Healthcare industry BW

New strategies against malaria

Malaria, which is a mosquito-borne disease caused by Plasmodium parasites, is still one of the worst infectious human diseases. The parasites have developed resistance against previously effective drugs and new strategies to combat malaria are urgently needed. Scientists from Heidelberg are investigating the molecular interactions between the parasite and the host with the goal to develop new approaches for treating and bringing malaria under control.

Anopheles mosquito with human blood after biting the skin.

Around 120 years ago, Ronald Ross, a British military physician living in India, and Giovanni Batista Grassi, a zoologist from Italy, discovered independently from each other that malaria was transmitted by mosquitoes. Ross was awarded the Nobel Prize in Physiology or Medicine in 1902 for this discovery, and was knighted in 1911. Ross discovered sporozoites, the infectious stages of one-celled parasites of the genus Plasmodium, in the salivary glands of malaria-infected female mosquitoes. The sporozoites are transmitted to the bloodstream of the human host when the mosquito pierces human skin. Generations of scientists have since explored the complex life cycle of the parasites and ways to combat the disease.

Although much progress in malaria control has been made in recent decades, the World Malaria Report published by the World Health Organisation on 28th November 2017 shows that there were still an estimated 216 million people infected with malaria tropica in 2016. Malaria tropica is a particular dangerous form of malaria caused by Plasmodium falciparum. In the same year, around 445,000 people died of the disease, especially children in Africa. The World Malaria Report 2017 states that although the number of malaria-free countries has continued to increase, worldwide progress in the prevention of malaria diseases and deaths has stalled. Innovative methods are urgently needed to gain control of the disease.

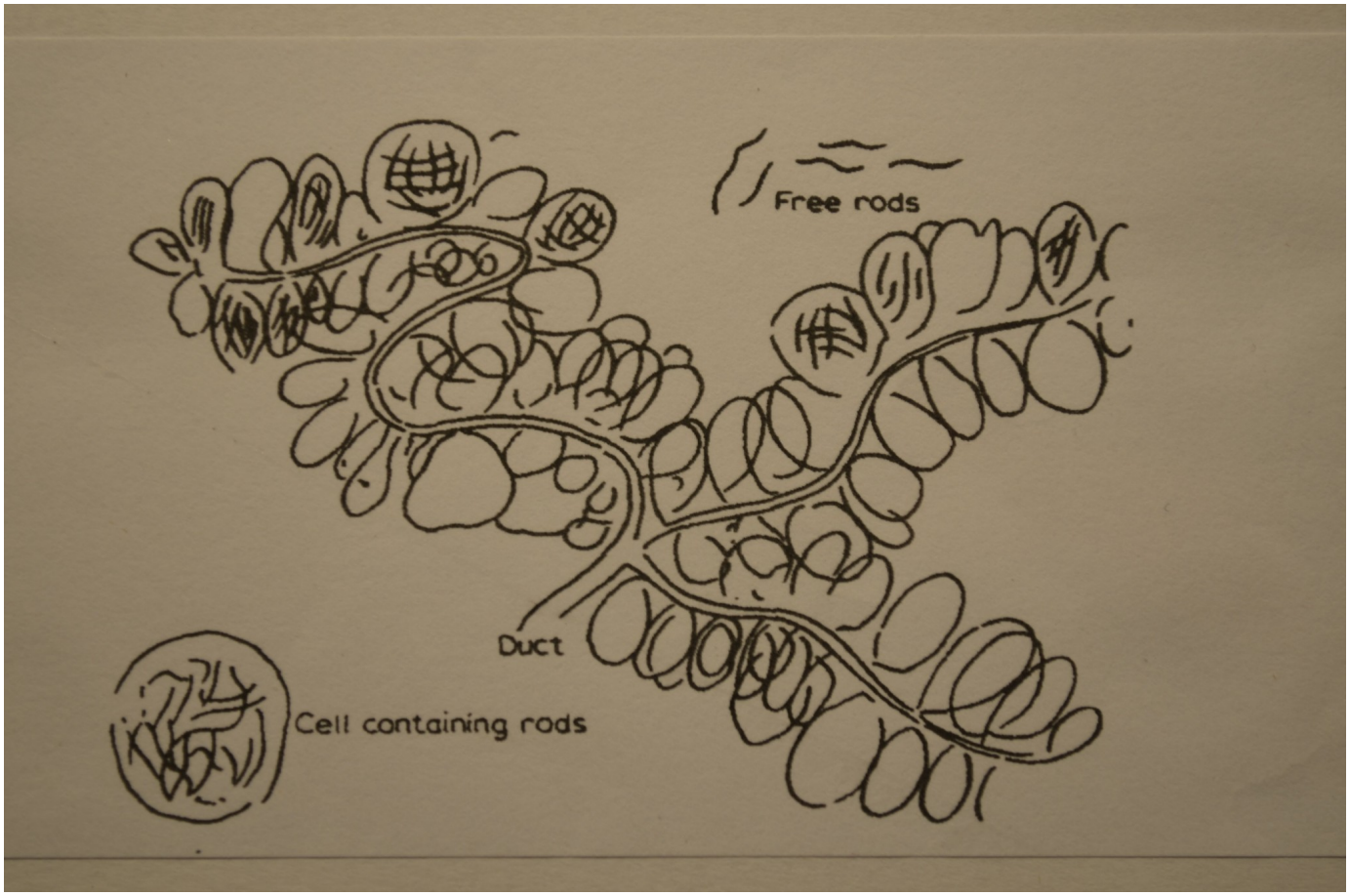
Major stages of the malaria pathogen life cycle

