UCL INSTITUTE OF CARDIOVASCULAR SCIENCE

List of Research Projects:

iBSc in Cardiovascular Science – CARD3002

Academic year 2018-19

V.2
21/09/2018

Research Project ID01

Mitochondrial and Genomic DNA as novel mediators of cardiovascular injury

Supervisor(s): Dr Robert Bell, Prof Derek Yellon

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Department/Group: ICS The Hatter Cardiovascular Institute, UCL

Project outline:

The pathophysiology of myocardial ischaemia/reperfusion injury is complex and only partially understood. Generation of reactive oxygen species (ROS) is an important component of ischaemia-reperfusion injury and can lead to injurious post-translational modifications to proteins and to the damage to both mitochondrial & nuclear DNA. Mitochondrial DNA (mtDNA) is different from genomic DNA (and similar to bacterial DNA), as it is devoid of histones and contain CpG motifs in which the cytosine is un-methylated which renders it more vulnerable to oxidation and is more immunogenic if released into the extracellular space. On the other hand nuclear DNA breakdown does cause histone release which in itself can cause significant injury to the cell. Interestingly, preliminary experiments have shown that administration of DNase1 – an enzyme capable of degrading DNA – reduces infarct size in hearts undergoing injurious ischaemia/reperfusion injury. In addition, we are also fortunate to having recently obtained a new anti-histone agent as a means of preventing myocardial injury. As DNA breakdown, as a result of ischaemia/ reperfusion injury correlates with myocardial injury it therefore represents a novel target for reducing such injury in the clinical context of acute coronary syndromes.

Key references:

- Hajizadeh S, DeGroot J, TeKoppele JM, Tarkowski A, Collins LV. Extracellular mitochondrial DNA and oxidatively damaged DNA in synovial fluid of patients with rheumatoid arthritis. Arthritis Res Ther. 2003;5:R234-240
- Destouni A, Vrettou C, Antonatos D, Chouliaras G, Patsilinakos S, Kitsiou-Tzeli S, Tsigas D, Kanavakis E. Cell-free DNA levels in acute myocardial infarction patients during hospitalization. Acta Cardiol. 2009;64:51-57
- Chen R, Kang R, Fan X_G, Tang D Release and activity of histones in diseases. Cell Death & Disease 2014; 5
- Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target.J Clin Invest. 2013 Jan;123(1):92-100.
- Hausenloy DJ, Yellon DM. The therapeutic potential of ischemic conditioning: an update.Nat Rev Cardiol. 2011 Jun 21;8(11):619-29

Research Project ID02

Novel means of cardioprotection by exploiting pathways activated by Stromal Derived Factor-1α

Supervisor(s): Dr Sean Davidson, Prof Derek Yellon

Email(s): s.davidson@ucl.ac.uk; d.yellon@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Heart attacks cause the death of cardiomyocytes. Stromal Derived Factor-1a (SDF-1α) can protect cardiomyocytes from death but its precise mechanism of action is not known.

There are two receptors for SDF-1α, CXCR4 and CXCR7. There is increasing interest in CXCR7 due to its emerging role in revascularization and regeneration. This project involves the generation of novel mice with inducible, endothelial-specific deletion of CXCR7 to investigate its role in cardioprotection. We will also use a unique antibody to SDF-1 that we developed to investigate its role before and after ischaemic injury. The ultimate aim is to develop cardioprotective strategies utilizing the protective and pro-angiogenic pathways activated by SDF-1α which will protect patients from myocardial reperfusion injury and subsequent heart failure.

Key references:

- Davidson SM, Selvaraj P, He D, Boi-Doku C, Yellon RL, Vicencio JM, Yellon DM. Remote conditioning involves signalling through the SDF-1α/CXCR4 signalling axis. Basic Res Cardiol 108(2013):377
- Bromage DI, Davidson SM, Yellon DM. Stromal derived factor 1α: A chemokine that delivers a two-pronged defence of the myocardium. Pharmacol Ther 143(2014):305-315
- Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013 Jan;123(1):92-100.
- Ding, B.S., et al. Divergent angiocrine signals from vascular niche balance liver regeneration and fibrosis. Nature 505, 97-102 (2014)
- Hausenloy DJ, Yellon DM. The therapeutic potential of ischemic conditioning: an update.Nat Rev Cardiol. 2011 Jun 21;8(11):619-29

Research Project ID03

Prevent today's cancer survivor from becoming tomorrow's cardiac patient.

Supervisor(s): Prof Derek Yellon & Dr Malcolm Walker

Email(s): d.yellon@ucl.ac.uk; malcolm.walker@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Improved cancer survivorship paradoxically exposes patients to acute and chronic cardiovascular consequences with anthracycline chemotherapy playing a prominent role in many cancer treatments. However anthracyclines can cause chronic irreversible cardiac damage/failure. Although the mechanism remains poorly understood, it has been suggested to include reactive oxygen species (ROS)-toxicity or mitochondrial permeability transition pore (mPTP) induction. Emerging data indicate cardiac damage begins early suggesting protective modalities delivered in the acute stage may confer prolonged benefit. Ischaemic Preconditioning (IPC), i.e. subjecting hearts to sub-lethal ischaemia followed by reperfusion, activates the pro-survival Reperfusion Injury Salvage Kinase (RISK) pathway is a highly protective procedure. We will examine the hypothesis that IPC conditioning can protect against anthracycline-induced cardiac injury.

Our overall aim in this research project is to prevent today's cancer survivor from becoming tomorrow's cardiac patient.

Key references:

- Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015 Jun 2;131(22):1981-8.
- Hausenloy DJ, Tsang A, Mocanu M, Yellon DM. Ischemic Preconditioning Protects by Activating Pro-Survival Kinases at Reperfusion. Am J Physiol Heart Circ Physiol. 2004 Aug;287(2):H841-9.
- Minotti G, Menna P, Salatorelli E, et al. Molecular advances and pharmacologic developments in antitumour activity and cardiotoxicity.. Pharmacol Rev. 2004 Jun;56(2):185-229.

Research Project ID04

Protecting the heart in the setting of diabetes

Supervisor(s): Dr Rob Bell, Dr Sapna Arjun, Prof Derek Yellon

Email(s): rob.bell@ucl.ac.uk; s.subrayan@ucl.ac.uk; d.yellon@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Acute myocardial infarction is a leading cause of death and morbidity in the word. Epidemiological studies demonstrate that hyperglycaemia at the time of presentation with an acute ST-elevation myocardial infarction (STEMI) correlates with higher 30-day and 1-year mortality compared with those with normal serum glucose – paradoxically this is particularly relevant in patients who are not diabetic.

Sodium glucose co-transporters (SGLT) have become a novel target for pharmacological intervention in diabetes, rapidly lowering blood glucose by inhibiting renal SGLT2. More recently SGLT1 has been demonstrated in the myocardium, but its role in the context of STEMI is unknown. We hypothesized that by inhibiting SGLTs, we can both lower circulating blood glucose and prevent excess uptake of glucose into the reperfused myocardium at the time of revascularization, to attenuate the impact of excess glucose and improve cardiovascular outcomes following presentation with STEMI.

