Host-directed therapy for the treatment of tuberculosis: rewiring the host to recover control

Heemskerk, M.T.

Curriculum Vitae

Born in Leiden on October 19th, 1989, Maarten Thomas (Matthias) Heemskerk grew up in Katwijk aan Zee. His interest in biology started at the age of 10, when he received a microscope as a gift. Armed with microscope slides, he explored the house, the neighbourhood, as well as blood obtained with the finger prick lancet from a friend's father. This interest was grown by the beta sciences oriented profile during his VWO education. After graduating high school in 2008, he enrolled in the bachelor Life Science & Technology at Leiden and Delft. During his Bachelor internship, he took part in a research project on identifying host factors that play a role in intracellular Chikungunya virus replication. Drawn in particular to cell biology, he did his master's in Life Science & Technology at Leiden. In his first Master internship, he worked on optimizing the simultaneous isolation of various T-cell populations using MHCI-Streptamer isolation technology. His second Master internship focused on short hairpin RNAs and improving their activity and biogenesis. Eager to learn more, he started his research to attain his Ph.D. at the Department of Infectious Diseases of the Leiden University Medical Center, in 2014, even prior to having graduated. Through teamwork and collaborations, he aimed for maximizing the impact of his work of which the results are described in this thesis. In 2020, he leveraged his skills and expertise to help develop a cell therapy manufacturing process fit for decentralized production at the start-up company CellPoint. By working on preclinical development, analytical development and quality control, he helped start clinical trials for three different cell therapy products. Currently, he leads the analytical development department at Galapagos and is responsible for developing the innovative release and testing strategy required for this next generation of cell therapy production.

List of Publications

Kilinç G, Boland R*, **Heemskerk MT***, Spaink HP, Haks MC, van der Vaart M, Ottenhoff THM, Meijer AH, Saris A. *Host-directed therapy with amiodarone in preclinical models restricts mycobacterial infection and enhances autophagy*. Microbiol Spectr. 2024 Aug 6.

Boland R*, **Heemskerk MT***, Forn-Cuní G, Korbee CJ, Walburg KV, Esselink JJ, Carvalho Dos Santos C, de Waal AM, van der Hoeven DCM, van der Sar E, de Ries AS, Xie J, Spaink HP, van der Vaart M, Haks MC, Meijer AH, Ottenhoff THM. *Repurposing Tamoxifen as Potential Host-Directed Therapeutic for Tuberculosis*. mBio. 2023 Feb 28.

Heemskerk MT, Korbee CJ, Esselink JJ, Dos Santos CC, van Veen S, Gordijn IF, Vrieling F, Walburg KV, Engele CG, Dijkman K, Wilson L, Verreck FAW, Ottenhoff THM, Haks MC. *Repurposing diphenylbutylpiperidine-class antipsychotic drugs for host-directed therapy of Mycobacterium tuberculosis and Salmonella enterica infections*. Sci Rep. 2021 Oct 4.

van Doorn CLR, Schouten GK, van Veen S, Walburg KV, Esselink JJ, **Heemskerk MT**, Vrieling F, Ottenhoff THM. *Pyruvate Dehydrogenase Kinase Inhibitor Dichloroacetate Improves Host Control of Salmonella enterica Serovar Typhimurium Infection in Human Macrophages*. Front Immunol. 2021 Sep 6.

Bakkum T, **Heemskerk MT**, Bos E, Groenewold M, Oikonomeas-Koppasis N, Walburg KV, van Veen S, van der Lienden MJC, van Leeuwen T, Haks MC, Ottenhoff THM, Koster AJ, van Kasteren SI. *Bioorthogonal Correlative Light-Electron Microscopy of Mycobacterium tuberculosis in Macrophages Reveals the Effect of Antituberculosis Drugs on Subcellular Bacterial Distribution*. ACS Cent Sci. 2020 Nov 25.

Moreira JD, Koch BEV, van Veen S, Walburg KV, Vrieling F, Mara Pinto Dabés Guimarães T, Meijer AH, Spaink HP, Ottenhoff THM, Haks MC*, **Heemskerk MT***. *Functional Inhibition of Host Histone Deacetylases (HDACs) Enhances in vitro and in vivo Anti-mycobacterial Activity in Human Macrophages and in Zebrafish*. Front Immunol. 2020 Feb 3.

Korbee CJ*, **Heemskerk MT***, Kocev D, van Strijen E, Rabiee O, Franken KLMC, Wilson L, Savage NDL, Džeroski S, Haks MC, Ottenhoff THM. *Combined chemical genetics and data-driven bioinformatics approach identifies receptor tyrosine kinase inhibitors as host-directed antimicrobials*. Nat Commun. 2018 Jan 24.

Herrera-Carrillo E, Gao ZL, Harwig A, **Heemskerk MT**, Berkhout B. *The influence of the 5´-terminal nucleotide on AgoshRNA activity and biogenesis: importance of the polymerase III transcription initiation site*. Nucleic Acids Res. 2017 Apr 20.

Roex MCJ, Hageman L, **Heemskerk MT**, Veld SAJ, van Liempt E, Kester MGD, Germeroth L, Stemberger C, Falkenburg JHF, Jedema I. *The simultaneous isolation of multiple high and low frequent T-cell populations from donor peripheral blood mononuclear cells using the major histocompatibility complex I-Streptamer isolation technology*. Cytotherapy. 2018 Apr 20.

Treffers EE, Tas A, Scholte FE, Van MN, **Heemskerk MT**, de Ru AH, Snijder EJ, van Hemert MJ, van Veelen PA. *Temporal SILAC-based quantitative proteomics identifies host factors involved in chikungunya virus replication*. *Proteomics*. 2015 Jul15.

* contributed equally

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