination campaign in Burkina Faso
© www.malariavaccine.org

The most advanced malaria vaccine candidate, RTS,S developed by GlaxoSmithKline (Mosquirix®) is based on a recombinant protein that is composed of parts of a P. falciparum surface protein (circumsporozoite protein, CSP) and the hepatitis B surface antigen. The vaccine, which is boosted by the addition of a special adjuvant, is designed to provide protection in the first phases of infection. A Phase III trial is currently being carried out at eleven sites in Africa (including Burkina Faso, see photo). The results gained in a clinical Phase II study suggest that it is possible to reduce the number of infections by 50 per cent. No information is available as to how long the protection provided by the vaccination lasts. The Phase III trial, which costs around 100 million US Dollar, is being financed by the Malaria Vaccine Initiative (MVI), a public private partnership working for the development of malaria vaccines and that is funded primarily by the Bill & Melinda Gates Foundation.

Combination strategies

It is envisaged that Mosquirix® will be launched in 2011 or sometime after. It is believed that the vaccine will save the lives of many children. The eradication of malaria, the stated goal of Bill and Melinda Gates' financial support in 2007, which they reiterated in January 2010, cannot be achieved with this vaccine alone. The researchers hope to achieve a multiplication effect with combination vaccines (e.g., in combination with a T-cell vaccine). MVI is now looking for partners to finance the development of vaccines that would prevent the transmission of the malaria parasites. Such vaccines would not directly better the lot of individuals, but rather combat the disease on the population level.

The University of Heidelberg is involved in many projects focusing on the fight against malaria. In 1999, the German Research Foundation (DFG) established the collaborative research centre entitled "Control of tropical infectious diseases" (SFB 544) in Heidelberg. Numerous SFB 544 projects deal with malaria. Dr. Hans-Georg Kräusslich, executive director of the Department of Infectiology (formerly Hygiene Institute), is the spokesman of the SFB which has a number of long-term collaborations, including the exchange of scientists, with the Centre de Recherche en Santé in Nouna, Burkina Faso. This research centre, which is also supported by the Baden-Württemberg government, was established as a joint project between the Burkina Faso Ministry of Health and the University of Heidelberg.

Attenuated, living parasites as antigens

Prof. Dr. Michael Lanzer

Scientists in the Department of Infectious Diseases/Parasitology led by Prof. Dr. Michael Lanzer have used a new strategy for developing a malaria vaccine based on the observation that the human immune system is to some degree able to fend off P. falciparum. People who have survived previous infections can still become infected but the progression of the disease is no longer life-threatening. Certain individuals have acquired a partial immunity to the parasite and scientists are now working to boost this immunological response.

The Heidelberg researchers used a Plasmodium strain found in rodents (P. berghei). The researchers silenced a gene (UIS3) which the parasite needs in order to turn into infectious blood stages. The attenuated pathogens were propagated in the alternate host, the Anopheles mosquito, and were transferred to the mice via a mosquito bite. Plasmodium then accumulated in the liver. However, the pathogens were unable to develop into merozoites, which enter the erythrocytes. The results gained with the mouse-malaria model are now being transferred to P. falciparum, which leads to severe malaria tropica infections in humans. P. falciparum requires the same genes for its development. The living, genetically attenuated parasites might possibly be used as experimental "whole-organism" vaccines. Dr. Kai Matuschewski was awarded the Joachim Siebeneicher Foundation research prize of 50,000 euros in 2006 for this work. In 2009, Matuschewski became the director of the Department of Parasitology at the Max Planck Institute for Infection Biology in Berlin.

MSP-1, a promising vaccine candidate

When he was head of Biological Research at Hoffman-La Roche in Basel, Switzerland, Prof. Dr. Hermann Bujard established a research programme to develop a malaria vaccine, research that he then continued when he moved on to the Centre for Molecular Biology in Heidelberg (ZMBH, 1986 – 2007).

Bujard's team is mainly interested in MSP-1 (merozoite surface protein), which is the major protein on the surface of the merozoite cells. MSP-1 plays a key role in the invasion of the erythrocytes through the merozoites. Bujard gives several reasons why MSP-1 is one of the most promising vaccine candidates for malaria tropica, for example: 1) Vaccination with MSP-1 leads to a humoral immune response in animal models. 2) There is a positive correlation between MSP-1-specific antibody titres and a decreased risk of re-infection. 3) The adoptive transfer of MSP-1-specific CD8+ cells also provides protection in the mouse model, which suggests that the liver exerts a cellular immune response against the infectious plasmodium stages. 4) The antigen has numerous T- and B-

Prof. Dr. Dr. h.c. Hermann Bujard

cell epitopes for a multivalent immune response directed against parasite growth. A vaccine based on the whole MSP-1 molecule is therefore believed to be suitable to counteract potential resistances and genetic differences in the immune response of recipients.

When Bujard was appointed Executive Director of the European Molecular Biology Organisation (EMBO) in 2007, the work with MSP-1 and vaccine development was continued by the Division of Parasitology of the Department of Infectiology (see link in top right-hand corner: BIOPRO article of 12th Feb. 2008: Hermann Bujard - a passionate basic researcher). The MSP-1 protein which is expressed in E. coli can be isolated in highly pure form. The production of the vaccine candidate is being prepared and Bujard envisages that the researchers will be able to commence a clinical Phase I trial in 2010. The subsequent field studies in Africa will most likely take three to four years.

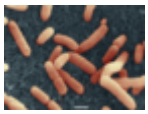
If one idea fails, other options remain

In the annual letter of the Bill and Melinda Gates Foundation published in January 2010, Bill Gates said: "The current tools alone will not be enough. To eradicate the disease we almost certainly need a malaria vaccine, which is the highest-risk malaria work we fund. The key here is that researchers are pursuing a lot of different ideas, so if one fails, there are still other options."

Article

15-Mar-2010
EJ
BioRN

The article is part of the following dossiers



Human infectious diseases: new threats

Vaccine development