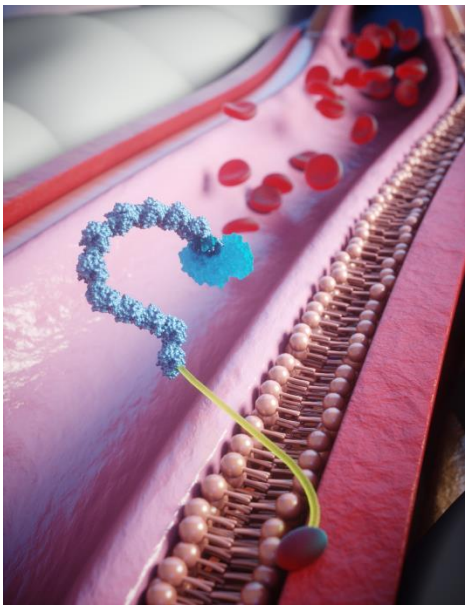
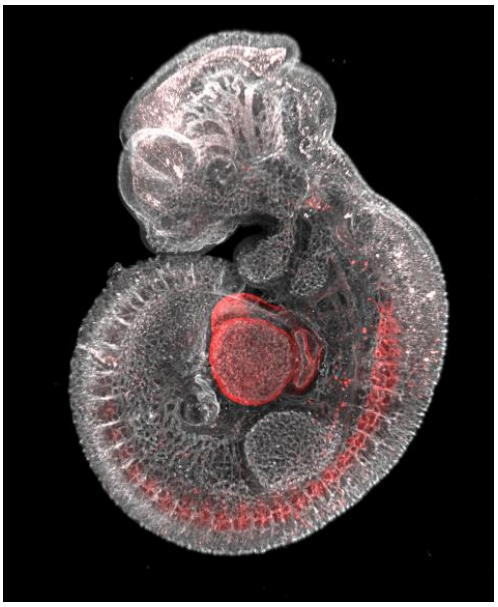
Oxford BHF Centre of Research Excellence

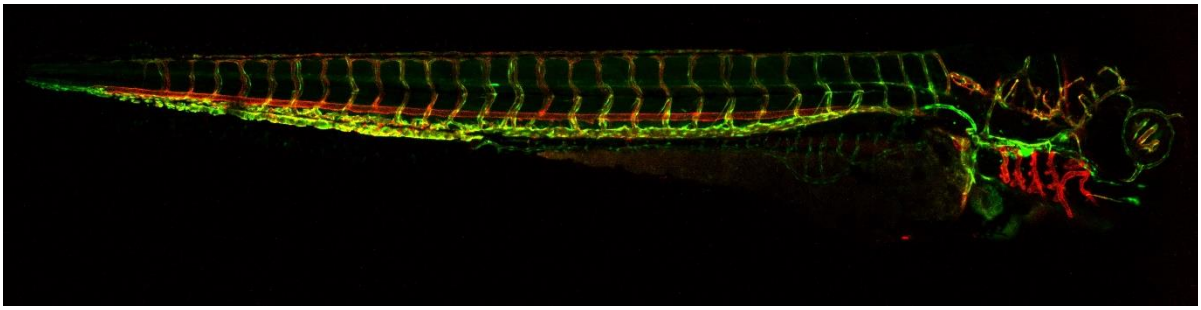
Annual Symposium

Wednesday 10th November 2021

Online via Zoom







Cover images contributed by (left to right and top to bottom):

1. Prof Ellie Tzima
2. Dr Richard Tyser
3. Dr Alice Neal

Speaker session 1 - 10:10 – 11:10

Oxford BHF CRE Transition Research Fellows

Chair: Professor Sir Rory Collins

Four of the current BHF CRE Transition Research Fellows give an overview of their research.