This study will encompass translation of experimental data in isolated cardiomyocytes, through ex-vivo models to the in-vivo animal, potentially leading to data that could be translated into first-in-man studies.

Key references:

- Deedwania P, et al. Hyperglycemia and Acute Coronary Syndrome: A Scientific Statement From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2008;117:1610-1619
- Banerjee SK, McGaffin KR, Pastor-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. Cardiovascular Research (2009) 84, 111–118
- Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target.
- J Clin Invest. 2013 Jan;123(1):92-100.
- Hausenloy DJ, Yellon DM. The therapeutic potential of ischemic conditioning: an update. Nat Rev Cardiol. 2011 Jun 21;8(11):619-29
- Zinman B et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG Outcome Study). N Engl J Med 2015; 373:2117-2128November 26,

Research Project ID05

Exosomes – endogenous nanoparticles that protect the heart

Supervisor(s): Dr Sean Davidson and Prof Derek Yellon

Email(s): s.davidson@ucl.ac.uk; d.yellon@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Exosomes are nano-sized lipid membrane vesicles that circulate in the blood at up concentrations of up to 10^9 per ml. Recent high-profile studies that show they can deliver miRNA and proteins between cells. However, we still know very little about what they do. We have shown that plasma exosomes are able to protect the heart against ischaemia and reperfusion injury, such as occurs during a heart attack. This project involves the study of exosomes using technology such as nanoparticle tracking analysis, fluorescent confocal imaging, and Western blot analysis, to investigate exosomes and cardioprotection, with a view to using them as therapeutic agents. Novel, highly purified, clinical relevant exosomes will be used in these studies in collaboration with the stem cell research company ReNeuron.

Key references:

- Vicencio JM, Yellon DM, Sivaraman V, Das D, Boi-Doku C, Arjun S, Zheng Y, Riquelme JA, Kearney J, Sharma V, Multhoff G, Hall AR, Davidson SM Plasma exosomes protect the myocardium from ischemia-reperfusion injury J Am Coll Cardiol 65(2015):1525-36
- Yellon DM, Davidson SM. Exosomes: nanoparticles involved in cardioprotection? Circ Res 114:(2014):325-32
- Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013 Jan;123(1):92-100.
- The therapeutic potential of ischemic conditioning: an update. Hausenloy DJ, Yellon DM. Nat Rev Cardiol. 2011 Jun 21;8(11):619-29
- Davidson SM, Vicencio JM, Riquelme JA, Doreth C, Khoo V, Boi-Doku C, Multhoff G, Yellon DM.Cardioprotection mediated by exosomes is impaired in the setting of type II diabetes but can be rescued by the use of non-diabetic exosomes in vitro. J Cell & Mol Medicine 2017 (Aug 25. doi: 10.1111/jcmm.13302)

Research Project ID06

Regulation of the inflammatory response by SDF-1α-CXCR4 after acute myocardial infarction

Supervisor(s): Prof Derek Yellon & Dr Daniel Bromage

Email(s): d.yellon@ucl.ac.uk; dan.bromage.13@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Stromal derived factor-1α (SDF-1α/CXCL12) is a CXC chemokine that is up-regulated in experimental and clinical studies of acute myocardial infarction and regulates chemotaxis of inflammatory and progenitor cells to sites of myocardial injury (1). Interestingly, transgenic mice with cardiomyocyte-specific deletion of the cognate SDF-1α receptor, CXCR4 (CM-CXCR4$^{-/-}$), are protected against ischaemia-reperfusion injury, although the exact mechanism is unknown. It is hypothesised that the cardio-protection in CM-CXCR4$^{-/-}$ transgenic mice is contingent on reduced inflammatory cytokine release, including monocyte chemoattractant protein 1, interleukin 6 and tumour necrosis factor 1α.(2-5) The project therefore aims are to investigate the importance of SDF-1α-CXCR4-mediated inflammation in cardio-protection. BHF PhD students will learn a broad range of techniques in this project including include real-time quantitative PCR using mouse inflammatory cytokine and receptor PCR arrays, mouse cardiomyocyte isolation and simulated ischaemia-reperfusion (hypoxia-reoxygenation), and characterisation of the inflammatory phenotype using FACS and immunohistochemistry. In addition the student will learn the isolated perfused mouse heart Langendorff preparation.

Key references:

- Bromage DI, Davidson SM, Yellon DM Stromal derived factor 1α: A chemokine that delivers a two-pronged defence of the myocardium Pharmacology & Therapeutics 2014;143: 305–315
- Shi J, Dai W, Kloner RA. Therapeutic Hypothermia Reduces the Inflammatory Response Following Ischemia/Reperfusion Injury in Rat Hearts. Ther Hypothermia Temp Manag. 2017.
- Schiraldi M, Raucci A, Munoz LM, Livoti E, Celona B, Venereau E, et al. HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4.
- J Exp Med. 2012;209(3):551-63.
- Huang XZ, Wu JF, Cass D, Erle DJ, Corry D, Young SG, et al. Inactivation of the integrin beta 6 subunit gene reveals a role of epithelial integrins in regulating inflammation in the lung and skin. J Cell Biol. 1996;133(4):921-8.
- Muhlstedt S, Ghadge SK, Duchene J, Qadri F, Jarve A, Vilianovich L, et al. Cardiomyocyte-derived CXCL12 is not involved in cardiogenesis but plays a crucial role in myocardial infarction. J Mol Med (Berl). 2016;94:1005-14.

Research Project ID07

Neuroprotection by remote ischaemic conditioning in acute ischaemic stroke

Supervisor(s): Prof Derek Yellon & Dr Maryna Basalay

Email(s): d.yellon@ucl.ac.uk marina.basalay@ucl.ac.uk

Department/Group: The Hatter Cardiovascular Institute, UCL

Project outline:

Ischaemic stroke is one of the leading causes of death worldwide. At present, timely restitution of blood flow by intravenous thrombolysis or thrombectomy is the sole existing treatment strategy, which is known to reduce infarct size in these patients. However, this treatment, even if successful, does not ensure full recovery in most of the treated patients. This indicates the need of additional therapeutic methods, alleviating ischaemia and reperfusion damage in the brain. Among such potential methods, the most promising is phenomenon of Remote Ischaemic Conditioning (RIC). RIC is a method whereby the application of brief episodes of ischaemia and reperfusion to an organ/tissue can significantly protect a remote organ (the heart or the brain) from subsequent injury. Initially described as a promising method to protect the heart, RIC is now known to be able to protect all the organs. We have demonstrated the neuroprotective effects of RIC in pilot studies in rats. The aims of this project are therefore; to establish whether the infarct-limiting effect of RIC depends on the duration of focal brain ischaemia; to determine the delay interval at reperfusion, within which RIC is neuroprotective. To investigate the potential mechanisms associated with protection observed following RIC. We shall be using protocols in which infarct size in the brain will be measured, histologically (TTC staining) and with the use of high-resolution magnetic resonance imaging (MRI). This is an ideal PhD project with potential to collaborate we have at the Stroke Unit at the University of Lyon in France.

