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Malaria vaccinology: from the development of a new malaria vaccine to the ethics of clinical trial participation

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Non scientific part

Portfolio

Nederlandse samenvatting

Curriculum vitae

List of publications

Acknowledgements

Portfolio

The main project of this PhD has been the GA2 project, the clinical trial involving the administration of genetically attenuated malaria parasites to healthy human participants. Much time and effort went into this project as I was in charge of it from beginning to end. I helped redact the application for using the genetically modified parasite GA2 in clinical research and then wrote the application for the medical ethical committee. I was the contact person for other collaborating departments within the Leiden University Medical Center and for our collaborators in the Radboud Medical Center in Nijmegen. I recruited and screened potential participants for the clinical trial, coordinated the study visits and collected data. I then analyzed the clinical data and worked in the lab to analyze part of the immunological data as well. Finally, I wrote the first draft of the manuscript and many revisions after that (**Chapter 1**).

Besides the GA2, I worked on several side projects, which, unfortunately, have not all resulted in publication. Among these was the endeavor meant to analyze the movement of different types of genetically attenuated and wild-type sporozoites using the confocal microscope. However, due to the lack of results, i.e. no tangible difference in the movement patterns of said sporozoites, this project was abandoned.

To place the GA2 in a broader context and discuss potential implications for its large-scale implementation, I wrote a review about existing genetically attenuated parasites, the process that lead to their development and their current test status (**Chapter 2**).

After that I decided to continue the work of a previous colleague, investigating and comparing the motivations of clinical trial participants in SARS-CoV2 vaccination (**Chapter 3**). A second article about a further comparison between motivations of phase 1 and controlled human infection study participants is in the make, yet not included in this thesis. Finally, I wrote an opinion piece dissecting the conceptual and ethical differences between phase 1 trials and controlled human infections (**Chapter 4**).

I furthermore collaborated on several of my colleagues' projects, helping recruit participants, being the study physician for the participants and reviewing the final manuscripts.

I have decided to include two collaborative projects in this thesis because I believe that they provide additional information to better understand the position of the GA2 in the current scientific panorama. **Chapter 5** describes the development and pre-clinical evaluation of GA2 and therefore represents, if you will, the fundaments upon which this thesis is built. In **Chapter 6** the efficacy of a lower dose of GA2, namely a single immunization with 50 mosquito bites, is reported. This chapter is a continuation of my

work and confirms once more not only the safety, but also the high protection rates (90%) achieved by this parasite.

For an overview of all publications presented in this PhD thesis please refer to **Table 1** and for an overview of all publications please refer to **Table 2**.

I was allowed to present my work on a couple of occasions: I did an oral presentation at the Dutch Malaria Day in Leiden, the Spring Meeting of the Dutch Society for Parasitology in Utrecht, the BioMalPar in Heidelberg and the Dutch Internist Days in Maastricht; I had a poster and short pitch at the Spring Meeting of the British Society for Parasitology in Edinburgh (**Table 3**).

During my PhD I also completed all mandatory courses (**Table 4**) and was involved in teaching activities, giving several lectures to medical students and co-supervising biomedical students writing their thesis. Additionally, working on most of the papers included in this thesis allowed me to get acquainted with R for data organization, statistical analysis and figure generation.

Table 1. PhD candidate contributions to each article according to the CRediT methodology

