Leids Universitair Medisch Centrum

News

NEWS 2012-2021

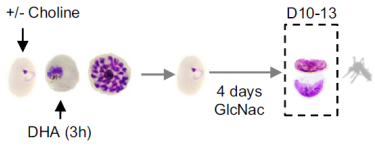
NEWS 2020

15/12

Approval was gained for use of a second generation GAP, GA2, in humans by the Dutch Ministry of Infrastructure and the Environment (GGO IM-MV 20-018).

This second generation genetically attenuated parasite, GA2, has been developed in Leiden (LUMC) for development of a genetically attenuated malaria vaccine. GA2 parasites arrests growth late during development in liver, compared to GA1 parasites, which arrest early during liver stage development and which have been used in the first clinical trial of a genetically attenuated vaccine (Science Translational Medicine). The late growth arrest of GA2 broadens the array of antigens displayed to the immune system and extends the duration of parasite exposure to the immune system (compared to GA1, which arrest early during liver stage development).

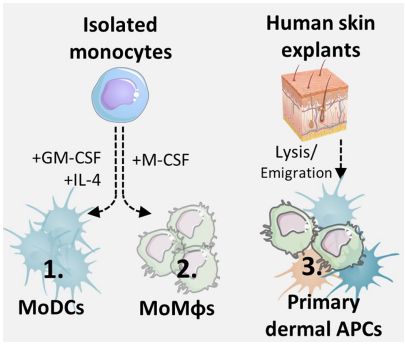
21/10



The Leiden malaria group contributed to a study showing artemisinin exposure at the trophozoite stage impacts Plasmodium falciparum sexual conversion

Using a robust assay using gametocyte-reporter parasite lines to accurately measure the impact of drugs on sexual conversion rates, independently from their gametocytocidal activity, it was found that exposure to subcurative doses of the frontline antimalarial drug dihydroartemisinin (DHA) at the trophozoite stage resulted in a ~ fourfold increase in sexual conversion. Published in Elife

11/09



The Leiden malaria group contributed to a study showing that sporozoites induce regulatory macrophages

In this study human professional antigen-presenting cells responses to recombinant circumsporozoite protein, whiole sporozoites and and anti-CSP opsonized sporozoites both in monocyte derived macrophages and dendritic cells. The results of this study are a first step in enhancing our understanding of pre-erythrocytic natural immunity and the pitfalls of intradermal vaccination-induced immunity. Published in PloS Pathogens

20/5

First clinical trial with genetically modified malaria vaccine completed

In an innovative study, LUMC and Radboudumc jointly tested a candidate vaccine based on a genetically weakened malaria parasite. The results of this clinical trial, published in Science Translational Medicine, show that the vaccine is safe and elicits a defense response against a malaria infection.

Read more ...

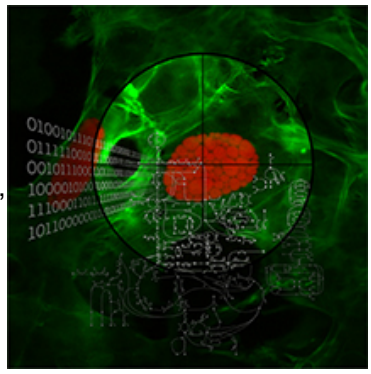
22/01

The Leiden malaria group contributed to preclinical evaluation of viral vector malaria vaccines expressing two liver stage antigens

Vaccination with a combination of the single-antigen vectors expressing PfLSA1 or PfLSAP2 was shown to improve protective efficacy compared to vaccination with each single-antigen vector alone. Vaccination with dual-antigen vectors expressing both PfLSA1 and PfLSAP2 resulted in responses to both antigens, particularly in outbred mice, and most importantly, the efficacy was equivalent to that of vaccination with a mixture of single-antigen vectors. Based on these promising data, dual-antigen vectors expressing PfLSA1 and PfLSAP2 will now proceed to manufacturing and clinical assessment under good manufacturing practice (GMP) guidelines. Published in Infection and Immunity

NEWS 2019

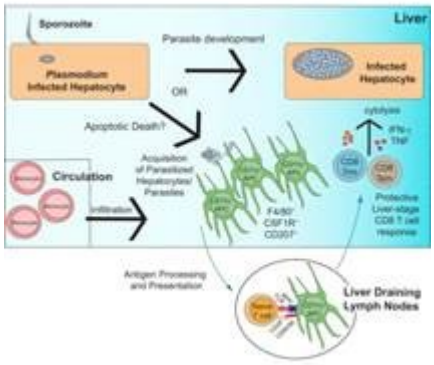
15/11



The Leiden malaria group contributed to a study of genome scale identification of essential metabolic processes of the Plasmodium liver stage

More than 1,300 barcoded P. berghei gene-deletion mutants were followed in a screen through the life cycle. We analyze the screen in the context of genomic, transcriptomic, and metabolomic data by building a thermodynamic model of P. berghei liver-stage metabolism. Seven metabolic subsystems were identified that become essential at the liver stages compared with asexual blood stages: type II fatty acid synthesis and elongation (FAE), tricarboxylic acid, amino sugar, heme, lipoate, and shikimate metabolism. Published in Cell

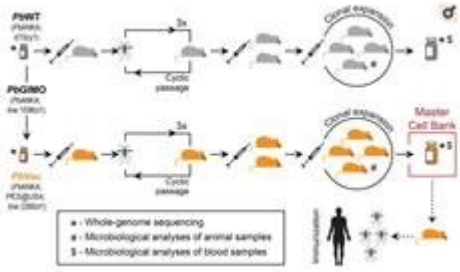
13/3



The Leiden malaria group contributed to a studyshowing that monocyte-derived CD11c+ cells acquire Plasmodium from hepatocytes to prime CD8 T cell immunity to liver-stage malaria

This study shows that a subset of liver-infiltrating monocyte-derived CD11c+ cells co-expressing F4/80, CD103, CD207, and CSF1R acquired parasites during the liver stage of malaria, but only after initial hepatocyte infection. These CD11c+ cells found in the infected liver and liver-draining lymph nodes exhibited transcriptionally and phenotypically enhanced antigen-presentation functions and primed protective CD8 T cell responses against Plasmodium liver-stage-restricted antigens. Published in Cell host Microbe

01/01

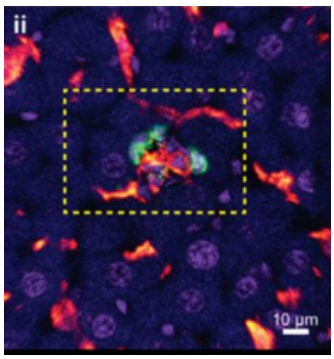


The Leiden malaria group contributed to Pre-clinical evaluation of a P. berghei-based whole-sporozoite malaria vaccine candidate

Recently, a transgenic line of the rodent malaria parasite P. berghei (Pb) that expresses the P. falciparum (Pf) circumsporozoite protein (PfCS), and it was shown that this parasite line (PbVac) was capable of (1) infecting and developing in human hepatocytes but not in human erythrocytes, and (2) inducing neutralizing antibodies against the human Pf parasite. In this study PbVac was analyzed in detail and tools were developed necessary for its use in clinical studies. This pre-clinical safety assessment demonstrates that PbVac possesses all characteristics necessary to advance into clinical evaluation. Published in NPJ Vaccines

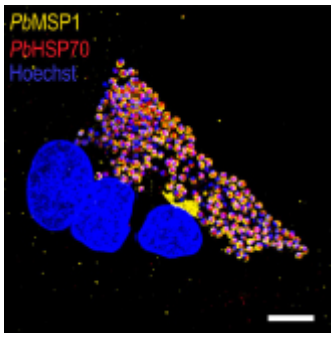
NEWS 2018

26/9



The Leiden malaria group contributed to a study developing a prime and target vaccination strategy that protects against liver-stage malaria in mice.
This alternative "prime and target" vaccination strategy aims specifically at inducing high numbers of tissue-resident memory T cells present in the liver at the time of hepatic infection. This approach bypasses the need for very high numbers of circulating T cells and markedly increases the efficacy of subunit immunization against liver-stage malaria with clinically relevant Ags and clinically tested viral vectors in murine challenge models. Translation to clinical use has begun, with encouraging results from a pilot safety and feasibility trial of intravenous chimpanzee adenovirus vaccination in humans. Published in SciTransl Med.

24/8

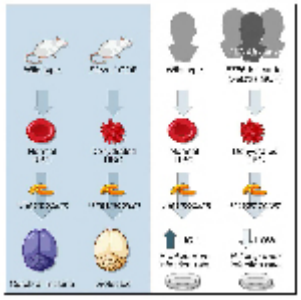


The Leiden malaria group contributed to a study aiming at development of a Plasmodium berghei sporozoite-based vaccination platform against human malaria.
A novel whole-sporozoite WSp malaria vaccine is described that employs transgenic sporozoites of rodent P. berghei (Pb) parasites as cross-species immunizing agents and as platforms for expression and delivery of PfCS (PbVac). PbVac is safe and induces functional immune responses in preclinical studies, warranting clinical testing and development. Published in NPJ Vaccines.

13/7

The Leiden malaria group contributed to a study showing that neutralization of the Plasmodium-encoded MIF ortholog confers protective immunity against malaria infection.
Plasmodium species produce an ortholog of the cytokine macrophage migration inhibitory factor, PMIF, which modulates the host inflammatory response to malaria. Using a novel RNA replicon-based vaccine, the impact of PMIF immunoneutralization on the host response is shown and improved control of liver and blood-stage Plasmodium infection, and complete protection from re-infection is shown.Published in Nat Commun.

08/3



The Leiden malaria group contributed to a study demonstrating that a common PIEZO1 allele in African populations causes RBC dehydration and attenuates Plasmodium infection.
A novel human gain-of-function PIEZO1 allele, E756del, present in a third of the African population, was identified. RBCs from individuals carrying this allele are dehydrated and display reduced Plasmodium infection in vitro. This paper was published in Cell.

05/3

The Leiden malaria group contributed to a study demonstrating that host antibody responses to gametocyte proteins are associated with reduced malaria transmission efficiency from humans to mosquitoes.
Transmission inhibition is significantly associated with antibody responses to Pfs48/45, Pfs230, and to 43 novel gametocyte proteins assessed by protein microarray. This paper was published in Nature Communications

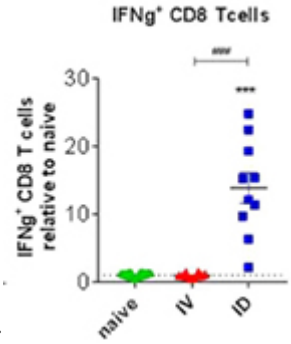
03/01

The Leiden malaria group contributed to a study showing that natural parasite exposure induces protective human anti-malarial antibodies.
In this study rare affinity-matured human NANP-reactive memory B cell antibodies elicited by natural Pf exposure were cloned and characterised that potently inhibited parasite transmission and development *in vivo*. This paper was published in Immunity

NEWS 2017

04/09

The LUMC Department of Parasitology have published a study that shows how protective immunity, after vaccination with attenuated malaria parasites, can vary depending on the route of administration and this is independent of the parasite load in the liver. This paper was published in Scientific Reports

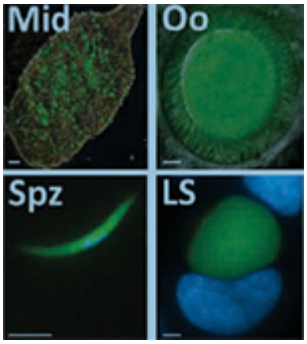


In humans and murine models of malaria, intradermal immunization with genetically attenuated sporozoites that arrest in liver induces lower protective immunity than intravenous immunization. Our results indicate that the lower protection efficacy is obtained after intradermal sporozoite administration and that this is not linked to low hepatic parasite numbers as presumed before, but correlates with a shift towards regulatory immune responses. Overcoming these immune suppressive responses is important not only for live-attenuated malaria vaccines but also for other live vaccines administered in the skin.

