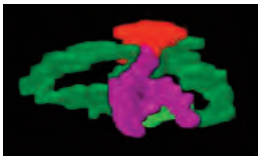
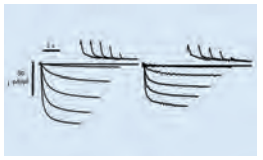
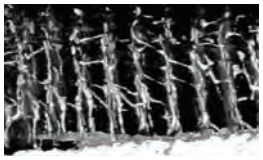
MANCHESTER 1824
The University of Manchester

Faculty of Medical and Human Sciences




Institute of Cardiovascular Sciences

2014-2015 Prospectus and Stategic Plans

Science is the torch which illuminates the world

Louis Pasteur

Contents


The Innovation
Centre
CTF & Incubator

Dean's introduction

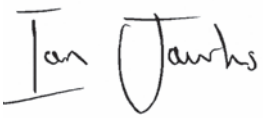
I am delighted to introduce the 2014-2015 Prospectus for the Institute of Cardiovascular Sciences, part of the Faculty of Medical and Human Sciences (FMHS) at The University of Manchester.

Our Faculty has now implemented a new strategy and structure which is intended to transform our contribution to research and education in medicine and health. We aim to build on the reputation of Manchester as a world leading centre for biomedical sciences and their clinical application.

The Faculty and the Institute of Cardiovascular Sciences are committed to achieving excellence through an ethos of collegiate and collaborative working involving all of our Faculty Schools and Institutes and the highest quality interactions with other University of Manchester Faculties, our NHS partners via Manchester Academic Health Science Centre (MAHSC) and our broader higher education and NHS partners in the new Greater Manchester Academic Health Science Network (GM-AHSN).

Importantly the Institute of Cardiovascular Sciences is part of a matrix structure (Figure 1) which is deliberately designed to break down barriers and encourage cross cutting interactions with staff in other Schools and Institutes. Staff are encouraged to affiliate to other Faculty structures and a high level of interaction is being achieved. This type of cross linking is crucial to achieving the full benefits for education and research of our unusual breadth of health disciplines.

This document provides an overview of the Institute of Cardiovascular Sciences in 2014 and is work in progress. In January 2014 the Institute hosted a visit by an international external advisory panel to help guide further developments. The Institute already has a set of truly outstanding achievements and excellent staff but we have a lot more to do to achieve our ambitious objectives. I am grateful to all of the academic and support staff in the institute for their contribution to the success to date and further plans.



Ian Jacobs
Dean, Faculty of Medical and Human Sciences
Vice President, The University of Manchester
Director of Manchester Academic Health Science Centre
Professor of Cancer and Women's Health

The University and Faculty

Our Academic and Support staff in the Faculty of Medical and Human Sciences (FMHS) number over 2,000 and work to deliver three core priorities:

- Development and delivery of the highest quality education and training for health professionals and scientists
- conducting outstanding, world-leading research in the biomedical and health sciences
- social responsibility to make a contribution to the 'greater good'.

Our University has a tradition of world-leading innovation which has led to a stepwise improvement in the health, wealth and wellbeing of populations across the world since the industrial revolution. Sitting at the heart of the City of Manchester, which is a global hub, excelling in arts, music, sport and commerce, the University is a beacon for research and education with a deep commitment to the economic transformation of Manchester and the North West of England. Tracing its origins back to John Dalton's Mechanic's Institute and John Owen's philanthropic desire to educate the local population, The University of Manchester was England's first 'civic' and now its largest campus-based university. No fewer than 25 Nobel Laureates have worked at the University and since the merger of the Victoria University of Manchester with UMIST in 2004 we have delivered in excess of 1,600 invention disclosures and formed 17 new companies attracting £117 million in third party benefit, demonstrating a formidable track record of commercialisation.

Each year we train over 400 doctors, 90 dentists, 150 pharmacists and 900 nurses, midwives and allied health professional staff. We are the largest supplier of healthcare graduates to the NHS within the North West of England but many of our graduates go on to deliver healthcare provision and scholarship in developed and developing health systems across the globe. Through the use of cutting edge technology, the highest quality workplace-learning environments and a highly trained educational faculty, we strive to deliver a personalised learning experience to each of our students so that they develop a real sense of identity and belonging to a world-class university. This in turn fully prepares them for life after graduation making the 'Manchester-made' graduate the first choice for healthcare employers. Our extensive postgraduate and continuing professional development programmes are hosted by our new Faculty Graduate School providing support and training to postgraduates undertaking a diverse range of study from short term professionally linked programmes through to research training in multidisciplinary areas. We believe that we are a complete resource for lifelong healthcare learning.

The scale, breadth and structure of our Faculty provide outstanding opportunities for basic biomedical research discoveries to be rapidly translated into effective new therapies with a strong emphasis on knowledge transfer and partnerships with industry. Our new matrix structure is designed to enhance opportunities for novel and multidisciplinary research (see figure 1). The matrix involves five schools (Medicine, Dentistry, Pharmacy, Psychological Sciences and Nursing, Midwifery & Social Work) and six research institutes (Cancer Sciences, Cardiovascular Sciences, Population Health, Brain, Behaviour & Mental Health, Human Development, Inflammation & Repair) with an emphasis on affiliation across these structures. The leadership team for each of the Institutes involves clinicians, basic scientists and healthcare researchers from both our own Faculty and our sister Faculty of Life Sciences. Our academics have the benefit of access to the large, stable population in the North West providing unique opportunities to study and address most causes of disease and deprivation. The opportunities are further enhanced by strong links to our partner Faculties (Humanities, Engineering and Physical Sciences, and Life Sciences) and the NHS through the Manchester Academic Health Science Centre (MAHSC). These partnerships facilitate rapid translation into practice and targeted biomedical, technological and psychosocial research based on clinical need.

In addition to our research and education activity, the Faculty is committed to make a major contribution to the greater good for society by contributing to solutions of the major challenges of the 21st century and the social and economic success of our local, national and global communities. We will ensure that social responsibility is embedded within all of our education and research activities, ensuring the highest ethical standards of professional practice from our staff and students. We are committed to equality and diversity in all our activities and to building on successful programmes such as the Manchester Access Programme, which targets talented students from underrepresented backgrounds, and a wide ranging global health programme, which will help deliver sustainable capacity building within the health systems of developing economies.

Whether you are a visitor or a prospective student, staff member or collaborator, we hope that you will be engaged by the enthusiasm and vibrancy of our students and staff, our commitment to improving health and quality of life and the diversity of opportunity in research, and education that our Faculty has to offer.

Faculty of Medical and Human Sciences Structure

Matrix of six Faculty Institutes and five Faculty Schools intended to facilitate cross cutting interactions

Figure 1

Faculty Structure – matrix of six Faculty Institutes and five Faculty Schools intended to facilitate cross-cutting interactions.

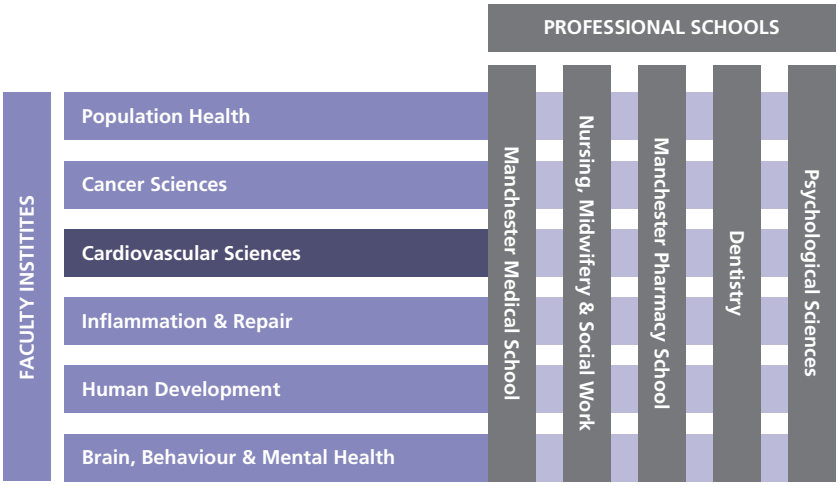


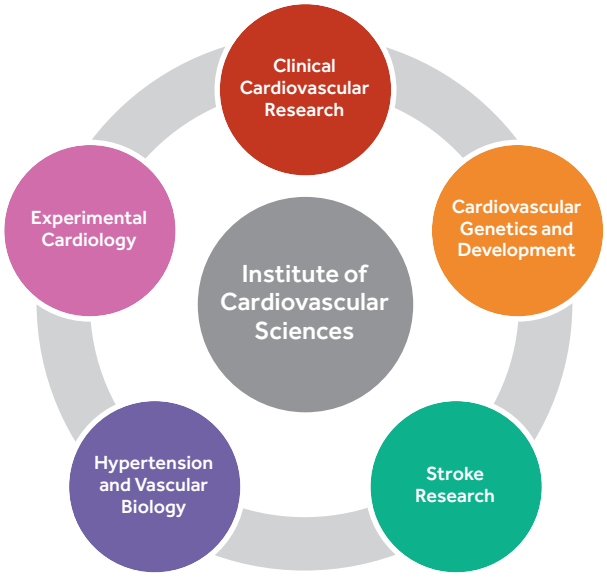
Figure 2

Institutes and Centres (May 2014)

Brain, Behaviour & Mental Health **Shôn Lewis**	Cancer Sciences **Sir Salvador Moncada**	Cardiovascular Sciences **Bernard Keavney**	Human Development **Peter Clayton**	Inflammation & Repair **Jane Worthington**	Population Health **Martin Tickle**
Clinical & Cognitive Neurosciences **Daniela Montaldi**	Haematological Oncology **John Radford**	Cardiac **David Eisner**	Hearing & Vision Research **Paul Bishop**	Musculoskeletal **Anne Barton**	Primary Care **Peter Bower**
Developmental Science & Disorders **Elena Lieven**	Personalised Therapy **Paul Townsend**	Vascular and Stroke **Pippa Tyrrell**	Endocrinology & Diabetes **Neil Hanley**	Gastrointestinal **Shaheen Hamdy**	Biostatistics **Graham Dunn**
Health & Risk Sciences **Jenny Shaw**	Paediatric, Teenage & Young Adult Cancer **Guy Makin**		Paediatrics & Child Health **Peter Clayton**	Dermatology **Chris Griffiths**	Epidemiology **Raymond Agius**
New Treatments & Understanding in Mental Health **Gill Haddock**	Women's Cancer **Andrew Clamp**		Genomic Medicine **Bill Newman**	Respiratory & Allergy **Angela Simpson**	Health Economics **Matt Sutton**
	Radiotherapy Related Research **Tim Illidge**		Women's Health **Melissa Westwood**	Tissue Injury and Repair **Judith Hoyland**	Imaging **Steve Williams**
	Manchester Centre for Cellular Metabolism (MCCM) **Michael Lisanti**			Immune Mechanisms **Tracey Hussell**	Health Informatics **Iain Buchan**