Main Articles			
Article Title	**Year of publication**	**Journal**	**Contribution**
Safety and Efficacy of Immunization with a Late-Liver-Stage Attenuated Malaria Parasite	2024	New England Journal of Medicine	Data curation Formal analysis Investigation Methodology Project administration Validation Visualization Writing – original draft Writing – review & editing
The path from early- to late-liver stage arresting genetically attenuated parasites as a malaria vaccination strategy	2025	NPJ Vaccines	Conceptualization Data curation Investigation Methodology Visualization Writing – original draft Writing – review & editing
What motivates SARS-CoV-2 vaccine trial participants? A pre- and post-participation survey study	2024	Trials	Conceptualization Data curation Formal analysis Investigation Methodology Software Visualization Writing – original draft Writing – review & editing
Risk in healthy volunteer studies: does it matter if the agent is a drug or a bug?	2025	Submitted, under peer-review at Trials	Data curation Formal analysis Investigation Methodology Project administration Visualization Writing – original draft Writing – review & editing
Collaborative projects			
Creation and preclinical evaluation of genetically attenuated malaria parasites arresting growth late in the liver	2022	NPJ Vaccines	Writing – review & editing
Single immunization with genetically attenuated PfΔmei2 (GA2) parasites by mosquito bite in controlled human malaria infection: a placebo-controlled randomized trial	2025	Nature Medicine	Investigation Writing – review & editing

Table 2. Overview of all publications in chronological order

Title	Author	Journal	Year
Opioid-related beliefs and prescription modalities for postoperative pain of Dutch and American physicians.	Lamers OAC, Kuck K, Okifuji A, Stuart, AR, Johnson KB and Rijsdijk M	Pain Management	2019
Treatment strategies for GLILD in common variable immunodeficiency: a systematic review	Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VA, Ho HE, Hurst JR, IJspeert H, Prevaes SM, Robinson A	Frontiers Immunology	2021
Creation and preclinical evaluation of genetically attenuated malaria parasites arresting growth late in the liver	Franke-Fayard BMD, Marin-Mogollon C, Geurten FJA, Chevalley-Maurel S, Ramesar J, Kroeze H, Baalbergen E, Wessels E, Baron L, Soulard V, Martinson T, Aleshnick M, Huijs ATG, Subudhi AK, Miyazaki Y, Othman AS, Kolli SK, Lamers OAC, Roques M, Stanway RR, Murphy SC, Foquet L, Moita D, Mendes AM, Prudêncio M, Dechering KJ, Heussler VT, Pain A, Wilder BK, Roestenberg M, Janse CJ	NPJ Vaccines	2022
Safety and infectivity of female cercariae in Schistosoma-naïve, healthy participants: A controlled human *Schistosoma mansoni* infection study	Koopman JPR, Houlder EL, Janse JJ, Casacuberta-Partal M, Lamers OAC, Sijtsma JC, de Dood C, Hilt ST, Ozir-Fazalalikhan A, Kuiper VP, Roozen GVT, de Bes-Roeleveld LM, Kruize YCM, Wammes LJ, Smits HH, van Lieshout L, van Dam GJ, van Amerongen-Westra IM, Meij P, Corstjens PLAM, Jochems SP, van Diepen A, Yazdanbakhsh M, Hokke CH, Roestenberg M	EBioMedicine	2023
Causal chemoprophylactic activity of cabamiquine against Plasmodium falciparum in a controlled human malaria infection: a randomised, double-blind, placebo-controlled study in the Netherlands	van der Plas JL, Kuiper VP, Bagchus WM, Bödding M, Yalkinoglu Ö, Tappert A, Seitzinger A, Spangenberg T, Bezuidenhout D, Wilkins J, Oeuvray C, Dhingra SK, Thathy V, Fidock DA, Smidt LCA, Roozen GVT, Koopman JPR, Lamers OAC, Sijtsma J, van Schuijlenburg R, Wessels E, Meij P, Kamerling IMC, Roestenberg M, Khandelwal A.	The Lancet Infectious Diseases	2023
Intradermal delivery of the third dose of the mRNA-1273 SARS-CoV-2 vaccine: safety and immunogenicity of a fractional booster dose	Roozen GVT, Prins MLM, Prins C, Janse JJ, de Gruyter HLM, Pothast CR, Huisman W, Koopman JPR, Lamers OAC, Kuijer M, Myeni SK, van Binnendijk RS, Hartog GD, Heemskerk MHM, Jochems SP, Feltkamp MCW, Kikkert M, Rosendaal FR, Roestenberg M, Visser LG, Roukens AHE	Clinical Microbiology and Infection	2024
Immunogenicity and reactogenicity of intradermal mRNA-1273 SARS-CoV-2 vaccination: a non-inferiority, randomized-controlled trial	Prins MLM, Roozen GVT, Pothast CR, Huisman W, van Binnendijk R, den Hartog G, Kuiper VP, Prins C, Janse JJ, Lamers OAC, Koopman JPR, Kruithof AC, Kamerling IMC, Dijkland RC, de Kroon AC, Azimi S, Feltkamp MCW, Kuijer M, Jochems SP, Heemskerk MHM, Rosendaal FR, Roestenberg M, Visser LG, Roukens AHE	NPJ Vaccines	2024