Key references:

- Hausenloy DJ, Yellon DM. The therapeutic potential of ischemic conditioning: an update. Nat Rev Cardiol. 2011 Jun 21;8(11):619-29
- Basalay M V., Davidson SM, Gourine A V., Yellon DM. Neural mechanisms in remote ischaemic conditioning in the heart and brain: mechanistic and translational aspects. Basic Res Cardiol 2018;113:25.
- Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, Lo EH, STAIR Group. Update of the stroke therapy academic industry roundtable preclinical recommendations.
- *Stroke* 2009;40:2244–2250.
- Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. New Engl J Med 2007;357:1121–1135.
- Savitz SI, Baron J-C, Yenari MA, Sanossian N, Fisher M. Reconsidering Neuroprotection in the Reperfusion Era. Stroke 2017;48:3413–3419.

Research Project ID08

Using a bioinformatic approach to describe a specific cardiovascular relevant process

Supervisor(s): Ruth Lovering; Rachael Huntley Email(s): r.lovering@ucl.ac.uk

Department/Group: Institute of Cardiovascular Science / Functional Gene Annotation

Project outline:

Bioinformatic resources are an essential tool for modern biologists and clinicians. This project will give you hands on experience of using these tools, understanding their limitations and enable you to confidently find the right resource for your future research. Gene Ontology (GO) is now an established standard for the functional annotation of gene products (www.geneontology.org/).

This project will involve in depth literature review and annotation of specific genes, such as NOTCH3, ITM2B or miR-124, with a known role in a dementia relevant process. Alternatively, we are happy for you to choose the research area that is of particular interest to you, for example: previous projects have focused on autism, hemochromatosis, folic acid metabolism and lipid metabolism. Your project will lead to the creation of detailed annotations for a limited number of gene products. You will then use a comparative genomics approach to transfer appropriate annotations to orthologous gene family members.

We anticipate a 12-week project will require reading around 30 scientific papers and summarising their contents by creating annotations (iBSc students will curate around 10 papers). Your annotations will be made public and contribute to the GO database.

Key references:

- Patel S, Roncaglia P, Lovering RC. Using Gene Ontology to describe the role of the neurexin-neuroligin-SHANK complex in human, mouse and rat and its relevance to autism. BMC Bioinformatics. 2015;16:186.
- The Gene Ontology Consortium. Expansion of the Gene Ontology knowledgebase and resources. Nucleic Acids Res. 2017;45(D1):D331-D338.
- Alam-Faruque Y, Huntley RP, Khodiyar VK, Camon EB, Dimmer EC, Sawford T, Martin MJ, O'Donovan C, Talmud PJ, Scambler P et al. The impact of focused Gene Ontology curation of specific mammalian systems. PLoS One. 2011;6(12):e27541.
- Khodiyar VK, Hill DP, Howe D, Berardini TZ, Tweedie S, Talmud PJ, Breckenridge R, Bhattarcharya S, Riley P, Scambler P et al. The representation of heart development in the gene ontology. Developmental biology. 2011;354(1):9-17.
- Huntley RP, Sitnikov D, Orlic-Milacic M, Balakrishnan R, D'Eustachio P, Gillespie ME, Howe D, Kalea AZ, Maegdefessel L, Osumi-Sutherland D et al. Guidelines for the functional annotation of microRNAs using the Gene Ontology. RNA. 2016.

Research Project ID14

Measuring reactive hyperemia in the gastrocnemius using near-infrared spectroscopy (NIRS): How important is occlusion duration?

Supervisor(s): Siana JONES **Email:** siana.jones@ucl.ac.uk
Alun HUGHES **Email:** alun.hughes@ucl.ac.uk

Department/Group: ICS- Population Science and Experimental Medicine (PSEM)

Project outline:
The prevalence of diabetes and cardiovascular disease is rising globally. Evidence suggests that vascular dysfunction manifests long before clinical diagnosis is made. There is a need to develop tests that assess micro-vascular function that they can be applied easily in clinical environments.

Post-occlusive reactive hyperaemia (PORH) can be used to assess both microvascular and large artery endothelial function by examining the response to a short period of ischaemia.(1, 2) The effect of different occlusion lengths on the flow mediated dilatation (FMD) in the large vessels has previously been described.(3) However the effect of altering occlusion duration on the microvasculature has not been closely investigated. Furthermore the effect of body position (supine or upright) on these measurements is unknown.

This project aims to investigate the effect of occlusion duration on the PORH measured using NIRS in the skeletal muscle of young, healthy individuals.

Key references:

- Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. Journal of the American College of Cardiology. 2002;39(2):257-65. Epub 2002/01/15.
- Willingham TB, Southern WM, McCully KK. Measuring reactive hyperemia in the lower limb using near-infrared spectroscopy. Journal of biomedical optics. 2016;21(9):091302. Epub 2016/04/07.
- Leeson P, Thorne S, Donald A, Mullen M, Clarkson P, Deanfield J. Non-invasive measurement of endothelial function: effect on brachial artery dilatation of graded endothelial dependent and independent stimuli. Heart. 1997;78(1):22-7. Epub 1997/07/01.

Research Project ID16

Statistical shape analysis of the aorta in Marfan population: a longitudinal study

Supervisor(s):	**Email(s):**
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Dr Silvia Schievano	s.schievano@ucl.ac.uk
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Miss Benedetta Biffi	b.biffi@ucl.ac.uk

Department/Group: ICS Clinical Cardiovascular Engineering Group

Project outline:

Marfan syndrome is a genetic disorder of the connective tissue, causing aortic anomalies such as enlargement and/or aneurysm. Regular monitoring of Marfan patients aortas is essential, in order to detect any morphological change and timely plan surgery, thus lowering the risk of abrupt aortic dissection.

The aim of this project is to perform statistical shape analysis of aortic 3D models derived from magnetic resonance images of a Marfan population. Providing quantitative information on the average aortic shape and time shape variations within the population, such analysis could help improve the understanding of the disease and predict of how it develops over time, ultimately impacting on patients management.

Key references:

Congenital heart disease, medical imaging, population study, image segmentation, statistical shape analysis

Research Project ID20

Population analysis of pulmonary artery from shape modelling perspective.

Supervisor(s): Dr Emilie Sauvage, Dr. Claudio Capelli, Dr Silvia Schievano

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Department/Group: Institute of Cardiovascular Science / Clinical Cardiovascular Engineering

Project outline:

In this analysis we perform a comprehensive shape analysis on pulmonary arteries (PA) that are identified as defective that due to various congenital conditions. The shape is often complex and may exhibit stenotic area. We hypothesize that a degenerative PA has a unique phenotype compared to the one in normal subjects and that 3D shape characterization can help improve diagnosis and risk evaluation for the patient.

