

## **Bristol Heart Institute – A Specialist Research Institute**

### **Strategic plan 2020-2025**

#### **Mission**

Continue to stand out as one of the leading academic cardiovascular centres in the UK and internationally.

To understand fundamental mechanisms of cardiovascular health and disease, translating insights into benefit for patients, the health care system and the wider population.

To provide the best environment where clinicians, basic scientists and clinical research methodologists can thrive, attract the most talented individuals and deliver world-class research.

Facilitate a smooth and timely transition to the next generation of cardiovascular clinicians/researchers, to build on our existing strengths.

Increase our network of interdisciplinary collaborations nationally and internationally to tackle ever more complex multi-morbidities.

#### **Background**

Specialist Research Institutes at the University of Bristol reflect strength and depth in key specialisms. The main strength of the BHI is its ability to translate fundamental laboratory discoveries and epidemiological identification of disease risk factors into clinical and patient benefit. Our expertise includes world-class adult and congenital cardiac surgery, the ability to assess diagnostic and therapeutic interventions in large animal models, cutting edge expertise in analysis of longitudinal populational data (e.g. ALSPAC, OMACS) and a broad range of fundamental discovery science that aims to understand the basis of cardiovascular health and disease.

The integration of clinical, translational and basic cardiovascular science with population health science is a major thrust of the current BHI strategy. This combination represented a key component in our highly successful £21m NIHR BRC award, underpinned our successful approach to the BHF 4-year PhD training programme and formed a core component of our successful BHF Accelerator award. We aim to enhance these large-scale awards and successfully obtain further substantial research funds, building capacity through training and supporting the next generation of world-leading scientists equipped to deploy data and population health science approaches to address cardiovascular challenges and to speed the translation of this research for the benefit of patients and the wider population.

#### **General ambition**

Translate our discoveries into improved patient care and public health interventions by:

- Understanding the genetic, molecular, cellular and integrative basis of the cardiovascular system, and the causes of cardiovascular wellness and disease.
- Identifying new diagnostic and therapeutic strategies.
- Developing personalized approaches to prevent, diagnose and treat cardiovascular disease.
- Improving the patients' potential to recover from cardiovascular events through novel regenerative therapies, including cell therapy, tissue engineering, and transfer of health-promoting genes.
- Performing first-in-human clinical trials which will lead to transformative change in clinical practice.
- Using mixed methods to identify, understand and address health inequalities in cardiovascular disease, access to treatment and outcomes.

## Specific objectives

The new BHI cardiovascular research purpose-built facility within the university/NHS trust precinct will for the first time concentrate a significant part of the cardiovascular expertise in one location. Given the strong translational nature of cardiovascular research activity, this building will provide easy access to the NHS clinical facilities (i.e. Bristol Heart Institute, Children's Hospital, CRIC, etc.), as well as direct access to the various world-class discovery science facilities such as the Wolfson Bio-Imaging Facility. Close alignment with cardiovascular population health investigators will also be critical and the recent BHF Acceleration Award will facilitate closer collaboration in this area.

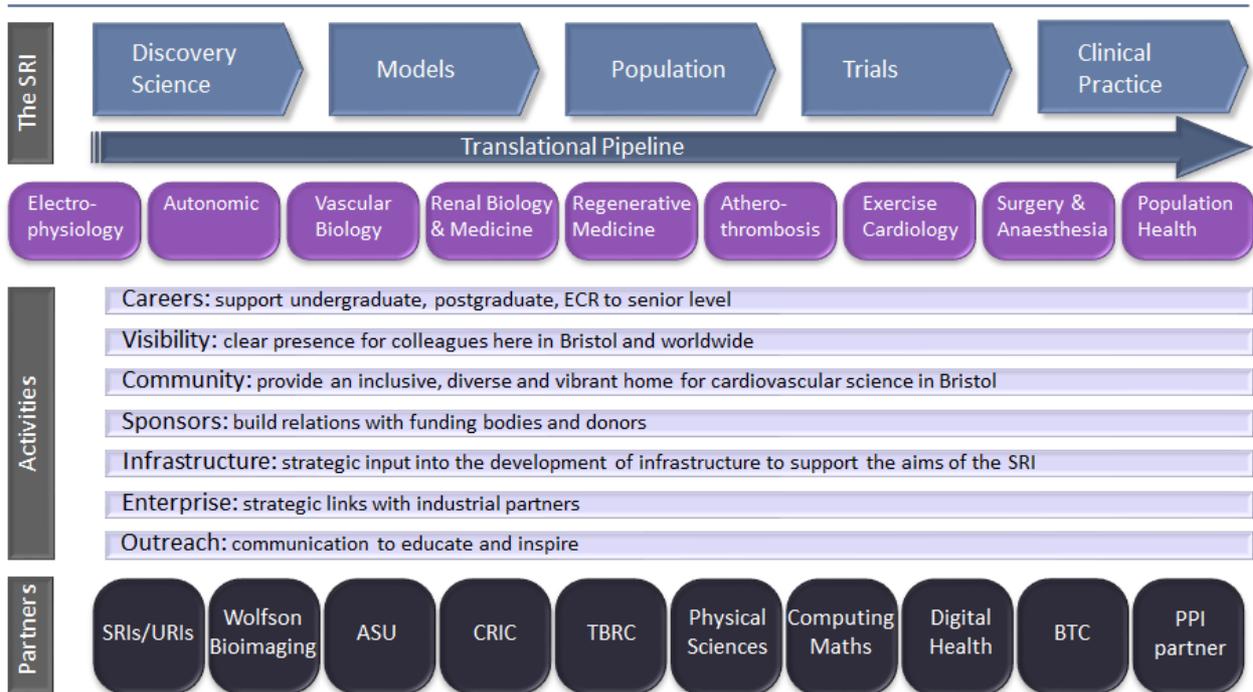
Detailed objectives:

- Renew the BHF Centre in Regenerative Medicine jointly with Edinburgh and Imperial College London (2021).
- Renew the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) with a strong and expanded cardiovascular component.
- Renew the BHF 4-year PhD Programme (2021).
- Increase integration and collaboration with other SRI's and research areas, particularly Population Health, Neuroscience and Regenerative Medicine.
- Appoint a Chair in Cardiology and development of joint NHS/university positions, to enable us to expand our translational strength and build on the research activity currently delivered by NHS cardiologists. It is our aspiration to develop a dedicated academic cardiology theme, with strengthened collaboration across all themes and an active program of postgraduate research within the next 5-year strategic plan.
- Enhance linkages with Population Health (Cardiovascular Epidemiology, Prof Deborah Lawlor, BHF chair application pending).
- Consolidate the Translational Biomedical Research Centre, which provides unique facilities for pre-clinical imaging and intervention studies in large animal models, as a facility of national relevance and excellence, fostering cross-fertilisation with other universities, and the Biomedical Industry.
- Establish a Sport Medicine Unit (in collaboration with Canon and Manchester United FC).
- Collaborate with the Bristol Trial Centre and the cross-cutting Translational Population Science (TPS) theme of the BRC. This will attract funding for clinical and basic science research (especially clinical research fellows) through fellowships and other program grants (NIHR, BHF, Medical and Engineering Research Councils and Wellcome Trust Investigator awards).
- Expand the successful Masters courses in Cardiovascular Translation and Perfusion Sciences (led by Prof S George) to increase the recruitment of national and international students.
- Exploit opportunities in robotics, in collaboration with the University of the West of England (UWE), and those provided by the SPHERE project led by Mechanical Engineering, which will develop and validate new home environmental monitoring bio-devices in high-risk patients including cardiovascular patients.
- Train the next generation of world-class cardiovascular scientists and clinical academics. We will continue to develop translational academic fellowship and PhD studentship programs in cardiovascular research that have international appeal and can attract the highest calibre undergraduate and postgraduate students and professionals. Aspire to further BHF chairs, Justified and defined by areas of excellence.

## Implementation strategy

Integrating discovery science, clinical science and population approaches will be achieved through the following activities:

### Bristol Heart Institute – Graphical Strategy



*'Nurture talent, support excellence, provide a home for cardiovascular scientists, ensure that our discoveries and progress are clearly visible and accessible, support infrastructure development to enable world class research and work with partners to ensure translational delivery of first-class science'*

#### Training and Careers

We will:

- Provide appropriate mentoring to support individuals at all career stages. We will mentor early career researcher, to enable progression to senior leaders.
- Provide tailored careers support through close collaboration with our partners in the University and beyond.
- Increase the number of externally funded fellows within the SRI.
- Maintain and enhance our postgraduate research training programmes.

In the short term we will:

- Appoint a Fellowship "early career champion" to identify support needs.
- Identify suitable candidates for fellowship schemes e.g. VC Fellowships and UKRI Future Leaders, liaise with School and Faculty Heads and RED to nominate and support applications.
- Identify emerging training needs to include in the evolving postgraduate research training program and renewals.
- Identify and maximise project supervision opportunities across University programs.

#### Visibility

We will:

- Work with our communication partners to ensure an up-to-date web presence and visibility across social media platforms to promote the work of the BHI within the university, nationally and internationally.
- Hold an annual BHI meeting reaching beyond Bristol in term of attendance.
- Continue to support subspecialty meetings.

In the short term we will:

- Maintain the webpages to reflect areas of research focus.
- Identify and appoint a social media and communication lead.
- Involve patients' representative groups at different stages of research development from preparation of grant proposals to communication of research results (see PPI below).

### *Community*

We will:

- Foster interdisciplinarity, bringing together novel groupings of scientists from different disciplines to drive scientific discovery within and outside Bristol.
- Ensure a connectivity across our community through away days, seminar programs and cross-bridging studentship programs.
- Establish an inventory of available infrastructure resources and expertise and a task force to identify new technologies necessary for accelerating the translational process.

### *Funders*

We will:

- Promote interactions with a range of funders.
- Develop relationships with donors to support our research activities.

In the short term we will:

- Identify funding opportunities and provide tailored support for Fellowship and grant applications offered by a variety of funders.
- Work with DARO to develop relationships with new Donors.

### *Infrastructure*

We will:

- Build a new Bristol Heart Institute cardiovascular research facility on the hospital campus to be completed in the summer of 2021.
- Develop a long-term vision for the new cardiovascular clinical laboratory hub and for the development of a new data science hub for populational cardiovascular approaches.
- Strive to equip our researchers with the latest infrastructures needed for world leading research.
- Ensure we are ready to respond to infrastructure opportunities.

In the short term we will:

- Identify infrastructure needs in emerging areas.
- Identify requirements for new and replacement small to medium sized (shared) equipment.

### *Enterprise*

We will:

- Play to our unique positioning in Bristol with strengths such as the TBRC and novel genetic approaches such as MR and polygenic risk scoring.
- Investigate new ways of establishing partnerships with industry and other centres of excellence.

In the short term we will:

- Map existing industrial partnerships.

