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Clonal hematopoiesis of indeterminate potential (CHIP) and inflammatory signaling in humanized atherosclerotic mice

Summary

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Supervisors:	Prof. Dr. Dagmar Kratky Dr. Andreas Reinisch
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Rationale and hypothesis:

CHIP arises from somatic mutations in hematopoietic stem cells that yield mutant clonal progeny in the blood.[1] CHIP frequency increases with age and has serendipitously emerged as an independent and strong risk factor for atherosclerotic disease.[2] Murine transgenic transplantation models suggest a direct link between CHIP, inflammatory signaling, and atherogenesis.[2-4] However, translating preclinical in vivo discoveries into clinical application is often hampered by significant species-related cellular and mechanistic differences. Overcoming these critical limitations by developing an atherosclerotic mouse model with humanized clonal hematopoiesis has the potential to provide new insights into basic human vascular biology and shine new light on the contribution of mutant human immune cells and inflammatory mediators to vascular health.

This PhD position is advertised in the frame of the new Med Uni Graz Research Flagship on Healthy Vascular Aging VASC HEALTH with joint supervision and ample cooperation possibilities.

Hypothesis and Objectives:

Hypothesis: Clonal human leukocytes harboring recurrent CHIP mutations and mutant leukocyte-derived inflammatory mediators critically impact atherosclerotic plaque formation.

Objective: The generation of a novel atherosclerotic mouse model harboring a humanized immune system with clonal hematopoiesis to investigate mutant human leukocytes and inflammatory mediators in atherosclerotic plaque development.

Methodology:

The successful applicant will be integral in developing a unique humanized mouse model with genome-engineered clonal hematopoiesis developing hyperlipidemia and atherosclerosis. You will then study the impact of human CHIP mutant immune cell infiltrates and leukocyte-derived inflammatory mediators on atherosclerotic plaque formation and composition and plasma lipid parameters in detail.

You will gain in-depth experience in mouse handling, including:

- Xenotransplantation for the generation of a humanized immune and blood system
- Isolation and analysis of mouse and human tissues
- Quantitative and qualitative analysis of atherosclerotic plaques and lipid parameters

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Furthermore, you will have the opportunity to develop key **in vitro** skills, including:

- Isolation and culture of primary human hematopoietic cells (including HSCs)
- Isolation of primary mouse cells

- Polychromatic flow cytometry: analysis, sorting
- Molecular biology: PCR, qRT-PCR, ddPCR, molecular cloning, Western blotting, Immunohistochmeistry, immuno-fluorescence
- CRISPR/Cas9 genome engineering of primary cells (knock-in and knock-out)

References:

1. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498.

2. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N Engl J Med*. 2017;377(2):111-121.

3. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science*. 2017;355(6327):842-847.

4. Rauch PJ, Silver AJ, Gopakumar J, et al. Loss-of-Function Mutations in Dnmt3a and Tet2 Lead to Accelerated Atherosclerosis and Convergent Macrophage Phenotypes in Mice. *Blood*. 2018;132.

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