16/07

The Leiden Malaria Group published a review on the use of transgenic parasites in malaria vaccine research. Published in Expert Rev Vaccines .

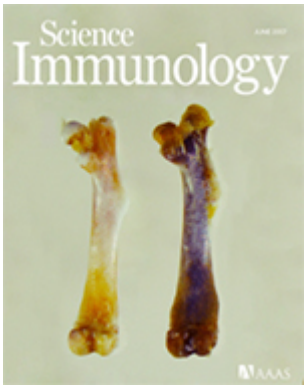
We review how transgenic malaria parasites are used, *in vitro* and *in vivo*, to determine protective efficacy of different antigens and vaccination strategies and to determine immunological correlates of protection. We describe how chimeric rodent parasites expressing *P. falciparum* or *P. vivax* antigens are being used to directly evaluate and rank order human malaria vaccines before their advancement to clinical testing. In addition, we describe how transgenic human and rodent parasites are used to develop and evaluate live (genetically) attenuated vaccines.



02/06

The Leiden Malaria Group contributed to studies showing that *Plasmodium* products persist in the bone marrow and promote chronic bone loss. Published in Science Immunology

It was found that malaria causes bone loss and growth retardation as a result of chronic bone inflammation induced by *Plasmodium* products. A malaria infection can severely suppress bone homeostasis, but the sustained accumulation of *Plasmodium* products in bone marrow induces MyD88-dependent inflammatory responses in osteoclast and osteoblast precursors, leading to increased RANKL expression and overstimulation of osteoclastogenesis that can result in bone resorption.

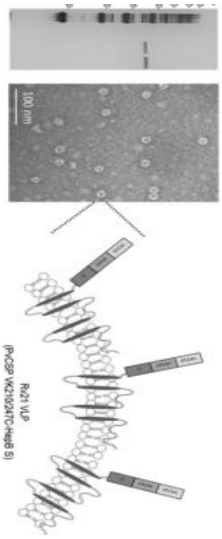


01/04

The Leiden Malaria Group contributed to studies identifying a protein (LIMP) that regulates sporozoite motility. Published in eLife

01/04

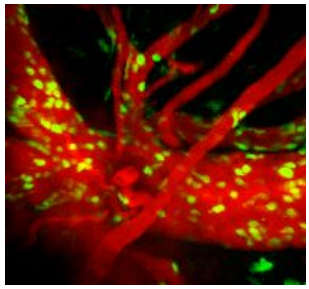
The Leiden Malaria Group contributed to studies characterising putative vaccine candidate antigens of *Plasmodium vivax.* Published in Scientific Reports and Clin Vaccine Immunol



In the first study the development of a highly protective CSP-based P. vivax vaccine is reported, a virus-like particle (VLP) known as Rv21, able to provide 100% sterile protection against a stringent sporozoite challenge in rodent models to malaria, where IgG2a antibodies were associated with protection in absence of detectable PvCSP-specific T cell responses. Protective efficacy against sporozoite challenge was assessed using novel chimeric rodent P. berghei parasites where the P. berghei csp gene has been replaced with either full-length P. vivax VK210 or the allelic VK247 csp. In the second study 4 vaccine platforms, each targeting the human malaria parasite P. vivax cell-traversal protein for ookinetes and sporozoites (PvCelTOS), were generated and assessed for protective efficacy. These platforms consisted of a recombinant chimpanzee adenoviral vector 63 (ChAd63), a recombinant modified vaccinia virus Ankara (MVA), PvCelTOS conjugated to bacteriophage Qβ virus-like particles (VLPs), and a recombinant PvCelTOS protein expressed in eukaryotic HEK293T cells. Protective efficacy against sporozoite challenge was assessed using a novel chimeric rodent P. berghei parasite (Pb-PvCelTOS). This chimeric parasite expresses P. vivax CelTOS in place of the endogenous P. berghei CelTOS and produces fully infectious sporozoites. Despite the induction of anti-PvCelTOS antibodies and PvCelTOS-specific CD8+ T-cell responses, only low levels of protective efficacy against challenge with Pb-PvCelTOS sporozoites were obtained using any immunization strategy.

01/02

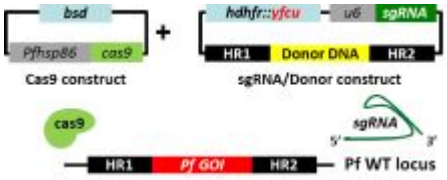
The Leiden Malaria Group contributed to a study showing the role of CD8+ T Cells during experimental cerebral malaria.



Published in PloS Pathogens
It is shown that CD8+ T Cells Induce Fatal Brainstem Pathology during Cerebral Malaria via Luminal Antigen-Specific Engagement of Brain Vasculature

01/01

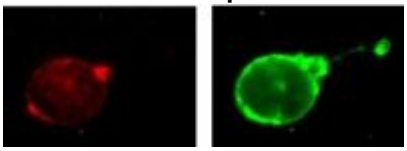
The Leiden Malaria Group developed Modified CRISPR/Cas9 Constructs and Selection Protocol for the Rapid Generation of Marker-Free P. falciparum Fluorescent Reporter Lines
Published in Plos One



The CRISPR/Cas9 protocol we developed provides a simple set of tools to rapidly generate genetically modified P. falciparum lines, in particular transgenic parasites or gene-disruption and gene-mutation mutants that are free of any drug resistance genes. The absence of drug-resistance genes is particularly important in the creation of live genetically attenuated parasites that can be used as a malaria vaccine.

01/1

The Leiden Malaria Group published a study demonstrating that Variant Exported Blood-Stage Proteins Encoded by Plasmodium Multigene Families Are Expressed in Liver Stages Where They Are Exported into the Parasitophorous Vacuole
Published in PloS Pathogens

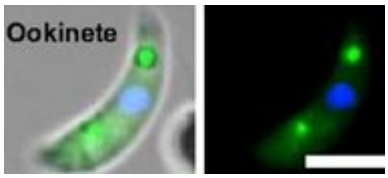


This is the first demonstration of expression of these proteins in the liver and evidence is presented that proteins of one family can transfer phosphatidylcholine in vitro. This is the first demonstration of a biological function of any exported variant protein family of rodent malaria parasites.

NEWS 2016

28/6

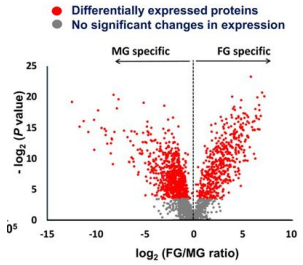
The Leiden Malaria Group contributed to a study identifying and characterizing a protein essential for the formation of the crystalloid and transmission of the malaria parasite. Published in Proc Natl Acad Sci U S A



We show that formation of the crystalloid - a unique and short-lived organelle of the Plasmodium ookinete and oocyst stage required for sporogony - is dependent on the precisely timed expression of an S-acyl-transferase, an enzyme involved in palmitoylation, a posttranslational modification of proteins (the addition of a C-16 long-chain fatty acid to a cysteine residue).

13/6

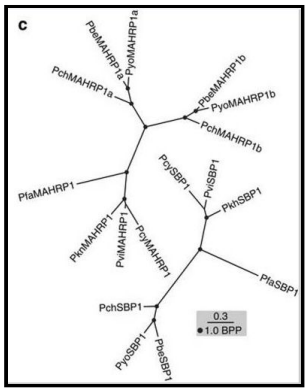
The Leiden Malaria Group contributed to a genome wide transcriptomic and proteomic analysis of separated male and female sexual cells of malaria parasites. Published in Nucleic Acids Research



This study revealed a large set highly expressed maternal transcripts without corresponding protein expression indicating large scale translational repression in *P. falciparum* female gametocytes for the first time.

26/05

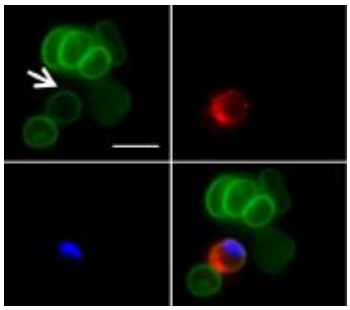
The Leiden Malaria Group contributed to a study showing that the machinery underlying malaria parasite virulence is conserved between rodent and human malaria parasites. Published in Nature Communications



Sequestration of red blood cells infected with the human malaria parasite *P. falciparum* in organs such as the brain is considered important for pathogenicity. A similar phenomenon has been observed in mouse models of malaria, but it is unclear whether the *P. falciparum* proteins known to be involved in this process are conserved in the rodent parasite. In this study two proteins, SBP1 and MAHRP1, are identified that are conserved between rodent and human malaria parasites and that play a role in sequestration and virulence. These findings reveal evolutionary conservation of the machinery underlying sequestration of divergent malaria parasites and support the notion that the P. berghei rodent model is an adequate tool for research on malaria virulence.

15/04

The Leiden Malaria Group contributed to the development of a murine model for pre-clinical studies on pathology associated to malaria in pregnancy. Published in Infect. Immun **.**



Malaria infection during pregnancy leads to abortions, stillbirth, low birth weight and maternal mortality. Infected erythrocytes (IEs) accumulate in the placenta by adhering to chondroitin sulphate A (CSA) via var2CSA protein exposed on the IE membrane. P. berghei IE infection in pregnant BALB/c mice is a model for severe PM. We describe a transgenic P. berghei parasite expressing the full length var2CSA extracellular region (domains DBL1X-DBL6ϵ) fused to a P. berghei exported protein (EMAP1) and characterized a var2CSA-based mouse model of placental malaria (PM).

08/04

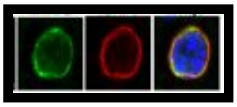
The Malaria Vaccines for the World (MVW)

The Malaria Vaccines for the World (MVW) meeting will take place this year in the LUMC (May 2-4th). This meeting, held once every 3 years, brings together the world's leading academic and industrial scientists, as well as international regulators, funders and government agencies.
The meeting will describe different aspects of vaccine development, assessment and deployment, as well as funding and regulatory aspects of vaccine implementation and testing. See here for more details.

