Final Report

6th Wael Almahmeed and IAS Research Training Fellowship

Fellow: Dr. Khatereh Shabanian, Pharm.D

Project Title: “Genetic Engineering of *Clostridium* sp. ASF356 to Prevent (Peri)Vascular Senescence and Extend Healthspan”

Host Institution: Cardiovascular Aging Lab, Center for Translational and Experimental Cardiology (CTEC), University of Zurich

Supervisor: Dr. Soheil Saeedi, Pharm.D, Ph.D, FESC

Dear Members of the Wael Almahmeed and IAS Research Training Fellowship Committee,

It is with great gratitude and enthusiasm that I submit this final report on the research and training activities supported by the *6th Wael Almahmeed and IAS Research Training Fellowship*, generously awarded by the *International Atherosclerosis Society (IAS)*.

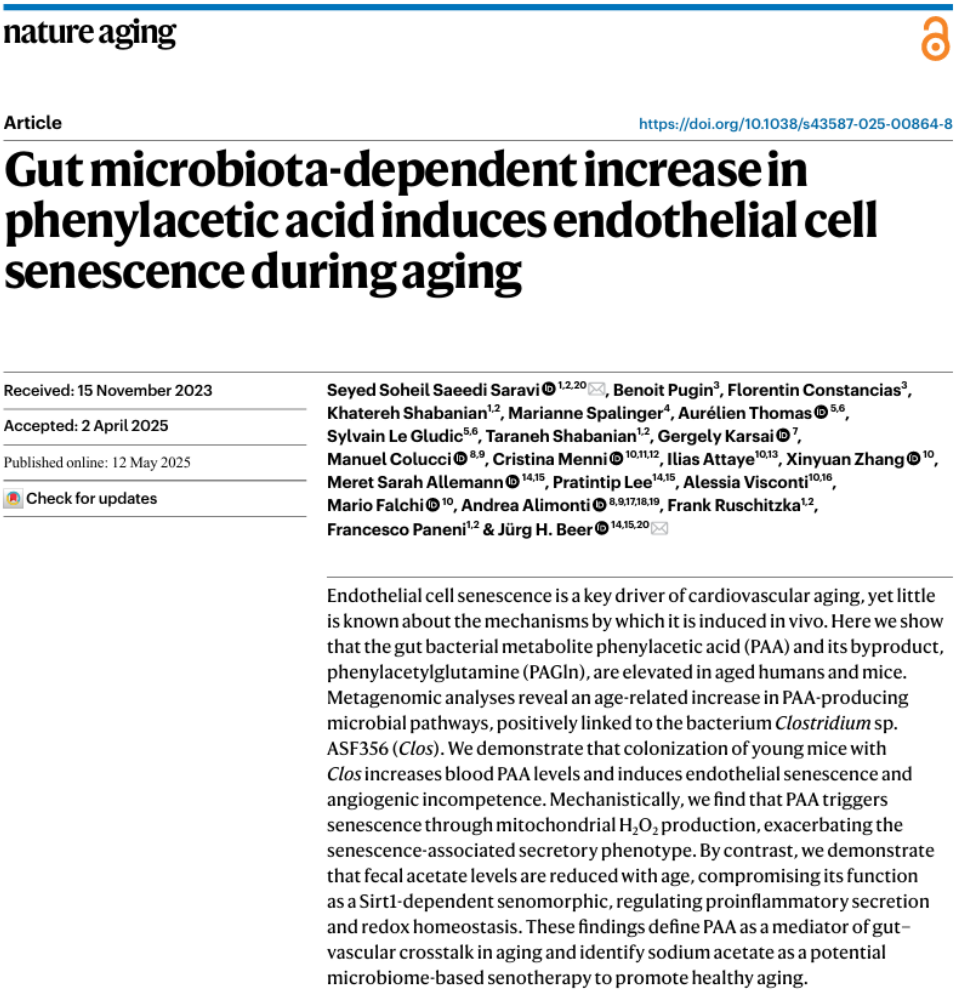
Over the past six months, I have had the privilege of working in the Cardiovascular Aging Lab at the University of Zurich under the guidance of Dr. Soheil Saeedi, contributing to multiple interdisciplinary projects at the interface of gut microbiome, vascular aging, and cardiometabolic disease. My fellowship project focused on the exploration of metabolic function and genetic engineering of *Clostridium* sp. ASF356 with the long-term goal of mitigating vascular senescence and enhancing cardiovascular healthspan.

