High throughput small molecule screening for inducers of epicardial cell EMT after myocardial infarction

Sophia Malandraki-Miller[1,5], Christophe Ravaud[1,5], Jia Zhao[1,5], Lorna Fiedler[4,5], Christopher Greaves[2,3,5], Irene Georgiou[2,3,5], Matthew Kennedy[2,3,5], Graham M. Wynne[2,3,5], Roger Patient[4,5], Angela J. Russell[2,3,5], Paul Riley[1,5]

1 Department of Physiology, Anatomy & Genetics, Sherrington, University of Oxford
2 Chemistry Research Laboratory, University of Oxford
3 Department of Pharmacology, University of Oxford
4 Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford
5 OxStem Ltd., Midland House, West Way, Botley, Oxford

Myocardial infarction (MI) results in the loss of millions of cardiomyocytes, and the formation of a non-contractile fibrotic scar, ultimately leading to heart failure. Despite more than a decade of research on cardiac regeneration, clinical study results using stem cell approaches have been disappointing. Currently there are no regenerative therapies available, and the only cure is heart transplantation.

Our group has previously demonstrated that the epicardium can be re-activated during MI. More specifically, epicardium-derived progenitor cells EPDCs when stimulated with thymosinβ4 undergo Epithelial-to-Mesenchymal Transition (EMT), migrate and contribute to the formation of coronary vessels, smooth muscle cells, as well as cardiomyocytes, in an adult mouse MI model. This provided proof-of-principle that reactivating adult epicardial cells might constitute a resident cell-based therapeutic approach post-MI.

The aim of this project is to identify novel small molecules that can activate the resident EPDCs, by promoting EMT, to both stimulate differentiation into cardiovascular cell types and release trophic signals to replenish lost cardiac tissue and preserve cardiac function after MI. To achieve this, we are conducting phenotypic screens based on an EMT assay of human ESC-derived EPDCs, miniaturised in a 384 well-plate format with an automated image analysis platform utilising machine learning. We have conducted a ”positive-candidate” small molecule screen for validation and are currently performing a 5,000 molecule pilot screen, with a proposed primary screen of 100,000 small molecules as the first stage of a drug-discovery programme.