NEWS 2015

13/08

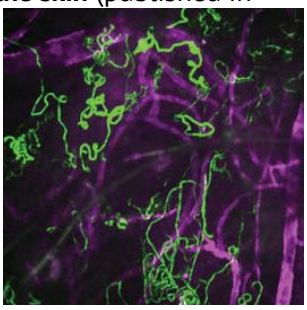
The Leiden Malaria Group contributed to a study that showed that the multidrug resistance-associated protein 2 (MDR2) is essential for malaria parasite development in the liver (published in Cell Microbiol)



Both *P. falciparum* MRP2-deficient parasites and *P. berghei* mutants lacking MRP protein expression abort in mid- to late liver stage development, failing to produce mature liver stages. The combined *P. berghei* and *P. falciparum* data are the first demonstration of a critical role of an ABC transporter during malaria parasite liver stage development.

13/08

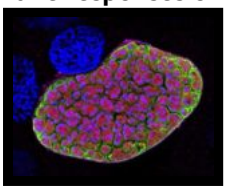
The Leiden Malaria Group contributed to a study that analysed motility of malaria parasites in the skin (published in Elife)



Sporozoite motility and their interaction with dermal blood vessels was analysed using intravital microscopy in mice. Evidence is provided that sporozoites exhibit different types of motility, which is important for successful exit from the inoculation site and invasion of blood vessels.

24/07

The Leiden Malaria Group contributed to a study that analysed cytosolic immune responses of host hepatocytes against malaria infection (published in Autophagy)



Both autophagy and nonselective cannonical autophagy events were analysed.

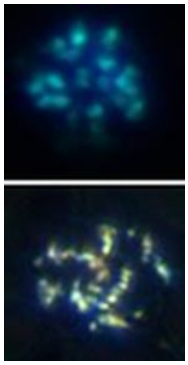
03/07

The Leiden Malaria Group contributed to a study that identified two protective liver-stage candidates (published in Sci Rep.)

Chimeric *P. berghei* parasites expressing the cognate *P. falciparum* antigen were used to test protective efficacy in mice that were immunised with 10 different *P. falciparum* vaccine candidate antigens

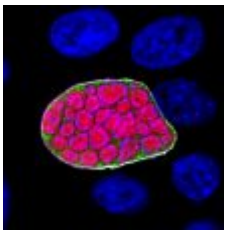
07/05

A Leiden study published in Journal of Experimental Medicine **showed that, unexpectedly, malaria parasites can develop without digesting haemoglobin** but are restricted to young red blood cells (reticulocytes) for their development and become insensitive to the action of chloroquine.



18/03

The Leiden Malaria Group contributed to a study that identified a phospholipase that is involved in disruption of the liver stage parasitophorous vacuole membrane (published in Plos Pathogens**)**



13/02

Dr. Meta Roestenberg, dr. Shahid Khan and prof. Ko Willems van Dijk (Departments of Parasitology and Human Genetics), received a Van de Kamp Fonds-grant (€ 250.000) for research on malaria parasite development in the liver

NEWS 2014

28/11

Dr. Meta Roestenberg received the Gisela Thier Fellowship for research on malaria; specifically to investigate the development of parasites in the liver.

19/11

The Leiden Malaria group in collaboration with RadboudUMC published a paper about a genetically modified parasite vaccine (GAP) against malaria, which is now ready for testing in humans (published ineLIFE **).**

This is an important milestone for malaria research in Leiden and is the culmination of studies that were first initiated here in the mid-90s:

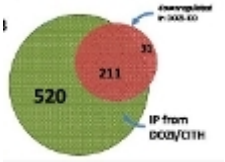
- The Leiden Malaria group was the first group to develop genetic modification in malaria parasites (2 papers published in Science in 1996 and 1997)

- Through analysis of gene-deletion mutants in rodent models of malaria, we discovered that it was possible to create attenuated parasites, which were able to invade the liver but were unable to proceed into the pathogenic blood stage infection. Importantly mice infected (immunised) with these live-attenuated parasites developed protective immunity against an infection with wild type parasites (published in PNAS in 2005).
- In 2008, in the group of Shahid Khan, we started to work on translating these findings into a human vaccine against malaria. This was performed in collaboration with the RadboudUMC (Nijmegen) and the US company Sanaria, and was supported by a grant provided by TI-Pharma. This involved testing and refining many live genetically-attenuated vaccines until we could demonstrate that one met all the necessary pre-clinical safety and protective efficacy standards; it is now ready to advance into testing in humans.

More details on the generation and pre-clinical characterisation of this vaccine can be found in 2 papers published in 2014; one published in the FASEB Journal in May and one that has just appeared in eLIFE .

3/11

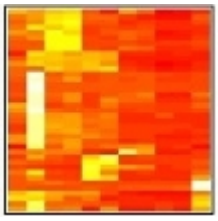
The Leiden Malaria Group contributed to a study that identified the maternal mRNA contribution to post-fertilization development of P. berghei using RNA immunoprecipitation and microarray analysis (published in Genome Biology **).**



Following fertilization, the early proteomes of metazoans are defined by the translation of stored but repressed transcripts; further embryonic development relies on de novo transcription of the zygotic genome. Evidence is presented that mRNA of >700 genes is translationally repressed in the female gametocyte which is the precursor cell of the female gamete. These mRNAs are associtated with DOZI and CITH which are translational repressor proteins.

30/10

The Leiden Malaria Group recently contributed to a paper entitled 'A comprehensive evaluation of rodent malaria parasite genomes and gene expression' (**published in** BMC Biology)



The consortium that contributed to this study consisted of teams from the Wellcome Trust Sanger Institute (UK), RUMC and LUMC (The Netherlands), NIMR, Univ. of Glasgow and Univ. of Oxford (UK). These analyses resulted in full-length gene models for more than 98% of predicted RMP protein-coding genes. Approximately 60% of these genes have functional annotation, which is comparable to the percentage of functionally annotated genes in the P. falciparum 3D7 reference genome. A high percentage (~90%) of the predicted RMP proteins have orthologs in primate malaria species. This high level of orthology and gene conservation between RMP and primate malaria genomes further supports the use of RMP as experimental models to characterize Plasmodium gene function.

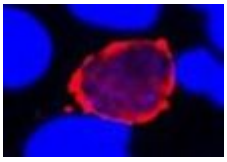
01/10

Dr Shahid Khan and Dr Chris Janse of the Leiden Malaria Research Group received a pilot grant of $70,000 from the PATH Malaria Vaccine Initiative (MVI) , an organization established and largely supported by the Bill & Melinda Gates Foundation. This pilot grant has been awarded to examine a novel live genetically-modified malaria-parasite vaccine, which is designed to provide immunity against multiple stages of the malaria parasite. This so called stage-transcending vaccine has been engineered to express malaria-vaccine candidate antigens from different points of the parasite life-cycle in sporozoites, the infectious forms of the parasite that are injected by the mosquito. The Leiden Malaria Research Group are pioneers and leaders in the field of genetic modification of malaria parasites and vaccine research. The pilot study will be first performed in rodents and, if successful, the intention in a second phase to develop this platform for human vaccination.

25/08

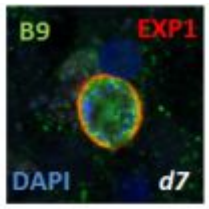
The Leiden Malaria Group have published a study on Plasmodium mutants expressing Ovalbumin (OVA)(published in Infect. Immunity **). They show that the subcellular location of Ovalbumin in Plasmodium berghei blood stages influences the magnitude of T-cell responses.**

20/02



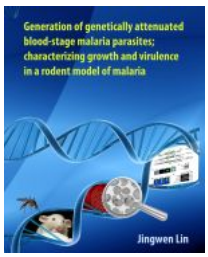
Dr Shahid Khan and Dr Chris Janse of the Leiden Malaria Research Group received a grant of $340,000 from the PATH Malaria Vaccine Initiative (MVI), an organization established and largely supported by the Bill & Melinda Gates Foundation. The grant has been awarded to develop a number of genetically modified rodent malaria parasites that express proteins from the most virulent human malaria parasite, *Plasmodium falciparum*. As evaluating malaria vaccine efficacy in humans is difficult, very expensive and highly time consuming these 'humanized parasites' will be used in rodents, to rapidly evaluate which vaccines against human malaria-parasite proteins are likely to be most effective in controlling a malaria infection. This research that is being carried out in collaboration with researchers from Seattle BioMed and Johns Hopkins University (both USA) and the best candidates will be directly translated into clinical trials and help inform the final composition of an effective malaria vaccine

02/02



The Leiden Malaria Group have published a study identifying and characterizing new members of the malaria parasite's 6-Cys family of proteins (published in FASEB J).
These proteins have critical roles throughout parasite development and are being pursued as targets in anti-malaria vaccination strategies. We show that a number of 6-Cys proteins have critical but distinct roles in the establishment and maintenance of a parasitophorous vacuole and subsequent liver-stage development. Specifically, we identify one member (B9) as a potential target to create genetically attenuated parasites suitable for vaccination.

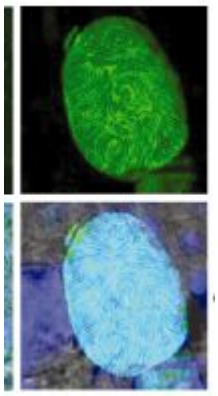
NEWS 2013



03/09

PhD thesis: Jingwen Lin (LUMC, Leiden). Generation of genetically attenuated blood-stage malaria parasites; characterizing growth and virulence in a rodent model of malaria. Read more ....

24/04



The Leiden Malaria Research group contributed to a study analysing malaria rhomboid proteases (published in Molecular Microbiology **)**
Rhomboid-like proteases cleave membrane-anchored proteins within their transmembrane domains. In apicomplexan parasites substrates include molecules that function in parasite motility and host cell invasion. While two*Plasmodium* rhomboids, Rhomboid 1 and rhomboid 4, have been examined, the roles of the remaining six rhomboids during the malaria parasite's life cycle are unknown. We present systematic gene deletion analyses of all eight *Plasmodium* rhomboid-like proteins as a means to discover stage-specific phenotypes and potential functions in the rodent malaria model, *P. berghei*.

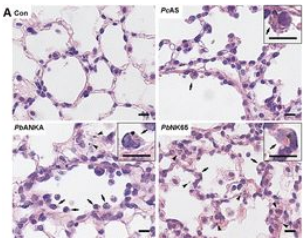
01/03

The Leiden Malaria Research group contributed to a study analysing anti-merozoite malaria vaccine candidates using the rodent model *Plasmodium berghei* (published in Science Reports **)**

An improved understanding of the mechanisms responsible for protection, or failure of protection, against *P. berghei* merozoites could guide the development of an efficacious vaccine against *P. falciparum*.

01/02

The Leiden Malaria Research group contributed to a study showing that Hemozoin induces lung inflammation and correlates with Malaria-Associated Acute Respiratory Distress Syndrome (published in Am J Respir Cell Mol Biol **.)**



Malaria-associated acute respiratory distress syndrome (MA-ARDS) is a deadly complication and its pathophysiology is insufficiently understood. Both in humans and mouse models, MA-ARDS is characterized by marked pulmonary inflammation. By quantifying hemozoin in the lungs and measuring disease parameters of MA-ARDS, we demonstrate a highly significant correlation between pulmonary hemozoin levels, lung weight, alveolar edema and pulmonary inflammation.