As important as the pioneering work of Sir Ronald Ross in the transmission of malaria was, knowledge of the life cycle of the unicellular Plasmodium parasite was, at that time, still in its infancy. The sporozoites disappeared from human blood within a few minutes of infection. It took another half century to discover that the parasites could persist in the liver cells without causing disease symptoms. After infecting liver cells, the sporozoites mature into schizonts, which go through several cell division rounds (schizogony), resulting in the release of merozoites. These return into the bloodstream and infect red blood cells (erythrocytes), where they persist in a specially formed vacuole and secrete numerous proteins into the cytoplasm of the host cell, thereby changing the cells' properties in favour of the parasite. The parasite feeds mainly on the haemoglobin of the host cells, and grows into a schizont, which ruptures and releases a large number of merozoites. After one to two days (in the case of malaria quartana after three days), the erythrocytes rupture and release merozoites into the blood. These can once again invade erythrocytes and repeat the cycle.

The merozoites are released from the blood cells almost synchronously and cause the fever attacks that are a characteristic hallmark of malaria. These periodic fever attacks are the reason why malaria is also called "intermittent fever". After multiple schizogony cycles, the merozoites differentiate into gamonts from which the male and female germ cells (gametocytes) develop. When ingested by an Anopheles mosquito during a blood meal from a person that is infected with malaria, the gametocytes enter the digestive tract of the mosquito where fertilisation takes place. The zygotes become mobile and invade the midgut wall of the mosquito where they develop into oocysts. The oocysts grow, undergo meiosis and after several cell divisions (sporogony), rupture and release up to a thousand sporozoites into the haemolymph (fluid that circulates in the mosquito's body), from where they make their way into the mosquito's salivary glands. This perpetuates the life cycle of the Plasmodium parasite.

Effective vaccine protection is still a long way off

Only a few parasites are able to invade the human skin during a blood meal of a mosquito. From there, the parasites travel at enormous speed into the blood vessels, enter the liver and hide in the hepatocytes. On their way into the liver, they move around ten times faster than the phagocytes of the immune system. They simply run away from them, as Friedrich Frischknecht from the Centre for Infectious Diseases at the Heidelberg University Hospital has impressively demonstrated. Frischknecht and his co-workers are investigating the molecular mechanism of the amazing gliding movement of the sporozoites and, by restricting the parasite's ability to move, they hope to be able to prevent the parasite from spreading and triggering malaria. Despite decades of research and huge investments from international development programmes such as the PATH Malaria Vaccine Initiative, no satisfactory vaccine against malaria is yet available. As already described, Frischknecht and his colleagues have produced genetically attenuated parasites through targeted modifications



The discovery of Plasmodium sporozoites in the salivary glands of the Anopheles mosquito in 1897; original drawing produced by Ronald Ross.

that have the potential to serve as the basis for an effective vaccine.