10:10 - 10:25

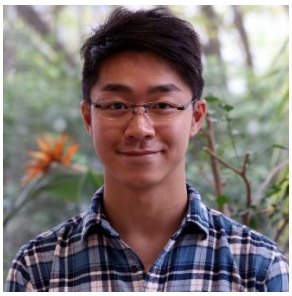
The crucial role of metabolism in cardio-oncology

Dr Kerstin Timm
Department of Pharmacology

Several chemotherapeutic agents, such as the anthracycline doxorubicin, have severe cardiotoxic side effects, which can lead to congestive heart failure in 5-10% of patients. There are currently no imaging techniques available to detect patients at risk of developing cardiotoxicity before the onset of functional decline and there are no specific cardio-protective drugs. My research focuses on both the early detection of cardiotoxicity using the clinically-translatable metabolic imaging technique, hyperpolarized magnetic resonance imaging (MRI), and the repurposing of existing drugs that target cardiac metabolism as potential cardio-protective therapy. I recently procured a high resolution respirometer, the Oroboros O2k oxygraphy to underpin metabolic imaging data with *ex vivo* mitochondrial function analysis. I am currently also establishing rodent models of cancer in which to assess new cancer therapies, the mitocans. These mitocans are based on inhibition of mitochondrial electron transport chain proteins, and I will test them for efficacy and cardiac safety using in *vivo* metabolic imaging of the heart and cancer and *ex vivo* respirometry of both tissues. These cancer models will furthermore allow me to test cardioprotective drugs in light of their potential benefit on the heart as well as additive or detrimental effects on tumour-treatment response.

10:25 - 10:40

Air pollution and cardiovascular health: what's more to know?



Dr Peter Ka Hung Chan
Nuffield Department of Population Health

Air pollution is widely considered as a leading risk factor of disease burden worldwide. The latest estimates from the Global Burden of Disease Study suggest that household air pollution from domestic use of solid fuels and ambient air pollution together contributed to over 7 million premature deaths in 2019, with cardiovascular disease being the predominant cause. Such estimates, however, have been based on epidemiological studies with longstanding limitations from the crude exposure assessment methods used and the lack of validation from actual personal exposure measurements, especially in low- and middle-income countries where most of the related disease burden lies. There is also inadequate evidence on the biological mechanisms underlying the cardiovascular effects of air pollution. In this talk, I shall explain the persistent knowledge gaps in this field, highlight the practical challenges in obtaining the necessary data, and present some preliminary findings from my current fellowship designed to address some of the limitations and advocate for better research in this field.

10:40 - 10:55

Cardiovascular outcomes in clinical trials: definitions of truth

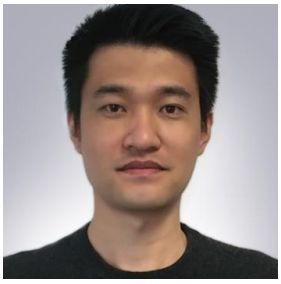
Professor Marion Mafham
Nuffield Department of Population Health

Large clinical trials are essential to reliably assess the effects of cardiovascular interventions on important outcomes. Currently, clinical trials collect outcome data in a labour intensive way: Data collected from participant reports or extracted from the medical records is manually recorded by trained research staff, then checked by study monitors against the original source, and then copies of the original medical records are reviewed by a committee of experts aiming to establish a 'ground truth'. This process of ensuring an accurate chain of custody from one perfect source of truth, has produced reliable results but is prohibitively expensive, meaning that people turn to non-randomised 'real world' studies which can be biased and misleading. An alternative approach is to use a range of data sources in clinical trials, including routinely collected healthcare data, which can be integrated to produce a 'best estimate' of the truth that is sufficiently accurate to produce reliable trial results. This approach has been used to produce rapid, reliable results among patients admitted to hospital with COVID-19 in the 44,000 participant RECOVERY trial and data from existing 'gold-standard' clinical trials will be used to assess the utility of such methods in long-term cardiovascular disease trials.

10:55 - 11:10

Virtual contrast dye' to replace gadolinium and needles:
How AI is advancing cardiac MRI

Dr Qiang Zhang
Department of Cardiovascular Medicine



The current gold-standard for imaging heart muscle disease is CMR, using late gadolinium enhancement (LGE). However, this requires injection of a contrast agent into the patient, which prolongs the scan, increases the cost, and is cautioned in some patients. Clearly, having a faster scan that provides the same information, but without the need for needles and contrast agents, would be very attractive to patients and doctors who need these scans.

We have developed an AI solution called 'virtual native enhancement' (VNE). This combines MR images that do not normally need contrast injections, and uses AI to train machines to predict what a contrast-enhanced image would look like. This approach can produce images that are similar to traditional contrast-enhanced images, but without the need to inject the contrast agent.

Tested first on hypertrophic cardiomyopathy, it was shown that these AI-enhanced images can produce as clear or better quality images than the traditional LGE, providing doctors with the same information. VNE is much faster and significantly cheaper than the conventional scans. With further development on more heart conditions, it could lead to a next generation of CMR scans that are cheaper, safer, needle-free and more patient-friendly.

