Angela Russell Group

Department of Chemistry, Chemistry Research Laboratory and Department of Pharmacology

AJR Group 2018–19

http://russell.chem.ox.ac.uk

@AJR_Group

angela.russell@chem.ox.ac.uk

angela.russell@pharm.ox.ac.uk

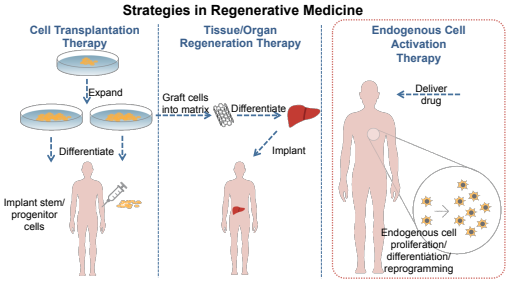
There are tremendous opportunities for chemistry to impact on biology and medicine. Progress can only occur through collaborations with the medical and life sciences, where the Russell group has already established highly successful projects.

Our research aims to identify small molecules to manipulate cell signalling processes and translate them into therapeutic agents, particularly for regenerative medicine. Our research areas include: 1) Stem cell chemistry "Stemistry" and regenerative medicine; (2) Modulation of gene expression to treat fatal genetic diseases such as Duchenne Muscular Dystrophy, DMD: (3) Anti-inflammatory agents for chronic inflammation, wound repair and regenerative medicine; (4) Cancer medicinal chemistry: we have developed several selective inhibitors of anti-cancer targets, inducers of cancer stem cell differentiation and probes to quantify a cancer biomarker.

Stem Cell Chemistry and Regenerative Medicine

Harnessing the potential of stem cells is a major current challenge in medicine and healthcare. The use of chemicals to control the destiny of stem cells is an emerging discipline which offers unprecedented advantages over other techniques in terms of speed, cost, reproducibility and the ability to influence stem cell fate reversibly.

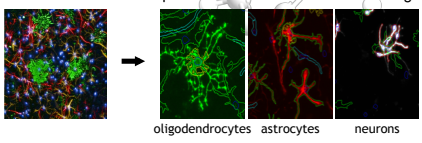
Most current therapies are based on manipulation of stem cells in vitro, followed by transplantation into the patient. Our approach is to stimulate adult stem cells with small molecules in situ, using the endogenous repair mechanisms that already exist within the body.

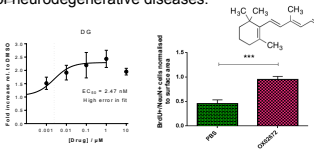


Small molecule activation of endogenous stem cell populations for neuroregeneration

*with **Francis Szele**, Physiology, Anatomy and Genetics, **Noel Buckley**, Psychiatry and **Steve Davies**, Chemistry*

Neural stem cells (NSC) are characterised as multipotent stem cells due to their capability to differentiate into multiple cell types (astrocytes, neurons and oligodendrocytes). Three nests of NSCs have been described in the brain: the subventricular zone (SVZ), the dentate gyrus (DG) and the hypothalamus. The control of the proliferation and differentiation of these cells in vivo holds tremendous potential for treatment of a wide range of neurodegenerative diseases.





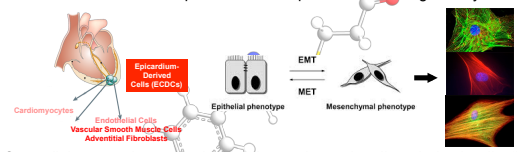
Neurogenesis in vitro (**left**) and in vivo in the anterior DG (**right**) following 3 x daily oral delivery of **OXS00672**

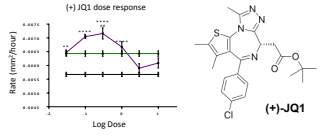
We have devised screening methods which have allowed us, for the first time to identify small molecules which increase neurogenesis both in vitro and in vivo upon oral administration. We are currently progressing our most promising pro-neurogenic small molecules into preclinical disease models of dementia, depression and brain injury.

Small molecule activation of the adult epicardium for cardiac repair

*with **Paul Riley** and **Nicola Smart**, Physiology, Anatomy and Genetics, **Roger Patient**, Weatherall Institute and **Steve Davies**, Chemistry*

The inability of the human heart to functionally repair itself in response to injury remains the biggest cause of morbidity and mortality in the global population. The most catastrophic injury, a myocardial infarction (MI), results in the instantaneous death of millions of cardiomyocytes that cannot be sufficiently regenerated by endogenous repair mechanisms. A new strategy to activate cardiac regeneration is the use of small molecules to stimulate proliferation, migration, differentiation and maturation, either in stem cell cultures prior to cell transplantation or acting directly on resident cardiac progenitors.





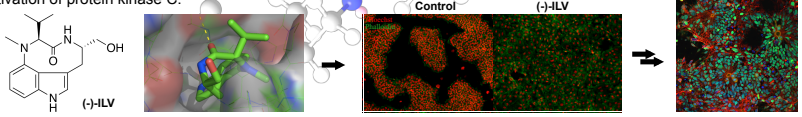
(+)-JQ1

Our collaborators have previously shown that epicardium-derived cells (EPDCs) can differentiate into cardiac myocytes, fibroblasts and vasculature. Furthermore, upon activation in vivo, endogenous epicardial cells migrate and differentiate into cardiomyocytes in situ following injury. However, this represents only a limited regenerative capacity and we have therefore established screens to allow for the discovery of small molecules that will augment this process. We have already identified several examples of candidate molecules showing activity in vitro.

