RTD Project MalarX

Together against malaria

MalarX is a prime example of the new generation of SystemsX.ch projects: applied, interdisciplinary research with a strong link to medicine. In this project, the scientists' goal is nothing less than to contribute significantly to the worldwide eradication of malaria.

Volker Heussler has been involved in malaria research for many years.

Malaria does not stop at Europe's doors. As recently as last year, an outbreak occurred in Greece. This comes as no surprise to parasitologist Volker Heussler, a scientist at the Institute of Cell Biology at the University of Bern and a member of the MalarX RTD Project consortium: "Malaria was widespread in Western Europe until the 20th century." He also knows why this disease sporadically flares up in Europe: "As soon as medical care is not fully functional, diagnostics, among other things, are cut back to save costs." Consequently, possible malaria infections remain undetected for many weeks. "This opens the floodgates to the disease", warns Heussler. If infected people are bitten by the Anopheles mosquito during this period, the malaria pathogen spreads before the danger has even been identified.

Millions of new infections

"At our latitudes, only the form of malaria induced by *Plasmodium vivax* is prevalent", explains Volker Heussler. This pathogen is one of four different unicellular parasites, so-called plasmodia, known to cause malaria in humans.

Plasmodium vivax has largely been eradicated at our latitudes but is still the cause of most of the malaria cases in Asia, Latin and South America. "It is estimated that every year 130–400 million infections of *Plasmodium vivax* occur worldwide", says Heussler.

Even though mortality due to this form of malaria is low, it is still a serious disease: "It is like suffering several consecutive, severe bouts of flu." Typical symptoms include feverish episodes caused by toxins released when red blood cells burst.

Heussler explains what happens: "By way of a mosquito bite, the pathogens enter the bloodstream and travel to the liver where they multiply and mature. They then return to the bloodstream and infect red blood cells, where they again multiply until the cells burst." The freely floating parasites can once more be taken up by a mosquito when it bites an infected person, thus completing the cycle of infection.

In *Plasmodium vivax,* this cycle exhibits a distinctive feature: the liver phase can last several months or even years. Thanks to this time lag, the parasite can spend the mosquito-free months in a dormant state in the protected environment of the host organism.

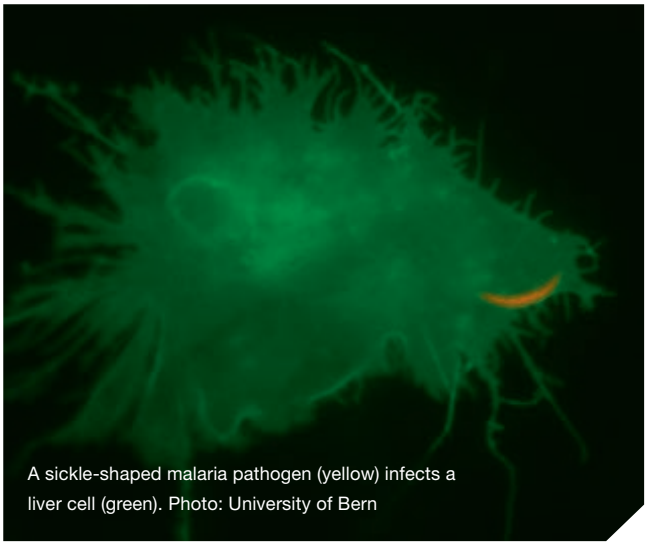
Eliminating parasites without affecting the liver

"To date, most research projects have focused on the blood phase, as it was long thought that this was where the key to new therapeutic approaches would be found", explains Volker Heussler. A mistake, as we now know. "It is not sufficient to kill the plasmodia in the bloodstream. The dormant parasites in the liver must also be eliminated. At present, the dormant phase is still a black box", says the scientist. Especially the events which take place between the parasite and the host cells at the molecular level. For example, experts do not know how the pathogen taps into its host's metabolism for survival. The MalarX RTD Project should help shed light

on this question and determine how the pathogen may be damaged without harming the liver cells.

A major challenge for modeling specialists

The MalarX team can count on project leader Vassily Hatzimanikatis' many years of experience to answer these questions. Hatzimanikatis, a bioengineer at the EPF Lausanne, is specialized in the development of mathematical models for biomedical purposes. But even for him this project presents a special challenge: "Interactions between an intracellular pathogen and the host cell are very complex." The reason for this is the fact that it is not sufficient to integrate the data of two organisms into a single model. The possible interactions between the two also need to be taken into account. Moreover, system biologists are venturing into uncharted territory: "To date, we have looked mainly into the behavior of growing organisms. Here, everything centers on a dormant organism."



A sickle-shaped malaria pathogen (yellow) infects a liver cell (green). Photo: University of Bern

The advantages of interdisciplinary collaborations

In order to be able to work as efficiently as possible, the scientists first develope a model based on the available data. The mathematicians can then formulate possible hypotheses as to how the parasite and liver cells might interact at the molecular level. The plausibility of these assumptions will subsequently be tested in laboratory experiments.

The most important factor in this approach is well-functioning communication between the involved experts. According to Hatzimanikatis, "experience gained during earlier SystemsX.ch projects demonstrates the importance of constant knowledge exchange between the research groups". At the beginning of a project, scientists from a wide variety of research fields need to find a "common language". The project leader is convinced that "in the long term, the advantages of interdisciplinary collaborations will prevail".

International integration and an overarching objective

Not only is MalarX an interdisciplinary project, it is also integrated into the international malaria project network. Experts working in many different countries meet on a regular basis to update each other on the state of their research. Recently, the MalarX team hosted such an event in Lausanne. "Typical competitive thinking is not found among most malaria experts. We are willing to discuss data that has not yet been published", reports Volker Heussler. This is, above all, due to the fact that all involved pursue an overarching objective: to eradicate malaria as quickly as possible.

MalarX at a glance

Principal investigator: Prof. Vassily Hatzimanikatis

Research groups:

- Prof. Vassily Hatzimanikatis, Laboratory of Computational Systems Biotechnology, EPF Lausanne – Mathematical modeling and computational analysis
- Prof. Volker Heussler, Institute of Cell Biology, University of Bern – Biology of Plasmodium liver stage parasites
- Prof. Dominique Soldati-Favre, Departement of Microbiology and Molecular Medicine, Faculty of Medicine, University of Geneva – Genetic manipulation of Plasmodium parasites
- Prof Gerard Hopfgartner, School of Pharmaceutical Sciences, University of Geneva – Metabolomics

Total budget (2014–2018): CHF 5.721 million, including CHF 2.85 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project

MalarX
Systems Medicine of Malaria