24/1

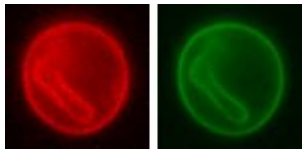
The Leiden Malaria Research group contributed to the generation of fluorescent *P. cynomolgi* liver stages enabling live imaging and purification of hypnozoite-forms (published in PloS One **).**

A major challenge for strategies to combat the human malaria parasite *P. vivax* is the presence of hypnozoites in the liver. These dormant forms can cause renewed clinical disease after reactivation through unknown mechanisms. The closely related non-human primate malaria *P. cynomolgi* is a frequently used model for studying hypnozoite-induced relapses. The generation of the first transgenic *P. cynomolgi* parasites that stably express fluorescent markers in liver stages enabled live imaging and purification of hypnozoite-forms (hypnozoites)

NEWS 2012

2/12

The Leiden Malaria Research group contributed to a study showing the rodent parasite Plasmodium berghei blood stages export a large and diverse repertoire of proteins into the red blood cell (published in Mol Cell Proteomics **).**

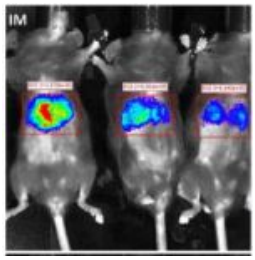


This study indicates that *P. berghei* traffics a diverse range of proteins to different cellular locations into the host red blood cell by mechanisms that are analogous to those employed by the human parasite *P. falciparum*. This information can be exploited to generate transgenic humanized rodent *P. berghei* parasites expressing chimeric *P. berghei/P. falciparum* proteins on the surface of rodent irbc, thereby opening new avenues for in vivo screening adjunct therapies that block sequestration.

28/11

The Leiden Malaria Research group contributed to a study showing that male gametes of malaria parasites evolve faster than female gametes (published in Evolution, Medicine and Public Health). Read more ..

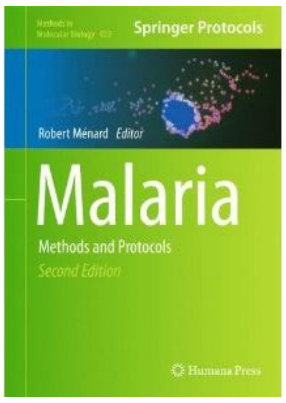
11/11



The Leiden Malaria Research group contributed to a study analysing different routes of administration of attenuated sporozoites to immunize mice (intravenous, intradermal, subcutaneous). Pubished in Vaccine

23/10

The Leiden Malaria group published four methods papers in the book: Malaria: Methods and protocols (Methods in Molecular Biology) edited by Robert Menard



- Screening inhibitors of P. berghei blood stages using bioluminescent reporter parasites. Link....
- Quantitative analysis of Plasmodium berghei liver stages by bioluminescence imaging. Link....
- Bioluminescence imaging of P. berghei Schizont sequestration in rodents. Link....
- Bioluminescence imaging of P. berghei Schizont sequestration in rodents. Link....

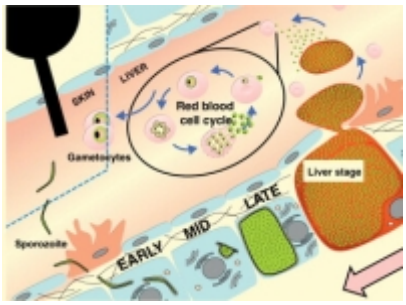
9/07

The Leiden Malaria Research group contributed to a study showing that malaria parasites interfere with the development of immunological memory through expression of an ortholog of macrophage migration inhibitory factor, MIF (published in PNAS **)**

Malaria parasites interfere with the development of immunological memory through expression of an ortholog of macrophage migration inhibitory factor (MIF). This cytokine enhanced inflammatory cytokine production and also induced antigen-experienced CD4 T cells to develop into short-lived effector cells rather than memory precursor cells.

15/05

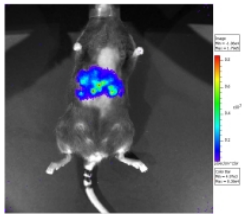
The Leiden Malaria Research Group and collaborators wrote a review on genetic engineering of attenuated malaria parasites for vaccination (published in Curr. Opin. Biotechnol **.).**



Vaccination with live-attenuated *Plasmodium* sporozoites that arrest in the liver can completely protect against a malaria infection both in animal models and in humans. Advances in genetic manipulation of *Plasmodium* has enabled new approaches to design genetically attenuated parasites (GAPs). Tthe principles in discovery and development of GAPs in preclinical models that are important in selecting GAP parasites for first-in-human clinical studies are dicsussed in this review. The challenges in manufacture, formulation and delivery of a live-attenuated whole parasite malaria vaccine are highlighted, as well as the further refinements that may be implemented in the next generation GAP vaccines.

15/02

The Leiden Malaria Research Group and collaborators report on an approach for assessing the adequacy of attenuation of genetically modified malaria parasite vaccine candidates (published in Vaccine **)**



The critical first step in the clinical development of a malaria vaccine, based on live-attenuated *Plasmodium falciparum* sporozoites, is the guarantee of complete arrest in the liver. We report an approach for assessing adequacy of attenuation of genetically attenuated sporozoites in vivo using the *Plasmodium berghei* model of malaria and *P. falciparum* sporozoites cultured in primary human hepatocytes.

08/02

The Leiden Malaria Research Group contributed to a paper discussing the role of animal models for research into development of new treatments for severe malaria (published in Plos Pathogens **)**

In light of the recent controversies over the role of animal models for research into the development of new treatments for severe malaria, particularly cerebral disease, a group of scientists came together to discuss the relative merits of a range of animal models and their overlap with the complex clinical syndromes of human disease.

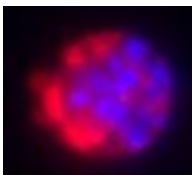
01/01

The Leiden Malaria Research Group developed and published a novel method (GIMO transfection) for transgene expression and gene complementation in rodent malaria parasites (published in PlosOne).

Compared to existing protocols the novel methods of GIMO-transfection greatly simplifies and speeds up the generation of mutants expressing heterologous proteins, free of drug-resistance genes, and requires far fewer laboratory animals. In addition we demonstrate that GIMO-transfection is also a simple and fast method for genetic complementation of mutants with a gene deletion or mutation.

01/01

The Leiden Malaria Research Group and collaborators showed that CD36-mediated tissue sequestration of malaria parasites is beneficial for growth of the parasites (published in J. Exp. Med **)** .



These results reveal for the first time the importance of sequestration to a malaria infection, with implications for the development of strategies aimed at reducing pathology by inhibiting tissue sequestration.

Leids Universitair Medisch Centrum

News 2009 - 2011

- 07/11

The Leiden Malaria Research group contributed to a study showing that malaria parasites can survive and develop in dendritic cells (published in PNAS, June 2011 **)**

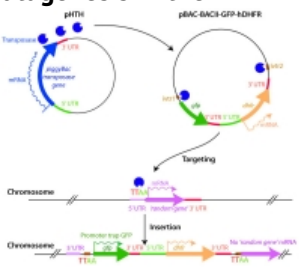
In this study it has been shown that blood stages of the rodent malaria parasite can survive and develop in CD317(+) dendritic cells. Small numbers of these cells released parasites that were infectious for erythrocytes in vivo.

- 06/2011

The Leiden Malaria Research Group and collaborators showed that the RNA binding protein pumilio (puf2) is a key regulator of the transformation of malaria parasites during transmission of the sporozoite from the mosquito to the liver of the mammalian host (published in Plos Pathogens)

- 03/2011

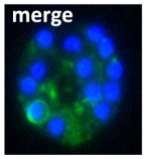
The Leiden Malaria Research Group developed the piggyBac transposable system for random mutagenesis in the malaria parasite Plasmodium berghei (published in BMC Genomics **).**

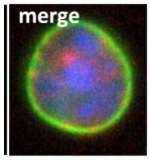


Transposable elements have been widely used to induce insertional mutagenesis in highly diverse biological systems. The TTAA-specific transposon *piggyBac* is rapidly becoming a highly useful transposon for genetic engineering of a wide variety of species, particularly insects. We have developed the piggyBac transposable system for random mutagenesis in the malaria parasite *Plasmodium berghei.* See also the commentary in BMC Biology .

- 02/2011

The Leiden Malaria Research Group published a review on sequestration of malaria infected red blood cells (PloS Pathogens **)**



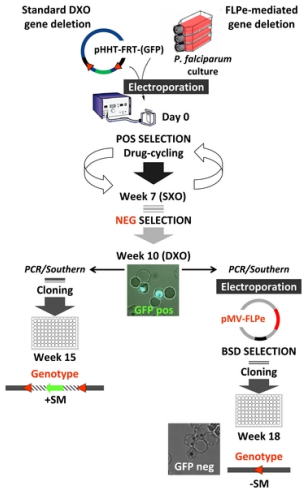


The sequestration of *Plasmodium falciparum*-infected red blood cells (irbcs) in the microvasculature of organs is associated with severe disease; correspondingly, the molecular basis of irbc adherence is an active area of study. In contrast to the human parasite *P. falciparum*, much less is known about sequestration in other malaria parasites, including those species that are used as models to study severe malaria. Here, we review the cytoadherence properties of irbcs of the rodent parasite *Plasmodium berghei* ANKA, where schizonts demonstrate a clear sequestration phenotype. The role of sequestration is discussed in the context of disease as are the general (dis)similarities of *P. berghei* and *P. falciparum* sequestration**.**

- 01/2011

The Leiden Malaria Research Group and collaborators developed a method for removal of heterologous sequences from the genome of malaria parasites using FLPe-recombinase (published in PloS One **).**

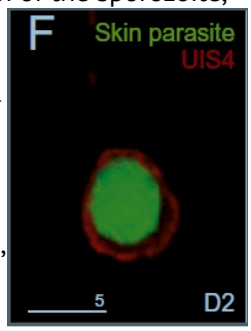
Genetically-modified mutants are now indispensable Plasmodium gene-function reagents, which are also being pursued as genetically attenuated parasite vaccines. Currently, the generation of transgenic malaria-parasites requires the use of drug-resistance markers. We developed of an FRT/FLP-recombinase system that enables the generation of transgenic parasites free of resistance genes. This method of removing heterologous DNA sequences from the genome opens up new possibilities in Plasmodium research to sequentially target multiple genes and for using genetically-modified parasites as live, attenuated malaria vaccines.



- 10/2010

The Leiden Malaria Research group contributed to a study showing that malaria parasites (sporozoites) can develop in the skin (PNAS, Oct 2010)

The first step of malaria parasite (*Plasmodium*) development in vertebrate host is the transformation of the sporozoite, the parasite stage injected by the mosquito in the skin, into merozoites, the stage that invades erythrocytes and initiates the disease. The current view is that, in mammals, this stage conversion occurs only inside hepatocytes. In this study it is shown the transformation of sporozoites of rodent-infecting malaria parasites into merozoites in the skin of mice. Therefore, during malaria in rodents, the skin is not just the route to the liver but is also the final destination for many inoculated parasites, where they can differentiate into merozoites and possibly persist. It has to be established if the same developmental processes also occur in human-infecting malaria parasites, but if they do, this will have major implications on what sort of immune responses will be generated against the parasite.



- 08/2010

The Leiden Malaria Research group published a paper describing the (use of the) RMgm-database (Trends Parasitol. July 2010).

