Spectrum of smooth muscle cell and fibroblast subtypes in atherosclerosis

R'Life kick-off seminar

November 27th, 2020

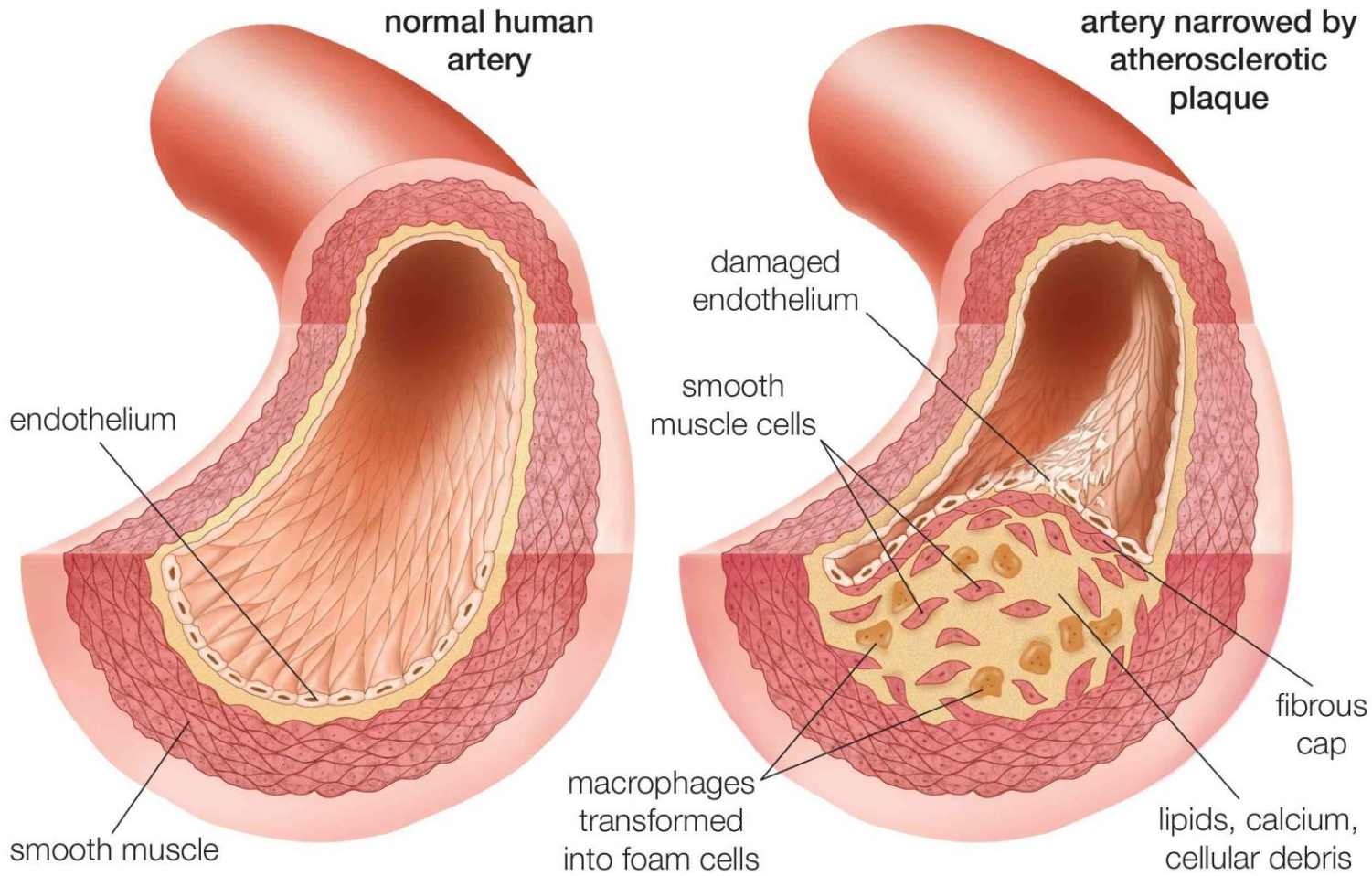
Minna Kaikkonen-Määttä,

University of Eastern Finland

UNIVERSITY OF EASTERN FINLAND