Current tools are able to describe shape features and identify 3D shape biomarkers from medical imaging (2016_Bruse). Others are capable of simulating blood flow on patient specific geometries subjected to realistic conditions and thus help design the most appropriate treatment. There is strong evidence that such tools provide essential information when selecting the proper treatment for the patient (2010_Capelli, 2010_Schievano).

The aim of this project is to analyse the shape of pulmonary artery from a cohort of 30 to 40 medical image sets. The student will identify outliers, mean geometry and cast the geometry into relevant groups using existing tools based on Principal Component Analysis method. The final stage involves fluid simulation performed on patient geometries in order to extract relevant flow quantities able to support the previous choice of shape casting.

Key references:

- 2010_Capelli: Capelli C, Taylor AM, Migliavacca F, Bonhoeffer P, Schievano S. Patient-specific reconstructed anatomies and computer simulations are fundamental for selecting medical device treatment: application to a new percutaneous pulmonary valve. *Philosophical transactions Series A, Mathematical, physical, and engineering sciences*. 2010;368(1921):3027-3038.
- 2010_Schievano: Schievano S, Taylor AM, Capelli C, Lurz P, Nordmeyer J, Migliavacca F, Bonhoeffer P. Patient specific finite element analysis results in more accurate prediction of stent fractures: application to percutaneous pulmonary valve implantation. *Journal of Biomechanics.* 2010; 43(4):687-693
- 2016_Bruse: Bruse J, McLeod K, Biglino G, Ntsinjana HN, Capelli C, Hsia TY, Sermesant M, Pennec X, Taylor AM, Schievano S. A statistical shape modelling framework to extract 3D shape biomarkers from medical imaging data: assessing arch morphology of repaired coarctation of the aorta. *BMC Medical ImagingBMC series – open, inclusive and trusted.* 2016; **16**:40

Research Project ID21

Artificial angiogenesis

Supervisor(s): Marcus Fruttiger **Email(s):** m.fruttiger@ucl.ac.uk

Department/Group: Institute of Ophthalmology

Project outline:

Our lab studies the molecular and cellular mechanisms that control angiogenesis during normal development and disease. In this project, we aim to investigate the growth of new blood vessels (angiogenesis) in a novel cell culture assay, which is based on recent progress made in bioengineering. The student will be studying biological processes contributing to vessel formation in a novel microfluidics device, using cell culture techniques, immunohistochemistry, and fluorescent and time lapse microscopy.

Key references:

- Orlova VV et al. Generation, expansion and functional analysis of endothelial cells and pericytes derived from human pluripotent stem cells. Nat Protoc. 9(6):1514-31 (2014)
- Kim J et al. Engineering of a biomimetic pericyte-covered 3D microvascular network. PLoS One 10, 1–15 (2015).
- Potente M et al. Basic and therapeutic aspects of angiogenesis. Cell 146, 873–887 (2011).
- Fruttiger M. Development of the retinal vasculature. Angiogenesis 10(2):77-88 (2007).

Research Project ID25

Functional and phenotypic 'switching' in vascular smooth muscle cells

Supervisor(s): Dr Markella Ponticos **Email(s):** m.ponticos@ucl.ac.uk

Department/Group: Inflammation/ Centre for Rheumatology and Connective Tissue diseases

Project outline:
Phenotypic modulation of vascular smooth muscle cells (VSMC) is associated with vascular remodelling in many cardiovascular diseases. Stimuli associated with specific disease processes such as endothelial dysfunction or inflammation initiate pathways that result in the de-differentiation of VSMC towards proliferative, embryonic-like and disease-associated phenotype. Many of these pathways concomitantly affect many cellular functions of VSMC which ultimately result in diseased vessels. The aim of this project is to investigate the pathways that result in the de-differentiation process which also relate to the loss of function of injured/diseased vessels and to identify target genes that activate these processes. We previously generated gene array data comparing healthy and de-differentiated VSMC identifying novel gene targets. Cellular and molecular biological techniques using VSMC in culture, inhibition/ RNA interference of target genes as well as in vitro and ex-vivo assays to assess function (proliferation, migration, contraction, apoptosis) will be utilised. Robust gene targets will be translated in vivo using conditional knock-out technology as examined for their impact on phenotypic switching in animal models of human vascular injury (for PhD only)

Key references:

- An overview of potential molecular mechanisms involved in VSMC phenotypic modulation. Zhang MJ, Zhou Y, Chen L, Wang YQ, Wang X, Pi Y, Gao CY, Li JC, Zhang LL. Histochem Cell Biol. 2016 Feb;145(2):119-30.
- Ponticos M, Smith BD. Extracellular matrix synthesis in vascular disease: hypertension, and atherosclerosis. J Biomed Res. 2014 Jan;28(1):25-39.
- Nguyen AT, et al., Smooth muscle cell plasticity: fact or fiction? Circ Res. 2013 Jan 4;112(1):17-22.
- Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. Cardiovasc Res. 2012 Jul 15;95(2):156-64.
- Ponticos M, Partridge T, Black CM, Abraham DJ, Bou-Gharios G. Regulation of collagen type I in vascular smooth muscle cells by competition between Nkx2.5 and deltaEF1 / ZEB1. Mol Cell Biol. 2004 Jul;24(14):6151-61.

Research Project ID27

Functional and phenotypic 'switching' in vascular smooth muscle cells

Supervisor(s): Dr Markella Ponticos **Email(s):** m.ponticos@ucl.ac.uk

Department/Group: Inflammation/ Centre for Rheumatology and Connective Tissue diseases

Project outline:

Phenotypic modulation of vascular smooth muscle cells (VSMC) is associated with vascular remodelling in many cardiovascular diseases. Stimuli associated with specific disease processes such as endothelial dysfunction or inflammation initiate pathways that result in the de-differentiation of VSMC towards proliferative, embryonic-like and disease-associated phenotype. Many of these pathways concomitantly affect many cellular functions of VSMC which ultimately result in diseased vessels. The aim of this project is to investigate the pathways that result in the de-differentiation process which also relate to the loss of function of injured/diseased vessels and to identify target genes that activate these processes. We previously generated gene array data comparing healthy and de-differentiated VSMC identifying novel gene targets. Cellular and molecular biological techniques using VSMC in culture, inhibition/ RNA interference of target genes as well as in vitro and ex-vivo assays to assess function (proliferation, migration, contraction, apoptosis) will be utilised. Robust gene targets will be translated in vivo using conditional knock-out technology as examined for their impact on phenotypic switching in animal models of human vascular injury (for PhD only)

Key references:

- An overview of potential molecular mechanisms involved in VSMC phenotypic modulation. Zhang MJ, Zhou Y, Chen L, Wang YQ, Wang X, Pi Y, Gao CY, Li JC, Zhang LL. Histochem Cell Biol. 2016 Feb;145(2):119-30.
- Ponticos M, Smith BD. Extracellular matrix synthesis in vascular disease: hypertension, and atherosclerosis. J Biomed Res. 2014 Jan;28(1):25-39.
- Nguyen AT, et al., Smooth muscle cell plasticity: fact or fiction? Circ Res. 2013 Jan 4;112(1):17-22.
- Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. Cardiovasc Res. 2012 Jul 15;95(2):156-64.
- Ponticos M, Partridge T, Black CM, Abraham DJ, Bou-Gharios G. Regulation of collagen type I in vascular smooth muscle cells by competition between Nkx2.5 and deltaEF1 / ZEB1. Mol Cell Biol. 2004 Jul;24(14):6151-61.