Chapter 1

Introduction to the Institute of Cardiovascular Sciences



Research Themes

Bernard Keavney
Head of Institute

AV Hill building

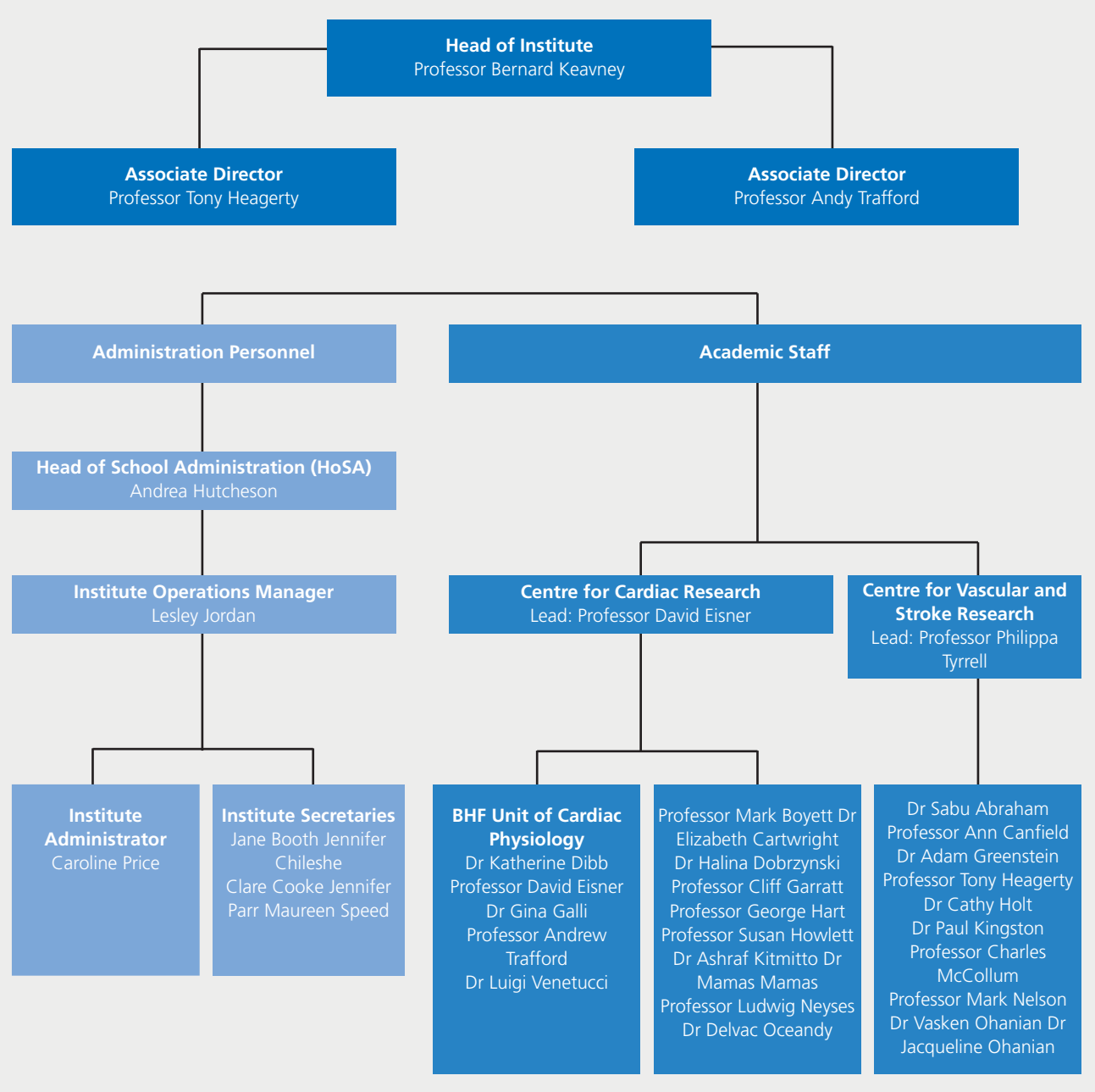
CTF building

Institute Director's message

It is a great pleasure to introduce the Prospectus and our plans for the Institute of Cardiovascular Sciences. Cardiovascular disease and stroke, considered together, will remain the world's most important source of morbidity and mortality for the foreseeable future. It is our mission to combat these diseases, through the conduct and application of the highest quality science, and to train the next generation of cardiovascular researchers both basic and clinical. We are a young Institute, having come into being only in late 2012, but our plans are ambitious. We aim to be recognized as one of a small number of elite international centres for cardiovascular research and education. Facilitated by our links with our National Health Service partner hospitals, we seek to translate our research advances into patient care, and through experimental medicine studies gain biological insights into clinically relevant phenotypes, biomarkers and disease processes. Our established strength in basic science makes us particularly well positioned to conduct "reverse translation" from clinical observations to biological insights, and we have several examples of outstanding successes in this type of work. We also have examples of truly "bench to bedside" research where basic insights gained in Manchester have achieved translation to late phase clinical studies of novel therapies conducted in our partner hospitals. Our Institute is closely aligned with the Manchester Academic Health Sciences Centre Cardiovascular Domain, through which a co-ordinated drive for excellence in research, teaching and patient care is facilitated between the University and our NHS partners. Our clinical staff are embedded in Central Manchester University Hospitals, University Hospital of South Manchester, and Salford Royal Hospital NHS foundation trusts, all members of MAHSC.

We look forward to sharing our achievements and ambitions for the future with you in the following pages.

Institute of Cardiovascular Sciences – Organisation chart



Links

www.inflammation-repair.manchester.ac.uk/

- Manchester Academic Health Science Centre
  www.mahsc.ac.uk
- Central Manchester University Hospitals NHS Foundation Trust
  www.cmft.nhs.uk
- University Hospital of South Manchester NHS Foundation Trust
  www.uhsm.nhs.uk
- Salford Royal NHS Foundation Trust
  www.srft.nhs.uk
- NIHR/Wellcome Trust Clinical Research Facility UHSM
  www.uhsm.nhs.uk/racrf
- NIHR/Wellcome Trust Clinical Research Facility CMFT
  www.wtcrf.nhs.uk

Institute of Cardiovascular Sciences Management Team

Professor Ann Canfield
Undergraduate Director

Professor David Eisner
Cardiac Centre Lead

Professor Tony Heagerty
Associate Institute Director

Mrs Andrea Hutcheson
Head of Administration

Professor Bernard Keavney
Institute Director

Dr Ashraf Kitmitto
Athena SWAN Champion
and Director of PGT

Dr Jaqui Ohanian
Postgraduate Research Director

Professor Andy Trafford
Associate Institute Director

Professor Pippa Tyrrell
Vascular and Stroke
Centre Lead

Institute overview

Structure

The Institute of Cardiovascular Sciences (ICVS) is one of six Institutes established by The University of Manchester Faculty of Medical and Human Sciences (FMHS) in August 2012 as part of a major reorganisation intended to transform research and education in medicine and healthcare. The Institute comprises the majority of the membership of the former Cardiovascular Research Group. Colleagues in Stroke Research have joined the Institute of Cardiovascular Sciences. The designation of our Institute firmly establishes Cardiovascular Research as an FMHS priority, which has been backed by the allocation of substantial resource towards new senior academic recruitment and laboratory space.

The Institute is presently comprised of 29 principal investigators, both clinicians and basic scientists. These include two Fellows of the Academy of Medical Sciences (Heagerty, Eisner), and one NIHR Senior Investigator (McCollum). Twelve PIs hold Chairs. Thirteen PIs are clinical academic staff, and honorary Chair appointments to six NHS clinicians have been made since 2008 (Keenan, Clarke, Bridgewater, Ray, King, O'Donoghue). External personal awards total over £5 million and include: BHF Chairs in Cardiac Physiology (Eisner), and Cardiovascular Medicine (Keavney); BHF Senior Basic Science Fellowship (Trafford); BHF Intermediate Basic Science Fellowships (Dibb, Oceandy); and BHF Intermediate Clinical Fellowships (Venetucci, Greenstein). Grant awards (2008-13) total £25 million. These include £14.6 million from BHF, £4.0 million from MRC, and £1.2 million from NIHR. Institute members hold Programme Grants from the BHF and MRC The Institute provides an excellent clinical and basic training programme in cardiovascular disease; its BHF four year PhD studentship scheme was renewed in 2012 (£0.5 million per year over five years), and the NIHR Integrated Academic Training (IAT) programme was renewed in 2013.

Several Institute members and NHS colleagues with honorary Institute appointments have national and international clinical leadership roles. These include Professor Heagerty, who served as President of the European Society for Hypertension (2009-2010), the International Society for Hypertension (2010-2011) and the British Hypertension Society (2011-2013); Professors Ray, Vice-President (Clinical Standards) and Garratt, Vice-President (Education and Research) of the British Cardiovascular Society; Professor Clarke, one of only four specialist cardiology reviewers for the national "Mothers and Babies: Reducing the Risk through Audits and Confidential Enquiries in the UK" (MBRRACE-UK) programme; Professor Pippa Tyrell, Associate Director of the Royal College of Physicians Stroke Programme and Chair of the Stroke association research awards committee; Dr Fraser, British Cardiovascular Intervention Society Council; Professor McCollum, National Screening for Abdominal Aortic Aneurysm committee; Dr Williams, British Heart Failure Association Council; Dr Arumugam, President of the British Nuclear Cardiology Society; and Professor Bridgewater, Director of Outcomes Publication at the Healthcare Quality Improvement Partnership on behalf of NHS England. Institute members include past chairs of the British Society of Cardiovascular Research (Eisner, Hart), and current council members of the BSCR and British Atherosclerosis Society (Holt).

The Institute has a strong track record of basic research with clear translational potential, particularly in cardiac physiology, heart failure, translational vascular biology and stroke. For example, the original observation that IL-1 Ra treatment could reduce inflammation-mediated injury following stroke in experimental animal models was made in Manchester (by Nancy Rothwell and Stuart Allan); this line of research has been advanced in Manchester as far as phase II studies of IL-1 Ra in stroke and subarachnoid haemorrhage (led by ICVS PI Pippa Tyrrell). Somewhat further back along the translational pathway, clinical studies of PMCA inhibitors in heart failure, following up on observations originally made in animal models by Ludwig Neyses, Delvac Oceandy and Elizabeth Cartwright, are in the planning phase. Institute staff have published over 450 papers (2008-13). There are currently 74 doctoral students (including 18 BHF four-year PhD students).

The Institute was organised at its inception into two Centres that aim to bring together researchers with common interests and facilitate collaboration across multiple sites. These are:

- Centre for Cardiac Research (lead Professor David Eisner)
- Centre for Vascular and Stroke Research (lead Professor Pippa Tyrrell)

The BHF Unit of Cardiac Physiology, led by BHF Professor David Eisner, lies within the Centre for Cardiac Research. Bernard Keavney joined the Institute as its inaugural Director in April 2013.

There are five broad scientific themes to the Institute's research effort: these are Heart Failure and Arrhythmias; Cardiovascular Genetics and Development; Clinical Cardiovascular Research; Hypertension and Vascular Biology; and Stroke.

Resources

Laboratory space comprises 1700 m^2 on one floor of a new building (occupied 2006) situated adjacent to Central Manchester Hospitals NHS Foundation Trust (CMFT), the Wellcome Trust/NIHR Clinical Research Facility (equipped with a state-of-the-art 3T MR scanner with cardiac capability) and the laboratories of the Faculty of Life Sciences. Two groups have laboratory space in the adjacent Michael Smith and AV Hill Building. An additional 600 m^2 of laboratory space in the same complex (AV Hill Building) to support the recruitment of new University funded Chair appointments is available for occupancy. The affiliated Transplantation Research Group has space co-located with the Transplant Unit at University Hospital of South Manchester (UHSM).

Major items of laboratory infrastructure available within the Institute include a comprehensive and fully equipped suite of rooms for cellular electrophysiology, a state-of-the-art setup for small vessel calcium imaging using spinning disk confocal microscopy, two further confocal microscopes, real-time PCR, MiSeq sequencing, pressure and wire myograph equipment, and small and large animal phenotyping facilities. Equipment for corneal confocal microscopy and retinal vessel analysis in human research participants is housed in the adjacent Wellcome Trust Clinical Research Facility which also houses a 3T magnet with cardiac capacity.

Core facilities equipped to a very high standard are available to Institute members. The Faculty of Life Sciences maintains a wide range of analytical facilities maintained by full-time expert staff, containing state-of-the-art equipment housed in custom-built laboratories (http://www.ls.manchester.ac.uk/research/facilities/). There are presently twelve such core facilities including Genomic Technologies (focusing largely on RNA analysis); Bioinformatics; and Bioimaging. The Manchester Centre for Genomic Medicine provides access to core facilities for high-throughput DNA sequencing (Illumina Hi-Seq and MiSeq platforms), high throughput genotyping (Illumina, Sequenom platforms) and bioinformatics analysis of DNA sequencing data.