A.I.VIRTANEN INSTITUTE

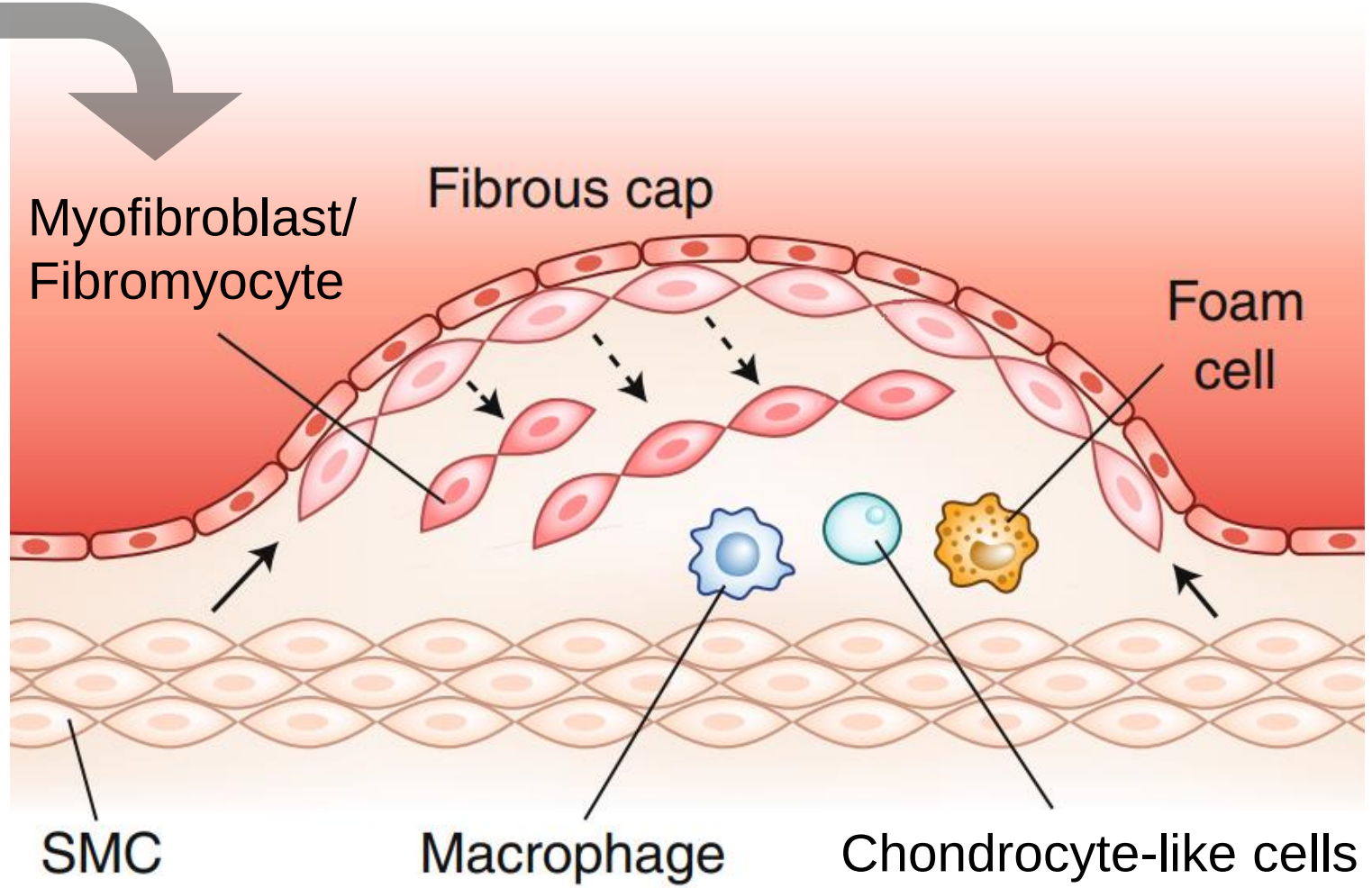
Many cell types are implicated in atherosclerosis



https://www.verywellhealth.com/

Smooth muscle cells take several fates in lesions

Contractile genes
(e.g. MYH11, TAGLN)