Small molecule-mediated scaleable culture of human stem cells

*with **Sally Cowley** and **William James**, Pathology, and **Steve Davies**, Chemistry*

One of the most significant hurdles in the application of stem cells for disease modelling, drug toxicity testing, cell therapies and, importantly for us, drug screening for regenerative medicine remains the ability to rapidly and reproducibly generate sufficient numbers of high quality pluripotent and tissue-specific stem cells. We have identified compounds which reversibly block differentiation and cell-cell contact in human pluripotent stem cells, allowing the efficient culturing of these cells in 2D and 3D suspension culture systems. These molecules are based on the teleocidin family of natural products and act through activation of protein kinase C.



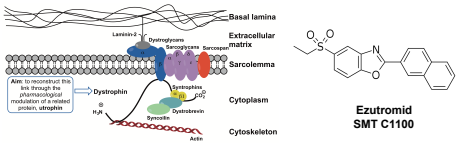
A combination of molecular modelling, chemiinformatics and ligand based-design is currently being employed to optimise these small molecules for the scaleable 3D suspension culture of human induced pluripotent stem cells (iPSCs).

References: Clunie-O'Connor *et al. Curr. Protocol.* **2016**; *J. Med. Chem.* **2015**, *58*, 2863; Russell, A. J. *ACS Med. Chem. Lett.* **2013**, 4, 365; Soncin, F. *et al. Stem Cells*, **2009**, *27*, 2069; Wilkinson, R. N. *et al. Dev. Cell* **2009**, *16*, 909.

New Therapy for Duchenne Muscular Dystrophy

*with **Kay Davies**, Physiology, Anatomy and Genetics & **Steve Davies**, Chemistry*

It has been shown that utrophin, the autosomal homologue of dystrophin can compensate for the aberrantly regulated protein in Duchenne Muscular Dystrophy (DMD). The regulation of the transcriptional activity of the utrophin gene has been studied and two promoter elements identified that may serve as targets for pharmacological therapy of DMD, through up-regulation of utrophin.

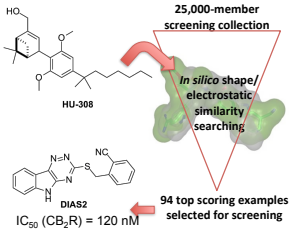


We have discovered small molecule modulators of utrophin and show that they rescue pathology in preclinical models of DMD. This has led to ezutromid, a first-in-class utrophin modulator, which recently completed a Phase 2 clinical trial, and next generation leads in prelinical studies. We are currently optimising these next generation leads and investigating their mechanism of action.

References: Guiraud, S. *et al.*, *Hum. Mol. Genet.* **2015**; Russell, A. J. and Wynne, G. M. in Orphan Drugs and Rare Diseases, Palmer, M. and Pryde, D. (Ed.), RSC, 2014, ISBN: 978-1-84973-806-4.

Anti-inflammatory agents

*with **David Greaves**, Pathology*



Reducing the inflammatory response is crucial in developing regenerative therapies as well as a stand alone therapies for chronic inflammation and wound healing. The endo-cannabinoid system is a signalling pathway involved in inflammation, pain modulation and atherogenesis. We have identified a new family of CNS-sparing highly selective canna-binoid receptor (CB2R) selective agonists through virtual screening. We are currently developing ligands to other immunometabolic receptors.

References: Gianella-Borridori, M. *et al.*, *Bioorg. Med. Chem.* **2015**, *23*, 214; Taylor, L. et al., Scientific Rep., 2015.

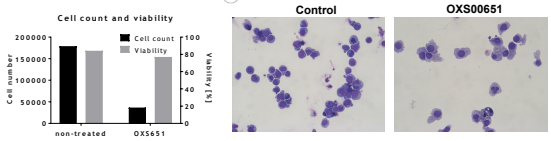
New Agents for Tumour Detection and Therapy

Through collaboration with cancer biologists, pharmacologists and structural biologists, the group aims to develop, advance and characterise chemical tools for use as bioprobes and as potential diagnostic agents and therapeutic molecules. We have been focussing on projects that span early stage, though less validated pathways, to projects and targets that are more mature.

Small molecule-induced differentiation of cancer stem-like cells

*with **Paresh Vyas** and **Tom Milne**, Weatherall Institute, **Tariq Enver**, UCL and **Steve Davies**, Chemistry*

Acute myeloid leukemia (AML) is a type of blood cancer characterised by a block of differentiation, leading to the accumulation of immature cells in the bone marrow. Current treatments aim to kill these abnormal cells via chemotherapy. Our approach is to overcome the differentiation block of AML blasts.



We have established an in vitro screen to detect differentiation of AML cells via flow cytometry. This has led to the identification of mutliple classes of small molecules which can block proliferation and overcome the differentiation block in AML blasts. We are currently optimising these molecules and investigating their mechanism of action.

References: Bataille C. J. R. *et al.*, *Bioorg. Med. Chem.* **2017**; Egleton, J. E. *et al.*, *Bioorg. Med. Chem.* **2014**, 22, 3030; Laurieri, N. *et al.*, *PLoS One* **2013**, *8*, e70600; Laurieri, N. *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 3238.