Another strategy is being pursued by immunologist Prof. Dr. Hedda Wardemann from the German Cancer Research Center (DKFZ) in Heidelberg. She explained: "Ideally, a vaccine will destroy the sporozoites in the blood before they are able to reach the liver. This would stifle malaria infection from the very onset." Although the number of sporozoites is too low to effectively stimulate the immune system, the scientists were able to isolate memory B cells that were directed against Plasmodium falciparum sporozoites in the blood of people from high-risk malaria areas. Such memory B cells form the memory of the immune system. They carry antibodies that they do not release into the blood on their surface. However, renewed contact with the pathogen can, at a later stage, lead to the production of large quantities of antibodies. Wardemann's research group has now identified the amino acid sequences of a sporozoite protein against which the antibodies of the memory cells are directed and which could serve as the basis of a new vaccine.

Race against resistance formation

The asexual reproductive capacity of the parasite by way of schizogony is highly effective. 20,000 tiny merozoites can be released from a single sporozoite when it enters a liver cell and grows into a schizont. According to Frischknecht, up to 40 percent of all erythrocytes can be infected if the schizonts are able to enter the bloodstream and undergo further schizogony cycles in the red blood cells. This corresponds to a total of more than 10 billion parasites with a mass of half a kilogramme.

For decades, chloroquine has been considered the antimalarial drug of choice. It kills the schizonts in the erythrocytes by preventing the degradation product that is produced when the parasite digests

the haemoglobin from being rendered harmless. The first chloroquine-resistant plasmodia were observed in 1957. Today, chloroquine is largely ineffective against the causative agent of malaria tropica, Plasmodium falciparum, anywhere in the world. In the last ten years, a combination therapy (ACT) with the plant drug artemisinin has been used successfully worldwide, so that the number of malaria deaths has decreased sharply. Meanwhile, Plasmodium falciparum strains that are resistant to this therapy have also emerged and already spreading rapidly across South East Asia. New antimalarial therapeutics are therefore urgently needed.

Prof. Dr. Michael Lanzer, director of the Department of Parasitology, Centre for Infectious Diseases, Heidelberg University Hospital

Prof. Dr. Michael Lanzer, director of the Department of Parasitology at the Centre for Infectious Diseases at Heidelberg University Hospital, and his team are investigating the development of chloroquine resistance. This resistance is the result of gene mutations of the pathogen that have spread independently in two areas – from South East Asia from where the resistance spread throughout tropical Africa, and in the Amazon lowland. Lanzer uses his extensive expertise in areas such as resistance mechanisms, antigen variations and ion and membrane transport processes in malaria parasites in the development of novel drugs. In cooperation with the biotechnology company 4SC in Martinsried, the researchers from Heidelberg have developed a promising low molecular weight active substance (SC83288), which targets calcium transport proteins in the intracellular membranes of Plasmodium falciparum. SC83288 has proven its efficiency in curing P. falciparum infections in a humanised mouse model and can now be used in clinical trials to treat severe malaria.

Therapeutic approach against malaria by inhibiting helper proteins

Lanzer was instrumental in turning Heidelberg into a focal point of modern malaria research in Europe. At the Centre for Infectious Diseases alone, eight research groups are working on the biology of plasmodia, their transmission through Anopheles and strategies to combat the disease. In October 2017, Dr. Jude Przyborski, one of Lanzer's former doctoral students, returned to Heidelberg on a Heisenberg scholarship to accept a position as group leader of a group of researchers focused on a transport system that plasmodia form in the erythrocytes. The researchers have found that an adhesion protein (EMP1) that is secreted by the parasite is incorporated into the membrane of erythrocytes, presumably with the help of chaperones (helper proteins). This helper protein ensures that the blood cells adhere to the wall of blood vessels.

"Usually, red cells are transported to the spleen, where old and damaged cells are removed,"

Przyborski explained. By sticking to the blood vessels, blood cells that are infected with plasmodia escape this control. A completely new approach for treating malaria tropica would open up if it were possible to counteract the adhesive ability of erythrocytes by inhibiting the chaperones. Michael Lanzer considers Przyborski's research area to be an ideal complement to the current research groups of his department: "While we are mainly focused on the interaction between the infected blood cell and its host, Jude Przyborski works at the cellular level." The only way to achieve long-lasting success against the parasite, whose sophisticated mechanisms help it to evade host control effectively, is to combine strategies that target different sensitive sites in the malaria cycle. This is the only way to bring one of humanity's most devastating epidemics under control.

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- Campaign to eradicate malaria
- Generating malaria parasite gene deletion mutants

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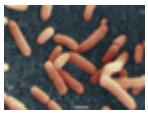

Human infectious diseases: new threats

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Rapid motility of Plasmodium sporozoites