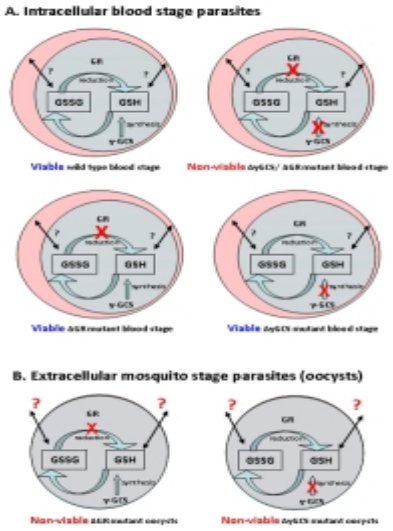
The RMgm database, www.pberghei.eu, is a web-based, manually curated, repository containing information on the genotype and phenotype of genetically modified rodent-malaria parasites generated by many labs worldwide. In addition it contains information on gene function, inferred from mutant phenotypes.
In the paper special emphasis has been placed on standardization of generating and describing mutant genotypes. See the table (PDF-file) containing suggestions for standardization of generating and describing rodent parasite mutants. In this paper the use of standardized vocabularies to describe mutant phenotypes and the use of Gene Ontology (GO) for annotating gene function of *Plasmodium* genes is discussed.

- 07/2010

The Leiden Malaria Research Group and collaborators analysed the enzyme glutathione reductase involved in glutathione (GSH) metabolism of malaria parasites.
It was shown that glutathione reductase (GR) is essential for the development of the malaria parasite in mosquitoes. In contrast, GR is not essential for growth and multiplication of the blood stages of this parasite. These studies provide new insights into the role of the GSH system in malaria parasites with implications for the development of drugs targeting GSH metabolism. For example, it was shown that GR-null parasites had the same sensitivity to methylene blue and Eosin B as wild type parasites demonstrating that these compounds target molecules other than GR in malaria parasites (see article in Journal of Biological Chemistry)

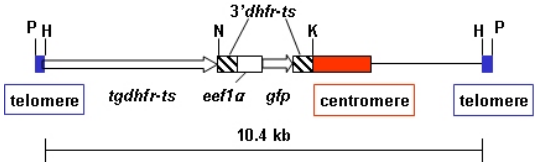
- 04/2010

The Leiden Malaria Research Group and collaborators identified malaria proteins that play a role in *Plasmodium* gamete fertility and fertilisation.
These proteins belong to a family of 10 structurally related proteins, the so called 6-cys family (see the article in PloS Pathogens).



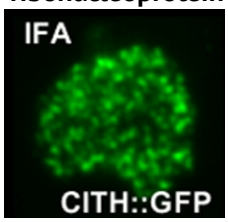
- 03/2010

The Leiden Malaria Research Group and collaborators generated a *Plasmodium* Artificial Chromosome, which can be stably segregated and maintained in parasites.
The artificial chromosome represents a useful tool for gene transfer, both as cloning vectors and in chromosome biology research (see article in CELL, Host & Microbe , Cicero and news item LUMC website)



- 02/2010

The Leiden Malaria Research Group and collaborators identified proteins associated with a messenger ribonucleoprotein particle (mRNP) that is involved in translational repression in malaria parasites.



Plasmodium female gametes contain mRNPs that withhold certain mRNA species from translation to provide coding potential for proteins during early post-fertilization development. Using affinity purification coupled with mass-spectrometric analysis we identify a messenger ribonucleoprotein (mRNP) from *P. berghei* gametocytes defined by a RNA helicase (DOZI) and the Sm-like factor CITH (homolog of worm CAR-I and fly Trailer Hitch). This mRNP includes 16 major factors, including proteins with homologies to components of metazoan P granules and archaeal proteins. This study defines *Plasmodium* P-granules as an ancient mRNP whose protein core has remained evolutionarily conserved from single-cell organisms to germ cells of multi-cellular animals and stores translationally silent mRNAs that are critical for early post-fertilization development during the initial stages of mosquito infection (see article in PloS Pathogens).

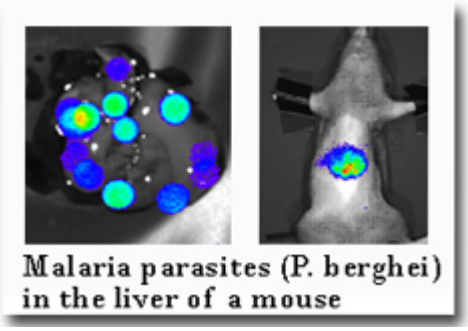
- 01/2010

The Leiden Malaria Research Group and collaborators generated virulence attenuated malaria parasites that induce protective immunity against experimental malaria

This study demonstrates, for the first time, that a single gene disruption in the rodent malaria parasite *P. berghei* can generate virulence-attenuated parasites that do not induce cerebral complications and, moreover, are able to stimulate strong protective immunity against subsequent challenge with wild-type parasites. Parasite blood-stage attenuation should help identify protective immune responses against malaria, unravel parasite-derived factors involved in malarial pathologies, such as cerebral malaria, and potentially pave the way for blood-stage whole organism vaccines (see article in Am. J. Pathol.).

- 11/2009

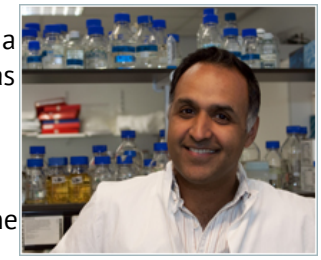
The Leiden Malaria Research Group and collaborators developed a method for visualisation and quantitative analysis of malaria liver stages by real time imaging.


Malaria parasites (P. berghei) in the liver of a mouse

A transgenic malaria parasite of rodents, *P. berghei*, expressing the bioluminescent reporter protein luciferase, is used to visualize and quantify parasite development in liver cells both in culture and in live mice using real-time luminescence imaging. For the first time the liver stage of *Plasmodium* is visualized in whole bodies of live mice and we were able to discriminate as few as 1-5 infected hepatocytes per liver in mice using 2D-imaging and to identify individual infected hepatocytes by 3D-imaging. The simplicity and speed of quantitative analysis of liver-stage development by real-time imaging compared to the PCR methodologies, as well as the possibility to analyse liver development in live mice, opens up new possibilities for research on *Plasmodium* liver infections and for validating the effect of drugs and vaccines on the liver stage of *Plasmodium*. (see article in PloS One)

- 10/2009

A Grand Challenges Exploration (GCE) Grant, funded by The Gates Foundation, awarded to the LMRG



Shahid Khan, one of the researchers of the Leiden Malaria Research Group, has been awarded a $100,000 grant from the Gates Foundation for exploratory research on malaria. His project was one of 76 selected from almost 3,000 proposals. To date 262 researchers representing 30 countries have been awarded these grants. Khan's winning project is entitled: 'Preventing Malaria in Both Host and Vector' and the aim of this project is to use genetically attenuated parasites as vehicles to not only protect the host but also kill the parasite in the mosquito. The grant covers research costs for 1 year, up to $100.000, which Khan's team (part of the Leiden Malaria Research Group (LUMC); headed by Chris Janse) will use to perform this exploratory research. See also the news items on the LUMC homepage and the TI Pharma website.

- 09/2009

The Leiden Malaria Group contributed to a study describing a cyclic GMP signalling module that regulates gliding motility of *Plasmodium* ookinetes, published in PloS Pathogens

Through genetic interaction a signalling module is described that identifies guanosine 3′, 5′-cyclic monophosphate (cGMP) as an important second messenger regulating ookinete differentiation and motility. In ookinetes lacking the cyclic nucleotide degrading phosphodiesterase δ (PDEδ), unregulated signalling through cGMP results in rounding up of the normally banana-shaped cells. This phenotype is suppressed in a double mutant additionally lacking guanylyl cyclase β (GCβ), showing that in ookinetes GCβ is an important source for cGMP, and that PDEδ is the relevant cGMP degrading enzyme.

- 09/2009

Member of Parasitology wins prize for 'outstanding' presentation

Aga Religa (PhD student) from the Leiden Malaria Research Group (Parasitology) was awarded a prize at the 2009 annual Molecular Parasitology Meeting, Woods Hole (MA, USA), for her 'outstanding' presentation of her research on the role of a histone deacetylase (SIR2) in malaria parasites. She found that the SIR2 protein, which is involved in regulation of chromatin structure and gene transcription, also plays an unexpected role in the parasites development inside the mosquito (see also the abstract of the presentation). The PhD project is a joint collaboration between Leiden Malaria Leiden Group at the LUMC (Chris Janse), the University of Glasgow (Andy Waters) and the Pasteur Institute, Paris (Artur Scherf). The prize consists of funding to attend and to present her work at the annual meeting of the American Society of Tropical Medicine and Hygiene in Washington DC (USA) in November 2009 as well as a one year subscription to the Journal Cellular Microbiology. See also the publication on the LUMC Albinusnet and an abstract of her research.

- 07/2009

Links between the malaria database PlasmoDB and the Leiden RMgm database:

In the new release of the malaria database PlasmoDB (www.plasmodb.org) there are direct links from appropriate gene pages to genetically modified rodent malaria parasites in the RMgm database (www.pberghei.eu) of the Leiden Malaria Research Group. In PlasmoDB see the 'external links – Databases': *Phenotypes from Genetically Modified Rodent Malaria Parasite database*. By clicking on this link, a list is shown of all mutants in the RMgm database which relate to the gene (e.g. gene has been disrupted, tagged, mutated, expressed as a transgene etc). Clicking on a specific mutant directs to the RMgm webpage and here one can find the more detailed information on the mutant. In the attachment you will find more information on the RMgm database (i.e. 'What is the RMgm database'; 'What the RMgm database offers'; 'How you can contribute to the database'; 'Preferred information (requirements) for a RMgm mutant entry'; etc).

- 04/2009

Molecular genetics and comparative genomics reveal RNAi is not functional in malaria parasites

RNA interference (RNAi) is an evolutionarily conserved mechanism found across a range of eukaryotes, where it plays a key role in post-transcriptional gene regulation. With its exquisite specificity for the target gene as well as its potent and reversible action, RNAi technology has now become a standard technique in the molecular toolbox for reverse genetic experimentation in many systems, providing a quick and easy means to gain valuable insight into gene function, in particular those that are essential to cell viability. The use of RNA interference (RNAi) to silence gene expression of malaria parasites would provide a powerful means to gain valuable insight in the function of genes that are essential for growth of the patahogenic blood stages.
The Leiden malaria Group and collaborators provide strong evidence that RNAi is absent in malaria parasites and therefore it is unlikely that RNAi-based gene silencing will prove to be a reliable approach to unravel the function of malaria proteins. See for more information the publication in Nucleic Acids Research .

- 03/2009

Updated and new information on our SharePoint website (containing the LMRG *P. berghei* protocols and databases).

