Final Report

7th Wael Almahmeed and IAS Research Training Fellowship

Fellow: Taraneh Shabanian

Project Title: “Discovering a Novel Cholesterol-Lowering Symbiotic to Prevent Atherosclerosis in Aging”

Host Institution: Cardiovascular Aging Laboratory, Center for Translational and Experimental Cardiology (CTEC), University Hospital Zurich, University of Zurich
Supervisor: PD Dr. Soheil Saeedi, PharmD, PhD, FESC

Summary of Progress

First, I would like to express my sincere gratitude to the International Atherosclerosis Society (IAS) and Dr. Wael Almahmeed for their generous support through the IAS Research Training Fellowship. This fellowship has provided me with a unique opportunity to join the Cardiovascular Aging Laboratory at the Center for Translational and Experimental Cardiology (CTEC), University Hospital Zurich, where I have received advanced training in cardiovascular biology, microbiome science, and translational research under the supervision of PD Dr. Soheil Saeedi. Beyond technical training, the fellowship has enabled me to contribute to an innovative international research program aimed at developing microbiome-based therapeutic strategies for preventing vascular aging and atherosclerotic cardiovascular disease.

The fellowship focused on the **Athero-Gut Project**, an interdisciplinary research initiative investigating how cholesterol-metabolizing gut bacteria can be harnessed as next-generation probiotic and synbiotic therapies to reduce cholesterol burden and delay vascular aging. Specifically, the project explores the therapeutic potential of newly

identified ***ismA*-encoding bacterial strains**, which convert intestinal cholesterol into poorly absorbable cholestenone, thereby limiting cholesterol absorption and reducing systemic exposure to one of the major drivers of atherosclerosis.

During the fellowship, I successfully completed comprehensive training in advanced experimental methodologies in cardiovascular aging and microbiome research. These included vascular senescence phenotyping, functional vascular assays, gut microbiome sequencing, microbial metabolite profiling, human cohort studies, and animal experimentation. This training substantially strengthened my technical expertise and established a solid foundation for conducting independent translational cardiovascular and microbiome research.

A major achievement of the fellowship was the successful establishment and optimization of experimental platforms required to evaluate the vascular protective properties of cholesterol-metabolizing probiotic candidates. I contributed to developing standardized endothelial senescence and vascular function assays that are now routinely implemented within our laboratory to investigate microbiome-host interactions during cardiovascular aging.

Importantly, significant scientific progress was achieved during the fellowship. Our studies identified novel ***ismA*-positive bacterial strains** with enhanced cholesterol-metabolizing capacity and demonstrated their potential to reduce cholesterol bioavailability and improve endothelial health. Using complementary bacterial culture systems, endothelial cell models, and preliminary translational analyses, we generated compelling evidence supporting the concept that modulation of gut microbial cholesterol metabolism may represent a promising therapeutic strategy for preventing endothelial dysfunction and age-associated atherosclerosis.

The fellowship also established the experimental framework for several ongoing translational studies that substantially extend these findings. These include validation of probiotic and synbiotic formulations in aged and atherosclerosis-prone *Ldlr*$^{-/-}$ mouse models, shotgun metagenomic sequencing to characterize cholesterol-metabolizing

microbial communities, LC-MS/MS-based metabolomic and lipidomic profiling to quantify cholesterol-derived metabolites, and advanced single-cell and spatial transcriptomic analyses to identify vascular cell-specific mechanisms regulated by microbiome-derived metabolic pathways. Together, these complementary approaches are providing unprecedented insight into the molecular mechanisms linking microbial cholesterol metabolism with vascular aging.

The scientific quality and translational significance of this work have already received outstanding international recognition. The project was selected for oral presentation at **the European Society of Cardiology (ESC) Congress 2025** in Madrid, Spain, one of the world's leading cardiovascular meetings. In addition, the work was selected for oral presentation at **the European Atherosclerosis Society (EAS) Congress 2026** in Athens, Greece, highlighting its relevance to the international cardiovascular and lipid research communities. Furthermore, these achievements led to the award of an **EAS Educational Grant**, which supported my participation in the EAS Congress and the presentation of our findings in Athens in May 2026. These recognitions underscore both the scientific excellence and the translational potential of the Athero-Gut Project.

