**PI profile**

**Keith Channon**

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| **C:\Users\DStafford\AppData\Local\Microsoft\Windows\INetCache\Content.MSO\B5CC007F.tmp** | **Professor Keith Channon**  **Titles**: Field Marshal Earl Alexander Professor of Cardiovascular Medicine  **Location**: Wellcome Centre for Human Genetics  **Department**: Radcliffe Department of Medicine  **Group**: Channon  **Webpage**: <https://www.well.ox.ac.uk/research/research-groups/channon-group-cardiovascular-functional-genomics-and-redox-signalling-1>  **Email**: keith.channon@cardiov.ox.ac.uk  **PA**: Dianne Stafford - channon\_pa@cardiov.ox.ac.uk |

GMS themes:

* Genomic and –omic technologies
* Functional genomics
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)
* From genes to clinic (target discovery, structural biology, medicinal chemistry)
* Application of genomics in the clinic (diagnostics and therapeutics)

**Research Overview :**

The Channon group bring together interdisciplinary expertise in biochemistry, vascular function, in vivo models of cardiovascular disease and immune cell biology to probe molecules involved in cardiovascular disease.  Our work is split over 4 main themes:

* The role of the endothelium and nitric oxide signalling in the development of vascular disease
* NOS-independent roles of tetrahydrobiopterin
* Leukocyte recruitment in cardiovascular inflammation
* Evaluating novel GWAS candidate genes in experimental models of cardiovascular disease

**Project areas:** Endothelial function, GWAS, Redox Biology, Inflammation, Immunometabolism,

**Specific project proposals:**

* Defining the function of new causal atherosclerosis genes from coronary artery disease GWAS loci using in vitro and in vivo models
* Investigating the role of immune-metabolic mediators in endothelial and immune cell biology

Please contact directly for further information.

***These pages were reviewed/updated: July 2021***

Page Break

**Project proposal**

**Title**: Defining the function of new causal atherosclerosis genes from coronary artery disease GWAS loci using in vitro and in vivo models

**Supervisors:** Dr Gillian Douglas, Professor Keith Channon

**Wet/dry lab mix (approx)**: 70% wet lab, 30% dry lab

**Description:**

Genome wide association studies have enabled us to identify genes which are associated with cardiovascular disease at the level of the whole genome. These novel genes, which are not associated with traditional risk factors, have the potential to identify novel treatment strategies for coronary artery disease. The work in my lab aims to establish the role of novel candidate genes in cardiovascular disease.

Working in close collaboration with bioinformaticians we identify novel candidate genes from GWAS implicated loci. Once candidate genes have been identified we use targeted cardiovascular disease relevant *in vitro* cell based assays in primary human cells to understand how the candidate gene impacts and cell function. Proteomic and genomic analysis is used to give an unbiased analysis of candidate gene function. This is complimented by advanced cellular imaging as well as molecular biology techniques. The information gained from these In vitro studies is then used in a targeted fashion to investigate the role of the candidate gene in models of In vivo cardiovascular disease, in particular the development and regression of atherosclerosis and models of altered vascular function such as vascular injury and ischaemia models. We also utilize data from local and international biobanks to investigate the role of candidate genes in vascular biology. Doctorial students have the flexibility to focus either on *in vitro* cell based assays or *in vivo* models of cardiovascular disease.

**Training Opportunities:**

This DPhil will be based in the Division of Cardiovascular Medicine at the Welcome Centre for Human Genetics. We are part of a wider scientific community with expertise in Cardiovascular Disease allowing for collaborative work with other senior scientist. By the end of this project the candidate will have developed a wide range of laboratory skills such as molecular biology techniques (protein and RNA analysis), cell culture techniques and *In vivo* models of cardiovascular disease. Training in scientific techniques as well as scientific presentation and writing will be given throughout the project.

**Background reading / references:**

* 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, doi:10.1093/cvr/cvz263. 2019
* [Endothelial Cell Tetrahydrobiopterin Modulates Sensitivity to Ang (Angiotensin) II-Induced Vascular Remodeling, Blood Pressure, and Abdominal Aortic Aneurysm.](https://www.rdm.ox.ac.uk/publications/835041) Chuaiphichai S. et al, (2018), Hypertension, 72, 128 - 138

**Project proposal**

**Title**: Unravelling the role of metabolic mediators in macrophages and endothelial cells

**Supervisors:** Professors Mark Crabtree and Keith Channon

**Wet/dry lab mix (approx)**: 80% wet lab, 20% dry lab

**Description:**

In cells, there is normally a fine balance between a group of chemicals collectively known as reactive oxygen species and another chemical, nitric oxide (termed NO-redox balance). Both of these chemicals are critical factors in cardiovascular function. They play important roles in the vessel wall, the heart, and in immune cells, and imbalance of these factors causes these cells to work differently. This dysregulation occurs in many cardiovascular disease states including the atherosclerotic plaque, the heart following a heart attack, and in immune cells that are recruited to repair areas of damage.

We have already demonstrated that this NO-redox balance is important to preserve normal cardiovascular function. However, studies using antioxidant therapies and cofactor supplementation in patients have failed, possibly as signalling through more complex mechanisms is involved and important new targets are as yet undiscovered. It is also known that macrophages are involved the inflammatory response to disease, and metabolic reprogramming of these immune cells is essential for both inflammatory as well as anti- inflammatory responses. Evidence is emerging for the targeting of these specific metabolic events as a strategy to limit inflammation in different contexts. We recently revealed that this reprogramming is dependent on NO-redox balance, and that NO orchestrates metabolic remodelling in inflammatory macrophages; through TCA Cycle regulation and by determining the accumulation of the anti-inflammatory metabolite itaconate, via redox alteration of the synthetic protein cis-aconitate decarboxylase (CAD; Bailey et al, 2019). For the first time, we now propose that repolarizing of immune cells towards a less inflamed phenotype by manipulating metabolism using small molecules maybe beneficial in cardiovascular disease.

**Training Opportunities:**

We use multi 'omics approaches, combined with molecular biochemistry using in vitro, in vivo, and human models, to determine the mechanism by which anti-inflammatory itaconate is produced, its role in immunometabolism, and its impact in human patients with cardiovascular disease. Specifically, in this rotation project the student will use a combination of biochemical (including Seahorse analysis of cellular metabolism, and redox-focused techniques) and metabolomic-based approaches to test the effects of itaconate supplementation on both macrophage metabolism and endothelial cell function.

**Background reading / references:**

1. McNeill E., Crabtree M.J., Sahgal N., Patel J., Chuaiphichai S., Iqbal A.J., Hale A.B., Greaves D.R., Channon K.M. (2015) Regulation of iNOS function and cellular redox state by macrophage Gch1 reveals specific requirements for tetrahydrobiopterin in NRF2 activation. Free Radic Biol Med. 79:206-16.
2. Bailey J., Diotallevi M., Nicol T., McNeill E., Shaw A., Davis S., Fischer R., Kessler B.M., McCullagh J., Channon K.M., and Crabtree M.J.(2019) Nitric oxide modulates metabolic remodeling in inflammatory macrophages through TCA regulation and itaconate accumulation. Cell Rep. 28, 218–230.