Two MAHSC partner Trusts (CMFT and UHSM) host tertiary cardiothoracic services which together encompass a catchment of 3.5 million people. This is among the largest clinical cardiovascular service affiliated with a single university in the UK. Primary Angioplasty services are provided in an integrated fashion between the two Trusts; the combined service is the UK's largest and has delivered nationally and internationally leading recruitments to several multicentre clinical research studies. Building on this successful integration, and as part of the Manchester Academic Health Science Centre (MAHSC) objectives in the five year redesignation period, we will develop MAHSC Centres for Inherited Cardiac Conditions and for Heart Failure involving the Institute and both NHS Trust partners, to advance service, training and research goals in these areas. UHSM hosts one of six nationally designated Cardiothoracic Transplant Centres, providing supra-regional services in Transplantation and Ventricular Assist Devices to a population of 6 million.

The Greater Manchester Comprehensive Stroke Centre at Salford Royal Foundation Trust [SRFT] provides hyperacute stroke care for people presenting within four hours of onset from across Greater Manchester, has the largest patient catchment in the UK, and provides an excellent recruitment base for our clinical stroke trials. The Stroke Group has clinical research space co-located with the NIHR Hyperacute Stroke Research Centre at SRFT. The basic science research in Stroke is performed in the Faculty of Life Sciences (Professors Rothwell and Allan).

The Greater Manchester CLRN (prior to the recent reorganisation into LCRNs) has had an excellent track record in recruitment to both non-commercial and commercial (where it was first of 25 CLRNs) clinical trials in cardiology/cardiovascular medicine. The effective organisation of CLRN funded infrastructure has ensured an environment optimal for the conduct of NIHR portfolio research and clinical research in general.

University Hospital of South Manchester NHS Foundation Trust

Central Manchester University Hospitals NHS Foundation Trust

Our Aims

1. To be an internationally recognised centre of excellence in cardiovascular research, whose outputs benefit the health of cardiovascular patients and decrease the likelihood of healthy people developing cardiovascular diseases.
2. To provide the highest quality teaching and research training for postgraduate and undergraduate students.
3. To be a leading national centre in the development of the next generation of clinical and basic science cardiovascular academics.

Objectives

We will deliver our five year aims through achievement of the following objectives:

1. Greater integration of our research programmes both within the Institute and through strategic collaborations with other FMHS Institutes and University Faculties.
2. Developing the clinical/basic science research dialogue, and pursuing the opportunities for translational research with NHS partners in the Manchester Academic Health Science Centre (MAHSC).
3. Focusing the Institute's research effort and resource in areas where we can achieve, or maintain, international competitiveness.
4. Increasing the value of grant income, especially from NIHR, EU and RCUK. Specifically, increasing the numbers of Programme Grants and senior personal awards held within the Institute from all sources.
5. A programme of strategic recruitment in areas that complement our existing research strengths.
6. Support and mentorship of current staff to achieve/maintain excellence in their research and educational careers.
7. Improve the quality and impact of published outputs through: increasing the translational relevance of our work; increasing collaboration to harness multidisciplinary skills; and focusing resource.
8. Increase the numbers of Postgraduate Research (PGR) students.
9. Develop our Postgraduate Taught (PGT) and Continuing Professional Development (CPD) offerings, continuing to deliver outstanding educational experiences while providing increased financial headroom for the Institute.
10. Maintain our contribution to undergraduate education within a culture characterised by parity of esteem between teachers and researchers performing at equal levels of excellence.
11. Deliver the necessary mentorship and support to develop our most promising junior and intermediate level clinical and basic science colleagues to independent research careers.

Interface with the Manchester Academic Health Science Centre (MAHSC)

MAHSC (mahsc.ac.uk) is a partnership between The University of Manchester and six NHS organisations. Our NHS partners are some of the most highly rated NHS Trusts in the country. We are one of only six centres in the country designated as an AHSC. AHSC designation recognises excellence across research, innovation, education and patient service, and in particular the potential to excel in translational medicine. Through partnership with the GM AHSN, MAHSC aims to act as a beacon within the local health system, providing clinical leadership and helping health care organisations reap the benefits of research and innovation to drive improvements in care. MAHSC brings together the potential capacity of 23,500 NHS staff and 9,700 academic staff, with the Faculty of Medical and Human Sciences teaching over 9,000 students and almost 6,000 multi-healthcare professionals trained across MAHSC partners. Income from research in the years 2011/12 was £49 million for NHS partners and an additional £77 million from health-related academic research.

ICVS staff hold clinical contracts with, or interact principally with colleagues at three of the NHS MAHSC partners. Central Manchester University Hospitals NHS Foundation Trust (CMFT) has a turnover of £850 million per annum and treats more than 1 million patients annually. CMFT partners the University in the NIHR BRU in Musculoskeletal Medicine and the Wellcome Trust Clinical Research Facility. University Hospital of South Manchester NHS Foundation Trust (UHSM) treats more than 570,000 patients every year and hosts regional centres for breast cancer and respiratory research, and supra-regional Cardiothoracic Transplantation services. Salford Royal NHS Foundation Trust (SRFT) includes the major e-health resource infrastructure, the Salford e-Health Record, which provides integrated primary and secondary care electronic health records. SRFT is home to NHS Quest and hosts the Greater Manchester Academic Health Science Network (GM AHSN).

MAHSC is organised into six Domains each mapping to one of the Faculty Institutes. Each Domain is Chaired by one of the NHS Chief Executives (Cardiovascular is co-chaired by Mike Deegan, Chief Executive of CMFT, and Attila Vegh, Chief Executive of UHSM). Bernard Keavney acts as Academic Lead and Professors Simon Ray (UHSM) and Danny Keenan (CMFT) act as co-Clinical Leads for the Cardiovascular Domain. MAHSC was redesignated by the Department of Health in December 2013. The goals of the Cardiovascular Domain in the five-year redesignation period are:

1. Delivering integrated, outcomes-driven and transparent care to patients with atherosclerosis and stroke, utilising both e-health records and clinician-specific outcomes data to predict and prevent adverse events.
2. Linking research excellence to improved clinical practice in heart failure and familial cardiovascular disease, by establishing cross-city interdisciplinary MAHSC Centres, using e-Health and conducting research using national audit datasets.

3. Implementing new preventive screening technology (Carotid plaque volume, Community diagnosis of AF) and rolling this out across the AHSN catchment.

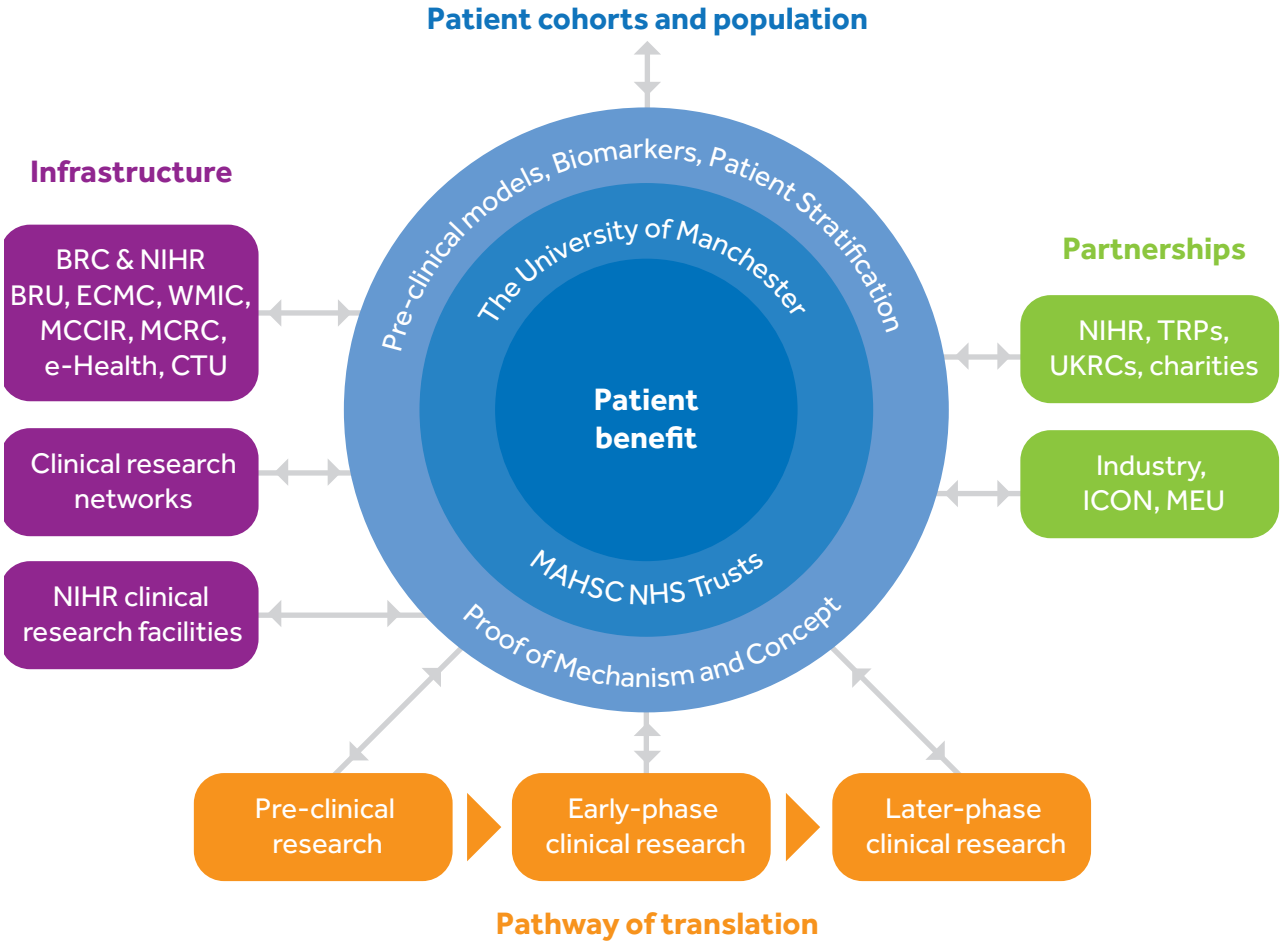
4. Rapidly taking early discovery and innovation from basic underpinning research through to novel therapies (IL-1Ra in stroke, PMCA1 and PMCA4 in heart failure, new targets for AF, biological pacemaking).

The Institute will play a central role in the achievement of these MAHSC goals, which will together deliver the overarching aim of the Cardiovascular Domain - to reduce cardiovascular and stroke morbidity and mortality by 5% more than the national average reduction over the redesignation period.

The AHSN and CLAHRC

Cardiovascular disease is the focus of both the Greater Manchester AHSN and the recently renewed Collaboration for Leadership in Applied Health Research and Care (CLAHRC). Manchester is a leading centre for applied healthcare research; this expertise is for the most part out with our Institute, but we have excellent examples of collaborative work that has delivered implemented clinical tools e.g. The GM-Stroke Assessment Tool (which has been adopted by the Stroke Association in the provision of six month post hospital discharge reviews), and the GM-Heart Failure Investigation Tool (GM-HFIT) developed by the CLAHRC and rolled out to three CCGs. This expertise and focus provide an ideal opportunity for interventions developed in the Institute and translated through MAHSC to be implemented promptly and effectively for patient benefit.