Speaker session 2 - 11:30 – 12:15

Chair: Professor Sarah De Val

A short-list of eight of the poster competition entrants present their posters.

Speaker session 3 – 13:45 – 14:30

Chair: Professor Manuela Zaccolo

13:45 – 14:00

Human stem cell models for defining cellular pathomechanisms in inherited cardiomyopathies

Dr Chris Toepfer
Sir Henry Dale Fellow, BHF CRE Intermediate Transition Fellow
Department of Cardiovascular Medicine

Human induced pluripotent stem cells (iPSCs) provide the opportunity to study human inherited cardiovascular diseases in a human model in the dish. Twinned with advances in CRISPR/Cas-9 and differentiation of iPSCs to cardiomyocytes we can begin to delve into mechanisms that define disease in patients that harbour hypertrophic (HCM) and dilated cardiomyopathy (DCM) variants. We use these cellular systems to phenotype variants and perform initial screens of potential therapies. In this session we describe the open access tools we have developed to move from genotype to phenotype and uncover fundamental disease mechanisms in HCM. Using this information we can begin to uncover therapeutic strategies by identifying potential druggable mechanisms of disease.

14:00 – 14:15

Human-based Computational Investigations into Cardiac Electromechanical Alterations Caused by Drugs and Hypertrophic Cardiomyopathy

Dr Francesca Margara
Research Associate
Department of Cardiovascular Medicine

The assessment of the cardiac safety and efficacy of therapeutic interventions remains a major challenge. Defining key disease- and patient-specific mechanisms is an important need for the development of pharmacological interventions that are safe and effective in the individual subject.

This work investigated the mechanisms explaining the cardiac safety and efficacy of pharmacological therapies in health and the genetic heart disease hypertrophic cardiomyopathy (HCM) through modelling and simulation of the human ventricular electromechanical function.

We constructed and evaluated a novel computational modelling and simulation framework of the human cardiomyocyte electromechanical function that enabled the simultaneous assessment and explanation of drug-induced effects on electrophysiology and contractility through mechanistic simulations informed by experimental data. Next, we developed a novel software tool for the automated analysis of calcium transients in cardiomyocytes enabling the phenotyping of primary and human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). We used this to analyse hiPSC-CM data under three mutations that are known to cause HCM in patients and pharmacological action. Finally, we integrated these experimental findings with mechanistic modelling and simulation and defined computationally the key pathomechanisms of each HCM mutation that determine drug efficacy.

This work demonstrates the use of experimentally-informed human-based computational methodologies for precision cardiology, by identifying key mechanisms that determine the cardiac safety and efficacy of pharmacological therapies in health and HCM.

14:15 – 14:30

Mechano-pulling the strings on atherosclerosis

Professor Ellie Tzima
Wellcome Trust Senior Fellow, Professor of Cardiovascular Biology
Department of Cardiovascular Medicine

The Tzima lab investigates the role of mechanotransduction in regulating cardiovascular function in health and disease. Our group has made significant conceptual advances in our understanding of flow sensing and systematically characterised one of the most comprehensive models of endothelial mechanotransduction available to date. This talk will focus on the recent discovery of a new class of mechanosensors which determine the site-specific distribution of atherosclerosis. I will discuss our current understanding of the molecular mechanisms by which vascular endothelial cells sense fluid shear stress to ultimately promote inflammation and atherogenesis.

Speaker session 4 - 14:45 – 15:30

Chair: Professor Cornelia van Duijn

14:45 – 15:00

Genetic insights from the Mexico City Prospective Study

Dr Jason Torres
Senior Genetic Epidemiologist
Clinical Trial Service Unit and Epidemiological Studies Unit,
Nuffield Department of Population Health

As the largest blood-based prospective study in Latin America, the Mexico City Prospective Study (MCPS) presents unprecedented opportunities to discover and resolve risk factors for disease and premature death in a non-European, middle-income country. Between 1998 and 2004, 150K adults were recruited from two districts in Mexico City and questionnaire data, physical measurements and a blood sample were taken. Through a recent partnership with the Regeneron Genetics Center, genome-wide array and whole exome sequencing (WES) data has been obtained for the full cohort, and whole genome sequencing (WGS) has been completed on a subset of 10K participants. Genetic analysis has revealed complex patterns of relatedness, population structure, and Mesoamerican admixture in the cohort. The incorporation of MCPS into a transethnic exome-wide association study of BMI has uncovered novel rare variant associations, including protein-truncating variants in *GPR75* that correspond to 54% lower odds of obesity. Genome-wide association analysis of type 2 diabetes has corroborated associations at the *SLC16A11* locus involving variants common in Mexico but less frequent in Europe. The availability of NMR-based metabolomic assays in combination with genetic data offer additional opportunities to resolve risk factors for non-communicable disease.