### *Outreach*

It is vital that we continue to reach out to the general public, explaining our science. This fulfils educational needs for interested parties including school children and is a critical activity to promote support for and from our funders, particularly our largest funders the BHF and NIHR. Most importantly, however, it provides the opportunity for a two-way conversation that helps inform and enhance our science.

We will:

- Establish regular outreach events to showcase the breadth of our research.

In the short term we will:

- Establish a regular 'Bristol Festival of the Heart' as a nucleus for our outreach activity.

Implementation will be coordinated through the BHI Steering Committee, whose members will be responsible for the areas of activity outlined above.

## Strategic priorities

### *Cardiac Surgery and Anaesthesia*

#### Major achievements:

We continue to stand out as the leading adult and paediatric academic cardiac surgery centre in the UK and amongst the foremost worldwide.

Massimo Caputo BHF Chair in Paediatric Heart Surgery.

Ben Gibbison Senior Lecturer in Cardiac Anaesthesia.

Umberto Benedetto Associate Professor in Cardiac Surgery.

BHF Accelerator Awards.

Cardiovascular Theme NIHR-BRC.

The 50th anniversary (2015) Jules Thorn programme grant awarded to M Caputo along with other project grants generating a total income of over £6M. These include several MRC and BHF grants awarded to Profs Madeddu, Caputo, Angelini, Ascione and the association of the BHI in the BHF network of cardiovascular regenerative medicine, to manufacture new tissue engineering products for the cure of neonatal and adult cardiac defects. This work figures strongly in the NIHR BRC and BHF Accelerator Award and has helped to establish Bristol as the central hub in the UK for research in congenital heart surgery.

#### Aims for the next 5 years:

- Facilitate a smooth and timely transition to the next generation of cardiovascular clinicians/researchers.
- Apply for a BHF Senior Fellowship in Cardiac Surgery, Umberto Benedetto.
- Reduce complications and increase the chance of survival for patients undergoing adult and paediatric cardiac surgery.
- Successfully conduct the OMACS and OMACp studies: Outcome monitoring after adult and paediatric cardiac surgery to improve the prediction of which patients will experience a serious acute event (SAE, including, blood loss, acute kidney injury, lung dysfunction, neurological complication, infection). Novel computer science and machine learning approaches will be applied to multiple- 'omics and clinical data collected pre-operatively. The aim is to accurately stratify surgical patients into different levels of risk of developing different types of SAEs and hence prepare for these peri-operatively.
- Conduct Mendelian randomization studies to identify metabolites and DNA methylation sites with causal effects on complications of cardiac surgery.
- Conduct machine-learning to predict operative risk in cardiac surgery: to develop and validate machine learning algorithm using the national adult cardiac surgery audit (NACSA) and the NIHR Health Informatics Collaborative (HIC).
- Deliver on the BBSRC funded grant: Development and integration of a **cortisol sensor** with real-time read-out to an ambulatory microdialysis sampling system (£633, 232).
- Deliver the **PEACOCK** Study: to characterise in a detailed and dynamic manner the hypothalamic pituitary adrenal axis physiology in children undergoing heart surgery and catheter procedures. This will allow us to understand who is deficient in cortisol and therefore, who may or may not benefit from steroid type drugs.
- Deliver **COMICS** study Conventional vs. Minimally Invasive Extracorporeal Circulation in Patients undergoing cardiac surgery, RCT (see below).
- Deliver **CO-2** study: Carbon dioxide insufflation in brain protection during open heart surgery. A multi-centre RCT, (EME-NIHR £1,256,395.66) on the use of CO<sub>2</sub> versus placebo (medical air) to investigate the mechanistic relationship between cerebral air embolus load and perioperative brain injury detected by MRI.

- Deliver **Prompt2** trial (NIHR EME) investigating the efficacy of propofol-supplemented cardioplegia on biomarkers of organ injury in patients having cardiac surgery using cardiopulmonary bypass.
- Create of a UK research network for congenital heart surgery for conducting large observational and randomised clinical studies.
- Obtain successful grant to study Delirium - Delirium affects about 50% patients on ICU and after cardiac surgery but depends on diagnostic criteria / tool used. There is currently no good way of “measuring” delirium on ICU. It is not collected by ICU National Audit (ICNARC). We will develop and test measurement “ruler” of ICU Delirium using psychometrics. Collaboration between BRC/ ICNARCLSHTM.
- Assess adrenal function after out-of-hospital cardiac arrest.
- Study stress, sleep and metabolism in ICU. Admission to hospital for major surgery such as heart surgery represents a major stressor, most obviously the normal rhythms of sleep and feeding. We plan to: (i) Identify dynamic biomarkers that could be markers of post-operative complications (e.g. delirium). (ii) Understand the acute effects of surgery on diurnal, circadian and ultradian physiological rhythms. (iii) Use the information to inform a more personalised approach to post-operative care.
- Enhance longevity of heart valves and vascular conduits. Bioengineer novel vascular prostheses (using cells from umbilical cord and placenta) that grow with the child, to repair congenital cardiac defects avoiding further operations. Develop heart valve bio-prostheses seeded with adventitial pericytes from patients’ saphenous vein to increase their longevity.
- Start our “first in man” studies on the tissue engineering products we are developing in Bristol.
- Understand the molecular basis of heart failure in congenital heart disease patients, with focus on accelerated senescence – develop new therapies targeting anti-aging mechanisms. Model specific congenital heart diseases in vitro using gene perturbations in stem cells to identify the earliest cellular and developmental consequences of disease
- Establish new collaborations with academic (renewal of the BHF regenerative medicine network) and industrial partners to combine our translational and clinical expertise with new discovery from material sciences.
- Generate a clear translational pipeline and strategic alignment between basic and clinical science including population health. Build on the established strong and successful collaboration between clinical science and several basic science groups, from regenerative medicine to engineering and imaging science. Enhance the links with population science ranging from PhD student supervision to collaboration in large epidemiological studies linking “omics” expression with deep imaging and clinical database phenotype in congenital heart disease.
- Develop exercise programs for cardiovascular rehabilitation in adult and congenital heart disease patients