- Shabanian K, Pugin B, Constancias F, **Shabanian T**, Spalinger M, Menni C, Zhang X, Hermann M, Feinberg MW, Paneni F, Ruschitzka F, Saeedi S. Gut ismA-expressing bacteria mitigate atherosclerosis by modulating cholesterol metabolism. *European Heart Journal*, 46(Suppl_1): ehaf784.4878 (2025). https://doi.org/10.1093/eurheartj/ehaf784.4878
- Shabanian K, Pugin B, Constancias F, **Shabanian T**, Menni C, Zhang X, Hermann M, Paneni F, Ruschitzka F, Saeedi S. Cholesterol-lowering ISMA-encoding gut bacteria mitigate atherosclerosis. *Atherosclerosis*, 407(Suppl_1): 120332 (2025). https://doi.org/10.1016/j.atherosclerosis.2025.120332

In addition, this fellowship provided me with an excellent opportunity to actively participate in the microbiome-atherosclerosis projects that resulted in publications in ***Nature Aging*** (PMID: 40355758) and ***BioRxiv.***

(https://doi.org/10.64898/2026.02.27.708541), as well as one under revision in ***Cell Reports***.

- Saeedi Saravi SS, Pugin B, Constancias F, Shabanian K, Spalinger M, Thomas A, Le Gludic S, **Shabanian T**, Karsai G, Colucci M, Menni C, Attaye I, Zhang X, Allemann MS, Lee P, Visconti A, Falchi M, Alimonti A, Ruschitzka F, Paneni F, Beer JH. Gut microbiota-dependent increase in phenylacetic acid induces endothelial cell senescence during aging. *Nature Aging*, 5(6): 1025-1045 (2025). https://doi.org/10.1038/s43587-025-00864-8
- Shabanian K, Constancias F, Pugin B, **Shabanian T**, Thomas A, Le Gludic S, Spalinger M, Mongelli A, Menni C, Zhang X, Da Dalt L, Colucci M, Biefer HRC, Dzemali O, Hermann M, Alimonti A, Norata GD, Paneni F, Ruschitzka F, Saeedi Saravi SS. Gut Microbiota Production of Phenylacetate Programs Vascular Niche Senescence and Drives Atherosclerosis. *BioRxiv*. (2026). https://doi.org/10.64898/2026.02.27.708541
- Shabanian K, **Shabanian T**, Constancias F, Pugin B, Thomas A, Le Gludic S, Spalinger M, Mongelli A, Menni C, Zhang X, Da Dalt L, Colucci M, Biefer HRC, Dzemali O, Hermann M, Alimonti A, Norata GD, Paneni F, Ruschitzka F, Saeedi Saravi SS. Gut Microbiota Production of Phenylacetic acid Programs Vascular Niche Senescence and Drives Atherosclerosis. *Under Revision in Cell Reports*. (2026).

Beyond the scientific achievements, the fellowship substantially enhanced my ability to critically design experiments, integrate multidisciplinary datasets, interpret complex biological mechanisms, and communicate scientific findings through presentations and collaborative discussions. Participation in laboratory meetings, journal clubs, and interactions with experts in cardiovascular biology, microbiology, metabolomics, and systems biology significantly broadened my scientific perspective and strengthened my capacity to conduct independent translational research.

Overall, the IAS Research Training Fellowship has successfully accomplished its primary objective of equipping me with advanced scientific knowledge, technical

expertise, and international collaborative experience in cardiovascular aging research. The fellowship has laid the foundation for future high-impact publications, competitive research funding, and the continued development of microbiome-based precision therapies aimed at preventing atherosclerosis and promoting healthy cardiovascular aging.

Conclusion

The Wael Almahmeed and IAS Research Training Fellowship has been an exceptional opportunity for my scientific and professional development. It has equipped me with advanced experimental skills, strengthened my expertise in cardiovascular aging and microbiome research, and enabled me to contribute to an innovative translational research program aimed at developing microbiome-based strategies for preventing atherosclerosis and promoting healthy vascular aging.

I am sincerely grateful to the International Atherosclerosis Society, Dr. Wael Almahmeed, my supervisor, PD Dr. Soheil Saeedi, and the CTEC, University of Zurich, for their generous support, mentorship, and commitment to fostering the next generation of cardiovascular scientists. The knowledge and experience gained during this fellowship will have a lasting impact on my future research career and my continued contributions to cardiovascular medicine.