Specifically: 1) *The effect of host (animal) diet upon rodent malaria parasite infections.* We have received several of enquiries about host diet and *P. berghei* infections. In our experience host diets can influence both the course of an infection and its virulence phenotype (and also on the quality of parasites for transfection). We have provided some additional information on host diet and its influence on rodent malaria parasite infections (see FAQ and the folder Shared Documents, subfolder Host diet). Since *P. berghei* is frequently (and increasingly) used to study host-parasite interactions we believe standardization of diets in experiments (and between labs) may be very useful. 2) *Problems using one of LMRG a standard DNA vectors (pL0037) for genetic modification: unwanted integration.* We have on many occasions successfully used our positive/negative selection vectors, pl0035 (available via MR4) and its close derivative pL0037, to target *P. berghei* genes by gene replacement and then using cloned lines of these mutant parasites we have been able to use negative selection (i.e. 5-FC) to 're-cycle' and remove the drug selectable marker cassette. Recently, however, we have noticed that a number of our transfections using pL0037 appear not to be integrating into the correct locus. For more information see NEWS item on our Sharepoint site.

Login details (username, password) for this Sharepoint-site can be requested by filling out the 'request for access/password' form on our website
forms.lumc.nl/lumc2/para_access

- 02/2009

The Leiden Malaria Group contributed to a study of the glutathione biosynthetic pathway, published in PloS Pathogens

Infection of red blood cells subjects the malaria parasite to oxidative stress. Therefore, efficient antioxidant and redox systems are required to prevent damage by reactive oxygen species. Malaria parasites have thioredoxin and glutathione (GSH) systems that are thought to play a major role as antioxidants during blood stage infection. This study demonstrates that gamma-glutamylcysteine synthetase (gamma-GCS), the rate limiting enzyme in de novo synthesis of GSH, is not essential for the growth of the pathogenic blood stages but is essential for development of the parasite in the mosquito.
These results have important implications for the design of drugs aiming at interfering with the GSH redox-system in blood stages and demonstrate that de novo synthesis of GSH is pivotal for development of *Plasmodium* in the mosquito

- 01/2009

The Leiden Malaria Group contributed to a study of fatty acid synthesis, published in CELL host & microbe

The Leiden Group contributed to a paper on fatty acid synthesis in malaria parasites. The fatty acid synthesis type II pathway has received considerable interest as a candidate therapeutic target in malaria infections. Synthetic chemistry and transfection studies demonstrate that the FabI enzyme of *Plasmodium* is not the target of the antimalarial activity of triclosan, an inhibitor of bacterial FabI. The lack of of fabI does not impede blood-stage growth. In contrast, the growth of the liver stafes of the parasite is markedly affected
These data illuminate key differences between liver- and blood-stage parasites in their requirements for host versus de novo synthesized fatty acids, and create new prospects for stage-specific antimalarial interventions.

- 01/2009

The Leiden Malaria Research Group has a new website:

www.lumc.nl/con/1040/81028091348221/810281121192556/

- 01/2009

The Leiden Malaria Research Group has set up a publically accessible database Pberghei.eu.

Pberghei.eu hosts a database containing information on genetically modified rodent malaria parasite lines generated by many labs worldwide.

Specifically, we are collating data that has been generated in the three rodent parasite species; *Plasmodium berghei*, *P. yoelii* and *P. chabaudi*. The aim of this database is to provide the research community access to detailed information on the generation (e.g. disruption, tagging, mutation, transgene expression) and phenotype (e.g. lethal, aberrant growth, failure of sporozoites to infect liver cells, expression of reporter genes) of genetically modified malaria parasites.
We are still technically improving the database and are in the process of adding in many more genetically modified parasite lines (and their associated information). At this moment we have information on around 100 parasite lines. We will not only provide information on 'successful' mutants with a clear phenotype, but also (un)published mutants **without** a clear phenotype and (un)published **negative trials** to disrupt genes.
Currently we are in discussion with PlasmoDB on the best way to link our RMGM database with theirs to best ensure availability and access of the collated information.

We would be pleased and would very much welcome everyone's comments to improve our RMGM database. Moreover, we would like to explore the possibilities of coordinating our activities with you and other researchers; such that individuals can submit and/or upload information on their rodent parasite mutants either directly onto the RMGM database or in an excel format that can be sent to the Leiden Malaria Research Group for uploading. We believe that the information on published and unpublished (rodent) malaria parasite mutants, all within one database, will help the research of all and may also prevent unnecessary duplication of work/experiments.

Downloads

- standardization generating and describing rodent parasite mutants [PDF]
- Woods Hole_Religa_abstract [PDF]
- prize_Aga_Woods_Hole_2009 [PDF]
- Gates_Grant_TI-Pharma_news_2009 [PDF]
- Gates_Grant_2009_LUMC_news [PDF]
- RMgm database [PDF]

Leids Universitair Medisch Centrum

News 2007 - 2008

- 11/2008

Gene Disruption of p52 of the human parasite *P. falciparum* results in attenuation of malaria liver stage development: implications for vaccine development
Researchers from Leiden (LUMC) and Nijmegen have characterized a large number of parasite proteins that may prove useful in the development of a human malaria vaccine (published in PLoS Pathogens).Collaborators had previously shown how to successfully vaccinate mice using a rodent malaria which had one of these liver stage genes removed, specifically p36p. In a related article, published October 28th in PLoS ONE, the researchers show the first transition of such a vaccination from the rodent system to humans, by inactivating the equivalent gene (p52) in the major human malaria parasite, *P. falciparum*. 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 promising possibilities for its use as a human vaccine. These studies show how results obtained in rodent models of malaria can be pipelined to form the basis for clinical development of antimalaria vaccines in humans.

Malariavaccin P52 in het nieuws 2008 (pdf)

- 09/2008

To better manage the Leiden Malaria Research Groups *P. berghei* protocols and reference databases this information has been placed in a 'SharePoint' environment (groepen-forms.lumc.nl/sites/leidenmalaria/default.aspx)

Login details (username, password) for this Sharepoint-site can be requested by filling out the 'request for access/password' form .
We do not send the password to 'general' e-mail addresses like hotmail, yahoo, gmail or plasa, only to institutional e-mail addresses!
In case you do not have an institutional e-mail address you have to find the methods in our published papers (see PubMed; we do not send papers to other groups/researchers).

- 05/2008

Update of the website of the Leiden Malaria Research Group, with special emphasis on the password protected area

Additional and/or new information, explanations and information updates on the website; based on questions we have received in the last two years from 'researchers in the field':

Protocols:
In addition to the 'general laboratory protocols', three protocols which we published in Nature Protocols on transfection and in-vivo imaging are available on the website including the videos showing purification of schizonts and transfection.

Transgenic P. berghei parasite lines

We have deposited at MR4 a number of our transgenic *P. berghei* lines expressing reporters such as GFP and Luciferase as well as transgenic lines that are deficient in expressing specific parasite proteins. Since these lines can now be obtained from MR4, we do not send any of these lines directly to other laboratories. We have provided additional information on our website about the lines that are present at MR4, in combination with their MRA-number. For obtaining other *P. berghei* lines (i.e. those not deposited with MR4) from our laboratory, we request you to fill out the parasite request form on this website.

Plasmids:
A collection of standard plasmids have been deposited at MR4. Details of these plasmids (e.g. sequence, plasmid map, integration locus, selectable marker cassette etc) can be found in an Excel sheet on our website. Two plasmids are now available that contain the drug-selection cassette, hDHFR and yFCU, as a fusion gene for both positive and negative selection procedures (MRA-849 = pl0034, MRA-850 = pl0035).

Databases:
In addition to the transcriptome and proteome data of blood stages and gametocytes of *P. berghei*, data is provided on the chromosome location and synteny of genes of the rodent malaria parasites (in comparison with *P. falciparum*). Biosafety issues of working with transgenic *P. berghei*: Information is provided about biosafety levels and health (monitoring) reports for mice infected with *P. berghei* lines.

- 12/2007

Translational repression in gametes and zygotes of malaria parasites: new insights from the Leiden Malaria Group

Translational repression (TR) during sexual development appears to be an ancient process for controlling the timing of expression of proteins. Unicellular eukaryotes of the genus *Plasmodium* use TR to regulate protein expression during gamete and zygote formation. Previously we have identified a *Plasmodium* protein (DDX6-class RNA helicase) involved in TR and which forms a complex with repressed mRNA's (Mair et al., 2006, Science 313:667-9). In a recent paper we now report the involvement in TR of specific regions/domains in the 3'- and 5'-UTR's of the repressed mRNA transcripts. These results demonstrate that TR in *Plasmodium* is mediated by both cis- and trans-acting factors that are closely analogous to those employed in TR of higher eukaryotes (Braks et al., (2007). A conserved U-rich RNA region implicated in regulation of translation in *Plasmodium* female gametocytes. Nucleic Acids Research 2007, 1-11 (23 December).

- 10/2007

A number of *P. berghei* transgenic/mutant lines generated in the Leiden Malaria Group are now available from Malaria Research and Reference Reagent Resource Center, MR4

See the following links:

MRA-865 , MRA-866 , MRA-867 , MRA-868 , MRA-869 , MRA-870 , MRA-871 , MRA-872 , MRA-440 , MRA-441 , MRA-442 , MRA-443 , MRA-444 .

- 03/2007

The *Plasmodium* homologue of Macrophage Migration Inhibitory factor (MIF) has been characterized in the Leiden Malaria Group:

MIF is an important regulator of inflammatory response in mammalians. MIF is an unusually versatile chemokine/cytokine in that it is involved in both pro- and anti-inflammatory response and cellular proliferation. In malaria infections host MIF response has been shown to correlate with disease severity and anemia. Surprisingly, analysis of the *Plasmodium* genome revealed the presence of a single MIF homologue. Since these parasites themselves do not have an immune system, we hypothesized that *Plasmodium* might produce a MIF homologue to interfere with the host immune response. In order to test this hypothesis, we undertook a functional characterization of the *Plasmodium* homologue of MIF using purified recombinant protein and genetic manipulation of *P. berghei* parasites. (Augustijn KD et al., (2007) Functional characterization of the *Plasmodium falciparum* and *P. berghei* homologues of macrophage migration inhibitory factor. Infect. Immun. 75:1116-28.

Leids Universitair Medisch Centrum

News 2004 - 2006

- 09/2006

The Leiden Malaria Group and collaborators published in Science

Mair et al. (2006). Regulation of sexual development of Plasmodium by translational repression. Science 313: 667-9

Timing the Sexual Development of Parasites (pdf) , Gevoelige achilleshiel (pdf) , Klaargelegd voor later (pdf)

- 09/2006

New insights in regulation of gene expression during sexual development of malaria parasites.

A protein with homology to the DDX6 family of RNA helicases is involved in translational repression of mRNA in female gametocytes and in regulating sexual development (Mair et al, (2006). Regulation of sexual development of *Plasmodium* by translational repression. Science 313: 667-9).