Research Project ID28

Prostate Cancer, Therapies and Cardiovascular risk

Supervisor(s): Riyaz Patel **Email(s):** Riyaz.patel@ucl.ac.uk

Department/Group: ICS, Farr Institute

Project outline:
There is uncertainty about the role of prostate cancer therapies and risk of cardiovascular disease (CVD). Some treatments like GnRH agonists are cheap and widely used but may cause cardiovascular disease. This work will develop evidence around testosterone replacement, GnRH agonists, antagonists and combined androgen blockers and risk of CVD.

The project is to perform a detailed and up to date systematic review through literature searches and if appropriate a meta-analysis of risk effect estimates. This data will lead to a paper, with a high chance of citation given the uncertainty in the field. This would be suitable for a BSc or an MSc standalone project.

For BHF PhD students, the systematic review would be combined with an observational epidemiological study in the CALIBER database, which includes 10M patients from primary care with linked records and outcomes (please note this will be outside the 6-12 week timelines). This will seek to determine if these therapies in real world setting associate with risk of CVD. A Mendelian Randomization study may also be possible depending on the interests of the candidate.

Key references:

- Bosco et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015
- Ziehr et al. Association of androgen-deprivation therapy with excess cardiac-specific mortality in men with prostate cancer. BJU Int 2015.
- Wallis et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet D&E 2016

Research Project ID31

Prevalence of traditional cardiovascular risk factors among young patients with coronary artery disease

Supervisor(s): Dr Riyaz Patel; Dr Leon Menezes **Email(s):** Riyaz.patel@ucl.ac.uk

Department/Group: ICS-UCL, Barts Heart Centre

Project outline:

An increasing number of young people are being identified to have premature coronary artery disease. Risk factors driving the disease in these people have been identified from old population studies or post mortem studies, which have various selection biases and do not reflect contemporary lifestyles and behaviours . With the advent of CTCA we can now assess coronary artery disease non-invasively to overcome this issue.

At the Barts Heart Centre over 3000 scans a year are conducted for assessment of chest pain, with a substantial proportion in people under 45years and of South Asian descent, groups under-represented in the literature.

This project will seek to identify the prevalence of core risk factors in this group of patients with a view to publishing findings as a descriptive report. The work will entail going through CTCA reports and creating a database of relevant variables, before running descriptive analyses.

If interested, please get in touch to discuss further.

Key references:

- Genest JJ1, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. Am J Cardiol. 1991 Jun 1;67(15):1185-9.

Research Project ID32

Prevalence and extent of coronary artery disease in patients with Familial Hypercholesterolaemia

Supervisor(s): Dr Riyaz Patel; Dr Leon Menezes **Email(s):** Riyaz.patel@ucl.ac.uk

Department/Group: ICS-UCL, Barts Heart Centre

Project outline:
Familial hypercholesterolaemia is a genetic disorder leading to high LDL cholesterol and premature coronary heart disease. However not everyone with FH has severe coronary disease. Previously assessment of coronary disease burden was challenging but now with the availability of CTCA, this can be more easily achieved.

At the Barts Heart Centre over 3000 scans a year are conducted for assessment of chest pain, with an unknown proportion among people with known or unknown familial hypercholesterolaemia. A large proportion of patients with FH have also been scanned at UCLH.

This project will seek to identify those patients with FH having a CTCA scan at both sites and then to evaluate the extent and burden of disease in these patients. This will then be related to duration of treatment and genetic diagnosis. We anticipate this work to inform local clinical practice and to be published as a paper.

If interested, please get in touch to discuss further.

Key references:

- Sharifi M1, et al. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. Atherosclerosis. 2017 Aug;263:405-411. doi: 10.1016/j.atherosclerosis.2017.05.015. Epub 2017 May 13.

Research Project ID33

Characterisation of paediatric hypertrophic cardiomyopathy caused by MYH7 mutations

Supervisor(s):
Dr Juan Pablo Kask, Ms Ella Field

Email(s):
j.kaski@ucl.ac.uk

Department/Group: Inherited Cardiovascular Diseases, Great Ormond Street Hospital

Project outline:

Most cases of HCM in childhood are caused by mutations in the sarcomere protein genes, inherited as autosomal dominant traits with age-related penetrance. MYH7 gene variants are among the two most common causes of sarcomeric disease. Disease onset is usually seen in late adolescence to early adulthood, and the clinical presentation and prognosis of childhood-onset disease is not well described. This retrospective cohort study will investigate the clinical features and outcomes of childhood-onset HCM caused by MYH7 gene variants.

Key references:

- Kaski JP, Syrris P, Esteban MT et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2009 Oct;2(5):436-41
- Moak JP, Kaski JP. Hypertrophic cardiomyopathy in children. Heart. 2012 Jul;98(14):1044-54
- Morita H, Rehm HL, Menesses A et al. Shared genetic causes of cardiac hypertrophy in children and adults. N Engl J Med. 2008 May 1;358(18):1899-908

Research Project ID38

Studying facets of inflammation in pulmonary arterial hypertension

Supervisor(s): Prof Lucie Clapp & Prof David Abraham
Email(s): l.clapp@ucl.ac.uk; david.abraham@ucl.ac.uk
Department/Group: UCL Institute of Cardiovascular Science and Division of Medicine

Project outline:
Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling of the pulmonary arteries and excessive proliferation of vascular cells leading to vessel stiffness [1]. Although the pathophysiology remains largely unknown increasing evidence to suggest an important role for inflammation [2-5]. Pulmonary vascular lesions identified in patients with PAH, as well as in animal models, have been found to contain various immune cells including B cells, T cell, macrophages, dendritic cells and mast cells [4]. In addition PAH also show altered circulating cytokine and complement levels some of which are characteristic of specific T cell subsets (TH1, TH2, TH17 and Tregs). The project aims to study in detail specific T cell sub-sets in PAH by examining circulating levels of T cells in PAH patient, cytokine profile and to examine tissues sections from PAH patients and an animal model for defined T cell sub-sets.

Specific aims are to:
1. Measure the levels of T cell sub-sets (in particular Tregs and complement induced cTregs) and T cell derived cytokines and complement factors and receptors in the circulation of patients with PAH.
2. Explore the expression of complement factors and receptors, and other novel markers on T cells from patients with PAH.
3. Examine the expression of T cell subsets (Treg/cTregs) in tissues of patient with PAH and in a mouse model of PAH and to assess the role of T cell derived complement.