## *Population Health*

### Major achievements:

In the last 5 years we have achieved, the renewal of core funding for the Avon Longitudinal Study of Parents and Children (ALSPAC; £8 million, Wellcome/MRC) and Born in Bradford (BiB; £3 million, MRC/ESRC) together with £1million from the BHF to foster more detailed assessments in the BiB children. In addition we obtained the Horizon2020 LifeCycle award (Euros 10 million, Euros 1 million to Bristol) which will generate, from existing birth cohorts, a pan-European cohort of ~300,000 participants with environmental, social, clinical and multi 'omics data collected from pre-conception to mid-adulthood and across generations. These awards together with substantial awards from the European Research Council, US NIH, the Bristol BHF Accelerator Award as well as the NIHR BRC are providing unprecedented opportunities for identifying modifiable risk factors in the development of adverse cardio-metabolic/-vascular outcomes (including congenital heart diseases), the occurrence of these diseases and their rapid adverse progression.

### Aims for the next 5 years:

- Bid successfully for a British Heart Foundation Chair Deborah Lawlor.
- Make the most efficient use of substantial amounts of data, including appropriate triangulation of evidence from different causal analyses and data sources
- Extend our 'omics research to a wider range of biofluids and tissues, including urine, placenta and waste tissue collection (OMACS-OMACp)
- Improve the translational pipeline between underpinning population science and clinical and public health practice  
Engage with disciplines who are and/or can make major contributions to cardiovascular science but who are not traditionally recognised as working in this area, including with obstetricians, perinatal health, renal health and endocrinology clinical and research professionals, as well as data scientists, mathematicians, informaticians The Cabot Institute for the Environment.

## *Exercise and Sports Cardiology and Inherited Cardiac Conditions*

### Major achievements:

Work over the last years led by G Pieles and G Stuart led to the establishment of a now internationally recognized research group in paediatric and adult sports/ exercise cardiology for patients with CHD and inherited cardiomyopathies. Expertise and international core collaborations lie in the following areas: exercise physiology (University of Exeter and Munich), CMR and cardiac MR spectroscopy (Oxford University), Cardiomyopathies and functional Echo Imaging (University of Toronto), Image processing and AI (University of Edinburgh), and Sports cardiology (UCL, University of Barcelona, Technical University Munich).

Overall, the core group work has attracted project as well as PhD studentship grants from NIHR EME, MRC, HR UK, Children with Cancer UK, the Canon Foundation of > £ 1 million. The work has established large scale long term non-educational sector partnerships with Canon Medical Systems UK, EU and Japan (AI, echo and MRI R&D, image processing development), and Manchester United FC (sports cardiology). Dr. Pieles is leading the to date largest paediatric sports cardiology research program in collaboration with Manchester United FC, FC Barcelona, Aspire Academy Qatar and the German Olympic Development Centre and the English FA and the German DFB. The group has published in journals such as NEJM, Lancet, Br. J. of Sports Med. and Nat. The research program links in closely with other research groups (Surgery in CHD, CRIC, genetics, electrophysiology) and the innovative imaging methods (exercise imaging, MR spectroscopy) constitute a core imaging laboratory for the BHI.

### Aim for the next 5 years.

The objective is to further develop the exercise and sports research program in paediatric and adult CHD and cardiomyopathies to become a clinical and research referral centre for exercise cardiology:

- Generate innovative sports and exercise imaging methodology (real time exercise imaging by Echo and CMR)
- Conduct metabolic and cellular phenotyping of the athlete heart and patients with CHD (e.g. exercise and hypoxia/ senescence)
- Conduct qualitative outcome research and multi-centre RCT for exercise intervention in CHD
- Develop automatic imaging tools and machine learning (Canon)
- Establish a dedicated sports research and clinical (imaging) centre and mobile research cardiology laboratories (pilot unit to go live in 2020)
- Use exercise phenotyping as an outcome tool in other related diseases/ trials/ research projects

A key component for success in these areas lies in continuing collaborations with other groups at the BHI, University collaborators and the agreed extension of our non-educational partnerships, in particular with Canon Medical Systems, the Manchester United and Michael Carrick Foundations and the FC Barcelona Innovation Hub, thereby utilising the agreed access to the unparalleled R&D facilities and expertise in sports science of the above institutions.

### *Vascular biology*

#### Major achievements:

In the last 5 years there have been multiple major achievements, a BHF Senior Research Fellowship (J Johnson), an Innovate UK award, along with multiple national and international project grants and numerous PhD studentships including those within the 4 year BHF programme and a prestigious NC3Rs studentship for a total income of around £5M. This work has contributed to the NIHR BRC and BHF Accelerator Award.

