Project title: In Silico drug and interventions screening for vascular-ageing

Project reference: DT4H_01_2024

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Aim of the Project

The present project aims to implement a user-friendly tool that will allow for simulations of drug and intervention screening for vascular ageing. The simulations will be based on directed cell-cell and transcription factor-gene networks reconstructed by combining integrated publicly available scRNAseq data with a newly collected in-house longitudinal mechanistic mouse scRNAseq dataset of the trajectories of vascular ageing and calcification. The following objectives will be addressed:

1. Develop a new network reconstruction and analysis workflow and tool for the reconstruction of directed cell-cell and transcription factor-gene networks.
2. Integrate methods, tools and datasets into a user-friendly web application that will allow intervention simulations on epigenetic networks and drug screening for vascular ageing and atherosclerosis.
3. Screen existing medications for their effect on vascular-ageing with an emphasis on the reduction of inflammation and enrichment in protective subtypes of smooth muscle cells.

Project Description

Despite major advances in our understanding and treatment of cardiovascular disease (CVD), there are likely molecular targets beyond traditional lipid measurements that can better inform the diagnosis and prognosis of CVD. One such marker is the burden of vascular calcification however major ambiguities remain regarding the mechanisms that induce atherosclerotic plaque development and calcification in the context of vascular ageing particularly related to the role of smooth muscle cell (SMC) subtypes and leucocytes. Single-cell RNA-sequencing (scRNA-seq) is a recently developed technique able to provide novel insights into the epigenetic molecular mechanisms of disease. We have recently integrated publicly available scRNA-seq datasets of vascular tissues from coronary arteries and carotid plaques identifying novel markers of modulated SMCs [1] and verifying culprit SMC populations that express large aggregating proteoglycans which are central to calcification development and patient outcomes [2]. Despite the recent advances, however, the design of novel therapeutic protocols still entails complex and expensive experiments on animal models and cell cultures which among others may not reflect completely the complex atherosclerosis epigenetic molecular mechanisms in humans. Moreover, from a technical point of view, network techniques to identify cell-cell communication patterns and reconstruct correlation networks (such as Cell-Chat, WGCNA) are solely based on literature networks and previously known transcription factors, while they fail to produce any directed link which makes them not suitable for in silico simulations and drug screening. Finally, the lack of public longitudinal mechanistic data restricts the validation of any potentially resolved mechanism of intervention hypothesis.

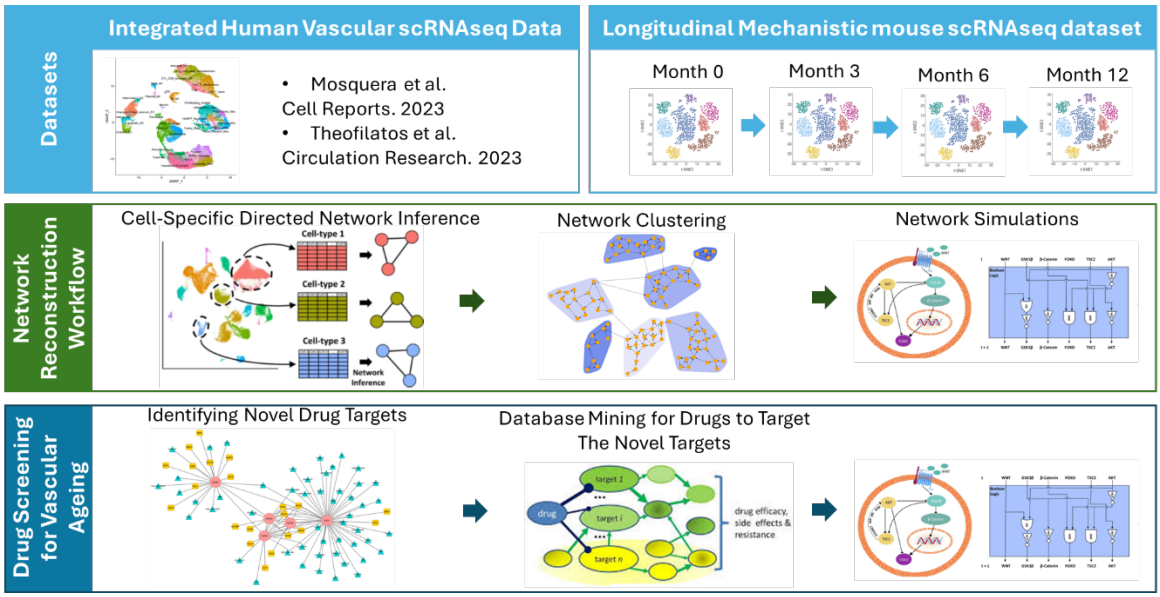
The present project aims to implement a user-friendly tool that will allow for simulations of drug and intervention screening for ageing/calcification. The simulations will be based on directed cell-cell and transcription factor-gene networks reconstructed by combining integrated publicly available scRNAseq data with a newly collected in-house longitudinal mechanistic mouse scRNAseq dataset based on a novel model of vascular ageing and calcification. The network reconstruction method will be based on a previously implemented method of the Project's supervisor [3], which utilized conditional mutual information to reconstruct directed molecular networks. This method will be expanded with additional directed reconstruction models (eg. probabilistic and fuzzy logic networks) and applied to integrated human scRNAseq data from coronary arteries and carotid endarterectomies [1]. The reconstructed network connections will be further verified and filtered using an in-house longitudinal mechanistic mouse scRNAseq dataset. As a next step, a user-friendly web application will be developed to allow simulations of interventions and drug screening for vascular ageing.
In the context of this project, the student will be trained on the basics of processing single-cell RNA-sequencing data and the basics of coding computational workflows with Python and R. Moreover, the student will be trained in managing and analyzing multi-omics datasets and the development of a web interface and application using Python-based framework tools. Finally, the student will be trained on the basics of atherosclerosis, SMC and leukocyte biology which will allow them to interpret and analyze the provided data.

Requirements:

Prior experience in programming is desired but not essential. The student's background could be either biomedical/cardiovascular research-oriented or computational.

Suggested reading:

1. Mosquera JV, Auguste G, Wong D, Turner AW, Hodonsky CJ, Alvarez-Yela AC, Song Y, Cheng Q, Cardenas CL, Theofilatos K, Bos M. Integrative single-cell meta-analysis reveals disease-relevant vascular cell states and markers in human atherosclerosis. Cell Reports. 2023 Nov 28;42(11).
2. Theofilatos K, Stojkovic S, Hasman M, van der Laan SW, Baig F, Barallobre-Barreiro J, Schmidt LE, Yin S, Yin X, Burnap S, Singh B. Proteomic atlas of atherosclerosis: the contribution of proteoglycans to sex differences, plaque phenotypes, and outcomes. Circulation research. 2023 Sep 15;133(7):542-58.
3. https://github.com/Cardiovascular-Bioinformatics/Direc-AP


Datasets
Integrated Human Vascular scRNAseq Data
• Mosquera et al. Cell Reports. 2023
• Theofilatos et al. Circulation Research. 2023
Longitudinal Mechanistic mouse scRNAseq dataset
Month 0
Month 3
Month 6
Month 12
Network Reconstruction Workflow
Cell-Specific Directed Network Inference
Cell-type 1
Cell-type 2
Cell-type 3
Network Inference
Network Clustering
Network Simulations
Drug Screening for Vascular Ageing
Identifying Novel Drug Targets
Database Mining for Drugs to Target The Novel Targets
drug
target 1
target i
target n
drug efficacy, side effects & resistance