I am deeply grateful to the International Atherosclerosis Society (IAS) for their generous financial support and the opportunity to be part of this unique program. The fellowship has not only enriched my scientific training but also opened doors to meaningful collaborations and impactful research that I am confident will shape the course of my academic career.

Throughout the fellowship period, I was actively involved in the lab's major gut microbiome–vascular aging axis studies, learning and applying high-throughput gut microbiome sequencing**,** metabolomic profiling, and molecular senescence analysis, along with (peri)vascular signal transduction studies using both murine models and human clinical cohorts, particularly the *Aging Heart Zurich Cohort* (in collaboration with University Hospital Zurich, University of Zurich) and the

TwinsUK Aging Cohort (in collaboration with King's College London). This intensive hands-on training has significantly enriched my technical and conceptual skills in translational cardiovascular science.

One of the most remarkable outcomes of this collaborative effort was the publication of a research article in ***Nature Aging***, titled: **"Gut microbiota-dependent increase in phenylacetic acid induces endothelial cell senescence during aging"** (https://doi.org/10.1038/s43587-025-00864-8), where the generous support of the *International Atherosclerosis Society* was duly acknowledged. This study has attracted attention from the cardiovascular research community and highlighted the key role of the microbial metabolite *phenylacetic acid (PAA)*, generated by *Clostridium* sp. ASF356, in promoting endothelial senescence and atherosclerosis. This work was reported by >60 prestigious international scientific media agencies (with over 18 million audience), such as Science Daily (https://www.sciencedaily.com/releases/2025/05/250528131555.htm), Eurekalert (https://www.eurekalert.org/news-releases/1085494), AlphaGalileo (https://www.alphagalileo.org/en-gb/Item-Display/ItemId/259055?returnurl=https://www.alphagalileo.org/en-gb/Item-Display/ItemId/259055), and the SRF1 radio (Schweizer Radio und Fernsehen).



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Gut microbiota-dependent increase in phenylacetic acid induces endothelial cell senescence during aging

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Endothelial cell senescence is a key driver of cardiovascular aging, yet little is known about the mechanisms by which it is induced in vivo. Here we show that the gut bacterial metabolite phenylacetic acid (PAA) and its byproduct, phenylacetylglutamine (PAGln), are elevated in aged humans and mice. Metagenomic analyses reveal an age-related increase in PAA-producing microbial pathways, positively linked to the bacterium *Clostridium* sp. ASF356 (*Clos*). We demonstrate that colonization of young mice with *Clos* increases blood PAA levels and induces endothelial senescence and angiogenic incompetence. Mechanistically, we find that PAA triggers senescence through mitochondrial H_2O_2 production, exacerbating the senescence-associated secretory phenotype. By contrast, we demonstrate that fecal acetate levels are reduced with age, compromising its function as a Sirt1-dependent senomorphic, regulating proinflammatory secretion and redox homeostasis. These findings define PAA as a mediator of gut–vascular crosstalk in aging and identify sodium acetate as a potential microbiome-based senotherapy to promote healthy aging.