#### Aims for the next 5 years:

- Develop and evaluate novel therapeutics and devices to improve treatment of patients with cardiovascular diseases including atherosclerosis, aneurysm, myocardial infarction, hypertension, and peripheral vascular disease. Identification of robust biomarkers to aid primary prevention and serve as endpoints for clinical trials.
- Contribute to the “first in man” studies on: gene therapy for late vein graft disease, biodegradable and drug delivery arterial stents for peripheral artery disease and aneurysms, tissue-engineered conduits for vein grafting.
- Continue the development of robust ex vivo models of select cardiovascular diseases to further reduce and potentially replace currently used animal models and enhance translational potential of novel therapeutic approaches.
- Develop stem cell models of cardiovascular tissues and diseases in vitro
- Integrate with the regenerative medicine activities (see below)

Clear translation pipeline and strategic alignment between basic and clinical science including population health:

- Build on long-standing and successful collaborations between multiple clinical science and basic science groups. Links with population health have been established through various projects, particularly via the 4-year BHF PhD programme.
- With the recent award of four Home Office Licences and the continuing progression of TBRC, we are now in a strong position to develop a unique translational pipeline to investigate underlying pathogenesis of multiple cardiovascular diseases, the development of novel therapeutics and devices, and evaluate their efficacy in human ex vivo and pre-clinical models.

## *Atherothrombosis*

### Major achievements:

Major investments included renewal (3<sup>rd</sup> renewal) for BHF Programme Grant to Poole, Madeddu & Hers, in collaboration with Riley (Oxford), to investigate how platelet secretion may regulate cardiac repair processes after ischaemic damage (>£1.5M)

NIHR i4i investment in development of novel clinical platelet analyser (>£500k)

### Aims for the next 5 years:

- Consolidate commercial partnership with major international medical devices company to develop further and commercialise the novel clinical platelet analyser.
- Bioengineer platelets outside the body, in scalable technologies, for transfusion medicine.
- Exploit the platelet secretome to engineer novel treatments to promote cardiac repair after ischaemia-reperfusion injury.
- Develop (re-purpose) and exploit novel antiprocoagulant antithrombotics for the control of thrombosis without bleeding adverse effect.
- Minimise bleeding associated with antiplatelet drugs.
- Understand how metabolic disorder leads to enhanced thrombotic risk.
- Develop novel chemistries to target thrombosis and specific vascular condition (pulmonary arterial hypertension).
- Conduct functional analysis of rare human genetic disorders to understand regulation of platelet number and function in health and cardiovascular disease in collaboration with A Mumford director of the South West Genomic Laboratory hub, with potential for extension to national prospective cohort piggybacking on National Genomics Test Directory
- Major challenges to the field: Minimising bleeding whilst maximizing antithrombosis, generating platelets outside the body in large quantities, exploiting platelet secretion for cardiac repair, Devising clinically predictive approaches to measure platelet function.

## *Regenerative medicine*

### Major achievements

BHF network of cardiovascular regenerative medicine, with two Units led by Profs Madeddu and Ascione associated to the Vascular Hub comprising Edinburgh, King's College and Imperial college. Madeddu's team has received several project and translational grants from the MRC, BHF, Heart Research UK for over £3 million to study new proangiogenic and antifibrotic treatment of myocardial and limb ischemia. Recruited VC fellow, Dr Victoria Mascetti, working in regenerative medicine.

Cell therapy and tissue engineering with human pericytes for the treatment of myocardial, limb ischemia and congenital heart disease, gene therapy with a polymorphic variant gene associated with extreme longevity, microRNA-based therapies, development of new cellular biomarkers predictive of cardiac death in ischemic patients etc.

Collaboration with National and International academic partners and industry. Collaboration with ReNeuron has fostered the first clinical trial of neuronal stem cells in the treatment of limb ischemia. Collaboration with Diamedica has led to the first trial of human kallikrein for the treatment of stroke. Prof Madeddu is Editor in Chief of Vascular Biology and member of the Regenerative Medicine committee (MRC).

### Aims for the next 5 years:

- Renew the BHF regenerative network and extension of our participation in the cardiac regenerative hub (Sian Harding lead at Imperial college): create a provisional right ventricle efflux chamber in patients with single ventricle defects.

- Interact with the vascular biology hub to study mechanisms transforming regenerative cells into dangerous cells detrimental to vascular homeostasis.
- Develop gene therapy and cellular therapy approaches further to treat myocardial ischemia and diabetic cardiomyopathy, with focus on mechanism improving health rather than combating disease.
- Use human pluripotent stem cells (hPSCs) and their differentiated cardiovascular progeny to model and repair CHDs in vitro and in utero, leading to understanding of mechanisms of diseases and establishing proof of principle for their prenatal repair.
- Introduce new models and technologies, such as generation of 3D heart on chip model for drug screening, development of liquid biopsies (cells from peripheral blood) to monitor myocardial arteriogenesis, omics to study epigenetic regulation of proteins implicated in heart repair (collaboration with Frankfurt on the cardiac sulfhydrylome).
- Understand the etiology of specific CHDs in vitro using gene perturbations in hPSCs and small animals to model the earliest molecular, cellular and developmental consequences of the disease in distinct cell types, thereby identifying its mechanistic basis.
- Introduce new models and technologies to exemplify prenatal regenerative medicine strategies for the repair of CHD defects, such as chimeric complementation in vitro, and the generation of patient stem cell-derived “living grafts”.
- Perform preclinical in utero transplants in small and large animal models to test efficacy towards repair of CHD in vivo by creating hPSC-derived ‘living prenatal grafts’ that grow and remodel, thus eliminating the need for future surgical intervention after birth and during adulthood.
- Focus on molecular mechanisms (matricellular proteins) implicated in infarct extension, assessment of circulating levels to follow-up scar remodeling in conjunction with CRMI.

