# Leveraging genomic approaches and genetic associations to identify potential new drug targets in cardiometabolic disease

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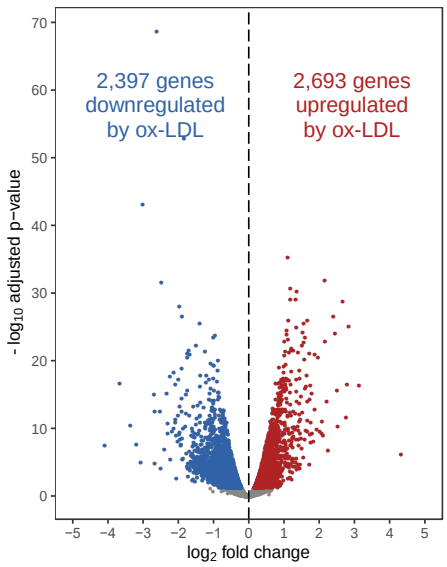
## Project outline

### Background

Cardiometabolic syndrome is a major cause of morbidity and mortality, especially from atherosclerotic vascular disease and consequent myocardial infarction or stroke. Factors contributing to cardiometabolic syndrome include hyper-lipidaemia, diabetes mellitus, obesity and hypertension—all traits that are associated with genetic variants in genome-wide association studies (GWAS). Despite some improvements in outcomes for cardiometabolic disease, there remains a substantial need to identify new drug targets for preventive or therapeutic intervention and there are strong arguments for using genetic information to guide target selection. For this reason, we are studying the responses to plasma lipid species of different cell types involved in cardiometabolic disease (e.g. *PLOS Genetics*, 2015).




Endothelial cells play a fundamental role in atherosclerosis and changes in endothelial cell function and activation arise at an early stage in atherosclerosis. Endothelial cells also play central roles in the function of the liver and kidneys, which can be affected in cardiometabolic syndrome resulting in non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) respectively. Our preliminary data demonstrate that in primary human arterial endothelial cells, low-density lipoprotein cholesterol (LDL-cholesterol) induces substantial changes in the openness of chromatin across the genome which are associated with potentially deleterious changes in gene expression (see Figure).

### Hypothesis

We hypothesise that mapping chromatin changes in the endothelial cell response to LDL-cholesterol with disease-associated genetic variants will identify new pathways in cardiometabolic disease and potential new drug targets.

**Aims**

1. To generate a genome-wide map of the changes in chromatin induced by LDL-cholesterol in primary human arterial endothelial cells using ATAC-seq, ChIP-seq/ChIPmentation and chromatin conformation capture.
2. To integrate these results with genetic information from GWAS in cardiometabolic disease to identify and prioritise new drug targets for cardiometablic disease.
3. To undertake focused *in vitro* experiments to assess selected targets further.

**Work to be undertaken**

This project will build on work undertaken using other cell types and pilot work using endothelial cells. In brief, ATAC-seq, ChIP-seq and ChIPmentation will be used to develop a genome-wide map of the changes induced in endothelial cells by oxidized LDL-cholesterol and this will be supplemented with RNA-seq data on gene expression and chromatin conformation capture data. Facilities are in place for cells to be grown under flow conditions as required. These genome-wide maps will be integrated with genetic information from GWAS for cardiometabolic traits to identify regions of chromatin where there is both a variant associated with disease risk and a change in chromatin accessibility. The prioritisation of these variants for further investigation will be based on information about the potential functional consequences of the variants including the extent of conservation, predicted binding motif and predicted function (e.g. promoter/enhancer/insulator status). Selected highly prioritised variants will be tested further to establish the functional consequences of the variants using cellular and molecular biology techniques including expression analysis, ChIP, electrophoretic mobility shift assay (EMSA) as described previously (*PLOS Genetics,* 2015, *EMBO J*, 2018).

**Contributions**

Chris O'Callaghan's group will provide experience and data using this approach, cells, ox-LDL, sequencing, sequencing analysis as well as downstream cellular and molecular biology. Joanna Howson's group will provide expertise in statistical and computational analysis of genetic variants for cardiometabolic traits.

**Supervisor's recent relevant publications:**


1. A genetics-led approach defines the drug target landscape of 30 immune-related traits. Fang H, ULTRA-DD Consortium, De Wolf H, Knezevic B, Burnham KL, Osgood J, Sanniti A, Lledo Lara A, Kasela S, De Cesco S, Wegner JK, Handunnetthi L, McCann FE, Chen L, Sekine T, Brennan PE, Marsden BD, Damerell D, **O'Callaghan CA**, Bountra C, Bowness P, Sundstrom Y, Milani L, Berg L, Gohlmann HW, Peeters PJ, Fairfax BP, Sundstrom M, Knight JC *Nature Genetics* 2019 Jul; 51(7):1082-1091.
2. Purine nucleotide metabolism regulates expression of the human immune ligand MICA. McCarthy MT, Moncayo G, Hiron TK, Jakobsen NA, Valli A, Soga T, Adam J, **O'Callaghan CA** *J Biol Chem* 2018 Mar 16;293(11):3913-3924

3. Intragenic transcriptional interference regulates the human immune ligand MICA. Lin D, Hiron TK, **O'Callaghan CA** *EMBO Journal* 2018 May 15;37(10). pii: e97138.
4. Genetic and environmental risk factors for atherosclerosis regulate transcription of phosphatase and actin regulating gene PHACTR1. Reschen ME, Lin D, Chalisey A, Soilleux EJ, **O'Callaghan CA** *Atherosclerosis*. 2016 May 2;250:95-105.
5. Lipid-induced epigenomic changes in human macrophages identify a coronary artery disease associated variant that regulates *PPAP2B* expression through altered C/EBP-beta binding. Reschen ME, Gaulton KJ, Lin D, Soilleux EJ, Morris AJ, Smyth SS, **O'Callaghan CA** *PLOS Genetics.* 2015 Apr 2;11(4):e1005061.
6. NF-kappa B regulates MICA transcription in endothelial cells through a genetically inhibitable control site. Lin D, Lavender H, Soilleux E, **O'Callaghan CA.** *J Biol Chem.* 2012 Feb 3;287(6):4299-310.