Modified from Pan & Reilly, Nature Medicine 2019

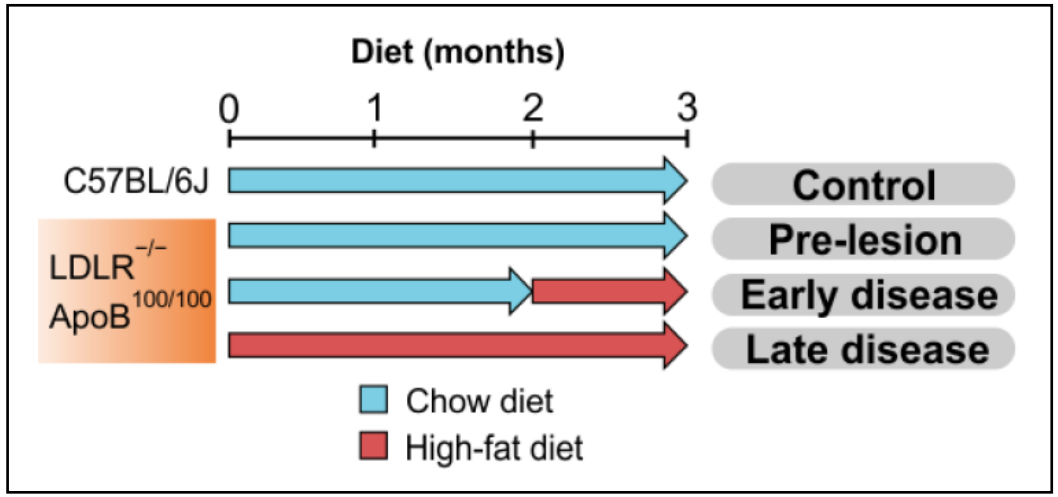
Aims of the R'Life-project

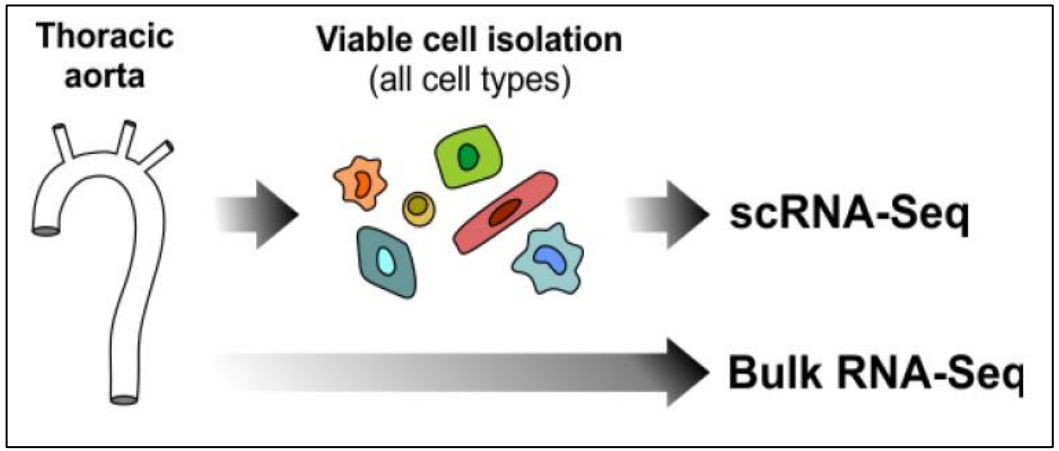
1. Characterization of the phenotypic spectrum of vascular smooth muscle cells (SMCs) and fibroblasts (FBs) using single cell sequencing *in vivo*
   - Unraveling the complexity and diversity of these cells in atherosclerosis
   - Understanding mechanisms (TFs, cell-cell interact.) driving pathological transformation