The MAHSC Experimental Medicine System



Experimental Cardiology

Aims

- To understand the normal physiology and electrophysiology of the healthy heart at the molecular, cellular, organ and whole animal levels.
- To understand the mechanisms that underlie the molecular, cellular, structural and functional remodelling leading to the development of heart failure
- To understand the cellular causes of cardiac arrhythmias including atrial fibrillation, hereditary channelopathies, and causes of pathological bradycardias.
- To develop new, more effective treatment strategies for heart failure and arrhythmias
- To understand the mechanisms whereby age, gender and exercise affect cardiac physiology

Expertise

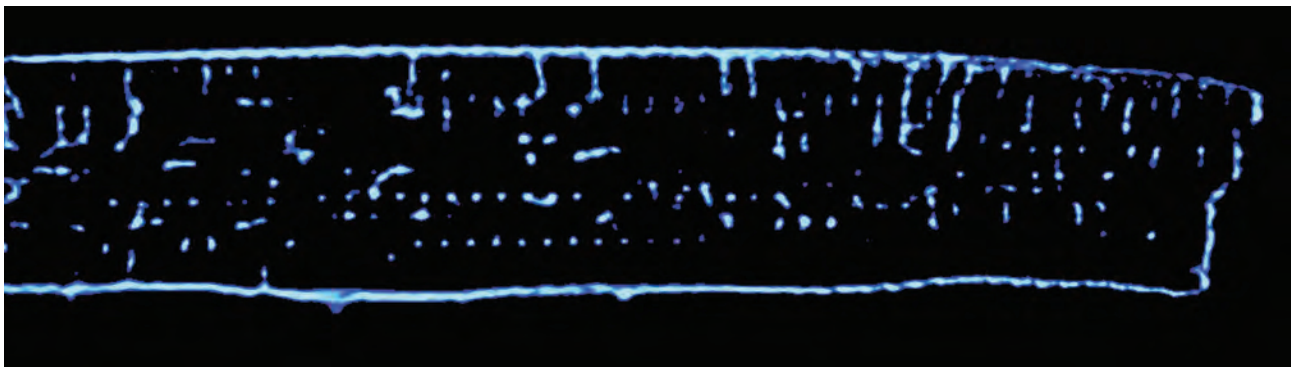
Our Principal Investigators are Professors Mark Boyett, David Eisner, George Hart, Susan Howlett (20% appointment), Ludwig Neyses (10% appointment), Andrew Trafford; and Drs Elizabeth Cartwright, Katharine Dibb, Halina Dobrzynski, Gina Galli, Ashraf Kitmitto, Oliver Monfredi, Delvac Oceandy, and Luigi Venetucci. We are closely allied to other researchers within the University including Professor Henggui Zhang (School of Physics and Astronomy) and Drs Holly Shiels and Xin Wang (Faculty of Life Sciences).

We have an international reputation for work in three areas: (i) the regulation of intracellular calcium and its link to cardiac excitability and contraction; (ii) the cardiac conduction system, which comprises the pacemaker of the heart (the sinus node), the atrioventricular node and His-Purkinje system; and (iii) molecular mechanisms and signalling pathways involved in the development of heart failure.

Our studies are conducted in a variety of animal models, human cellular models including induced pluripotent stem cells, human tissues and experimental medicine approaches. We have a wide range of methodological expertise including:

- *in vivo* cardiovascular measurements and interventions, e.g. echo, ECG, pacemaker implantation and ablation
- *in vitro* heart measurements, e.g. electrophysiology of the Langendorff-perfused heart
- the electrophysiology of isolated heart tissue preparations e.g. the isolated sinus node
- patch clamping of isolated cardiac myocytes
- measurement of intracellular calcium and other ions using fluorescent indicators
- whole heart imaging using micro-CT
- expression (at the mRNA and protein levels) of ion channels and components of the extracellular matrix underpinning cardiac arrhythmias
- transgenesis and gene knockout technology
- cardiac molecular biology and biochemistry
- histology and immunohistochemistry
- cardiac structural biology and biophysics
- imaging, including 3D electron microscopy, transmission EM, and confocal microscopy
- iPSC and hESC modelling
- regulation of expression by transcription factors and micro-RNAs
- single myocyte to whole heart computer modelling

We have a wide range of collaborations in the UK and internationally as well as strongly established collaborations with industry.



Transverse (T) tubules are a prominent feature of atrial myocytes from large mammals including man. Single ovine atrial myocyte stained with a membrane dye showing prominent intracellular t-tubule staining

Research

Research in this theme is focused in three areas: understanding the regulation of intracellular calcium signalling; investigating the properties of the cardiac conduction system in health and disease; and dissecting the molecular and cellular mechanisms responsible for heart failure and cardiac remodelling.

Regulation of intracellular calcium

(i) Basic mechanisms responsible for the regulation of intracellular calcium

Our work has focussed on the properties of the intracellular calcium store, the sarcoplasmic reticulum (SR) and, in particular, on the channel through which Ca is released on each beat (the Ryanodine Receptor). Eisner and Trafford have characterized the way in which the cell "autoregulates" the calcium content of the SR and the consequences that this has for the regulation of contractility.

(ii) The link between disordered calcium signalling and cardiac arrhythmias

Venetucci (with Eisner and Trafford) is studying the relationship between intracellular calcium waves and the origin of ventricular ectopic beats. Work concentrates on how making the Ryanodine Receptor leaky produces these waves. Of particular interest is understanding the changes in genetic arrhythmia syndromes such as CPVT (catecholaminergic polymorphic ventricular tachycardia).

(iii) Atrial calcium signalling in health and disease

Dibb (BHF Intermediate Basic Science Fellow) identified the presence of transverse tubules in the atrium. Previously, these structures were thought to exist only in the ventricle. The transverse tubules disappear almost entirely in heart failure. Current work concentrates on two topics: the functional effects of this loss of tubules; and the molecular mechanisms responsible for laying down the normal network.

(iv) The effects of gender on calcium signalling and contraction

Howlett has shown important gender differences between hearts from males and females and current work is studying how these relate to the protective effects of female gender on the development of heart disease.

(v) The effects of ageing on cardiac calcium signalling and contraction

Age is the largest risk factor for a variety of cardiovascular diseases. Trafford, Dibb and Howlett are using a variety of animal models to investigate the mechanisms linking ageing to the increased risk of heart failure and atrial fibrillation.

(vi) Reptilian and fish cardiovascular biology

Galli is interested in calcium signalling in non-mammalian species. As well as addressing fundamental biological questions, comparison with human studies provides important insights into human disease.

The Cardiac Conduction System in health and disease

(i) Understanding the cardiac conduction system

Although the three main parts of the cardiac conduction system are the sinus node, atrioventricular node and His-Purkinje system, there are other tissues that can be considered part of the cardiac conduction system (including the paranodal area, atrioventricular rings and retroaortic node and possibly the outflow tract). These other regions are known to be responsible for a variety of arrhythmias and Dobrzynski is mapping their distribution and establishing their characteristics. As much as possible of this is being done on the human heart.

(ii) Understanding failure of the cardiac conduction system in heart failure and other cardiac diseases.

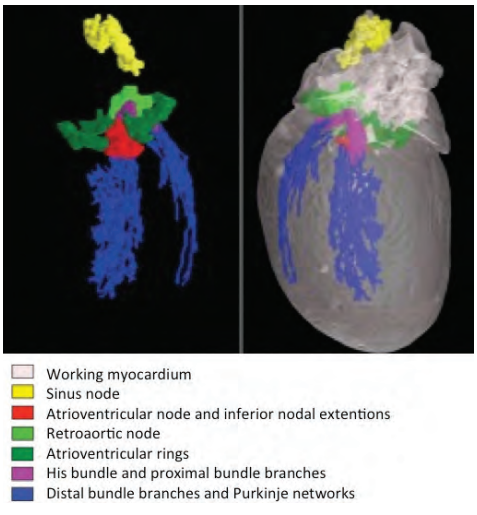
Failure of the cardiac conduction system results in sick sinus syndrome, heart block and bundle branch block, the only treatment for which is the implantation of an electronic pacemaker. With funding from a BHF programme grant Boyett, Dobrzynski, Hart and Cartwright are showing the underlying reason to be a 'remodelling' of the ion channels and related proteins.

(iii) Understanding arrhythmias in the athlete.

Athletes are thought to be the healthiest members of the population and yet they are prone to cardiac arrhythmias and even sudden cardiac death. Monfredi and others are investigating the underlying causes and have shown that the low resting heart rate of athletes is once again the result of a remodelling of the ion channels and related proteins.

(iv) Fixing the broken heart (or at least the broken cardiac conduction system).

As well as identifying the cause of dysfunction of the cardiac conduction system, Boyett and others are also experimenting with gene therapy to cure the dysfunction. For example, rather than implant an electronic pacemaker if the cardiac conduction system fails, it may be possible to use gene therapy to correct the underlying dysfunction (for example, by correcting the expression of an ion channel).



3D model of extended CCS only (myocardium removed) viewed from dorsal surface and 3D model of heart (with transparent myocardium) viewed from ventral surface.

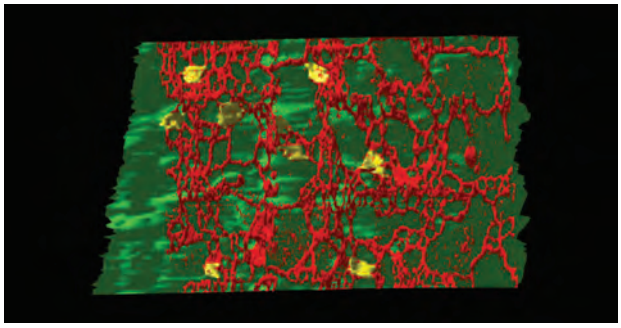
Mechanisms of Heart Failure and Remodelling

Heart failure is a major cause of morbidity and mortality worldwide; in the UK alone there are nearly 1 million people with heart failure and approximately 68,000 new cases are diagnosed each year. Studies have shown the lifetime risk of developing heart failure to be one in five and this incidence rises dramatically with age. However, despite the prevalence of this disease current treatments are inadequate and prognosis remains poor.

Heart failure is associated with extensive cardiac remodeling which leads to structural and functional changes. These changes include cellular hypertrophy, fibrosis, myocyte loss, and alterations in calcium handling, excitation-contraction coupling and electrical conductance. Underpinning these changes are alterations in gene expression and activity and cell signalling. The bioscientists and clinicians within the Institute work together to understand how and why this remodelling occurs and how it affects cardiac structure and function.

(i) Structure-function mechanisms underlying impaired ventricular contractility

One of the most common causes of heart failure (HF) is impaired ventricular contractility. Contractile function is regulated by calcium (Ca^{2+}) through a process termed calcium-induced calcium release that underlies excitation-contraction coupling. Funded by a BHF programme grant, Kitmitto, Trafford and Cartwright are studying how changes to calcium signalling (as well as to the extracellular matrix) contribute to decreased contractility in heart failure. Importantly, this work is done in a translationally-relevant model (the sheep). Among current projects, we are investigating the processes and proteins that hold the T-tubules (TTs) in apposition to the junctional sarcoplasmic reticulum (jSR) to form a dyadic cleft, a microdomain that is the site for local Ca^{2+}-control, which underpins E-C coupling. Defective cardiac E-C coupling concomitant with degradation of the ventricular TT membrane network are recognized characteristics of heart failure. Recently, Kitmitto has employed a novel type of EM, serial block face scanning electron microscopy (sbfSEM), to the study of the ultrastructure of whole cardiac myocytes to understand morphological changes that occur in the failing heart.



The novel use of serial block face scanning electron microscopy to reconstruct the 3D structure the SR membrane (red) close to the cell membrane (green) and regions of putative calcium release are coloured in yellow.

We have determined the first high resolution 3-D structure of both the TT system and the SR network for intact cardiac myocytes providing a unique understanding of dyad cleft organisation at the cell-wide level. Significantly, we have shown that in heart failure there is remodelling of the TT system and also a loss and re-arrangement of the SR. Understanding the mechanisms that lead to the structure-function changes that we have described may lead to entirely novel therapeutic approaches to HF. Kitmitto and Cartwright are also investigating remodeling of Ca^{2+} microdomains in models of diabetic cardiomyopathy.

(ii) Molecular mechanisms and signalling pathways

Research focuses on the molecular mechanisms underlying heart failure and associated remodelling. There is general agreement that hypertrophic remodelling is a determinant of the clinical course of heart failure and research conducted by Neyses, Cartwright, Oceandy and Wang has identified the role of novel genes, including several kinases, that are critical to the development of cardiac hypertrophy and subsequent heart failure. Several Ca^{2+} dependent signalling pathways are known to control aspects of the cardiac remodelling associated with heart failure. Current research funded by an MRC programme grant (Neyses, Cartwright and colleagues) is addressing how the cardiac cell uses calcium for signalling against the background of very large swings in calcium concentration during excitation contraction coupling. As a result we have identified several therapeutic targets for the treatment of hypertrophy and heart failure.