Timing the Sexual Development of Parasites , Gevoelige achilleshiel (pdf) , Klaargelegd voor later (pdf)

- 09/2006

Several (genetically modified) P. berghei parasite lines has been deposited at MR4

1. *Reference lines of the ANKA strain of P. berghei (cl15cy1; HPEcy1m50cl1)*
   - The cl15cy1 clone is a reference clone of the ANKA strain and used by different labs. It is derived from the 8417HP clone and produces wild type numbers of gametocytes, ookinetes, oocysts, sporozoites. This line has been used to sequence the genome of *P. berghei* (Hall et al., 2005; Science 307. 82-6).
   - The HPEcy1m50cl1 (ANKA strain) is also derived from 8417HP and produces no gametocytes. It has been used in our lab as a reference non-gametocyte producer clone and has also been used to analyse transcription in pure, synchronised asexual blood stages (Hall et al., 2005; Science 307. 82-6)

2. Genetically modified lines/clones
   - Four published, 'reference' lines (259cl2 (=GFPcon); 354cl4; 507m6cl1; 676m1cl1) that express reporter genes GFP or the fusion protein GFP-Luciferase under different promoters (Janse et al., 2006; Mol Biochem Parasitol. 145: 60-70). These have been sent to different labs and are used to visualise parasite development.
   - Two published knock-out parasites lines (137cl8; 270cl1) lacking the expression of the gametocyte/gamete specific proteins P48/45 and P47 respectively (van Dijk et al. 2001, Cell 104, 153-164; Khan et al., 2005, Cell 121: 675-87). Since these lines are defective in either male or female fertility, these lines are used by different labs for crossing experiments to test the fertility of gametes of other knock-out mutants.

- 09/2006

Two videos showing *P. berghei* protocols have been placed onto the password protected area of our website

- Purification of cultured mature schizonts using Nycodenz-gradient centrifugation
- Transfection of purified schizonts using the Amaxa Nucleofector device

- 07/2006

Three detailed protocols from our group have been published in Nature Protocols.

High-efficiency transfection and drug selection of genetically transformed blood stages of the rodent malaria parasite *Plasmodium berghei*

Selection by flow-sorting of genetically transformed, GFP-expressing blood stages of the rodent malaria parasite, *Plasmodium berghei*

Real-time in vivo imaging of transgenic bioluminescent blood stages of rodent malaria parasites in mice

- 07/2006

A negative selection marker has been developed in the Leiden Malaria Group for the use in reverse genetics of *Plasmodium berghei*

yFCU; which combines a fusion of yeast cytosine deaminase and uridyl phosphoribosyl transferase (UPRT) with in vivo selection using the prodrug 5-fluorocytosine (5-FC). The combination of a positive and negative selectable marker allows for rapid analysis of the phenotype by targeted disruption of a gene and further associate phenotype and function by genotype restoration (Braks JA et al., Nucleic Acids Res. 34: e39.) This negative selection system is also adapted to facilitate drug-selectable marker (vector) recycling which in principle will allow unlimited manipulation of a single parasite clone. A standard vector for genetic modification of *P. berghei* has been made that contains a fusion of the negative selectable marker yFCU with the positive selectable marker hDHFR and which allows for excision of the drug-selectable markers from the genome through homologous recombination. In this manner it should also prove possible to perform 'hit and run' mutagenesis on *P. berghei*. This vector has been send to MR4 and is described in the plasmid database on our Sharpoint environment .

- 07/2006

The plasmid database **on the password protected area of our website has been updated**

and all plasmids have been sent to MR4 . It also contains a standard vector for drug-selectable marker recycling using positive/negative selection

- 03/2006

Information about the organization of the genomes of the rodent malaria parasites (RMP) genomes is placed onto the password protected area of our website

This information consists of:

1. The chromosome location of all predicted *P. berghei*, *P. yoelii* and *P. chabaudi* genes with *P. falciparum* orthologs. The position of these genes is described relative to the chromosomal location of their *P. falciparum* orthologs (2 Excel files).
2. All available RMP sequence contigs with sequence homology to *P. falciparum* aligned along the composite chromosomes of rodent malaria parasite (RMP) and aligned along the *P. falciparum* chromosomes (information in 2 Excel files)
3. A schematic representation of the synteny map of the RMP genome and the *P. falciparum* genome, showing all 14 chromosomes, regions of synteny, breakpoints of synteny, centromere locations etc (pdf file).
4. Lists of *P. falciparum* specific genes for which an ortholog has not been found in the RMP genome and also a list of RMP-specific intersyntenic genes (information in 4 tables; *P. falciparum* subtelomeric genes, intersyntenic genes and intrasyntenic genes; RMP intersyntenic genes)

All information is based on the published study by Kooij et al (2005). A Plasmodium whole-genome synteny map: Indels and synteny breakpoints as foci for species-specific genes; PLoS Pathogens, 23, 1(4):e44

- 02/2006

PhD thesis: Taco Kooij (LUMC, Leiden). Rodent Malaria Parasites: Genome Organization and Comparative Genomics.

Genome Organization & Comparative (pdf)

- 01/2006

The Leiden Malaria Group and collaborators published in PLoS Pathogens

The Leiden Malaria Group and collaboratorsKooij et al (2005). A *Plasmodium* whole-genome synteny map: Indels and synteny breakpoints as foci for species-specific genes. PLoS Pathogens, 23, 1(4):e44published in PLoS Pathogens

- 11/2005

All standard plasmids for genetic modification of *P. berghei* from the Leiden Malaria group are now available from the Malaria Research and Reference Reagent Resource Center (MR4)

Detailed information about these plasmids can be found in an excel file on the password protected area of our website .

- 11/2005

Several novel technologies have been published that improve larger scale genetic modification of *P. berghei*

1. Sakamoto H. et al. (2005). Towards systematic identification of *Plasmodium* essential genes by transposon shuttle mutagenesis. Nucleic Acids Res., 33(20):e174. (from the group of Robert Menard, Pasteur Institute, Paris).
2. Ecker A. et al. (2005). Generation of gene targeting constructs for *P. berghei* by a PCR-based method amenable to high throughput applications. Mol Biochem Parasitol. 145(2): 265-8 (from the group of Oliver Billker and Bob Sinden, Imperial College, London).
3. Janse C. J. et al.. (2005). High efficiency transfection of *P. berghei* facilitates novel selection procedures. Mol Biochem Parasitol. 145(1): 60-70 (from the group of Andy Waters and Chris Janse, Leiden University Medical Center, Leiden)

- 08/2005

The Leiden Malaria Group and collaborators published in PNAS

van Dijk, M.R. et al (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)

Malaria Vaccines: Back to the Future? (pdf) , Herkansing voor malariavaccin (pdf)

- 08/2005

The Leiden Malaria Group used *Plasmodium berghei* is used as a model to investigate genetically modified, attenuated sporozoites as a vaccine

van Dijk, M.R. et al (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)

Malaria Vaccines: Back to the Future? (pdf) , Herkansing voor malariavaccin (pdf)

- 08/2005

Information on standard plasmids for genetic modification of *P. berghei* on our website is updated

The excel database contains information of plasmids (sequence, plasmid maps etc.) used for disruption, mutating or tagging of genes and for expression of transgenes, including tags such as TAP, c-myc and GFP and transgenes such as GFP, RFP and luciferase.

read more (password protected area)

- 08/2005

The Leiden Malaria Group and collaborators published in PNAS

Franke-Fayard B. et al. (2005). Murine malaria parasite sequestration: CD36 is the major receptor, but cerebral pathology is unlinked to sequestration. Proc Natl Acad Sci U S A. 102. 11468-73

Deep-organ malaria parasite not associated with cerebral complications (pdf)

- 08/2005

The Leiden Malaria Group developed a method for in *vivo* visualization of sequestration of schizonts of *P. berghei* (sequestered infected blood cells) in life animals using luciferase-expressing parasites

Franke-Fayard B. et al. (2005). Murine malaria parasite sequestration: CD36 is the major receptor, but cerebral pathology is unlinked to sequestration. Proc Natl Acad Sci U S A. 102. 11468-73

Deep-organ malaria parasite not associated with cerebral complications (pdf)

- 06/2005

Proteome data *Plasmodium berghei* male and female gametocytes is placed on our website

Proteome data is available in excel databases with *P. berghei* gene models linked to their *P. falciparum* gene orthologs. In addition we present a comparison of proteome data of *P. berghei* and *P. falciparum* of different published studies.

read more (password protected area)

- 06/2005

Phenotype data pertaining to kinase deficient mutant *P. berghei* parasites

(i.e. either MAP2 or NEK4) has been incorporated into the Excel database which conatins information on all genetically modified *P. berghei* mutant parasite lines

read more (password protected area)

- 06/2005

Proteome analysis of separated male and female gametocytes (the precursor cells of the male and female gametes) is published

Shahid M. Khan, Blandine Franke-Fayard, Gunnar R. Mair, Edwin Lasonder, Chris J. Janse, Matthias Mann & Andrew P. Waters. Proteome analysis of separated male and female gametocytes reveals novel sex specific *Plasmodium*. Cell (2005) 121:675-687

Revealing the Molecular Determinants of Gender in Malaria Parasites (pdf) , De malariacirkel (pdf) , Proteomes of Plasmodium gametocytes (pdf)

- 06/2005

The Leiden Malaria Group and collaborators published in Cell

Proteome analysis of separated male and female gametocytes reveals novel sex specific *Plasmodium*.
Cell (2005) 121:675-687

Revealing the Molecular Determinants of Gender in Malaria Parasites (pdf) , De malariacirkel (pdf) ,
Proteomes of Plasmodium gametocytes (pdf)

- 02/2005

Plasmodium berghei is used as a model to investigate genetically modified, attenuated sporozoites as a vaccine

Mueller AK, Labaied M, Kappe SH, Matuschewski K. Genetically modified *Plasmodium* parasites as a protective experimental malaria vaccine. Nature (2005)433:164-7.
See also Parasitology. Malaria vaccines: back to the future? (pdf) Waters AP, Mota MM, van Dijk MR, Janse CJ. Science. (2005), 307:528-30.

- 01/2005

Transcriptome data of the blood stages of *Plasmodium berghei* (including gametocytes) is placed on our website

An Excel database with *P. berghei* gene models linked to their *P. falciparum* gene orthologs

read more (password protected area)

- 01/2005

The genome of *Plasmodium berghei* is published

with transcriptome and proteome analyses
Hall N, Karras M, Raine JD, Carlton JM, Kooij TW, Berriman M, Florens L, Janssen CS, Pain A, Christophides GK, James K, Rutherford K, Harris B, Harris D, Churcher C, Quail MA, Ormond D, Doggett J, Trueman HE, Mendoza J, Bidwell SL, Rajandream MA, Carucci DJ, Yates JR 3rd, Kafatos FC, Janse CJ, Barrell B, Turner CM, Waters AP, Sinden RE.
A comprehensive survey of the *Plasmodium* life cycle by genomic, transcriptomic, and proteomic analyses.
Science (2005) 307:82-6.