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Peer review information *Nature Aging* thanks Tohru Minamino and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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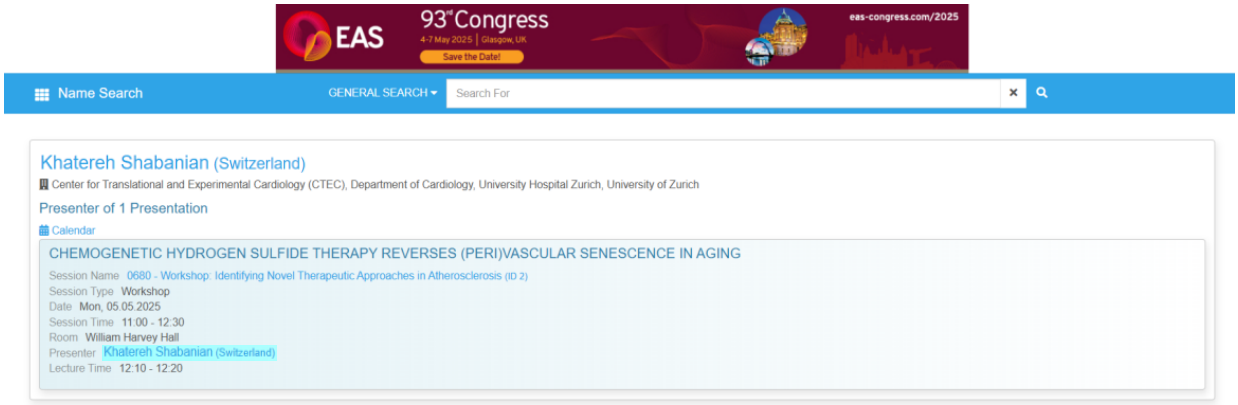
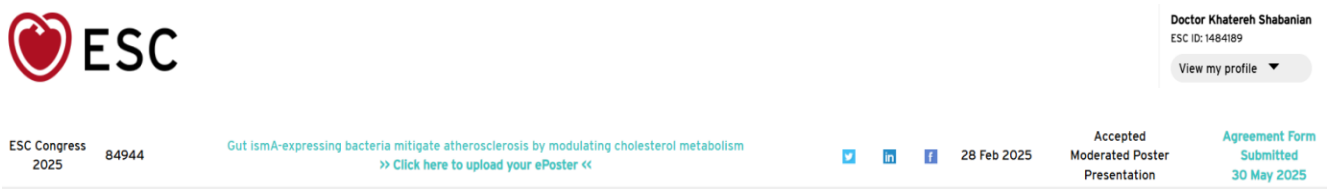
In addition to this, I was honored to receive the **AGLA Walter Riesen Award** by the Swiss Atherosclerosis Society with the work entitled **"AQP1 Differentially Orchestrates Endothelial Cell Senescence"**, published in ***Redox Biology*** (https://agla.ch/de/veranstaltungen/preistraeger/walter-riesen-award-2024).

I was also selected to deliver an *oral presentation* at the 93rd European Atherosclerosis Society (EAS) Congress in May 2025 in Glasgow, Scotland. My presentation, titled: **"Gut *Bacteroides thetaiotaomicron*-derived Ceramides Promote Perivascular Adipose Tissue-Endothelial Senescence in Aging"**, was met with highly positive feedback from renowned experts including Prof. Charalambos Antoniades (University of Oxford) and Prof. Alexander Bartlett (LMU Munich).



Another collaborative project to which I have contributed, **"Cholesterol-lowering *ismA*-encoding Gut Bacteria Mitigate Atherosclerosis"**, has been accepted as a moderated e-poster with *oral presentation* at the upcoming European Society of Cardiology (ESC) Congress 2025 in Madrid, Spain. At the EAS congresses, I was proud to acknowledge the IAS at the end of my presentations and display the IAS logo on my slides. I will do the same at the upcoming ESC congress.



Looking Ahead: Request for Fellowship Extension

As my current fellowship term comes to a close, I would like to respectfully express my strong interest in extending this program for an additional 6 months, should such an opportunity be available. I am presently in the final stages of a major research project—leading as the *first author*—on a manuscript that has been invited for submission by ***Nature Microbiology*** to its *Nature Human Microbiome Collection*.

This study builds directly upon the insights gained during my current IAS fellowship and involves the integration of molecular senescence, endothelial–PVAT cross-talk, gut microbiome metabolomics, and clinical tissue analysis. As part of this work, I am currently engaged in collecting aorta and perivascular adipose tissue (PVAT) from atherosclerotic CVD patients undergoing coronary artery bypass graft (CABG) surgery, which will provide the foundation for an important translational link between bench and bedside.

Key Highlights of the Paper (for your attention):

- Age-dependent increase in gut microbial metabolite PAA causally promotes aortic PVAT senescence
- PAA indirectly accelerates PVAT senescence through SASP
- PAA-exposed ECs release senescence-messaging secretome toward PVAT
- SASP upregulates Notch1 signaling, leading to PVAT dysfunction
- Senolytic therapy restores PVAT function
- PAA-induced PVAT senescence contributes to atherosclerosis progression

An extension of this fellowship would allow me to complete this project with continuity, further develop my scientific independence, and contribute another high-impact manuscript that highlights the mission of the IAS in advancing cardiovascular research globally.

In closing, I would like to extend my heartfelt appreciation to the International Atherosclerosis Society and the the Wael Almahmeed and IAS Research Training Fellowship Committee for generous granting me this unique and transformative training opportunity. This fellowship has significantly accelerated my development as a young cardiovascular scientist and opened exciting new directions for future research.

With sincere appreciation and hope for continued collaboration,

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