Results from these experiments will provide information on the role of T cells in inflammation in PAH and increase the evidence that alteration in T cell subsets or their function may predispose to development of PAH and may serve as useful and effective targets for therapeutic advantage.

Key references:
- Homeostasis and Inflammation in the Pathogenesis of Pulmonary Arterial Hypertension. Bello-Klein A, Mancardi D, Araujo AS, Schenkel PC, Turck P, de Lima Seolin BG. Role of Redox. Curr Med Chem. 2018;25(11):1340-1351.
- Challenges and opportunities in treating inflammation associated with pulmonary hypertension. Voelkel NF, Tamosiuniene R, Nicolls MR. Expert Rev Cardiovasc Ther. 2016 Aug;14(8):939-51.
- Inflammation in pulmonary hypertension: what we know and what we could logically and safely target first. Cohen-Kaminsky S, Hautefort A, Price L, Humbert M, Perros F.. Drug Discov Today. 2014 Aug;19(8):1251-6.
- Inflammation in pulmonary arterial hypertension. Price LC, Wort SJ, Perros F, Dorfmüller P, Huertas A, Montani D, Cohen-Kaminsky S, Humbert M. Chest. 2012 Jan;141(1):210-221.

Research Project ID46

Studying the mechanism underlying vascular changes in hypertensive mice

Supervisors: Dr Vishwanie Budhram-Mahadeo, Vaishali Yogendran
Email: v.budhram-mahadeo@ucl.ac.uk, l.mele@ucl.ac.uk.
Department/Group: Pre-clinical & Fundamental Science

Project outline:
Using a knockout mouse model, we have identified new roles for transcription factors in controlling extracellular matrix proteins (ECM) in blood vessels such as the aorta. Excess production of some ECM proteins e.g. collagen or disruption of elastin fibres are strongly associated with cardiovascular diseases such as arterial stiffening linked to hypertension.
This project will aim to analyse the changes found in blood vessels of mutant and wild-type mice using histological techniques such as trichrome staining, immuno fluorescent staining and collagen imaging using two photon second harmonic generation microscopy.

Research Project ID49

Ethnic differences in atherosclerosis in relation to cardiovascular risk

Supervisors: Alun Hughes, Sophie Eastwood, Nish Chaturvedi
Email(s): a.hughes@ucl.ac.uk

Project outline:

People of different ethnicities living in the UK experience different risks of coronary heart disease (CHD) and stroke. Compared with Europeans, people of South Asian ethnicity have a markedly increased risk of CHD and stroke, whereas people of African-Caribbean ethnicity have a lower risk of CHD, but an elevated risk of stroke.[1] These ethnic differences not understood, but differential atherosclerotic plaque vulnerability due to differences in plaque composition is a possible explanation.

This project will use data collected from the Southall and Brent Revisited (SABRE) study,[2] a longitudinal study of European, South Asian and African-Caribbean people resident in West London. All participants had an ultrasound scan of their carotid arteries, to identify atherosclerotic plaque.[3,4] The aim of the study is to establish whether number of plaques, extent of plaques (plaque area) or plaque composition differs by ethnicity and to examine the associations of plaque and plaque characteristics with cardiovascular risk factors in the different ethnic groups, particularly the potential role of diabetes. The project will involve the analysis of plaque area and composition using image-analysis techniques, and the statistical analysis of the resultant data. Full support and training in these techniques will be provided.

References

- Tillin T, Hughes AD, Mayet J, et al. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study. *J Am Coll Cardiol* 2013; **61**(17): 1777-86.
- Tillin T, Forouhi NG, McKeigue PM, Chaturvedi N. Southall And Brent REvisited: Cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins. *Int J Epidemiol* 2012; **41**(1): 33-42.
- Bots ML, Evans GW, Tegeler CH, Meijer R. Carotid Intima-media Thickness Measurements: Relations with Atherosclerosis, Risk of Cardiovascular Disease and Application in Randomized Controlled Trials. *Chin Med J (Engl)* 2016; **129**(2): 215-26.
- Park TH. Evaluation of Carotid Plaque Using Ultrasound Imaging. *J Cardiovasc Ultrasound* 2016; **24**(2): 91-5.

Research Project ID50

Investigating the role of nedd9 in zebrafish models of angiogenesis.

Supervisor(s): Dr Paul Frankel **Email(s):** p.frankel@ucl.ac.uk

Department/Group: Cardiovascular Biology and Medicine

Project outline:

Angiogenesis, the physiological process through which new blood vessels form from pre-existing vessels is essential for development and in disease. p130Cas belongs to a family of adaptor proteins including nedd9, which have emerged as key signalling nodes with important regulatory roles in normal and pathological angiogenesis (Barrett et al, 2013; Evans et al, 2017). Whereas global deletion of p130Cas in the mouse has been reported to be embryonic lethal, global deletion in the Zebrafish appears to be viable. We hypothesise that other Cas family proteins and in particular nedd9 is able to compensate for the lack of p130Cas, allowing survival of these animals. This project aims to investigate if and how the Cas family protein nedd9 could be mediating redundant pathways required for angiogenesis in p130Cas-deficient zebrafish. Transient (morpholino) and stable (CRISPR/Cas9) deletions of nedd9 on a wildtype or p130Cas-deficiency background will be established and used to investigate developmental angiogenesis in the zebrafish model.

Laboratory skills / Techniques to develop during project:

- Zebrafish husbandry: handling of adult zebrafish, staging of embryos, identification of fluorescent reporter transgenes
- Genetic manipulation of zebrafish embryos: Microinjection of DNA, RNA and use of morpholinos
- Zebrafish Imaging
- Molecular biology skills: PCR, sequencing, Western Blot, qPCR.

Key reference(s) (max. of 5):

- Barrett, A., Pellet-Many, C., Zachary, I. C., Evans, I. M. & Frankel, P. p130Cas: A key signalling node in health and disease. *Cellular Signalling* **25**, 766-777, doi:10.1016/j.cellsig.2012.12.019 (2013).
- Evans, I. M. *et al.* Neuropilin-1 signaling through p130Cas tyrosine phosphorylation is essential for growth factor-dependent migration of glioma and endothelial cells. *Mol. Cell. Biol.* **31**, 1174-1185, doi:10.1128/MCB.00903-10 (2011).
- Honda, H. *et al.* Cardiovascular anomaly, impaired actin bundling and resistance to Src-induced transformation in mice lacking p130Cas. *Nat. Genet.* **19**, 361-365, doi:10.1038/1246 (1998).
- Rccomagno, M. M. *et al.* Cas adaptor proteins organize the retinal ganglion cell layer downstream of integrin signaling. *Neuron* **81**, 779-786, doi:10.1016/j.neuron.2014.01.036 (2014).

