Keyhole limpet hemocyanin challenge model for studying adaptive immune system responses in early-phase clinical drug development

Saghari, M.

APPENDICES

CURRICULUM VITAE

Mahdi Saghari was born on the 11th of October 1989 in Herat, Afghanistan. After completing bilingual VWO at secondary school CVO Farelcollege (Ridderkerk, the Netherlands) in 2008, he studied Medicine at Erasmus University Rotterdam (Rotterdam, the Netherlands). He obtained his bachelor's degree in Medicine in 2012. Due to his interest in both academic research and medicine he simultaneously studied Neuroscience and Medicine, for which he obtained a Master's degree in 2014 and 2017, respectively. His primary focus during Neuroscience was the preclinical development of novel antisense oligonucleotide (ASO) therapy for Angelman syndrome in the lab of prof. dr. Ype Elgersma at the Erasmus Medical Center (Rotterdam, the Netherlands). His research served as the starting point for further evaluation of ASO therapy in Angelman syndrome, with promising results (Milazzo et al. 2021, DOI: 10.1172/jci.insight.145991).

Upon obtaining his medical degree in 2017, he started his career as a research physician and project leader at the Centre for Human Drug Research (CHDR, Leiden, the Netherlands). Here Mahdi began his PhD trajectory as described in this thesis under supervision of dr. M. Moerland, prof. dr. R. Rissmann and prof. dr. J. Burggraaf. In addition to performing clinical research described in this PhD thesis, he also contributed to many other clinical studies across different therapeutic areas including dermatology, immunology and cardiology. Whilst working at CHDR, he became a board-certified Clinical Pharmacologist in 2022.

In 2023 Mahdi worked as a medical intern at the dermatology department of the Admiraal de Ruyter ziekenhuis (ADRZ, Goes, the Netherlands). Since April 2024 he works as a medical intern in occupational health medicine at HumanCapitalCare B.V. (Capelle aan den IJssel, the Netherlands), with the aim to become an occupational health physician.

LIST OF PUBLICATIONS

Rousel, J., Nădăban, A., **Saghari, M.**, Pagan, L., Zhuparris, A., Theelen, B., Gambrah, T., van der Wall, H. E. C., Vreeken, R. J., Feiss, G. L., Niemeyer – van der Kolk, T., Burggraaf, J., van Doorn, M. B. A., Bouwstra, J. A., Rissmann, R. (2023). Lesional skin of seborrheic dermatitis patients is characterized by skin barrier dysfunction and correlating alterations in the stratum corneum ceramide composition. *Experimental Dermatology*. https://doi.org/10.1111/exd.14952

Rousel, J., **Saghari, M.**, Pagan, L., Nădăban, A., Gambrah, T., Theelen, B., de Kam, M. L., Haakman, J., van der Wall, H. E. C., Feiss, G. L., Niemeyer – van der Kolk, T., Burggraaf, J., Bouwstra, J. A., Rissmann, R., van Doorn, M. B. A. (2023) treatment with the topical antimicrobial peptide omiganan in mild-to-moderate facial seborrheic dermatitis versus ketoconazole and placebo: results of a randomized controlled proof-of-concept trial. *International Journal of Molecular Sciences.* https://doi.org/10.3390/ijms241814315

Saghari, M., Gal, P., Grievink, H.W., Klaassen, E.S., Zhuparris, A., Itano, A., Bodmer, M., McHale, D., Moerland, M. (2023). Evaluation of single-strain Prevotella histicola on KLH-driven immune responses in healthy volunteers: a randomized controlled trial with EDP1815. *Medicine in Microecology.* https://doi.org/10.1016/j.medmic.2023.100088

Itano, A., Maslin, D., Ramani, K., Mehraei, G., Carpenter, N., Cormack, T., **Saghari, M.**, Moerland, M., Troy, E., Caffry, W., Wardwell-Scott, L., Abel, S., McHale, D., & Bodmer, M. (2023). Clinical translation of anti-inflammatory effects of Prevotella histicola in Th1, Th2, and Th17 inflammation. *Frontiers in Medicine, 10*. https://doi.org/10.3389/fmed.2023.1070433

ten Voorde, W., **Saghari, M.**, Boltjes, J., de Kam, M. L., Zhuparris, A., Feiss, G., Buters, T. P., Prens, E. P., Damman, J., Niemeyer-van der Kolk, T., Moerland, M., Burggraaf, J., van Doorn, M. B. A., & Rissmann, R. (2023). A multimodal, comprehensive characterization of a cutaneous wound model in healthy volunteers. *Experimental Dermatology.* https://doi.org/10.1111/exd.14808

Saghari, M., Gal, P., Grievink, H. W., Klaassen, E. S., Itano, A., McHale, D., & Moerland, M. (2022). Impact of oral administration of single strain *Lactococcus lactis spp. cremoris* on immune responses to keyhole limpet hemocyanin

immunization and gut microbiota: A randomized placebo-controlled trial in healthy volunteers. *Frontiers in Immunology, 13*. https://doi.org/10.3389/fimmu.2022.1009304

Saghari, M., Jansen, M. A. A., Grievink, H. W., Rissmann, R., & Moerland, M. (2022). Characterization of KLH-driven immune responses in clinical studies: a systematic review. *Frontiers in Drug Discovery, 2*. https://doi.org/10.3389/fddsv.2022.992087

Saghari, M., Gal, P., Gilbert, S., Yateman, M., Porter-Brown, B., Brennan, N., Quaratino, S., Wilson, R., Grievink, H. W., Klaassen, E. S., Bergmann, K. R., Burggraaf, J., Doorn, M. B. A., Powell, J., Moerland, M., & Rissmann, R. (2022). OX40L inhibition suppresses KLH-DRIVEN immune responses in healthy volunteers: a randomized controlled trial demonstrating proof-of-pharmacology for KY1005. *Clinical Pharmacology & Therapeutics, 111(5)*, 1121–1132. https://doi.org/10.1002/cpt.2539

Saghari, M., Gal, P., Ziagkos, D., Burggraaf, J., Powell, J. F., Brennan, N., Rissmann, R., Doorn, M. B. A., & Moerland, M. (2021). A randomized controlled trial with a delayed-type hypersensitivity model using keyhole limpet haemocyanin to evaluate adaptive immune responses in man. *British Journal of Clinical Pharmacology, 87(4)*, 1953–1962. https://doi.org/10.1111/bcp.14588

Gal, P., Klaassen, E. S., Bergmann, K. R., **Saghari, M**., Burggraaf, J., Kemme, M. J. B.,Sylvest, C., Sørensen, U., Bentzen, B. H., Grunnet, M., Diness, J. G., & Edvardsson, N. (2020). First clinical study with AP30663 - a KCa2 channel inhibitor in development for conversion of atrial fibrillation. *Clinical and Translational Science, cts.12835*. https://doi.org/10.1111/cts.12835

In 't Veld, A. E., Grievink, H. W., **Saghari, M**., Stuurman, F. E., de Kam, M. L., de Vries, A. P. J., de Winter, B. C. M., Burggraaf, J., Cohen, A. F., & Moerland, M. (2019). Immunomonitoring of tacrolimus in healthy volunteers: the first step from PK- to PD-based therapeutic drug monitoring? *International Journal of Molecular Sciences, 20(19)*. https://doi.org/10.3390/ijms20194710

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