(iii) Relationship between genes regulating cardiac hypertrophy and cancer growth

Another focus of our research is the investigation of the close relationship between genes that regulate cardiac hypertrophy and cancer growth (Oceandy, BHF Intermediate Basic Science Fellow). The main objective of this research is to understand the regulatory role of tumour suppressor genes during cardiac hypertrophy, remodelling and failure.

(iv) Cardiac regeneration and the therapeutic use of stem cells

Due to more effective interventions an increasing number of people are able to survive a myocardial infarction; however, those that survive may develop heart failure due to cardiac cell loss. Recently, stem cell therapy in which damaged cells are replaced with stem cell-derived cardiomyocytes has emerged as potential therapeutic approach for HF. Our current research approaches are two-fold (i) to identify and characterise novel regulators of cardiomyocyte proliferation that can be targeted to induce cardiomyocyte regeneration (Oceandy & Cartwright); and (ii) development of a pre-clinical large animal model (the pig) in which to evaluate the beneficial effects of delivery of stem cells carrying a targeted gene modification on cardiac remodelling post myocardial infarction (Holt & Malik).

Cardiovascular Genetics and Development

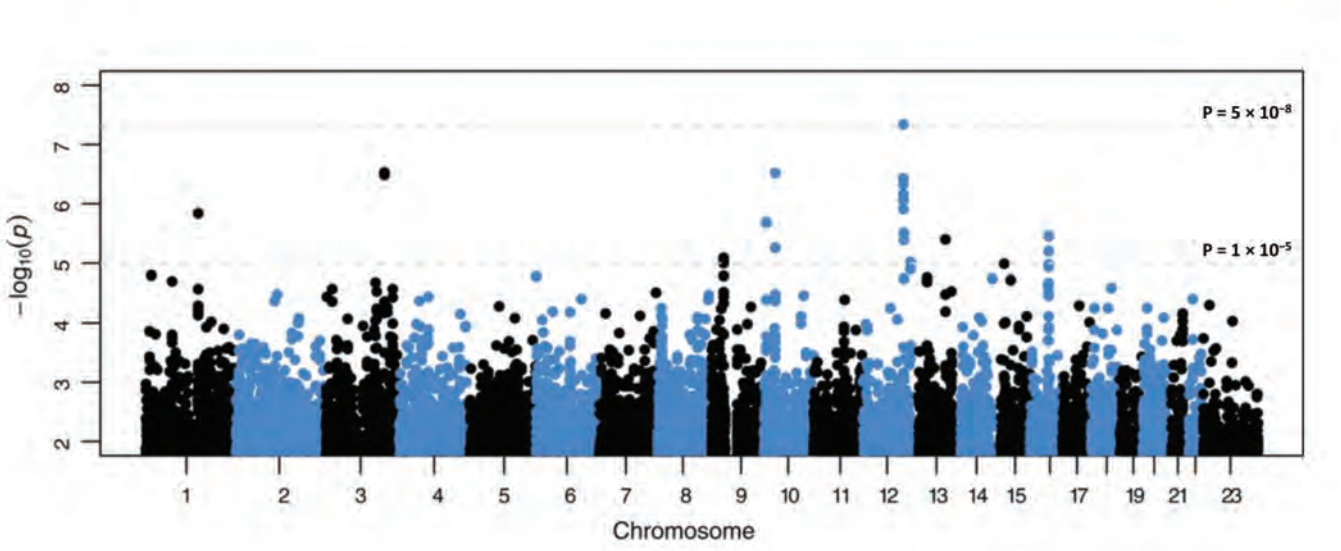
Aims

- To understand how genetic variation contributes to the risk of complex cardiovascular diseases and to develop novel approaches to prevention, screening, counselling and treatment based on this knowledge.
- To conduct translational research studies in patients with single-gene cardiovascular conditions, discovering novel causative variants and developing stratified approaches to patient care.

Expertise

Our PIs are Professors Bernard Keavney, Clifford Garratt, Bernard Clarke, and Drs Sabu Abraham and Luigi Venetucci. We have internationally recognised expertise in the study of complex cardiovascular genetics, and substantial recent expertise in next-generation sequencing studies of Mendelian conditions. We have extensive experience of:

- Study design, including large case-control, trio family, and extended pedigree designs.
- Detailed patient phenotyping for many cardiovascular conditions, including coronary artery disease, left ventricular structure and function, vascular and autonomic function, ambulatory blood pressure, predisposition to arrhythmias, congenital heart disease and associated malformations.
- Specific clinical expertise in inherited arrhythmias and sudden death provided by a designated Regional Inherited Cardiac Conditions Clinic (Garratt/Newman/Metcalfe)
- Fieldwork, including handling consent appropriately in children and vulnerable populations, and obtaining and storing biological samples.
- Biobanking, including international advisory roles to large initiatives such as UK Biobank and the Wellcome Trust/NIH H3 Africa Programme.
- Largescale genotyping and sequencing.
- Transcriptomic and focused gene expression analysis in a variety of tissues, including cell type-specific approaches using laser microdissection.
- Analysis and interpretation of single nucleotide polymorphism and sequencing data in genetic association and Mendelian family studies
- Fine-mapping of expression QTLs to identify causative genes in regions of GWAS association
- Meta-analysis of genetic data and Mendelian randomisation studies.
- In vitro and ex vivo angiogenesis models
- Retinal angiogenesis and choroidal neovascularisation (CNV) models
- Transgenic mouse models
- Gene knockdown using siRNA/ shRNA technologies
- Cell signaling and cell biology
- Confocal microscopy and image analysis



The Manhattan plot of a genome-wide association study that identifies loci associated with a congenital heart condition, Tetralogy of Fallot. Cordell et al. Human Molecular Genetics 2013. Reproduced with permission.

(i) Complex disease genetics

Our complex disease studies are conducted within a collaborative framework including colleagues within the Institute (e.g. iPSC modelling of the consequences of particular variants in cardiomyocytes, with the Heart Failure group), the wider Faculty (eg next-generation sequencing studies with colleagues in the Manchester Centre for Genomic Medicine), the Faculty of Life Sciences (e.g. the use of genome editing approaches to investigate cellular phenotypes consequent on particular genetic changes, mouse modelling of congenital heart disease) and beyond Manchester (e.g. population collection, statistical genetics, large-scale population sequencing studies). A MAHSC Cardiovascular Tissue Biobank is in the process of setup; this will provide us with the capacity to conduct tissue-specific studies of eQTLs, epigenetics, and proteomics. GWAS studies of a variety of cardiovascular diseases, conducted by many groups worldwide, have provided unprecedented numbers of clues to novel biological pathways to disease that may be suitable for intervention. However, at most loci, although statistical association between non-coding and presumed regulatory variation has been conclusively established, mechanistic insight is lacking and the responsible gene in the region has not been conclusively identified. In order to achieve such mechanistic insight in complex diseases, it is likely that highly multidisciplinary approaches will be required. Manchester provides an outstanding environment in which to pursue such approaches.

(ii) Single gene disease

The rapid and continuing developments in gene sequencing have the potential to significantly advance research and improve the care offered to patients and families with single-gene inherited cardiac conditions, through a more comprehensive knowledge of the mutational spectrum in particular conditions, an enhanced understanding of the consequences of individual genetic mutations and, potentially, stratified approaches to care. In this regard, access to large, well-phenotyped cohorts of patients is a key requirement. The Inherited Cardiac Conditions clinic run by Professor Garratt based at Central Manchester University Hospitals Trust has existed since 2006 and has been designated as the Greater Manchester/Cheshire Regional ICC clinic since 2010. It runs on a weekly basis and is staffed by Professor Garratt, Dr Luigi Venetucci and a Genetic Counsellor seconded from the Department of Genetic Medicine. The clinic has full cardiac nurse support and "same day" availability of electrocardiography, echocardiography and treadmill exercise electrocardiography. Five new patients and up to 10 review patients are seen in each clinic. The majority of referrals to this service are 1) adult patients with known or suspected ion channelopathies or cardiomyopathies (referred for advice about further clinical management or genetic testing) 2) relatives of young sudden death victims (referred for clinical/genetic screening) or 3) patients with idiopathic VF or their relatives. The service has immediate access to specialist clinical cardiac electrophysiological services including ajmaline testing, invasive electrophysiological studies and defibrillator implantation (transvenous and subcutaneous). Specialist imaging (contrast or exercise echocardiography and cardiac magnetic resonance imaging) is available on-site, as is paediatric and maternity cardiological expertise and specialist cardiac surgery (including myomectomy).

The service is supported by 2 bi-monthly multidisciplinary review meetings, one held with clinical geneticists with a cardiological interest (Dr Kay Metcalfe and Professor Bill Newman) and one with cardiac imaging specialists from both Central and South Manchester University hospitals (Helen Dormand, Dr Matthias Schmitt), interventional cardiology from South (Dr Chowdhary) and cardiac surgery from Central (Mr. Andreas Hoschtitzky). Clinical outcomes of individuals seen by this service are extremely good and have demonstrated low requirements for implantable defibrillators based on careful selection criteria. In addition to clinical cardiac research associated with the clinic, the service acts as a resource for clinical genetic research studies in collaboration with the Department of Genetic Medicine. Next generation sequencing techniques have been used to construct a "cardiac gene panel" that is currently undergoing testing for diagnostic accuracy and reliability. Studies in preparation include genetic characterisation of a large cohort of individuals with catecholaminergic polymorphic ventricular tachycardia. We will integrate the service offered to patients with structural genetic cardiac conditions (eg. Marfan's, Turner's, Loeys-Dietz syndromes) with the existing arrhythmia/cardiomyopathy focused ICC clinic to provide a comprehensive service to families which will facilitate cross-city clinical and research collaborations. At UHSM, Schmitt has established a cohort currently comprising >100 patients with HCM, and women with Turner's syndrome, extensively phenotyped with cardiac MRI.

Members of our Institute contribute their expertise to the development of national policy in inherited cardiac disease. For example, Professor Garratt was a member of the National Cardiac Genetics services review (2008-10) undertaken by the PHG Foundation, an independent international non-profit organisation. The final report (Heart to Heart; inherited cardiovascular conditions services) formed the basis for national commissioning guidelines in this area. He was a member of the Department of Health National Sudden Cardiac Death Delivery Group (2008-2010) and the national Steering Group for the now newly formed Association for Inherited Cardiac Conditions (2009-11). He brought together and co-chaired a national multidisciplinary team (nurses, cardiac electrophysiologists, heart muscle specialists, patient representatives) to produce guidelines for management of familial sudden cardiac death syndromes under the auspices of Heart Rhythm UK. In addition he is Medical Advisor to SADSUK, an independent patient organisation focusing on sudden unexpected death (2009-present).

Research

Cardiac developmental genetics

We have conducted large genetic epidemiological studies of a variety of complex cardiovascular traits including the risk of myocardial infarction, and quantitative traits related to cardiovascular risk. Most recently, supported by Programme Grants from the British Heart Foundation, and an EU FP7 award, we established among the largest international genetic studies of the risk of sporadic, non-syndromic congenital heart disease, organising an international collaboration involving seven UK paediatric cardiology units, four UK universities and six overseas partners. We recently reported the first genome-wide association studies (GWAS) of congenital heart disease, identifying loci on chromosomes 12 and 13 associated with Tetralogy of Fallot (TOF), the commonest cyanotic CHD condition; and on chromosome four associated with atrial septal defect (which accounts for some 7% of all CHD). We also reported the first large-scale study of the role of genomic copy number variation in sporadic, non-syndromic congenital heart disease, demonstrating an excess of rare genic CNVs in CHD cases and an important role for de novo events. We recently identified a causal gene for the association of outflow tract malformation with duplication at the 1q21.1 region of the genome; copy number variations at this region are the second most common microscopic chromosomal cause of CHD after 22q11 deletion. A focus of our future work will be to understand the mechanisms underlying the genetic associations with CHD, both of SNPs and CNVs, that we have discovered in work to date. We will conduct eQTL analyses in relevant tissues, model the developmental consequences of particular variants in hESC and iPSC derived systems, utilize CRISPR/Cas9 genome editing to confirm the causal role of particular SNPs in an isogenic context, and use transcriptomic and proteomic approaches to identify gene networks perturbed by hypothesised causal variants.

