Medical University of Graz

# Apolipoprotein mimetics as novel pro-resolving mediators

## Summary

*Otto Loewi Research Center (Pharmacology), Medical University of Graz*

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| Supervisor: | PD Dr. Gunther Marsche |
| Availability: | This position is available. |
| Offered by: | Medical University of Graz |
| Application deadline: | Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich) |

## Description

Background:

Lipoproteins are supra-molecular nanostructures that play important roles in cell function, lipid metabolism, and disease progression. Their main constituents are phospholipids and apolipoproteins, forming a capsule that encloses a hydrophobic core of triglycerides and cholesterol esters. High-density lipoproteins (HDL), primarily composed of apolipoprotein A1 (apoA-I) and phospholipids play a pivotal role in reverse cholesterol transport. HDL also interacts and modulates the function of immune cells and endothelial cells, key players in the innate and adaptive immune system [1]. Attractive alternatives to using full length apo-A-I as building blocks for HDL are short synthetic peptides, termed apoA-I mimetics, which have amphipathic α-helical structures comparable to apo-AI. HDL-mimetics offer a multitude of avenues through which disease therapies may be approached.

Hypothesis and Objectives:

Among the sought properties of apoA-I mimetics are lipid-associating ability, activation of enzymes involved in HDL maturation and remodeling, promotion of cholesterol efflux, binding of oxidized lipids, anti-inflammatory and antioxidant effects, and ultimately inhibition of disease progression in vivo. Yet, basic knowledge of their physicochemical properties: molecular organisation, size, structure, dynamics, and the impact of these parameters on potential biological effects is scarce. In this project, pro-resolving activities of apoA-I mimetics on primary blood neutrophil effector responses, endotoxin inactivation, endothelial function will be tested. In addition, apoA-I mimetics will be tested in models of in vivo chemotaxis and lung inflammation.

Methodology:

Techniques that the student will acquire include native gel electrophoresis, Western blotting, flow cytometry to determine the expression of receptors and adhesion molecules, multiplex ELISA to measure cytokine release, immunofluorescence microscopy, assays to detect reactive oxygen species, phagocytosis, degranulation and neutrophil-endothelial adhesion under flow. Endothelial barrier function will be investigated by electrical impedance measurements. The student will learn how to isolate leukocytes and platelets from peripheral blood. Functional responses of neutrophils and endothelial cells will be investigated in assays of shape change, integrin up-regulation, chemotaxis and Ca2+ signaling, in vivo chemotaxis.

References:

[1] Trakaki, A.; Marsche, G. Current Understanding of the Immunomodulatory Activities of High-Density Lipoproteins. *Biomedicines* **2021**, *9*, 587. https://doi.org/10.3390/biomedicines9060587

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