### *Renal Biology and Medicine*

#### Major achievements:

Bristol Renal interests include basic laboratory research into mechanisms of renal (particularly glomerular) and vascular disease, genetics, population cohorts, clinical trials and health services research.

Renal Radar (a UK registry for rare kidney diseases which now contains >25,000 patients).

NURTuRE (National Unified Renal Translational Research nurse Enterprise) cohort of highly phenotyped (including by multi-omics platform) patients set up with 6 industry partners with funding of £4.2 million. MRC stratified medicine award £3.2 million

1/ EQUAL and European cohort of 1700 people over 65 years with advanced CKD, highly phenotyped with baseline biomaterial.

Partners in BEAt-DKD FP7 European consortium in diabetic nephropathy total funding 29 million Euro. We lead work package 3 (mechanistic insights).

Cell lines licensed to over 50% of top 20 pharma companies worldwide generating income >£1.6 million to date and will be the focus of an impact case study for the REF in UOA1.

A £1.8m NIHR HTA-funded multi-centre ‘registry trial’ comparing high-volume HDF and high-flux HD on cardiovascular- and infection-related morbidity and mortality.

Excellent training record with NIHR, MRC and Wellcome fellowships including a current MRC senior clinical fellow and Wellcome Trust career development fellow.

New Renal Gene Therapy spinout company – Term sheets secured for £45M Stage A funding.

#### Aims for the next 5 years:

- Deliver on precision medicine in nephrotic syndrome.
- A new NURTuRE cohort for stratified medicine in diabetic nephropathy.
- Use linked intensive care data from the HIC, linked to registries, to do pseudo RCTs of interventions to improve renal outcomes following admission to intensive care.

- Define mechanisms of links between renal disease (chronic kidney disease and proteinuria) and cardiovascular disease.
- Conduct clinical translational of endothelial glycocalyx restoration therapies for renal and systemic vascular protection.
- Bioengineer the kidney for disease models and regenerative medicine.
- Gene therapy for kidney disease
- Work towards MRC centre application.

Clear translation pipeline and strategic alignment between basic and clinical science including population health:

- Translational pipeline from mechanistic experimental studies include clinical science, population genetics, patient cohorts, industrial partners, development of novel treatments e.g. with MRC T funding, clinical trials and health services research.
- Current applications for MRC DPFS grants and Wellcome Innovation grants for gene therapy and small molecule projects to move towards first in man therapy.
- Strong links with population health sciences e.g. George Davey-Smith and Tom Gaunt co-applicants on MRC stratified medicine award, work closely with UK Renal Registry e.g. a current project linking renal and cardiac registries to investigate access for renal patients to coronary intervention using mixed methods, including renal and cardiac registry linkages, to investigate kidney heart health inequalities.

### *Autonomic*

#### Major achievements:

We have published numerous high impact papers in peer reviewed journals (including Nature Medicine, Circulation Research and Journal of American College of Cardiology), multiple industry funded and BHF funded investigator led clinical studies, set up a secondary care hypertension clinic, which sees 200 new cases of difficult to control hypertension every year (also essential for recruitment), and discovered new targets for treatment in hypertension which have led to phase I and phase II clinical trials.

#### Aims for the next 5 years:

- Make advancements in the understanding of the development of heart failure with preserved ejection fraction (majority of cases develop in people with hypertension and there is no current treatment to prolong lifespan) and improve exercise prescription and outcomes in heart failure. We are applying for significant funding to UKRI and NIHR, with the aim to secure project grants, a research for patient benefit grant and an experimental challenge grant from the MRC.
- Strengthen our collaborations with population health by completing several projects linked to the development of hypertension and the problem of blood pressure levels during physical activity.
- Continue our training of both clinical and basic science researchers (continuing our track record of securing clinical training and basic science fellowships), which is key to the progression of our group and the completion of experimental clinical studies.
- Our research has a clear translational pipeline, we have taken work in animal models of disease and translated it into humans and completed phase I clinical trials. Population health is important for our work as it helps us identify possible targets in humans. We plan to work with population health and understand the physiological function of some of these targets identified. Finally, a potential limiting step for our group is the continuity of CRiC, where our experimental medicine laboratory is currently situated.

## *Electrophysiology*

### Major achievements:

The work in this group has been supported by programme grants from the MRC and the BHF, together with additional research project and training fellowship funding for a total income of >£7.0M.

There has been an output of >90 research publications ranging from basic science to clinical-basic science collaborative work (European Heart Journal, Circulation Research and Proceedings of the National Academy of Science (USA)).

MRC and BHF Clinical Research Training Fellowships have facilitated training of cardiology trainees in preclinical electrophysiology.

New insights into arrhythmia mechanisms and potential therapeutic targets in congenital arrhythmia syndromes and acquired conditions (atrial fibrillation, heart failure).

Involvement in inherited Genomics England arrhythmia gene panels to be used in national clinical genetics testing.

Involvement in global pharma/regulatory agency/academic initiative to improve cardiac safety pharmacology screening paradigm world-wide for novel therapeutics.

