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Curriculum vitae

Catherin Yizet Marin Mogollon was born on 30th December 1985, in Bogota, Colombia (South America). She completed a Bachelor's degree in Bacteriology and Clinical Laboratory Science in 2007 at Colegio Mayor University of Cundinamarca. During her Bachelor studies she performed a 12 month internship at the Department of Molecular Biology of Fundacion Instituto de Inmunologia de Colombia (FIDIC), where she gained an interest and experience in molecular biology of the parasites that cause malaria in humans, *Plasmodium falciparum* and *P. vivax*. From 2007 until 2010 she performed her Master's degree studies in Biochemistry at the Universidad Nacional de Colombia, where she completed a Master thesis entitled "Identification, expression and characterization of nicotinamide/mononucleotide adenylyltransferase of *Plasmodium falciparum*" under the guidance of Dr. Maria Helena Ramirez Hernandez. From 2011 until 2012 she worked as a research assistant in the Molecular Biology Laboratory of the Caucesco Scientific Research Center in Cali, Colombia, on the production of the recombinant protein P48/45 of *P. vivax* as a target for transmission blocking vaccines. From 2012 until 2013 she worked in the Laboratory of Biochemistry at Colegio Mayor de Nuestra Señora del Rosario University (Bogota, Colombia) as a research assistant investigating the relationship between hypoxia and metabolism in cancer cells. In 2013 she was enrolled as a PhD student in the Leiden Malaria Research Group (LMRG) of the Department of Parasitology within the Leiden University Medical Center (LUMC, The Netherlands), with support from a Colciencias-Colfuturo PhD fellowship (Call 568 from 2012 Resolution 01218 Bogotá, Colombia). In Leiden she carried out her PhD project under supervision of Dr. Shahid Khan and Dr. Chris Janse. The results of the studies in Leiden are presented in this thesis. After finishing her PhD, Catherin Marin will continue as a post-doc in the Department of Parasitology (LUMC, Leiden) focussing on *P. falciparum* genetic modification, to both study the biology malaria parasites and to develop attenuated parasite vaccines. After this period she intends to return to Colombia and apply the knowledge that she has gained to scientific projects in her country.



List of publications

1. **C Marin-Mogollon**, M van de Vegte-Bolmer, GJ van Gemert, FJA van Pul, J Ramesar, Othman AS, H Kroeze, J Miao, L Cui, KC Williamson, R Sauerwein, CJ Janse and SM Khan. The *Plasmodium falciparum* male gametocyte protein P230p, a paralog of P230, is vital for zygote formation and mosquito transmission. *Sci Rep*, 2018. **8**(1): p. 14902.
2. **C Marin-Mogollon**, FJA van Pul, S Miyazaki, T Imai, J Ramesar, AM Salman, BMF Winkel, Othman AS, H Kroeze, S Chevalley-Maurel, A Reyes-Sandoval, M Roestenberg, BM Franke-Fayard, CJ Janse and SM Khan. *Chimeric Plasmodium falciparum parasites expressing Plasmodium vivax circumsporozoite protein fail to produce salivary gland sporozoites*. *Malar J*, 2018. **17**(1): p. 288.
3. Othman AS, JW Lin, BM Franke-Fayard, H Kroeze, FJA van Pul, S Chevalley-Maurel, J Ramesar, **C Marin-Mogollon**, MM Jore, MJ Morin, CA Long, R Sauerwein, A Birkett, K Miura, CJ Janse and SM Khan. *Expression of full-length Plasmodium falciparum P48/45 in P berghei blood stages: A method to express and evaluate vaccine antigens*. *Mol Biochem Parasitol*, 2018. **224**: p. 44-49.
4. Othman AS, BM Franke-Fayard, T Imai, ETI van der Gracht, A Redeker, AM Salman, **C Marin-Mogollon**, J Ramesar, S Chevalley-Maurel, CJ Janse, R Arens and SM Khan. *OX40 Stimulation Enhances Protective Immune Responses Induced After Vaccination With Attenuated Malaria Parasites*. *Front Cell Infect Microbiol*, 2018. **8**: p. 247.
5. LE Contreras-Rodríguez, **C Marin-Mogollon**, LM Sánchez-Mejía, MH Ramírez-Hernández. *Structural Insights into Plasmodium falciparum nicotinamide mononucleotide adenylyltransferase: oligomeric assembly*. *Mem Inst Oswaldo Cruz*, 2018. **113**(9): p. e180073.
6. Othman AS*, **C Marin-Mogollon***, AM Salman, BM Franke-Fayard, CJ Janse and SM Khan. *The use of transgenic parasites in malaria vaccine research*. *Expert Rev Vaccines*, 2017. **16**(7): p. 1-13.*Authors contributed equally to this study.
7. CA Nieto, **CY Marin**, LE Contreras, MH Ramírez. *Study of specific Region of Plasmodium falciparum Nicotinamide/Nicotinate Mononucleotide Adenylyl Transferase (PfNMNAT): Characterizing a Possible Therapeutic Target*. *J Mol Genet Med*, 2017. **11**(12).
8. **C Marin Mogollon**, FJ van Pul, T Imai, J Ramesar, S Chevalley-Maurel, GM de Roo SAJ Veld, H Kroeze, BMD Franke-Fayard, CJ Janse and SM Khan, *Rapid Generation of Marker-Free P. falciparum Fluorescent Reporter Lines Using Modified CRISPR/Cas9 Constructs and Selection Protocol*. *PLoS One*, 2016. **11**(12): p. e0168362.
9. M Arévalo-Herrera, AF Vallejo, K Rubiano, Y Solarte, **C Marin**, A Castellanos, N Céspedes, S Herrera. *Recombinant Pvs48/45 antigen expressed in E. coli generates antibodies that block malaria transmission in Anopheles albimanus mosquitoes*. *PLoS One*, 2015. **10**(3): p. e0119335.
10. M Arévalo-Herrera, Y Solarte, **C Marin**, M Santos, J Castellanos, JC Beier, SH Valencia. *Malaria transmission blocking immunity and sexual stage vaccines for interrupting malaria transmission in Latin America*. *Mem Inst Oswaldo Cruz*, 2011. **106 Suppl 1**: p. 202-11.
11. AM Salman, **CM Mogollon**, JW Lin, FJ van Pul, CJ Janse and SM Khan. *Generation of Transgenic Rodent Malaria Parasites Expressing Human Malaria Parasite Proteins*. *Methods Mol Biol*, 2015. **1325**: p. 257-86.