Title	Author	Journal	Year
Clinical tolerance but no protective efficacy in a placebo-controlled trial of repeated controlled schistosome infection	Koopman JPR, Houlder EL, Janse JJ, Lamers OAC, Roozen GVT, Sijtsma JC, Casacuberta-Partal M, Hilt ST, van der Stoep MYEC, van Amerongen-Westra IM, Brienen EA, Wammes LJ, van Lieshout L, van Dam GJ, Corstjens PL, van Diepen A, Yazdanbakhsh M, Hokke CH, Roestenberg M	The Journal of Clinical Investigations	2024
Safety and Efficacy of Immunization with a Late-Liver-Stage Attenuated Malaria Parasite	Lamers OAC, Franke-Fayard BMD, Koopman JPR, Roozen GVT, Janse JJ, Chevalley-Maurel SC, Geurten FJA, de Bes Roeleveld HM, Iliopoulou E, Colstrup E, Wessels E, van Gemert GJ, van de Vegte-Bolmer M, Graumans W, Stoter TR, Mordmüller BG, Houlder EL, Bousema T, Murugan R, McCall MBB, Janse CJ, Roestenberg M	New England Journal of Medicine	2024
What motivates SARS-CoV-2 vaccine trial participants? A pre- and post-participation survey study	Lamers OAC, Roestenberg M, de Vries MC, Hoogerwerf MA	Trials	2024
Single immunization with genetically attenuated PfΔmei2 (GA2) parasites by mosquito bite in controlled human malaria infection: a placebo-controlled randomized trial	Roozen GVT, van Schuijlenburg R, Hensen ADO, Koopman JPR, Lamers OAC, Geurten FJA, Sijtsma JC, Baalbergen E, Janse JJ, Chevalley-Maurel S, Naar CM, Bezemer S, Kroeze H, van de Stadt HJF, de Visser B, Meij P, Tihaya MS, Colstrup E, Iliopoulou E, de Bes-Roeleveld HM, Wessels E, van der Stoep MYEC, Janse CJ, Murugan R, Franke-Fayard BMD, Roestenberg M	Nature Medicine	2025
The path from early- to late-liver stage arresting genetically attenuated parasites as a malaria vaccination strategy	Lamers OAC, Franke-Fayard BMD, Roestenberg M, Krol JMM	NPJ Vaccines	2025
Correlative humoral and cellular immunity to genetically attenuated malaria parasites in humans	Colstrup E, Nakajima R, Krol JM, Lamers OAC, de Assis RR, Jain A, Jasinskas A, Iliopoulou E, de Bes-Roeleveld HM, Franke-Fayard BMD, Roestenberg M.	iScience	2025

Table 3. Overview of courses completed

Course	Year
BROK	2020, requalification in 2024
Leiden University Onboarding Programme Inform & Connect	2022
Basic methods and reasoning in Biostatistics	2022
Communication training	2022
Job orientation training	2024

Table 4. Overview of conferences attended

Conference	Year	Presentation
British Society of Parasitology Spring Meeting	2023	Poster and pitch
Dutch Society for Parasitology Spring Meeting	2023	Presentation
Dutch Malaria Day	2023	Presentation
BioMalParXX	2024	Presentation
Travelers' medicine	2024	Not applicable
Regional training evening on infectious diseases	2024	Not applicable
Dutch internist days	2025	Presentation