### Aims for the next 5 years:

- Elucidate further the underlying basis of normal and aberrant cardiac muscle electrophysiology, ion handling and contraction, employing appropriate molecular, cellular and animal models.
- Validate/translate preclinical data to develop novel therapeutic approaches.
- Reconcile the wealth of genetic and genomic data from exome/genome sequencing with underlying (patho)physiological mechanisms of arrhythmias and sudden death. These range from monogenic disorders of inherited arrhythmias, such as the Long QT and Brugada Syndromes, through polygenic disorders to acquired diseases, such as heart failure and atrial fibrillation
- In 2018, North Bristol NHS Trust was awarded one of 7 UK Genomic Laboratory Hubs. Building on a close association between basic researchers and clinical cardiologists and geneticists is key to exploiting the opportunities for translation research that this brings.
- Link with population approaches, to explore ways of functionally interrogating findings on novel determinants of cardiac (electro)physiology.

## *Patient and public involvement (PPI)*

### Major achievements:

The Heart of the Matter led by Giovanni Biglino, was supported through grants awarded by the Wellcome Trust, the Arts Council England, the Blavatnik Family Foundation, Above&Beyond and private donations. The project culminated in 2018 with an exhibition that toured important venues across the country including the Royal West of England Academy (RWA) in Bristol, the Victoria & Albert Museum and the Copeland Gallery in London, the Great North Museum: Hancock in Newcastle. In 2019-20, pieces from the exhibition continue being shown nationally and internationally, including the Royal College of Physicians in London (Under the Skin exhibition) and the Villa Rot Museum in Germany. Another configuration of the work will be presented at the Elephant West art space in 2020, in collaboration with Prof Sian Harding (Imperial College London), offering more opportunities for PPIE at the Invention Rooms, as a demonstration also of collaboration across institutions.

Other achievements also include running a preliminary workshop with patients affected by Takotsubo (stress) cardiomyopathy funded through the Brigstow Institute and leading to an NIHR RfPB grant application for a national project.

Funding secured through the BHF to organize a meeting around the concept of narrative cardiology, exploring concepts of narrative medicine applied to cardiac patients, involving philosophers, narratologists, cardiologists, cardiac surgeons, patients, psychologists and artists. This was held at the Chocolate Factory in Bristol.

### Aims for the next 5 years:

- Become a leading example of a culture of true involvement of patients in research, which will involve carefully exploring aspects of training, signposting and safety, in liaison also with UHBristol (PPI Lead Tony Watkin). The possibility of more creative work could also be part of the future strategy, exploring the possibility of supporting visiting artists/researchers. The running of an annual narrative cardiology event is another opportunity to engage both colleagues, patients and members of the public in exploring the experiential dimension of heart disease.
- Promote a culture of engagement and having produced nationally and internationally recognized work to engage patient audiences and general audiences, a major theme will be to extend the actual involvement work towards engagement. Two main areas are a) conducting studies with patient co-researchers and b) including patients in teaching activities currently being piloted in collaboration with Great Ormond Street Hospital to train and involve a patient with congenital heart disease around the use of 3D printing technologies, and b) including a session on patient experience and narrative medicine in the MSc Perfusion taught in Bristol, involving a patient ambassador in preparing and delivering the lecture. Both aspects can be greatly expanded in the future.
- Promote interdisciplinary activities to facilitate PPIE, including working with visual artists and musicians, but also exploring opportunities with the University of Bristol, e.g. with the Centre for Health Humanities and Sciences.

### *Cardiovascular imaging (BHI and CRIC)*

#### Major achievements:

Bristol cardiovascular imaging has had a central role in the national delivery of important RCTs in collaboration with Leeds, Leicester, and Glasgow and internationally. This has led to REF returnable publications (CE-MARC 2 study published in JAMA 2016, and MR-INFORM study published in NEJM 2019).

Awarded 3 pilot grants (£100K) for studies on advanced imaging in cardio-oncology, valvular and congenital heart disease, and ischemic heart disease

Co-investigator on the MRC Capital Bid for TBRC (2.77M)

Secured successful training and research grants from the European Society of Cardiology and European Association of Cardiovascular Imaging for a total of £200K

Contribution and authorship in 2 major ESC clinical guidelines: 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation; and 2018 ESC/AHA/ACC/WHF Fourth Definition of Myocardial Infarction.

C Bucciarelli-Ducci has been invited as member of the research steering group, National Institute for Cardiovascular Outcome and Research (NICOR).

Established Bristol as a centre for functional and exercise cardiac imaging – G Pieles

#### Aims for the next 5 years:

- Create a programme of cardiovascular imaging in structural heart disease together (deep imaging phenotyping with 4D flow and CMR relaxometry) – C Bucciarelli-Ducci, M Caputo, G Biglino
- Explore heart and brain interaction using MRI – C Bucciarelli-Ducci
- Create a programme of 3D printing and imaging in structural heart disease – G Biglino
- Develop Bristol as a centre for conducting multicentre trials using cardiovascular imaging – C Bucciarelli-Ducci.
- Generate a clear translation pipeline and strategic alignment between basic and clinical science including population health – C Bucciarelli-Ducci, M Caputo
- Cardio-oncology presents an opportunity for basic and clinical science synergies (collaboration with professor C Emanuelli at Imperial College on mRNA) – C Bucciarelli-Ducci, G Biglino

- Both cardio-oncology, imaging phenotyping and imaging clinical trials are prone to synergies with population science and mendelian randomisation approaches which we aim to explore.

### *Translational Biomedical Research Centre*

#### Major Achievements:

TBRC opened in June 2016 as a unique national large animal facility operating at NHS-type, GLPMA and Home Office standards (<http://www.bristol.ac.uk/health-sciences/research/tbrc/>). The key objective is to bridge the translational gap between basic science and bedside. Current pipeline of ongoing research projects has a factored value of >£20M.