Our studies to date have identified rare sequence variants, copy number variants and single nucleotide polymorphisms, which, when considered together, explain around 10-15% of cases of CHD of various types. We will conduct large-scale sequencing studies in our sporadic CHD samples to identify additional rare and de novo variants. At present, studies focused on Tetralogy of Fallot are in process; these will be expanded to other CHD phenotypes. We will work with the UK 100K Genomes Project to identify families potentially suitable for investigation under their auspices. We will extend our international collaborative network to enable the conduct of meta-analyses of GWAS, CNV and ultimately sequencing data in CHD.

Genetics of familial arrhythmic conditions

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic arrhythmia syndrome characterised by the onset of life threatening arrhythmias during adrenergic stimulation of the heart. This typically occurs during exercise or emotional stress. In around 70% of cases CPVT it is caused by mutations of the RYR2 gene that encodes for the cardiac ryanodine receptor. A small number of cases are caused by mutations of the CASQ2 gene that encodes for the cardiac calsequestrin. We have characterised the mechanisms responsible for the onset of arrhythmias in CPVT. In addition, we have identified novel treatment strategies. For the last five years the St Mary's Clinical Genetics Department has been the national testing centre for RYR2 mutations - to date they have tested around 500 samples. Using this route Dr Venetucci, in collaboration with Professor Garratt (Manchester Heart Centre) and Professor Newman (St. Mary's Clinical Genetic Department) and colleagues nationwide, plans to build a national cohort of patients with CPVT. This will enable us to translate our basic science findings into clinical practice. Our clinical research programme will pursue three main lines of investigation. (i) Identify new disease causing genes: Over the last five years several studies have attempted to identify new genes responsible for CPVT. Mutations of CAM1, KCNJ2 and TRDN have been identified in small numbers of patients. Using next generation sequencing we plan to study our cohort of patients to identify novel genes responsible for CPVT. We also plan to test the functional effects of these mutations using two alternative approaches: expression in heterologous cells systems and inducible pluripotent stem cells derived directly from patients. (ii) Test novel treatment strategies: The main treatment for CPVT is β-blockers, which are effective in around 60-70% of cases. Recent reports have demonstrated that the addition of flecainide (a sodium channel blocker) to β-blockers improves arrhythmia control in most of the patients. We have recently demonstrated that in a mouse model of CPVT, Omega-3 fatty acids are very effective in preventing arrhythmias following challenge with adrenaline. In addition novel inhibitors of the RyR have been developed (Dantrolene and Rycal). Our cohort of patients will enable us to test these various treatment strategies. We will use iPSC modelling to test the efficacy of the various agents on each mutation, potentially informing stratified therapeutic approaches. (iii) Investigate clinical outcomes in patients with CPVT: CPVT is a rare disorder with a prevalence estimated at 1:10000. There is very little information regarding the natural history of the disease and risk predictors of sudden death. The largest cohort study to date includes just 101 patients with CPVT. Development of a nationwide cohort of patients with CPVT will enable more detailed study of the clinical characteristics and natural history of the condition, and potentially inform a risk prediction model for CPVT.

Genetics of atrial fibrillation

Atrial fibrillation (AF) is the most prevalent clinical arrhythmia, which is increasing in incidence as the population ages, and for which treatments remain suboptimal. A detailed understanding of the molecular mechanisms underpinning AF is lacking. Results from GWAS studies of lone AF indicate that there appears to be a key role of developmentally expressed genes in AF risk. The strongest common variants identified are in the transcription factor PITX2 which in early development is a determinant of "leftness". Also, a recent meta-analysis of GWAS studies of heart rate showed that variants associated both with relative bradycardia and relative tachycardia were associated with AF risk, including the key developmental gene Nkx2.5. As yet it is not understood whether the mechanism determining additional risk involving either of these genes is operating during development or postnatal life; clearly this is a key issue in deciding whether pathways involving these genes are potential drug targets for the prevention of AF. We have investigated ten genes in regions whose association with AF is supported by meta-analysis of GWAS data, which we will extend in our Cardiovascular Tissue Biobank. We will model the effects of putatively functional SNPs in an isogenic context using genome editing in iPSC and hESC models, differentiating these cells to cardiomyocytes for detailed cellular electrophysiological investigation by colleagues in our Institute. We will explore the effects of putative novel factors influencing AF risk (for example, certain micro-RNAs) on the expression of AF target genes and cellular electrophysiological properties in an allele-specific manner.

Genetic epidemiological studies in the UK Biobank resource

The UK Biobank (ukbiobank.ac.uk) has recruited 500,000 participants aged between 45 and 69 years, and carried out detailed baseline phenotyping, collection of biological samples, and obtained consent for medical record linking. UK Biobank is in the process of conducting genome-wide genotyping on all 500,000 participants, using a custom-designed chip. UK Biobank genome-wide data will start to become available from 2014 and will constitute a resource unique in the world for genomic epidemiology. Working together with other UK colleagues, we will pursue questions in keeping with our interest in cardiovascular development, structure and arrhythmogenesis in the Biobank resource. In this regard, UK Biobank plans to carry out comprehensive cardiac and vascular MRI studies on 100,000 people and these data will be of particular interest to examine for associations with genomic variation (for example, bicuspid aortic valve, aortic dimensions, and left ventricular mass).

Although most UK Biobank studies under discussion so far focus on common SNPs, the size of the resource will allow systematic study of rare CNVs, which will be scorable on the UK Biobank genotyping chip. Our group has a strong track record with respect to investigating the relationship between rare CNVs and cardiac structure and function. Since such CNVs are individually very uncommon in control populations, the Biobank resource will prove invaluable to determine accurate population prevalences and refine associations. It is already clear that certain deletions may have broad phenotypic impacts with very variable penetrances (e.g. 1q21.1); genomic factors influencing the phenotypic consequences of particular CNVs have not in general been systematically studied in large numbers of people. UK Biobank also provides a potentially unique opportunity to investigate rare variants by sequencing extreme individuals for cardiovascular phenotypes of interest.

Biology of vascular development

Blood vessels support all essential functions of various organ systems and the process of vessel formation is called angiogenesis. In a number of human diseases affecting the cardiovascular system, but also other organs such as the eye, and in cancer, abnormal vessel growth contributes to the pathology of the disease. Even though vascular blocking agents such as Avastin which block VEGF are in the clinic, there is an insufficient understanding of mechanisms controlling vascular growth and vessel patterning in development and disease. Dr Abraham is involved in the research that unraveled the novel roles of proteins such as Lrg1 (Wang et al 2013, Nature 2013) and Apelin (McKenzie et al Am J Pathol. 2012) in aberrant angiogenesis and intends to extend studies on Apelin, which is a GPCR ligand, and its role in diabetic retinopathy. We are also interested in identifying novel angiogenic factors and regulators using extensive in vitro, in vivo and ex vivo angiogenic assays that are being established in the lab. A better understanding of the cellular mechanisms and the molecular regulation of physiological and pathological angiogenesis will enable us to identify potential targets for future therapies.

Chapter 5

Clinical Cardiovascular Research

Aim

To improve the understanding of cardiovascular disease, improve diagnosis, provide more effective and individualised treatment, and ultimately improve the cardiovascular health and wellbeing of the North West and beyond through the application of our clinical research outputs.

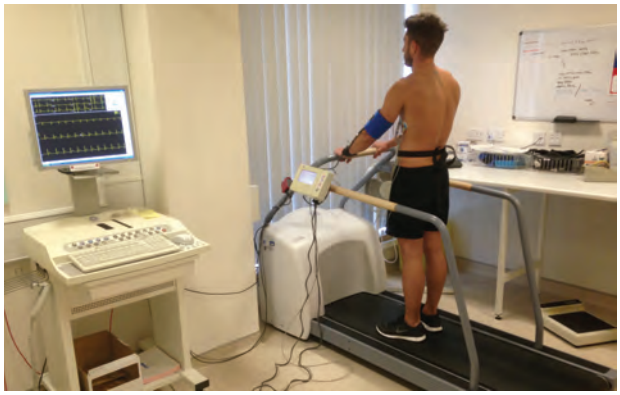
Expertise

Clinical cardiovascular research is conducted both by substantive Institute members and by a large number of NHS colleagues with honorary appointments across three large cardiac, vascular and stroke units at Central Manchester NHS Foundation Trust (CMFT), University Hospital South Manchester NHS Foundation Trust (UHSM) and Salford Royal NHS Foundation Trust (SRFT), all of which are MAHSC partners. These units together provide the highest quality specialist care to a population of around 3.5 million people with additional provision of a nationally designated adult congenital heart disease (CMFT) and a cardiopulmonary transplantation and ventricular assist device service (UHSM). This represents one of the largest population catchments for tertiary cardiac services in Europe and offers a unique resource for multi-disciplinary clinical translational research and advances in patient care.

Specialist clinical services

Heart Failure

The specialist heart failure (HF) services provided at CMFT (led by Dr Mamas) and UHSM (led by Dr Williams) represent amongst the largest cohorts of HF patients in the UK. Clinical research interests are focused around atrial fibrillation, diabetes, cardiac devices and inflammation. The Cardiac transplant centre based at UHSM is one of only five national heart and lung transplant units in the UK, with a patient catchment area of over six million led by Dr Steve Shaw who manages advanced heart failure patients, including those on mechanical circulatory support with both short term extracorporeal devices and long term implantable devices and post cardiac transplantation. Dr Shaw is a representative at CTAG (Cardiothoracic Advisory Group) to the NHS and also the VAD Advisory Group guiding the national delivery of advanced heart failure services.



Six minute walk test in cardiology laboratory

Hypertension

Professor Tony Heagerty and Dr Adam Greenstein run the Hypertension clinical service in Manchester formally recognized by the European Society for Hypertension as an International Centre of Excellence. The service provides international clinical expertise to patients referred from all over the Northwest of England for investigation and management of hypertension. Patients are recruited from the hypertension clinic to participate in their small artery research programme, which investigates why weight gain increases blood pressure to identify new treatments for obesity-related hypertension.

Interventional Cardiology

The primary PCI (PPCI) service provided by the interventional cardiologists across CMFT and UHSM to patients presenting with ST-elevation Myocardial infarction (STEMI) is the largest such service in the UK with a catchment of 3.5million, and one of the largest in Europe, with over 1200 PPCI procedures undertaken each year. Principal investigators across both CMFT and UHSM are nationally recognised. We are represented on the British Cardiovascular Interventional Society (BCIS) Council and BCIS research working group, with several colleagues acting as national chief investigators in numerous RCT and clinical registries. The integrated service provides an unparalleled UK resource for clinical research studies for patient benefit.

Vascular surgery

The Vascular surgery units at CMFT and UHSM work closely to provide comprehensive city-wide cover. Manchester has led nationally in screening programs for abdominal aortic aneurysms (AAA). Greater Manchester was the first conurbation to implement AAA screening through Professor Charles McCollum's work with the National Screening Committee, and represents the largest AAA screening programme in the UK. The Vascular Laboratory run by Professor Charles McCollum is the largest service for the minimally invasive investigation of vascular disease in the UK employing 40 technologists who undertake over 60,000 investigations for vascular disease per year.

Obstetric Cardiology

The CMFT joint obstetric cardiology clinic run by Professor Clarke and Dr Vause provides specialist care for pregnant women with cardiovascular disease from across the North West of England, North Wales and the Isle of Man (population 7 million), and has recently received an All Party Parliamentary Group for Maternity care award (2011), and a Royal College of Midwives award for excellence in maternity care (2012).