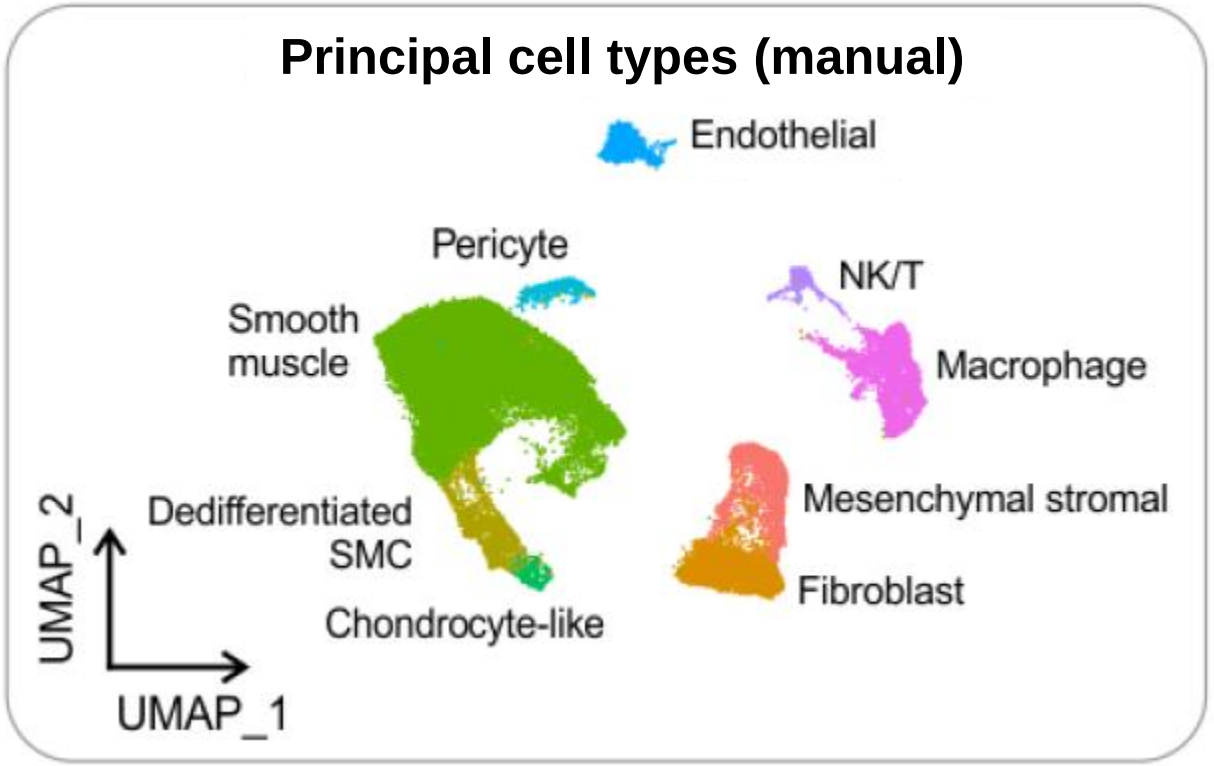
2. Discovery of master regulators that modify the SMC/FB phenotypes using *in vitro* modeling and CRISPR-screens
   - Identification/validation of transcription factors and signaling pathways acting that mediate the cellular transformation associated with atherogenesis

Better understanding of molecular and cellular regulons driving the pathological transformation of cells could translate into mechanism-based advances in prevention and treatment of coronary artery disease

scRNA seq in mouse model of atherosclerosis (WP1)