*Cardiovascular preclinical models in large animal available at TBRC for development/testing of new drugs, stem cells, biomedical devices:*

Closed chest balloon MI, Ischemic Heart failure.

Open vascular replacement surgery: Coronary, Carotid, Femoral, Pulmonary.

Cardiac surgery with cardiopulmonary bypass and cardioplegic arrest – adult and paediatric.

Valve replacement surgery, New congenital models.

Percutaneous coronary and vascular stenting, Acute arrhythmias.

*Major challenges to the field:*

Heart Failure, Inflammation/Fibrosis/Regeneration, Acute MI.

Advanced development/testing of platelet inhibition during MI or vascular replacement procedures

Comparative Immunology, Genome editing.

#### Aims for the next 5 years:

- Testbed small to large animal for Pharma.
- More partnerships with Biomedical Industry – drug/devices.
- On site unique colonies : inbred, mini-pig.
- Genome editing platform.
- Prenatal surgery and transplant in large animal.
- Xeno-transplantation and comparative immunology.
- On site outposts with Institutions and Industry to form a TBRC Institute of national/international relevance.

### *Bristol Trials Centre*

#### Major achievements

The Bristol Trials Centre (BTC) works with collaborators to design and deliver randomized clinical trials and observational studies. It delivered several early phase small randomized trials in cardiac surgery through our collaboration with researchers involved in the NIHR BRC, including:

- **Peacock** study (see cardiac surgery and anaesthesiology)
- **Thermic-3** trial investigating the effect of intermittent antegrade warm blood versus cold blood cardioplegia on myocardial ischaemia/reperfusion injury in children undergoing open heart surgery. Recruitment to the trial will be complete by spring 2020. Children are followed for 3 months and the trial will report late 2020/early 2021
- **Invite** trial investigating effectiveness on post-operative recovery of using 'off pump' self-expanding tissue valves (IPVR) versus 'on pump' conventional tissue valves (PVR) for pulmonary valve replacement.
- **Codec** study supported the local hospital charity, Above and Beyond, an observational pilot study investigating the neural mechanisms of cognitive decline after Cardiac surgery with resting state fMRI.

- **COMICS** pilot trial recruiting in 11 centres across 7 countries worldwide, comparing conventional versus minimally Invasive extra-corporeal circulation a composite of post-operative adverse events occurring up to 30 days in adults undergoing cardiac surgery
- Established and providing on-going support for data and sample collection in the **OMACS and OMACp** cohort of adults and paediatric patients undergoing cardiac surgery in Bristol.

The BTC has also collaborated with clinical colleagues to secure NHIR funding for several multi-centre cardiovascular trials including

- **GAP** trial evaluating the effectiveness, cost effectiveness and safety of gabapentin as an adjunct to multimodal pain regimens.
- **CO2** trial (see cardiac surgery and anaesthesiology).
- **Prompt2** trial investigating the efficacy of propofol-supplemented cardioplegia on biomarkers of organ injury in patients having cardiac surgery using cardiopulmonary bypass.
- **Inspire** trial investigating the effectiveness and cost-effectiveness of inspiratory muscle training for reducing postoperative pulmonary complications.
- **Cardioman** cross-over pilot trial of bezafibrate treatment of Barth Syndrome.

#### Aims for the next 5 years:

- Continue to collaborate with clinical colleagues to develop high-quality research funding applications addressing cardiovascular-related questions of importance to the NHS, patients and the public
- Work with colleagues to develop the next generation of Chief Investigators through fellowships and the infrastructure available through the BTC
- Develop further cross collaborations building on our network of collaborations within the cardiovascular arena and beyond, including identifying opportunities for maximizing the value of research, for example by extending the research beyond cardiovascular arena as has been done for the GAP and Inspire trials. These trials are recruiting across three surgical specialties (cardiovascular, abdominal and thoracic) and are powered to answer the research question in all three specialties, thereby maximising the value of the research investment.
- Exploit opportunities for trials across the SRI themes, not just cardiac surgery.
- Complete and report on the current portfolio of trials and studies
- Exploit opportunities to maximise the value of the investment into the OMACS study

By March 2022 OMACs will have amassed 1300+ patient samples and consent to use data for around 3700 patients. This will support work to predict outcomes in cardiac surgery patients using metabolomic, genomic and proteomic analyses, plus the development of statistical models (see cardiac surgery and anaesthesiology). Consent is in place for the collection of waste tissue and pericardial fluid which has yet to be exploited. Strengthen collaborations with other BRCs by extending the OMACS study to another cardiac surgery centre for the collection of data and samples.

Supplement the current prospective data collection with data available from routine sources. Consent is in place to for obtaining data from NHS Digital and there and there is the potential of linking with the cardiovascular HIC to obtain a wider cohort of in-hospital data.

Work with collaborators to develop proposal(s) for funding future work using the OMACs bio resource. There is on-going pilot work into the prediction and causal contributions of acute kidney injury (led by Nic Timpson). 135 pre-op urine and plasma samples sent to Warwick Dunn (Birmingham) in May 2019 for metabolomic analysis. All samples were of high quality. Candidate metabolites predictive of AKI were identified, and further funding is needed to allow the analyses of these metabolites in a much larger sample of patients to allow definitive linkage of the potential early predictors to AKI

A stage 1 grant application has been submitted to the NIHR in response to a commissioned call for research into the development of a model to predict post-operative atrial fibrillation (led by Umberto Benedetto). If funded this project will use the OMACS data set. A grant application is in preparation to study outcomes in adults with a congenital heart condition, which would draw data and samples collected in OMACS.