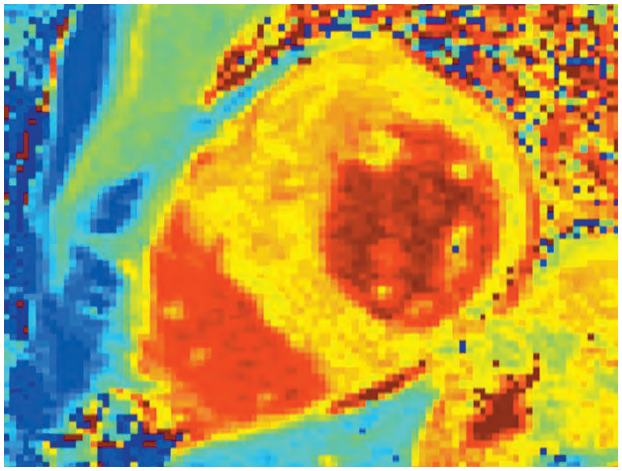
Adult congenital heart disease

CMFT is the regional centre providing Adult Congenital Heart Disease (ACHD) services to the North West, North Wales and the Isle of Man covering a population of about 7.2 million. This is done in a hub and spoke model whereby CMFT functions as the hub and the spokes being at Liverpool Heart and Chest hospital and Blackpool Victoria Hospital. The service currently is one of the largest services in the United Kingdom in terms of patient volume and also procedures such as interventional cardiac catheterisation and corrective cardiac surgery. A wide range of complex congenital Surgical and Catheter Interventions and electrophysiology procedures in adults are undertaken.
The service also has a large population of adult congenital patients receiving advanced pulmonary hypertension therapy.

Infrastructure

Imaging

High quality imaging is key to leading edge cardiovascular research. We have expertise in advanced cardiac imaging across CMFT (cardiac PET and PET-CT) and UHSM (cardiac MR and CT). There has been a rapid development of cardiac enabled MR scanner infrastructure in the Greater Manchester area including a dedicated 1.5T Siemens at UHSM with plans for a further cardiac 3T scanner and cardiac CT scanner that will go online in 2014. The UHSM based Cardiac MR research group is led by Matthias Schmitt (Hon Senior Lecturer) with the purpose of facilitating university and city wide cross-modality imaging research, establishing methodologies to a wider spectrum of disease populations including diabetes and chemotherapy induced cardiotoxicity with support of the UK Cancer Research sponsored Cardiotox programme. Further cardiac enabled scanners include a 1.5 T Philips scanner at the Wolfson Medical Imaging Centre (WMIC) and a 3T Philips equipped with a dedicated coil for Phosphorus spectroscopy. The vascular surgical group at UHSM has acquired 3D duplex ultrasound systems (amongst the first in Europe) in which they demonstrated 3D duplex imaging was more accurate in the measurement of carotid plaque volume than MR imaging or CT. A state of the art SPECT service at CMFT led by Arumugam is one of only two centres in the UK to provide a cardiac perfusion PET service that has rapidly progressed from being a research tool to a modality that can be used in clinical practice. The low radiation dose, fast patient throughput, ability to quantify myocardial perfusion reserve and good diagnostic accuracy make it an important complementary investigation in assessing CAD with the capability of fusion imaging to combine anatomy coronary CT with functional imaging (PET and SPECT)



Native (non-contrast) T1 map in hypertrophic cardiomyopathy demonstrating evidence of myocardial fibrosis in the hypertrophied septum (raised T1 levels denoted orange/red against yellow muscle background)

Health Informatics

We have internationally leading health informatics research and e-health innovation (Buchan), including the MRC-supported Health eResearch Centre (HeRC, www.herc.ac.uk) of the national Farr Institute for Health Informatics Research. ICVS leverages this concentration of methodology to enhance its work with national audits in cardiac surgery, interventional cardiology and heart failure, using data from national societies at the National Institute of Cardiovascular Outcomes Research (NICOR), and analyses and tools from HeRC provided collaboratively to Mamas and Bridgewater. In addition to its national role as a methodology hub for the Farr Institute, HeRC provide a regional network of health informatics research and education covering North England's 15 million population in concert with the Northern Health Science Alliance and N8 universities. HeRC is hosted by the Centre for Health Informatics in the Institute of Population Health, which has delivered some of the UK's strongest research outputs in health informatics and spun out a services arm, embedded in the NHS, known as Northwest eHealth (www.nweh.org.uk). Over the past five years this combination of research and applications has generated around £50 million investment in the regional economy, mainly from RCUK and industry. Collaborations with the ICVS are currently focused on: 1) statistical automation and novel statistical methods for clinical governance analysis and decision-support; and 2) software for networked clinical governance analysis.

Research Achievements

Miller and Schmitt performed the most comprehensive histological validation to date of T1 mapping / extracellular volume fraction quantification, an emerging CMR application that has the potential to significantly improve cardiovascular risk stratification and treatment monitoring, particularly in heart failure, valvular heart disease and genetic cardiomyopathies such

as HOCM. This work has led to an international research collaboration between UCL, Pittsburgh University, The Karolinska Institute and Manchester involving T1 mapping outcome-based research. Miller and Schmitt are members of the T1 Mapping Development Group, an international group that aims to facilitate the path of T1 mapping and myocardial extracellular volume quantification into clinical practice.

Mamas and colleagues studied the impact of access site choice in Primary PCI outcomes using both meta-analysis and UK national audit data from the British Cardiovascular Interventional Society / NICOR, showing a one-third lower mortality in patients treated via the transradial access site, a similar magnitude of mortality benefit to that observed in moving from thrombolysis to primary PCI. These findings have served to accelerate the adoption of radial access for primary PCI across the UK and internationally. More recently we have shown that the magnitude of mortality benefit observed in primary PCI is related to baseline bleeding risk and that paradoxically those patients at highest risk of bleeding complications (and hence at greatest risk of mortality) are less likely to receive PCI through the transradial access site.

Fitzpatrick (CMFT) has developed a device for the rapid diagnosis of AF in general practice, and working with the North West NHS Innovation Service (TRUSTECH) has spun out a company (RapidRhythm) to commercialise and manufacture the invention.

McCollum and colleagues have developed a national risk prediction model for elective abdominal aortic aneurysm repair using data derived from the Vascular Society of Great Britain and Ireland that will for the first time provide patient-specific estimates of in-hospital mortality risk for open AAA repair or EVAR.

Body (Consultant in Emergency Medicine, CMFT, and NIHR Postdoctoral Fellow) and colleagues have shown the high negative predictive value of undetectable high-sensitive troponin T at presentation in the setting of suspected acute MI, and are evaluating the performance of a clinical decision rule (the Manchester Acute Coronary Syndrome [MACS] Decision Rule), developed by the group, to reduce unnecessary admissions to hospital with chest pain of suspected cardiac origin.

Our Research Strategy

Our research strategy focuses around four clinical themes:

- Heart failure and its co-morbidities (including arrhythmias)
- Atherosclerosis and vascular surgery
- Cardiovascular imaging
- Adult congenital heart disease and obstetric cardiology.

The four clinical themes will span the spectrum from early discovery to clinical trials thereby providing a framework to allow maximisation of collaborations with basic scientists.

Health informatics will underpin these four clinical themes, in which the infrastructure will be provided by Professor Iain Buchan and his team at the North England's Health eResearch Centre (HeRC) and the Manchester Node of the Farr Institute, applying advanced methods to unlock and harness real-world evidence from health data across the north of England and nationally. This will create a world- leading multidisciplinary, multi-themed clinical e-research environment for health discovery and innovation.

Heart Failure and its co-morbidities

The future clinical research strategy around heart failure (HF) and its co-morbidities include a full clinical translational spectrum of work from investigations into immunological mechanisms that contribute to HF development through to studying the impact of co-morbidities and predicting HF outcomes using e-health records and health informatics. The overall aims of this workstream in heart failure include:

i) Defining mechanisms that contribute to the development of heart failure:

Investigating and modulating the immunological mechanisms of cardiac tissue damage and repair in human tissue from recipients of ventricular assist devices, whole cell proteomics and transcriptomics in explanted hearts with corresponding computational analysis and systems biology approaches to define signalling mechanisms in heart failure. Investigating the mechanisms underlying LV fibrosis and hypertrophy in aortic stenosis.

ii) Predicting HF development and outcomes:

Development and validation of omics based biomarkers of heart failure as part of a FP7 European programme to guide diagnosis and treatment of patients with heart failure; development of risk stratification scores for mortality and re-hospitalisation in acute heart failure syndromes using British Society of Heart Failure (BSH) National Heart Failure Audit.

iii) Investigation of the prognostic impact and management of co-morbidities in HF:

Use of health informatics to inform the impact of comorbidities such as atrial fibrillation and diabetes on heart failure outcomes using e-health records and national datasets such as the British Heart Failure Society / NICOR National Heart Failure audit to inform national practice.

iv) Define state-of-the-art device based therapy:

Determine the utility of leadless pacing technology in patients with advanced heart block and its cost-effectiveness in patients requiring immediate pacing following extraction of infected pacemakers who normally require prolonged hospitalisation; studying the utility of pacing at multiple sites in the left ventricle rather than a single site in biventricular pacing for heart failure; studying the utility of renal denervation in targeting insulin resistance in HF; role of long term circulatory support devices in advanced heart failure.

Atherosclerosis / Vascular surgery

The future clinical research strategy around atherosclerosis will focus in four areas:

i) Performance of stent technology during treatment of coronary artery disease.

We will continue our programme of systematic bench testing, micro CT and computer modelling of metallic and bioresorbable coronary stent platforms to provide insight into their mechanical limitations and performance during treatment of complex coronary artery disease.

ii) Risk stratification of interventional cardiology and cardiac surgery.

We will use national audit data from NICOR derived from the British Cardiovascular Interventional Society and British Cardiac Surgical Society. We will interrogate national BCIS and BCS databases and e-Health records to implement optimal practices in interventional cardiology and cardiac surgery.

iii) Lead and contribute to multicentre studies

To define optimal treatment strategies of coronary artery disease in both the acute and stable setting, with studies to define optimal revascularisation strategies.

iv) A personalised medicine approach for the surgical management of abdominal aortic aneurysms (AAA).

We will develop alogrithms that calculate when AAA repair optimises survival for an individual, through calculation of growth rate and risk of rupture for each individual AAA and derivation of a risk prediction score for perioperative mortality and for long-term survival.

Cardiovascular imaging

The overall aims of research focused around imaging include: to develop and validate novel imaging biomarkers of cardiovascular disease; use imaging biomarkers to better phenotype cardiovascular health and disease; assessment of the efficacy of imaging biomarkers as tools to better guide treatment, monitor disease and thus improve prognosis; lead and contribute to multicentre studies of imaging technologies and clinical trials that use imaging biomarker end-points and aid in the diagnosis and management of cardiac implantable electronic device infections.

Future methodological research based around CMR at UHSM will aim to establish 'missing link' techniques including blood oxygen level dependent imaging (allowing assessment of myocardial oxygenation), arterial spin labelling (allowing non-contrast perfusion imaging), spectroscopy (phosphorous and proton; allowing assessment of myocardial metabolism and lipid) and diffusion tensor tractography (allowing detailed assessment of myocardial fibre arrangement). CMR technologies will be applied to valvular heart disease, ischemic heart disease and non-ischemic heart disease (and are in the process of setting up a multi-centre, multi-national registry of metabolic cardiomyopathy) and the early detection and development of prediction models of chemotherapy cardiotoxicity. A programme of work around myocardial perfusion reserve with Rubidium PET to detect early microvascular dysfunction in diabetes, hypertension, and smokers is underway with use of 18-F NaF to predict vulnerable plaque and guide prognosis and interventional strategy.

Work at CMFT has demonstrated the clinical utility 18F-FDG PET combined with CT in the diagnosis of early cardiac implantable electronic device (CIED) infection with high sensitivity and specificity. This work will be the basis of a multi-centre national study to develop imaging pathways to define a strategy for the investigation and management of CIED.