15:00 – 13:15

Transcriptional regulation of arterial-venous patterning

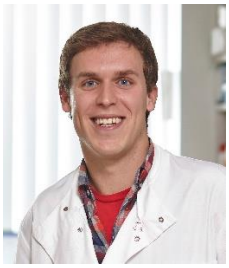
Dr Alice Neal
BHF Senior Fellow
Department of Physiology, Anatomy & Genetics

Venous and arterial endothelial cells are molecularly and functionally distinct and the correct patterning of arterial-venous gene expression is essential for vascular development. We have discovered DNA enhancer elements that drive gene expression exclusively in endothelial cells of embryonic veins. Analysis of these enhancer elements has shown that venous endotheli cell specific gene expression requires the combination of ETS and SMAD1/5 transcription factor binding downstream of VEGF and BMP signalling. Using a combination of mouse and zebrafish transgenic

models we have recently uncovered additional transcription factors that are essential for venous gene expression. We are currently working towards an integrated model of how combinations of transcription factors can achieve specific patterns of gene expression in endothelial cell subtypes to drive venous endothelial cell fate acquisition. We are using these animal models to investigate the mechanisms that drive development of the coronary vasculature and it's regeneration after injury.

15:15 – 15:30

Defining Cardiac Progenitors During Early Human Heart Development
Dr Richard Tyser
BHF Immediate Research Fellow
Department of Physiology, Anatomy & Genetics



On average our hearts beat around 3.5 billion times during our lifetime, but how does it form during human development? The human heart starts to form at around 20 days post fertilisation with the largest morphological changes occurring by 7 weeks, coinciding with the period in which the heart is most vulnerable to congenital defects. Congenital heart defects are the most common type of birth defect, being diagnosed in at least 1 in 150 births: equating to around 13 babies each day in the United Kingdom. It is therefore important to understand the cellular composition of the heart and the transcriptional programs that regulate early human cardiac development. We have begun to characterise these early stages of human cardiac development, gaining a unique insight into the cell types which make up the forming heart at both an anatomical and transcriptional level. This has revealed a surprising diversity in the cardiomyocyte and endocardial cell types present within the early heart and defined the transcriptional profile of the emerging human epicardium *in vivo*. Understanding how this vital organ forms not only addresses questions of fundamental biological significance but also provides clinically relevant insight into the potential origins of congenital heart disease and reparative therapies to treat heart disease.

Speaker session 5 – 16:00 – 17:00

KEYNOTE LECTURE

Toward Genetic Therapies for Cardiovascular Disease

Professor Eric Olson
UT Midwestern Medical Center

Biography

Eric Olson is the founding Chair of the Department of Molecular Biology at UT Southwestern Medical Center. He also directs the Hamon Center for Regenerative Science and Medicine and the Wellstone Center for Muscular Dystrophy Research at UT Southwestern. He holds the Robert A. Welch Distinguished Chair, the Pogue Chair Distinguished Chair in Cardiac Birth Defects and the Annie and Willie Nelson Professorship in Stem Cell Research.

Eric Olson and his trainees discovered many of the key genes and mechanisms responsible for development and disease of the heart and other muscles. His most recent work has provided a new strategy for correction of Duchenne muscular dystrophy using CRISPR gene editing.

Dr. Olson is a member of the U.S. National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. His work has been cited over 110,000 times in the scientific literature with an h index of 190.

Eric Olson has co-founded multiple biotechnology companies to design new therapies for heart and muscle disease.

