Principal Investigator:

David R. Greaves

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Current Appointment: University Lecturer in Cellular Pathology

Research Focus: The role of macrophages in inflammation including the role of GPCRs in cardiovascular disease and drug repurposing for CVD.

Lab Space / Department: Sir William Dunn School of Pathology

Current Research Group: **3** DPhil students.

CURRENT and RECENT DPhil STUDENT SUPERVISION:

Joshua Stott (2022 -) Medicinal chemistry applied to drug repurposing
Co-supervision with Angela Russell

Kacper Kurzyp (2021 -) Macrophage interactions with *Neisseria gonorrhoea*
Co-supervision with Chris Tang and Rachel Exley

Annabell Roberti (2020-) Drug repurposing to study macrophage inflammation

Vincent Luscombe (2019-) Chemical biology of the GPR84 receptor

** Laura Chafey (2018-2023) Drug repurposing and macrophage biology.

** Agata Rumianek (2017- 2022) New Methods to study Macrophage Biology in vitro and in vivo
Currently a senior cardiovascular scientist with a CardiaTec start-up company in Cambridge UK

** Daniel Lucy (2015 – 2019) Targeting GPR84: a receptor involved in regulating inflammation
Currently a postdoctoral fellow at Imperial College London

Sophia Valaris (2014-2018) The role of chemerin and chemerin receptors during acute inflammation
a postdoctoral fellow at Harvard Medical School, Massachusetts General Hospital

Theodoros Kappelos (2013-2017) Critical assessment of the role of the cannabinoid CB2 receptor in Inflammation
Currently a *Junior group leader Comprehensive Pneumology Center @ Helmholtz Center Munich*

** Lewis Taylor (2013-2017) Assessment of the role of CB2 in innate immune cell trafficking
Currently a research fellow in Nuffield Department of Clinical Neuroscience, University of Oxford

** Daniel Regan-Komito (2012-2016) The role of chemerin peptides in inflammation
Currently a Senior Scientist at Roche, Basel, Switzerland

** = BHF 4-year students, all submitted within 4 years

LAST 5 PUBLICATIONS:

Kinetic insights into agonist-dependent signalling bias at the pro-inflammatory G-protein coupled receptor GPR84.
Luscombe VB, Baena-López LA, Bataille CJR, Russell AJ, Greaves DR.
Eur J Pharmacol. 2023; 956:175960. doi: 10.1016/j.ejphar.2023.175960.

Drug repurposing in cardiovascular inflammation: Successes, failures, and future opportunities.
Chaffey L, Roberti A, Greaves DR.

Frontiers in Pharmacology. 2022; 13:1046406. doi: 10.3389/fphar.2022.1046406.

Bruton's TK regulates myeloid cell recruitment during acute inflammation.
Purvis GSD, Aranda-Tavio H, Channon KM, Greaves DR.
Br J Pharmacol. 2022; 179(11):2754-2770. doi: 10.1111/bph.15778.

A human CD68 promoter-driven inducible Cre-recombinase mouse line allows specific targeting of tissue resident macrophages.
Rumianek AN, Davies B, Channon KM, Greaves DR, Purvis GSD
Frontiers in Immunology 2022; 13:918636. doi: 10.3389/fimmu.2022.918636

Inhibition of Bruton's Tyrosine Kinase regulates macrophage NF-kB and NLRP3 inflammasome activation in metabolic inflammation
Purvis GSD, et al. Br J Pharmacol. 2020; 177: 4416-4432. doi: 10.1111/bph.15182

Project Title: **Targeting inflammation in atherosclerosis**

Project Outline:

Monocyte recruitment and macrophage differentiation within major arteries drives the development of atherosclerotic plaques. A characteristic feature of atherosclerotic plaques is the presence of macrophage derived foam cells that have taken up modified forms of LDL. Atherosclerotic plaques grow in situ and can rupture or act as foci for platelet activation and thrombosis leading to myocardial infarction, ischaemic stroke and peripheral artery disease.

In the Greaves Laboratory we study how macrophages contribute to inflammation and tissue repair. In recent work we have used macrophage reporter cells to identify existing medicines that target both NF-kB activation and NLRP3 inflammasome signalling. Using drug repurposing approaches we have identified FDA approved anti-cancer medicines including Bruton's Tyrosine Kinase (BTK) inhibitors that have significant anti-inflammatory effects *in vivo*. Importantly we have shown that long term dosing of *Ldlr*$^{-/-}$ mice with ibrutinib reduces atherosclerotic plaque size and causes a switch from pro-inflammatory M1 to pro-repair M2 macrophages.

In one initial lab rotation, the student would explore the possibility of developing a cell-based assay that could be used to identify small molecules that promote M2 macrophage differentiation. This project would build on successful drug repurposing screens to identify FDA approved drugs that inhibit NF-kB activation and inflammatory cytokine production in macrophage reporter cells.

We have shown that the GPR84 receptor is a pro-inflammatory G protein coupled receptor that is expressed in neutrophils and activated macrophages. In a second project the student would follow up our observation that the GPR84 receptor is expressed in murine and human atherosclerotic plaques by using the technique of RNA Flares. In addition, the student could study the effect of activating the GPR84 receptor with novel chemical agonists on lipid accumulation and reverse cholesterol transport in M1 macrophages exposed to apoB containing lipoproteins.

Our ultimate goal is to identify pathways that can be targeted to re-direct macrophage differentiation for therapeutic benefit in cardiovascular disease.

Key references to project (2 to 3):

(1) Purvis GSD, et al. Br J Pharmacol. 2020; 177: 4416-4432. doi: 10.1111/bph.15182
(2) Lucy D et al. ACS Chem Biol. 2019; 14(9):2055-2064. doi: 10.1021/acschembio.9b00533.