Revealing the Molecular Determinants of Gender in Malaria Parasites (pdf) ,
Malaria of mice and men; Using models to understand disease (pdf) , Malaria-onderzoekers leren hun vijand kennen (pdf) , De familie malaria (pdf)

The Leiden Malaria Group and collaborators published in Science

Hall N, Karras M, Raine JD, Carlton JM, Kooij TW, Berriman M, Florens L, Janssen CS, Pain A, Christophides GK, James K, Rutherford K, Harris B, Harris D, Churcher C, Quail MA, Ormond D, Doggett J, Trueman HE, Mendoza J, Bidwell SL, Rajandream MA, Carucci DJ, Yates JR 3rd, Kafatos FC, Janse CJ, Barrell B, Turner CM, Waters AP, Sinden RE.
A comprehensive survey of the *Plasmodium* life cycle by genomic, transcriptomic, and proteomic analyses.
Science (2005) 307:82-6

Revealing the Molecular Determinants of Gender in Malaria Parasites (pdf) ,
Malaria of mice and men; Using models to understand disease (pdf) , Malaria-onderzoekers leren hun vijand kennen (pdf) , De familie malaria (pdf)

- 01/2005

A picture of the natural host of *P. berghei*, *Grammomys surdaster*, on our website

The picture is obtained from the Institute of Tropical Medicine, Department of Parasitology, Antwerp. The animal shown is from a small breeding colony in the Institute of Tropical Medicine in Antwerp that originated from about fifty animals that were trapped in an area of 5 km around Kaindu, 20 km nort west of Mumbwa near the Kafua National Park (Zambia) in 1996. Determination of the species was based on analysis of the cytochrome B sequence of mitochondrial DNA at the Department of Animal Ecology of the University of Antwerp. In some handbooks *Grammomys surdaster* is called *Grammomys dolichurus* (woodland thicket rat) (Kingdon, J. (1974). East African Mammals. Vol.II part B (Hares and Rodents). London, Academic Press; R.M. Nowak, Walker's mammals of the World, vol. 2; Johns Hopkins University Press) but the taxonomy of thicket rats is still in a state of flux and in review. Based on differences in mitochondrial DNA *G. surdaster* and *G. dolichurus* are well separated species and the differences warrant to group them in different taxa (pers. comm. prof. dr. H. Leirs, University of Antwerp).
More information on *Grammomys dolichurus*

- 11/2004

Improvement of transfection efficiency in *P. berghei*

Using a new method of transfection, the AMAXA non-viral nucleofector^{tm} technology, we obtain transfection efficiencies in the range of 10^{-2}-10^{-3} (with the standard transfection technology the efficiency was 10^{-6}-10^{-9}). The methods have not been published yet but are described in our transfection protocols.

read more (password protected area)

- 11/2004

New on our website

Molecular protocols used in our laboratory are placed here (password protected area)

- 11/2004

The malariagroup of the LUMC has a new professor, Andy Waters

Andy Waters was promoted to the position of full professor with effect from October 1th 2004.

Malariahoogleraar (pdf)

- 9/2004

A reference line of *P. berghei*, expressing Green Fluorescent Protein (GFP) in all life cycle stages

We generated a transgenic line of *P. berghei* that expresses GFP at a high level in all life cycle stages. This line shows similar growth characteristics to wild type *P. berghei* parasites of the ANKA strain, both in the vertebrate and mosquito host.
More information: Molecular & Biochemical Parasitology paper (abstract) (pdf) ; information in our database
'Mutant lines (knockout, transgene, tagging) and natural lines of *P. berghei*'. article in Cicero: Parasiet geeft licht (pdf)

- 7/2004

Our website has been updated

Our website has been updated, in particular we have significantly changed the part on the 'Plasmodium berghei Research Model of Malaria'. A part of the information provided is no longer freely accessible, such as protocols and databases. For this information a password is needed.On a regular basis the password will change and you will be required to register again. It is a simple and brief process but it allows us to keep only active researchers as subscribers. In the password protected part of the website we now provide the following information:
- Detailed protocols on 'P. berghei: general parasitological methods', 'Molecular Methods', 'P. berghei: transfection methods', including information about transfection using the Amaxa method
- Excel databases with information on the basic plasmids we use for transfection of P. berghei and information on all mutant lines (gene knockout, transgene, tagging) that have been made in our laboratory or that have been described in the literature, with emphasis on the phenotype characteristics of the mutant lines
This part of our website is still under construction and comments or additional information are welcome. We will regularly update the protocols and databases and in the future more data concerning genome structure, transcriptomes and proteomes of P. berghei will be added. The relevant data will also be linked in to public databases such as PlasmoDB and GeneDB
Please follow the link and fill in the form for request of the password.

- 5/2004

Researchers from the Leiden malaria Group contributed to two papers published in Cell

Blandin S, Shiao SH, Moita LF, Janse CJ, Waters AP, Kafatos FC, Levashina EA.
Complement-like protein TEP1 is a determinant of vectorial capacity in the malaria vector Anopheles gambiae. Cell 2004 Mar 5;116(5):661-70.

Billker O, Dechamps S, Tewari R, Wenig G, Franke-Fayard B, Brinkmann V.
Calcium and a calcium-dependent protein kinase regulate gamete formation and mosquito transmission in a malaria parasite. Cell 2004 14;117(4):503-14

- 4/2007

New book 'Malaria Parasites: Genomes and Molecular Biology' (2004), edited by Andy Waters and Chris Janse

Internationally renown experts provide up-to-date reviews of the most important aspects of post-genomic malaria research: Genomes and Molecular Biology (pdf)
See also review: Postgenetic *Plasmodium* (pdf)

- 2/2004

Prize for a poster from Shahid Khan (LUMC, Leiden)

'Sensitive comparative proteomic analysis of highly purified Plasmodium male and female gametocytes' presented at the Molecular Approaches to Malaria' meeting (2004; Lorne, Victoria, Australia)

Sensitive comparative proteomic analysis of highly purified *Plasmodium* male and female gametocytes (pdf)

Downloads

- Malariahoogleraar [PDF]
- Sensitive comparative proteomic analysis of highly purified Plasmodium male and female gametocytes [PDF]
- Postgenomic Plasmodium [PDF] Genomes and Molecular Biology [PDF]
- Genomes and Molecular Biology [PDF] Parasiet geeft licht [PDF]
- Molecular & Biochemical Parasitology [PDF] De familie malaria [PDF]
- Malaria-onderzoekers leren hun vijand kennen [PDF]
- Malaria of mice and men Using models to understand disease [PDF]
- Proteomes of Plasmodium gametocytes [PDF] De malariacirkel [PDF]

- Revealing the Molecular Determinants of Gender in Malaria Parasites [PDF]
- Deep-organ malaria parasite not associated with cerebral complications [PDF]
- Herkansing voor malariavaccin [PDF] Malaria Vaccines: Back to the Future? [PDF]
- Genome Organization & Comparative [PDF] Klaargelegd voor later [PDF]
- Timing the Sexual Development of Parasites [PDF] Gevoelige achilleshiel [PDF]

Leids Universitair Medisch Centrum

News 2001 - 2003

- 12/2003

Interview met Dr. Andy Waters in Mediator Plus Ultra

December 2003, jaargang 1, nr 4:

'Waters' genetische tools voor malariabestrijding' (pdf)

- 11/2003

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Molecular Parasitology Meeting (pdf)

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Genome and Post-Genome Research in *P.berghei*

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Malaria researchers from Leiden contributed to the publication of the genome and partial proteome of two malaria parasites

In the Journal Nature, 5 papers were published on the sequencing of the genome of the human malaria parasite and a model rodent malaria parasite (with over 100 authors). Two additional papers reported the initial exploitation of whole genome data and presented significant attempts to report the protein complement (the proteome) of a number of life cycle stages of the two parasites.
Malaria researchers from contributed to to the publication of two of these papers (one proteome and one genome).

Lasonder E, Ishihama Y, Andersen JS, Vermunt AM, Pain A, Sauerwein RW, Eling WM, Hall N, Waters AP, Stunnenberg HG, Mann M (2002) Analysis of the Plasmodium falciparum proteome by high-accuracy mass spectrometry. Nature 2002 Oct 3; 419(6906): 537-42.

Carlton JM, Angiuoli SV, Suh BB, Kooij TW, Pertea M, Silva JC, Ermolaeva MD, Allen JE, Selengut JD, Koo HL, Peterson JD, Pop M, Kosack DS, Shumway MF, Bidwell SL, Shallom SJ, Van Aken SE, Riedmuller SB, Feldblyum TV, Cho JK, Quackenbush J, Sedegah M, Shoaibi A, Cummings LM, Florens L, Yates JR, Raine JD, Sinden RE, Harris MA, Cunningham DA, Preiser PR, Bergman LW, Vaidya AB, Van Lin LH, Janse CJ, Waters AP, Smith HO, White OR, Salzberg SL, Venter JC, Fraser CM, Hoffman SL, Gardner MJ, Carucci DJ. (2002). Genome sequence and comparative analysis of the model rodent malaria parasite Plasmodium yoelii yoelii.
Nature 2002 Oct 3; 419(6906): 512-9.

The largest part of the sequencing effort has been conducted at TIGR in the US and at the Wellcome Trust Sanger Institute in the UK.

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PhD thesis: Resie van Spaendonk (LUMC, Leiden)

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Dr. M. van Dijk (LUMC) received the 'Merial Award 2001 for Parasitology' for her research on malaria

(from: Trends in Parasitology (2002) 18, 203)
The Merial Award for Parasitology is granted under the auspices of The Netherlands Society for Parasitology to a post-doc researcher from the Benelux countries, who has conducted important and innovative research in parasitology. The 2001 Merial Award went to a medical parasitologist, Milly van Dijk (University of Leiden, The Netherlands). van Dijk was the first to report stable genetic modification of the blood-stage malaria parasite, which was carried out in Andy Waters and Chris Janse's group (Leiden University Medical Centre, The Netherlands). The development of this technique has opened up new possibilities for malaria researchers and has been adopted to investigate the structure and function of proteins of malaria parasites, in addition to defining new targets for drug and vaccine development.

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P. berghei Genome Sequencing Project

P. berghei has an estimated genome size of 25-27Mb organised into 14 chromosomes in the size range of 0.6 Mb to 3.8 Mb, numbered in ascending order of size (based on the size of chromosomes of the reference clones 8417 and cl15cy1 of the ANKA strain). A project funded by the Wellcome Trust has been initiated by the Sanger Centre in the U.K. to sequence the genome of *P. berghei* to 3x coverage. DNA for this sequencing project was obtained in our laboratory from asynchronous bloodstages of clone 15cy1 of the ANKA strain of *P. berghei* which had been filtered repeatedly through Plasmodipur filters prior to DNA isolation. Here is the link to the to the project web page at The Sanger Centre and associated Blast server: www.sanger.ac.uk/Projects/P_berghei/

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Melissa R. van Dijk, Chris J. Janse, Joanne Thompson, Andrew P. Waters, Joanna A.M. Braks, Huub J. Dodemont, Henk G. Stunnenberg, Geert-Jan van Gemert, Robert W. Sauerwein and Wijnand Eling (2001)
A Central Role for P48/45 in Malaria Parasite Male Gamete Fertility. Cell 104: 153-64

Summary: Fertilisation and zygote development are obligate features of the malaria parasite life cycle and occur during parasite transmission to mosquitoes. The surface protein PFS48/45 is expressed by male and female gametes of *Plasmodium falciparum* and PFS48/45 antibodies prevent zygote development and transmission. Here, gene disruption was used to show that Pfs48/45 and the orthologue Pbs48/45 from a rodent malaria parasite P. berghei play a conserved and important role in fertilisation. p48/45 - parasites had a reduced capacity to produce oocysts in mosquitoes due to greatly reduced zygote formation. Unexpectedly only male gamete fertility of p48/45 - parasites was affected, failing to penetrate otherwise fertile female gametes. P48/45 is the first surface protein of malaria parasites with a demonstrable role in fertilisation.
For more information see Cicero, 9 february 2001, #2.

Anticonceptie voor malariaparasieten (pdf)

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