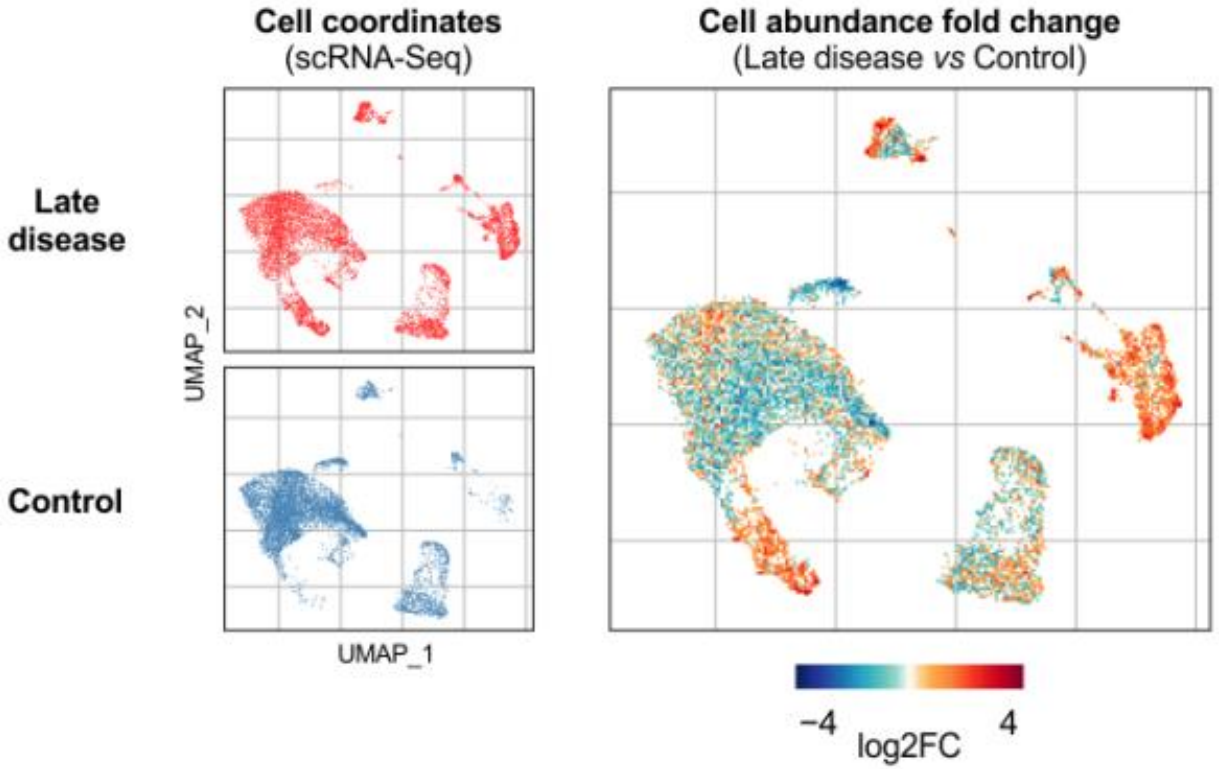


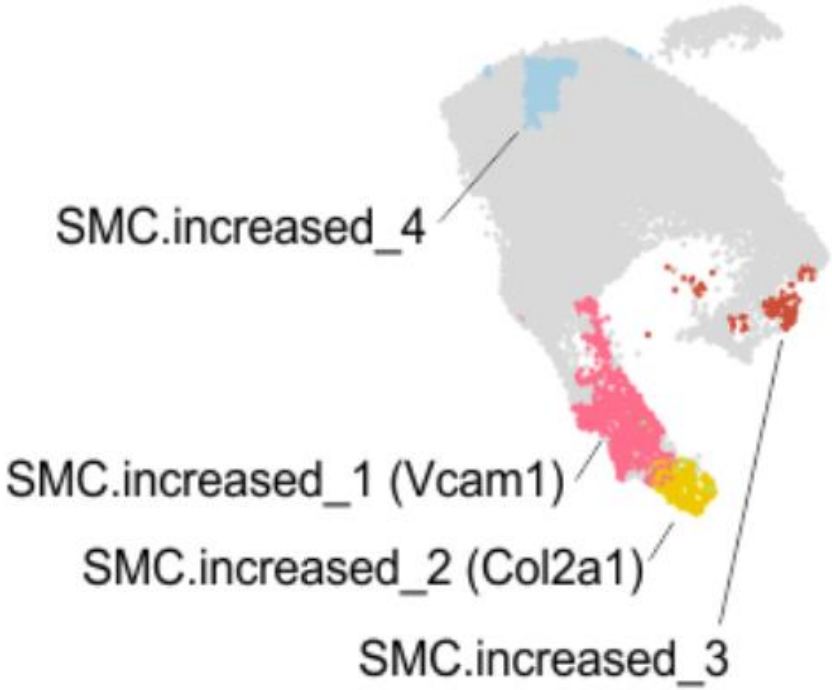




Örd *et al*, unpublished

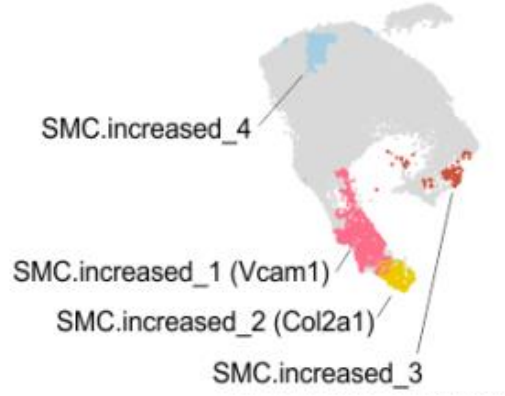
Atherosclerosis-associated cell abundance changes

