Targeting novel coronary artery disease-related genes for therapeutic intervention

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Project outline

Background: Genome-wide association studies (GWAS) and collaborative meta-analyses have identified many common genetic variations that contribute to increased coronary artery disease risk. Given the focus of current treatments on lipid lowering, genes which do not associate with lipid QTLs but rather implicate other aspects of plaque biology have the potential to uncover novel mechanisms and identify targets for future therapies. Indeed, many variants identified by genetic studies map onto the vascular wall and in particular the endothelial cell layer. However, most current drugs do not explicitly target the vessel wall. Therefore, targeting this area could be a key preventative strategy in the treatment of coronary artery disease.

Hypothesis: Identification of novel coronary artery disease-associated genes that modulate the function of the endothelial cell layer have the potential to offer a new strategies for atherosclerosis treatment.

This project will compliment and expand upon an ongoing collaboration between the Douglas lab and NNRCO which is prioritising novel coronary artery disease genes to take forward for further analysis. We have already established a successful workflow for the identification and characterisation of novel coronary artery disease-associated genes. This work flow utilises *in vitro* and *in vivo* human data as well as murine models to identify a key role for novel genes in atherosclerosis. This collaborative project brings together experts in endothelial cell biology, bioinformatics and clinical outcomes and will utilise a proven work flow to identify causal SNPs and characterise their associated novel genes, focusing on genes which mediate there effect via the endothelial cell layer.

Aims: To identify and characterize the therapeutic potential of novel coronary artery disease-related genes we will:
1) Interrogate the role of our genes of interest on endothelial cell function
2) Identify the putative causal SNPs and determine their regulatory function
3) Use organoid co-culture models to investigate the role of our genes in cell-cell interactions

3) Interrogate the role of our genes of interest in atherosclerosis using data from vascular-specific biobanks and in vivo model systems.

Description of Work: In this project we will take forward three candidate genes, identified by our current collaboration with NNRCO, for extensive mechanistic analysis. **Aim 1:** Genomic approaches will be used to interrogate the causal SNPs and to establish the role of novel genes in physiological and pathological endothelial cell function. This aim will combine assays in model systems such as zebrafish with *in vitro* cell analysis after CRISPR/Cas9-targeted gene deletion. **Aim2:** The regulatory role of the putative causal SNP will be determined using in vivo models including F0 tol2-mediated transgenic zebrafish, an approach already successfully used in GWAS screens for other novel cardiac genes. **Aim 3:** Organoid co-culture systems composed of endothelial cells (in which expression levels of the genes of interest are modulated), vascular smooth muscle cells and monocytes will be used to interrogate cell-cell interactions and communication in response to atherogenic stimuli. **Aim 4:** Once the cellular role of the candidate genes has been established, Oxford-based biobanks will be used to interrogate the role of our genes of interest in vascular function. For the most promising candidates, this will be complemented with data from *in vivo* model systems such as PCSK9 induced atherosclerosis studies in genetically modified mice.

Contributions of Oxford and NNRCO supervisors

Gillian Douglas is an expert in pre-clinical coronary artery disease models and will manage the overall project , leading the primary cell and *in vivo* work. **Sarah De Val** is a prominent authority in endothelial cell biology and will lead the SNP enhancer analysis and zebrafish gene knockdown study**. Anuj Goel** is a specialist in the analysis and interpretation of coronary artery disease GWAS data and large omics datasets and will manage the human Biobank analysis and SNP prioritisation. **Keith Channon** is a pre-clinical and clinical coronary artery disease expert who will support the Biobank analysis and provide clinical insight. **Jo Howson** is the senior director of genetics at NNRCO with a wealth of experience in statistical and computational analysis of genetic variants and pharmaceutical oversight.

Supervisor's recent relevant publications (5 max per supervisor):

1. **Douglas G**, Mehat V, Al Haj Zen A, Akoumianak I, Goel A, Rashvrook VS, Trelfa L, Donovan L, Drydale E, Chuaiphichai S, Antoniades C, Watkins H, Kyriakou T, Tzima E, **Channon KM.** A key role for the novel coronary artery disease gene *JCAD* in atherosclerosis via shear stress mechanotransduction. Cardiovascular Research. 2020
2. Regulatory pathways governing murine coronary vessel formation are dysregulated in the injured adult heart. Payne S., Gunadasa-Rohling M., Neal A., Redpath AN., Patel J., Chouliaras KM., Ratnayaka I., Smart N., **De Val S**. Nat Commun. 2019
3. Robust estimates of heritable coronary disease risk in individuals with type 2 diabetes, Grace C, Hopewell C.J, Watkins H, Farrall M, **Goel A**. Genet Epidemiol 2021
4. Chuaiphichai S, Rashbrook VS, Trelfa L, Hale AB, McNeill E, Lygate, CA, Channon KM, **Douglas G**. Endothelial Cell Tetrahydrobiopterin Modulates Sensitivity to Angiotensin II-induced Resistance Vessel Remodelling, Blood pressure and Susceptibility to Aortic Abdominal Aneurysm. Hypertension. 2018: 72 (1) 128-138.
5. Jones PD, Kaiser MA, Ghaderi Najafabadi M, Koplev S, Zhao Y, **Douglas G**, Kyriakou T, Andrews S, Rajmohan R, Watkins H, **Channon KM**, Ye S, Yang X, Björkegren JLM, Samani NJ and Webb

TR. JCAD Gene at the 10p11 Coronary Artery Disease Locus Regulates Hippo Signaling in Endothelial Cells. ATVB. 2018: 38 1711-1722

6. **Douglas G**, Hale, AB, Patel J, Chuaiphichai S, Haj Zen A, Rashbrook VS, Trelfa L, Crabtree MJ, McNeill E, **Channon KM**. Roles for endothelial cell and macrophage Gch1 and tetrahydrobiopterin in atherosclerosis progression. Cardiovascular Research. 2018: 114 (10) 1385-1399