Research Project ID51

Cardiac manifestations in congenital myotonic distrophy

Supervisor(s): **Elena Cervi** **Email(s): elena.cervi@nhs.net**

Department/Group: Cardiology at Great Ormond Street Hospital

Project outline:

Cardiac involvement in myotonic dystrophy especially with cardiac conduction disease and ventricular tachycardias with associated risk of sudden death is a well-established manifestation in adult cardiac practice. Less is known about cardiac manifestations in infancy in children affected with the most severe form of the neuromuscular condition, congenital myotonic dystrophy. We have recently established a pathway of care with the neuromuscular team and we will review our collected data to assess their manifestations and stratify their risk.

Key references:

- Myotonic Dystrophy And The Heart. G Pelargonio, A Dello Russo, T Sanna, G De Martino, F Bellocci. Heart 2002;88:665–670
- Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. G. Bassez, MD; A. Lazarus, MD; I. Desguerre, MD; J. Varin, MD; P. Laforêt, MD; H.M. Bécane, MD; C. Meune, MD; M.C. Arne-Bes, MD; Z. Ounnoughene, MD; H. Radvanyi, MD, PhD; B. Eymard, MD, PhD; and D. Duboc, MD, PhD. Neurology 2004;63 1939-41.
- Cardiac Abnormalities in Congenital and Childhood Myotonic Muscular Dystrophy Type 1. Anjali Sharma Sandeep Singh Shri K. Mishra. Neuropediatrics 2017;48:42–44.

Research Project ID53

Long-term cardiovascular outcomes in patients with mitochondrial diseases

Supervisor(s): Dr Konstantinos Savvatis **Email(s):** k.savvatis@nhs.net

Department/Group: Inherited Cardiovascular Diseases, Barts Heart Centre and UCL Institute of Cardiovascular Science

Project outline:

Mitochondrial diseases are systemic diseases secondary to defects in the structure or function of mitochondria, which are responsible for energy production in the organism. Mitochondria are under the dual control of nuclear and mitochondrial DNA. Mitochondrial diseases present with wide range of clinical expression with involvement of the nervous system and skeletal muscles being common. Cardiac disease can occur and can range from asymptomatic changes to severe cardiomyopathy.[1, 2] [3]The purpose of this project is the description of the natural history and clinical outcomes in patients with genetically confirmed mitochondrial diseases. Data will be obtained from the database of the Mitochondrial Diseases Service, UCL and the ICVD Service at Barts, and the cardiac phenotype, as well as long-term outcomes will be analysed.

Key reference(s) (max. of 5):

- Wahbi, K., et al., *Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases.* Eur Heart J, 2015. **36**(42): p. 2886-93.
- Ng, Y.S., et al., *Sudden adult death syndrome in m.3243A>G-related mitochondrial disease: an unrecognized clinical entity in young, asymptomatic adults.* Eur Heart J, 2016. **37**(32): p. 2552-9.
- Keshavan, N. and S. Rahman, *Natural history of mitochondrial disorders: a systematic review.* Essays Biochem, 2018. **62**(3): p. 423-442.

Research Project ID54

MSc Cardiovascular Science project: The association between sleep quality and risk of CVD: A tri-ethnic study using data from the Southall and Brent REvisited Study (SABRE)

Supervisor: Dr Victoria Garfield
Email: v.garfield@ucl.ac.uk

Project outline:

The association between sleep duration and CVD is well established, whilst the relationship between sleep quality and risk of CVD is less well understood and whether there are ethnic differences remains to be determined. We have sleep quality data collected in the Southall and Brent REvisited Study (SABRE) at baseline (1988) and follow-up data for participants up to 30 years later. This epidemiological study aims to primarily, investigate the association between sleep quality and risk of cardiovascular disease (CVD) in a UK community sample and as a secondary aim, examine whether this differs by ethnicity in adults of Europeans, South Asians and African Caribbeans. This project would suit a student who would be keen to gain experience in statistical modelling and has an interest in the analysis of prospective epidemiological studies.

Research Project ID55

Tissue characterization with MRI in paediatric hypertrophic cardiomyopathy #1

Supervisor(s): Vivek Muthurangu **Email(s):** v.muthurangu@ucl.ac.uk

Department/Group: Translational Cardiovascular Imaging

Project outline:

Great Ormond Street hospital has the largest paediatric population of patients with hypertrophic cardiomyopathy (HCM). We have pioneered the use of cardiac MRI for assessment of these children and have one of largest phentotyped populations in the world. Conventionally, HCM is diagnosed by increased left ventricular wall thickness and this has been shown to predict outcome. However, it is known that HCM causes inflammation and scarring in the myocardium. MRI is the best non-invasive method of assessing tissue characteristics. The student will help with the analysis of tissue biomarkers in a large population of children with HCM (extra-cellular volume, myocardial oedema) and preparation of the accompanying manuscript.

Research Project ID56

Tissue characterization with MRI in paediatric hypertrophic cardiomyopathy #2

Supervisor(s): Vivek Muthurangu **Email(s):** v.muthurangu@ucl.ac.uk
Department/Group: Translational Cardiovascular Imaging

Project outline:

Great Ormond Street hospital has the largest paediatric population of patients with hypertrophic cardiomyopathy (HCM). We have pioneered the use of cardiac MRI for assessment of these children and have one of largest phentotyped populations in the world. Conventionally, HCM is diagnosed by increased left ventricular wall thickness and this has been shown to predict outcome. However, it is known that HCM causes inflammation and scarring in the myocardium. MRI is the best non-invasive method of assessing tissue characteristics. The student will help with the analysis of tissue biomarkers in a large population of children with HCM (extra-cellular volume, myocardial oedema) and preparation of the accompanying manuscript.

Key reference(s) (max. of 5):

Sado DM, Flett AS, Banypersad SM, White SK, Maestrini V, Quarta G, Lachmann RH, Murphy E, Mehta A, Hughes DA, McKenna WJ, Taylor AM, Hausenloy DJ, Hawkins PN, Elliott PM, Moon JC. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart. 2012;98:1436–41.

Research Project ID57

The prognostic utility of MRI in paediatric pulmonary hypertension

Supervisor(s):Vivek Muthurangu **Email(s): v.muthurangu@ucl.ac.uk**

Department/Group: Translational Cardiovascular Imaging

Project outline:

Great Ormond Street hospital is national centre for paediatric hypertension and we have pioneered the use of cardiac MRI for assessment of these children. We have previously shown that cardiac MRI provides prognostic information in a small population of patients. We have now collected nearly 1000 MRI examinations over a 10-year period. This is the largest paediatric pulmonary hypertension population examined with MRI in the world. The student would be involved in analysis of this data (processing of MRI data and collection of outcome information) and preparing the manuscript for publication

Key reference(s) (max. of 5):

Moledina S, Pandya B, Bartsota M, McMillan MR, Mortenson KH, Quyam S, Taylor AM, Haworth SG, Schulze-Neick I, **Muthurangu V**. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013

Research Project ID58

New MRI biomarkers in paediatric pulmonary hypertension

Supervisor(s): Vivek Muthurangu **Email(s):** v.muthurangu@ucl.ac.uk

Department/Group: Translational Cardiovascular Imaging

Project outline:

Great Ormond Street hospital is national centre for paediatric hypertension and we have pioneered the use of cardiac MRI for assessment of these children. We have previously shown that cardiac MRI provides prognostic information in a small population of patients. However, we currently use simple volumetric measures of cardiac function. Recently, we have shown in adults that assessment of the regional components of cardiac function may be more prognostic. In this study, the student will help with the analysis of regional cardiac function measured using a novel MRI techniques (tissue phase mapping) and preparation of the accompanying manuscript.