Presentation abstract

We seek to delineate the mechanisms that govern development, disease and regeneration of the heart and other muscles and to build upon this knowledge to restore muscle function during disease and aging. In one approach, we are optimizing strategies for CRISPR-mediated gene editing to eliminate disease-causing mutations responsible for Duchenne muscular dystrophy (DMD) and various genetic cardiomyopathies. We refer to this approach as myoediting. We have optimized myoediting for DMD and cardiomyopathies in human cardiomyocytes derived from iPS cells generated from blood samples of affected patients and in animal models of these disorders. In another approach, we have discovered a collection of previously unrecognized micropeptides with key roles in many aspects of muscle and cardiac development, disease, and physiology. Among these is the cardiac-specific transmembrane peptide DWORF, which stimulates calcium cycling in cardiomyocytes by activating the SERCA pump. DWORF expression is downregulated in heart failure and viral delivery of DWORF in mice with heart failure is sufficient to enhance cardiac contractility. Opportunities and challenges in the path toward correction of genetic forms of heart disease through gene therapy will be discussed.

POSTER INDEX

Poster No.	Presenting Author	Poster Title
1	**Zeki Ilkan**	TMEM16A Channel is a Key Regulator of Cerebral Blood Flow at the Capillary Level
2	**Kyung Chan Park**	Using a mouse model of an inborn error of metabolism to identify novel epigenetic responses in the heart caused by elevated propionyl-CoA, a ubiquitous metabolic intermediate
3	**Rebecca Capel**	Acidic calcium stores in the cardiac atria: Insights from health and disease
4	**James Bae**	Development of Small Molecule PAK1 Activators for the Treatment of Heart Failure
5	**Kathryn Aguilar-Agon**	The role of microRNA-31 in cardiac fibrosis associated with atrial fibrillation
6	**Sevasti Zervou**	Mechanisms of homoarginine supplementation in the heart: β1 adrenergic receptor signalling and other targets.
7	**Kirsten Lee**	C16:0-ceramide as a potential modulator of redox signalling in human aortic endothelial cells
8	**C. Fielder Camm**	Independent effects of adiposity measures on risk of atrial fibrillation in men and women: A study of 0.5M individuals
9	**Parag Gajendragadkar**	Myocardial *NOS1AP* overexpression increases arrhythmia inducibility and slows conduction velocity whilst shortening QT duration in mice
10	**Henry West**	Epicardial adipose tissue volume measured by an automated computed tomography deep learning network predicts mortality and cardiovascular events
11	**Zakariye Ashkar**	Novel insights into abnormal haemodynamics in hypertrophic cardiomyopathy from 4D flow cardiac magnetic resonance
12	**Mark Cassar**	Longitudinal assessment of cardiopulmonary health and symptoms in moderate to severe COVID-19

13	**Rosemary Walmsley**	Allocation of time between machine-learned movement behaviours and risk of incident cardiovascular disease
14	**Marco Spartera**	Pro-thrombotic Left Atrial Flow characteristics are found in patients with stroke risk factors regardless of Atrial Fibrillation
15	**Ying-Chi Chao**	Selective regulation of cardiac Troponin I by PDE4D9
16	**Gunasekaran Subramaniam**	Nuclear PDE3A inhibits PKA phosphorylation of HDAC1 and decreases expression of the hypertrophic regulator GATA4
17	**Andia Redpath**	Transcription factor WT1 mediates HSPG-dependent signalling by directly regulating endosulfatase expression in the embryonic epicardium
18	**Sam Bose**	IP_3-mediated Ca^{2+} release regulates atrial Ca^{2+} transients through stimulation of adenylyl cyclase 1 and cAMP
19	**Adam von Ende**	Smoking and COVID-19 outcomes: a Mendelian randomisation study using UK Biobank
20	**Milda Folkmanaite**	*In Silico* Human Induced Pluripotent Stem Cell Derived Cardiomyocyte Electro-Mechanical Modelling and Simulation
21	**Konstantinos Lekkos**	Comparison of the regenerative capacity of six wild-type zebrafish strains reveals inter-strain variations in the wound healing process, cardiomyocyte proliferation and apoptosis levels following ventricular cryoinjury.
22	**Lara Scofano**	Effect of altered lipid trafficking on the modulation of vascular tone by the TMEM16A chloride channel
23	**Lucia Moreira**	Calcitonin signalling system regulates function and arhythmogenicity of atrial cardiomyocytes
24	**Mi Jun Keng**	Simulation model for lifetime prediction of complications in people with diabetes without previous cardiovascular disease using ASCEND risk equations
25	**Helen Potts**	Characterising differences between the regenerative and non-regenerative immune response in *Astyanax mexicanus*
26	**Anan Huang**	Investigation of the Possible Roles of Cardiomyocyte derived Extracellular Vesicles in Hypertrophic Cardiomyopathy