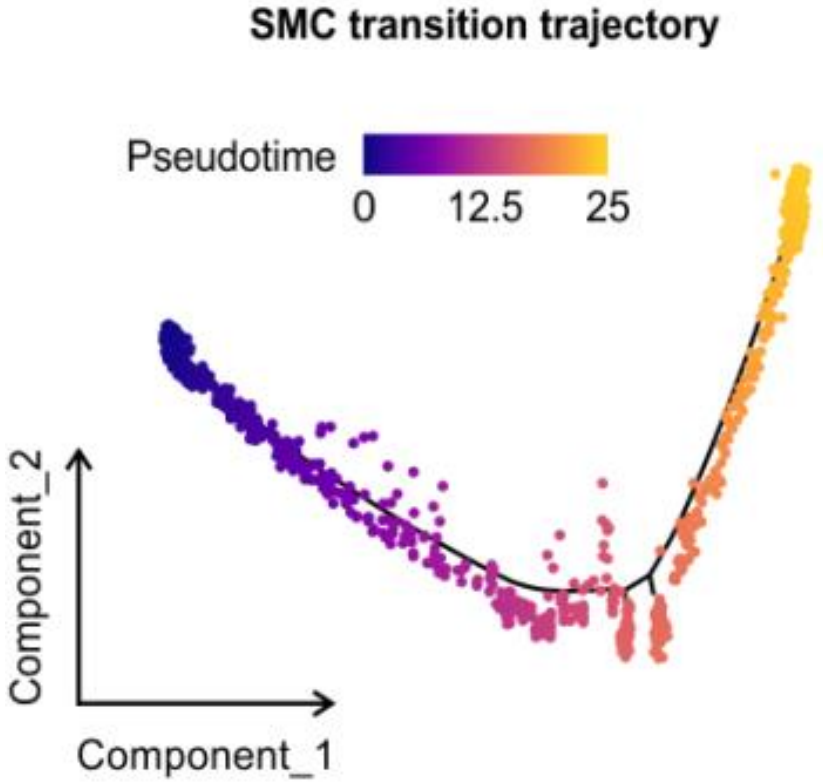


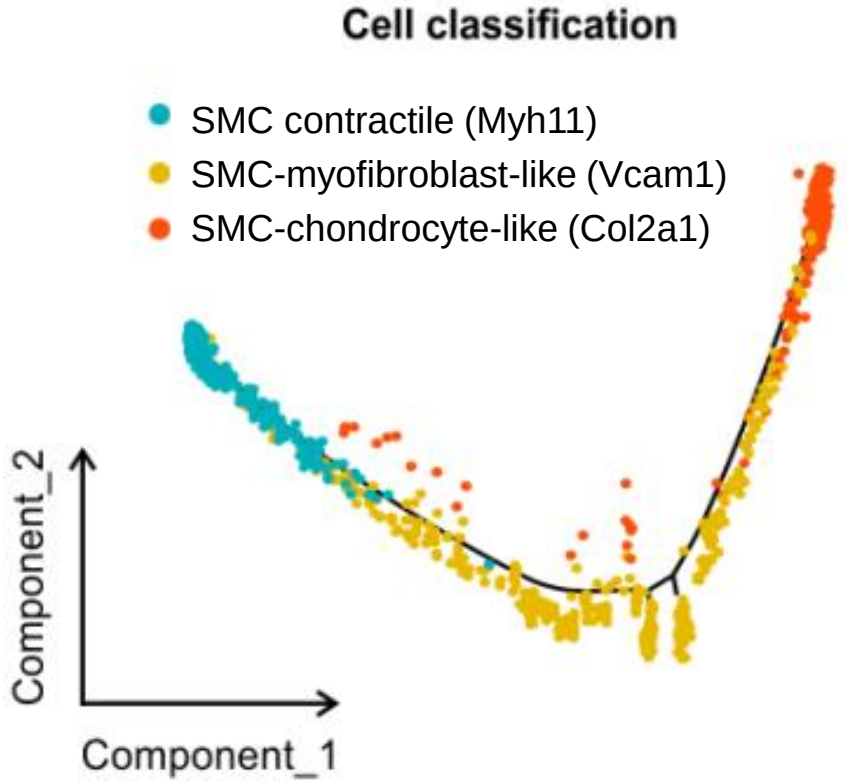


Örd *et al*, unpublished

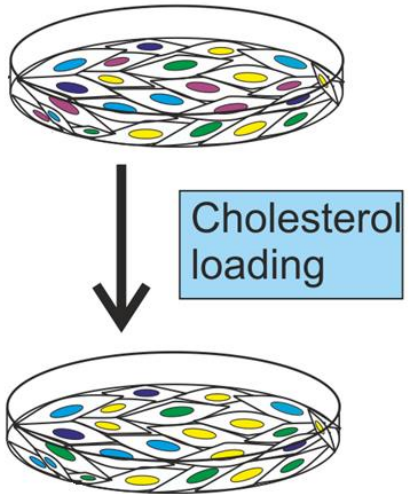
SMC differentiation trajectory

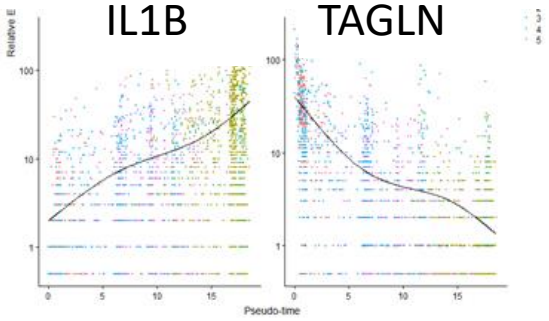


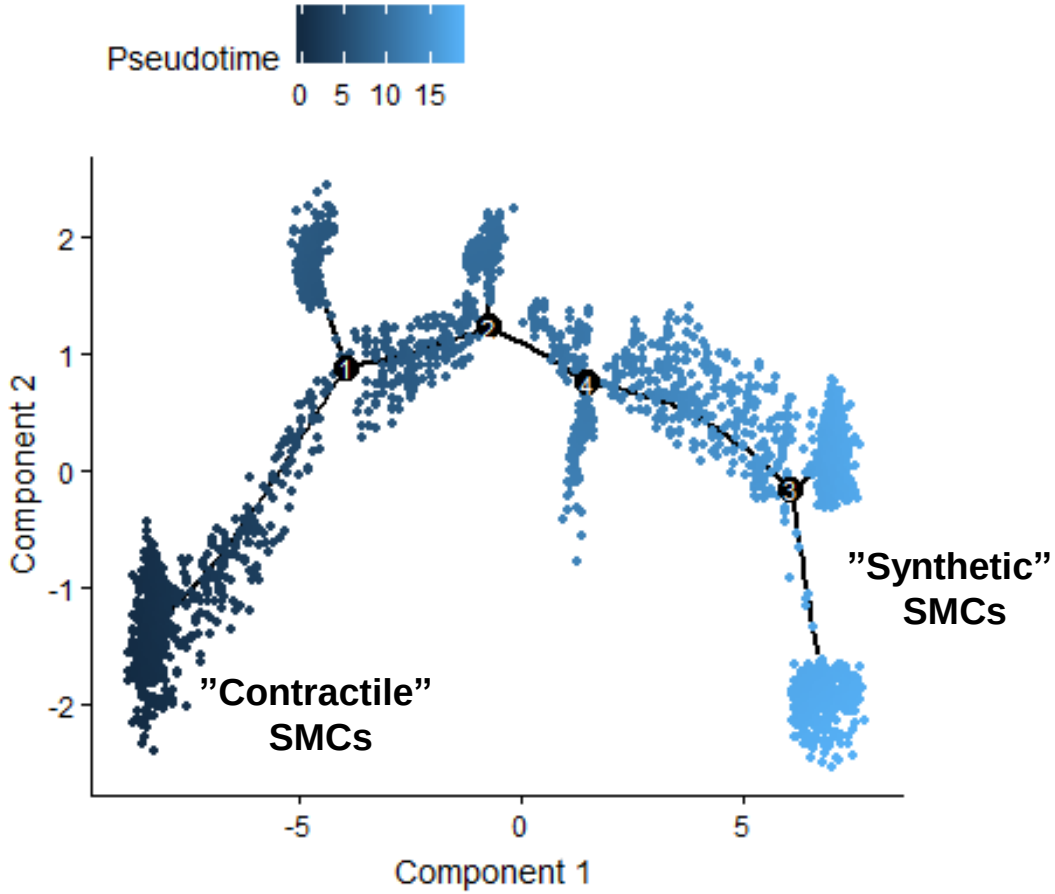




Modeling gene function in SMC plasticity *in vitro* (WP2)







Conclusions and future work

- SMCs represent the most heterogenous population of cells in the atherosclerotic aorta
- SMC transition into myofibroblast-like (Vcam1+) cells and further into chondrocyte-like cells (Col2a1+) is the most prominent cell-state change during disease progression
- Trajectory modeling allows understanding the changes in TF activity, ligand-receptor expression and CAD risk genes that can be validated by *in vitro* CRISPR-screens
- Ultimate goal is to **provide a path toward novel, mechanism-based translational advances in clinical practice**

Acknowledgements

CARDIOVASCULAR GENOMICS - group

Kadri Õunap, PhD

Tiit Örd, PhD

Uma Thanigai Arasu, PhD

Anu Toropainen, MSc

Valtteri Nurminen, MSc

Maykel Lopez Rodrigues,PhD

Tuula Salonen, technician

Aarthi Ravindran, MTec

Pierre Moreau, MSc

Ilakya Selvarajan, MSc

Oscar Liu, MSc

Vanesa Tomas Bosch, MSc

Eloi Schmauch, MSc

Nicholas Downes, BSc

COLLABORATORS

Einari Aavik, UEF

Tapio Lönnberg, Univ. Turku

Mete Civelek, Univ. Virginia

ACADEMY OF FINLAND

R'Life