Key reference(s) (max. of 5):

- Moledina S, Pandya B, Bartsota M, McMillan MR, Mortenson KH, Quyam S, Taylor AM, Haworth SG, Schulze-Neick I, **Muthurangu V**. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013
- Knight DS, Steeden JA, Moledina S, Jones A, Coghlan JG, **Muthurangu V**. Left ventricular diastolic dysfunction in pulmonary hypertension predicts functional capacity and clinical worsening: a tissue phase mapping study. J Cardiovasc Magn Reson. 2015 Dec 29;17:116. doi: 10.1186/s12968-015-0220-3.

Research Project ID68

Prediction of number of replicates required to enhance the reliability of three-dimensional speckle tracing echocardiography.

Supervisors: Alun Hughes **Email:** alun.hughes@ucl.ac.uk
Lamia Al Saikhan **Email:** lamia.saikhan.16@ucl.ac.uk

Department/Group: Population Science & Experimental Medicine

Project outline:

Three-dimensional (3D) speckle tracking echocardiography (3D-STE) is a novel advanced imaging technique used to analyse left ventricular (LV) myocardial deformation from acquired LV full-volume data sets. Theoretically, 3D-STE is believed to overcome some of the limitations of two-dimensional STE (2D-STE) providing a comprehensive quantification of advanced LV myocardial mechanics from a single 3D data set. This includes LV strain (longitudinal and circumferential shortening and radial lengthening in addition to the new 3D strain, a composite measure of longitudinal and circumferential strain; LV twist and rotations; LV mechanical dyssynchrony; and LV volumes. However, the reliability of 3DSTE LV derived measures varies. For example, twist has modest reliability being highly vulnerable to variability as opposed to other measure such as volumes. Reliability also varies between different LV strain measures. Reliability is often assessed by intra-class correlation coefficient (ICC). Spearman-Brown formula is a formal which can be used to predict the number of replicates required to achieve a desired degree of reliability. This project aims to test whether applying this formula is useful in enhancing the overall reliability of 3D-STE LV derived measures. This will be achieved by comparing the predicted ICC for 'x' replicates estimated from ICC of a single replicate and the actual averaged ICC estimated from actual 'x' replicates of measurements. It is hoped that this study will give insights of the usefulness of implementing the Spearman-Brown formula in the medical imaging field.

Key references:

1. Muraru D, et al. Three-dimensional speckle-tracking echocardiography: benefits and limitations of integrating myocardial mechanics with three-dimensional imaging. Cardiovasc Diagn Ther 2018;8(1):101-117. doi: 10.21037/ cdt.2017.06.01.
2. Lang RM, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging. 2012;13(1):1-46.
3. Mor-Avi Vet al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr. 2011;24(3):277-313.
4. Opdahl A, et al. Strain, strain rate, torsion, and twist: echocardiographic evaluation. Curr Cardiol Rep. 2015;17(3):568.
5. Surkova E, Muraru D, Aruta P, Romeo G, Bidviene J, Cherata D, et al. Current Clinical Applications of Three-Dimensional Echocardiography: When the Technique Makes the Difference. Curr Cardiol Rep. 2016;18(11):109.
6. Tsang W, Kenny C, Adhya S, Kapetanakis S, Weinert L, Lang RM, et al. Interinstitutional measurements of left ventricular volumes, speckle-tracking strain, and dyssynchrony using three-dimensional echocardiography. J Am Soc Echocardiogr. 2013;26(11):1253-7.
7. Spearman, Charles, C. (1910). Correlation calculated from faulty data. British Journal of Psychology, 3, 271–295.
8. Brown, W. (1910). Some experimental results in the correlation of mental abilities. British Journal of Psychology, 3, 296–322.
9. https://personalpages.manchester.ac.uk/staff/graham.dunn/MSc%20Biostatistics/Measurement%20Models_0
10. https://en.wikipedia.org/wiki/Spearman%E2%80%93Brown_prediction_formula

Research Project ID69

The impact of using different software versions in assessing left ventricular volumes, strain, torsion and dyssynchrony by three-dimensional speckle tracking echocardiography.

Supervisors: Alun Hughes **Email:** alun.hughes@ucl.ac.uk
Lamia Al Saikhan **Email:** lamia.saikhan.16@ucl.ac.uk

Department/Group: Population Science & Experimental Medicine

Project outline:

Three-dimensional (3D) speckle tracking echocardiography (3D-STE) is a novel advanced imaging technique used to analyse left ventricular (LV) myocardial deformation from acquired LV full-volume data sets. 3D-STE provides a comprehensive quantification of LV geometry and function including complex LV myocardial mechanics from a single 3D data set. This includes LV strain (longitudinal and circumferential shortening and radial lengthening in addition to the new 3D strain, a composite measure of longitudinal and circumferential strain; LV twist and torsion; LV mechanical dyssynchrony; and LV volumetric measures. While the reproducibility both intra- and inter-observer of 3D-STE is generally acceptable to good, this technology suffers from inter-vendor variability and standardization between different vendors is needed. However, little is known regarding the impact of using different software versions of the same manufacturer in 3D-STE derived LV measures. This project aims to use two different versions of vendor independent software to analyse LV full-volume 3D data sets.

Key references:

1. Muraru D, Niero A, Rodriguez-Zanella H, Cherata D, Badano L. Three-dimensional speckle-tracking echocardiography: benefits and limitations of integrating myocardial mechanics with three-dimensional imaging. Cardiovascular diagnosis and therapy. 2018;8(1):101-17.
2. Gayat E, Ahmad H, Weinert L, Lang RM, Mor-Avi V. Reproducibility and inter-vendor variability of left ventricular deformation measurements by three-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr. 2011;24(8):878-85.
3. Yuda S, Sato Y, Abe K, Kawamukai M, Kouzu H, Muranaka A, et al. Inter-vendor variability of left ventricular volumes and strains determined by three-dimensional speckle tracking echocardiography. Echocardiography. 2014;31(5):597-604.
4. Park CM, March K, Williams S, Kukadia S, Ghosh AK, Jones S, et al. Feasibility and reproducibility of left ventricular rotation by speckle tracking echocardiography in elderly individuals and the impact of different software. PLoS One. 2013;8(9):e75098.
5. Opdahl A, Helle-Valle T, Skulstad H, Smiseth OA. Strain, strain rate, torsion, and twist: echocardiographic evaluation. Curr Cardiol Rep. 2015;17(3):568.
6. Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. J Am Coll Cardiol. 2017;69(8):1043-56.