Obstetric Cardiology / ACHD

Future research in obstetric cardiology will focus on: i) risk stratification of women with cardiovascular disease to be able to accurately predict pregnancy outcomes ii) optimal medical management of women during pregnancy with CV disease. The obstetric cardiology group will investigate whether a cardiopulmonary exercise test (CPET) during pregnancy can predict pregnancy outcomes in pregnant women with CV disease. There is surprisingly little data on the response to exercise testing in normal pregnancy at different gestations, and therefore no normal ranges for pregnancy and minimal data relating to women with CV disease. Over the next five years, the obstetric cardiology group will develop a programme of research focused around risk stratification in pregnancy using CPET testing.

The management of women with prosthetic heart valves in situ embarking during pregnancy is unclear, with a lack of good quality data relating to optimal anti-coagulation strategy with multiple different anti-coagulant regimes currently in clinical use. The recent European Society for Cardiology guidelines called for research to identify the best anti-coagulant treatment for pregnant women. Various expert groups have suggested that women themselves should make an 'informed choice' about which regime to use - but currently there is very little evidence to aid them in this choice. A population based study initiated by the obstetric cardiology group in collaboration with the National Perinatal Epidemiology Unit, University of Oxford and facilitated by the UK Obstetric Surveillance System (UKOSS) data collection system will aim to report the incidence of fetal and maternal complications in women with prosthetic heart valves in pregnancy, using different anticoagulation regimes.

Further research in ACHD will include studies looking at systemic right ventricular function and fibrotic markers in patients with transposition of the great vessels. The clinical service is collecting patients for genetic studies of CHD. We are creating animal models of pulmonary valvular regurgitation and diseases of other valves.

Hypertension and Vascular Biology

Aim

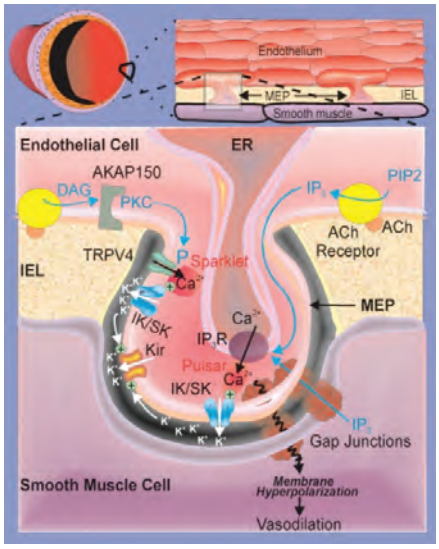
To study vascular structure and function in health and disease and understand better the mechanisms that lead to increased circulatory mortality and morbidity. By doing so, to develop new therapeutic strategies that will improve patient care.

Expertise

Our PIs are: Ann Canfield, Adam Greenstein, Anthony Heagerty, Cathy Holt, Paul Kingston, Mark Nelson (20%), Jaqui Ohanian, and Vasken Ohanian. We have expertise in the investigation of arterial calcification, lipid second messenger traffic, arterial ageing, atherosclerosis, perivascular adipose tissue function and ion channel activity and smooth muscle function. This is applied to clinical phenotypes such as hypertension, heart failure, coronary artery disease, obesity and diabetes. The bulk of this group's activity is located in our state-of-the-art laboratories on the third floor of the Core Technology Facility adjacent to the Wellcome Trust Clinical Research Facility where human tissues for in-vitro vascular studies can be obtained from carefully classified patients. We therefore have the capacity to study cellular and molecular mechanisms of function in small arterial tissue either in dispersed cells or after culture or in intact segments from models of disease or human tissue.

Specific technical expertise includes:

- wire and pressure myography
- calcium imaging using confocal microscopy
- gene transfer to modulate function
- lipid second messenger assays
- vascular electrophysiology and patchclamping
- differentiation assays and imaging
- mouse models of atherosclerosis
- rodent models of vascular calcification in chronic renal failure.
- large animal (pig) model of stenting and myocardial infarction



Signalling pathways between endothelial and smooth muscle cells

Research is supported by the MRC, BBSRC, Wellcome Trust, BHF, EU, Heart Research UK, NIH and industry. The group has multiple skills and together with collaborators in the Faculty of Life Sciences presents a multidisciplinary approach to clinical questions. We also have a number of highly successful collaborations with colleagues in Psychiatry, Rheumatology and Immunology.

Research

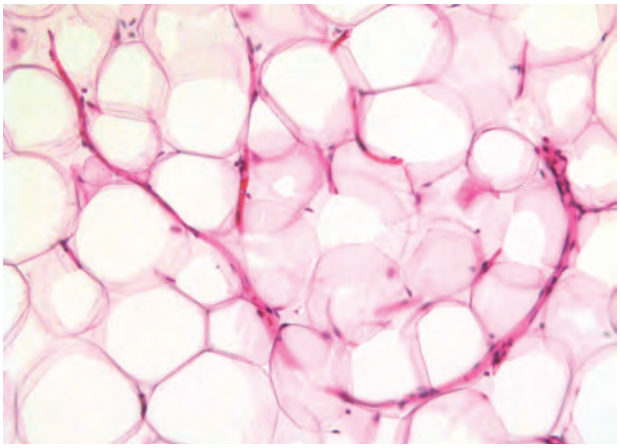
Recent achievements

Sarah Withers established an in-vitro method of investigating the effects of changes in extravascular pressure on arterial reactivity which mimics uterine contraction (Withers et al Placenta 2013). Canfield reported that mesenchymal stroma/stem cell fate and vascular induction are regulated by inhibiting PDGF receptors or depleting fibronectin (Ball et al Stem Cells 2013). Greenstein and Heagerty demonstrated that weight reducing surgery improves adiponectin bioavailability in adipose tissue and restores normal perivascular anticontractile function despite the persistence of morbid obesity (Aghamohammadzadeh et al JACC 2013). Holt showed that encapsulated glucagon-like peptide-1-producing mesenchymal stem cells have a beneficial effect on the failing heart (Wright et al Stem Cells Transl Med 2012). Izzard reported that intrinsic genetically determined changes in myogenic tone may contribute to stroke susceptibility (Delaney et al J Hypertension 2012). Kingston used his expertise in virus-mediated gene transfer to increase expression of HCN2 and increase pacemaker rate of the atrial pacemaker tissue (Morris et al Cardiovascular Res 2013). Nelson discovered that specialised myoendothelial projections serve as bidirectional signalling hubs between endothelial and smooth muscle cells and recently showed that elementary calcium signals through fewer than three TRPV4 channels per cell is sufficient to cause maximum vasodilatation through activation of calcium-sensitive potassium channels. (Sonkusare et al Science 2012). The Ohanian group demonstrated that endothelin 1 stimulates arterial VCAM-1 expression through p38MAPK-dependent activation of neutral sphingomyelinases (Ohanian et al J Vasc Res 2012).

Future research strategy

Small artery function in health, hypertension and obesity

Obesity is a pandemic condition with profound effects on cardiovascular risk. A substantial proportion of the adverse effects of obesity on cardiovascular health stem from the increase in blood pressure associated with higher body mass index (BMI). We have an established international profile in characterising the effects of perivascular adipose tissue (PVAT) on small artery function, having discovered a novel role of this tissue in regulating small artery function in 2009. In health, PVAT has a vasodilatory effect on the arteries which it surrounds through the release of a variety of hormones, including adiponectin.



Fat cells surround a small artery.

However, in obesity, the vasodilator function of PVAT is lost and the ensuing increase in contractility of small arteries contributes to the development of hypertension. PIs in the vascular biology group will pursue different aspects of PVAT function in health and disease. We will characterise the adipokine profile released from healthy PVAT, its dysregulation in disease states and the responsible mechanisms. We will do this in animal models and in tissues harvested from intensively phenotyped patients and healthy controls, collaborating with colleagues in Diabetes, and the bariatrics service. We will further investigate the mechanisms underlying the role of inflammatory cells in PVAT structure and function, which we recently discovered. We will investigate the effects of renal denervation on PVAT function and susceptibility to Type II Diabetes. By identifying the mechanisms whereby PVAT function is impaired in obesity, we will aim to develop strategies to restore the lost PVAT function in obesity, and potentially prevent the rise in blood pressure that accompanies increased BMI.

We will seek to better understand the importance of local calcium signalling in small vessels in physiological and pathological states. Using unique mouse models including genetically encoded calcium biosensors in the vascular endothelium (GCaMP2) and models offering the capacity to make smooth muscle-specific ratiometric measurements of calcium (GCaMP5-mCherry) we will examine the effects of chronic stress, Ang-II induced hypertension, and cerebral hypoperfusion on neurovascular coupling. We will use a mouse model of CADASIL, a monogenic form of small vessel disease resulting from mutations of the NOTCH3 gene) to characterise cerebral arterial smooth muscle function in this condition. Recent results support the concept that endothelial-dependent vasodilation of resistance arteries is enabled by MEP-localised AKAP150, which ensures the proximity of PKC to TRPV4 channels and coupled channel gating necessary for efficient communication of the endothelium to the smooth muscle cells in arteries. This molecular configuration is disrupted in mouse models of hypertension. We will explore these same mechanisms in the endothelium of intact resistance arteries from humans (control and obese). We will also investigate the role of calcium signalling via the BKCa channel in modulating the activity and function of PVAT.

Dysfunction of the extracellular matrix (ECM) plays an important role in the development of cardiovascular disease. We are investigating ECM proteins in different animal models of hypertension and stroke, and seeking to define the molecular basis of vascular smooth muscle cell mechanosensing in cardiovascular disease. We are also investigating, using state-of-the-art proteomics and glyomics, the cell matrix biology of the progenitor cell niche, with a view to understanding how specific molecular and cellular components of the niche regulate cell fate and vascular regeneration. These cell matrix studies are conducted in collaboration with colleagues in the Wellcome Trust Centre for Cell Matrix Research, part of the Faculty of Life Sciences.

Cardiovascular Ageing

We have recently shown novel roles for the plasma membrane calcium ATPase type 1 (PMCA1) and the AMP-activated protein kinase (AMPK) on small vessel contractility and remodelling, particularly in the context of ageing, in mouse models. We will continue mechanistic investigation of these observations, focusing particularly on the effects of other cardiovascular risk factors on the development of vascular disease in the setting of PMCA1 under-expression, and on the potential role of AMPK as a developmental modulator of adult cardiovascular disease.

Cardiovascular ageing is characterised by tissue fibrosis. Working with Lisanti (Institute of Cancer Sciences), we are investigating the role of caveolin-1 in this process. We have shown that caveolin-1 ablation in the mouse results in vascular changes consistent with premature ageing, and will investigate the impact of caveolin-1 ablation on the development and progression of atherosclerosis (by crossing with the ApoE knockout mouse) and cardiac hypertrophy. We recently showed that the phosphoinositide signalling system is activated solely in lipid rafts/caveolae in small arteries and that disruption of these domains affects the contractile response. Work is on-going to establish the specific role of lipid second messengers in vascular ageing. Increased arterial stiffness is a key age-related factor in the development of hypertension; we are investigating arterial stiffness at different length scales using a variety of different techniques including atomic force microscopy and micro-CT. In the brain, impaired autoregulation has been reported in a mouse overexpressing amyloid protein, raising the possibility that small artery function may be a contributory factor in the development of some types of dementia. We will explore the myogenic properties of cerebral arteries in a mouse model of Alzheimer disease. Our expertise in virus-mediated and non-viral gene transfer to the cardiovascular system will enable us to conduct studies investigating the capacity of antifibrotic transgene expression as a means of preventing or reversing pathologies of small vessels, the myocardium, and the conducting system characterised by fibrosis during ageing.

Vascular biology of atherosclerosis

We have active research programmes in vascular calcification, sphingolipid signalling, and novel therapeutic approaches to atherosclerosis and its consequences. We are determining the mechanisms whereby specific signalling pathways (e.g. Axl and Wnt, sphingomyelinases), inflammatory proteins (eg TSG6), glycosaminoglycans, and the tissue environment regulate vascular calcification. We will evaluate the potential of newly identified agents (eg farnesyl transferase inhibitors) to prevent vascular calcification associated with chronic kidney disease in vivo. We are assessing the scope of non-viral gene transfer to deliver therapeutic genes to the vasculature and the heart. We have recently developed novel non-viral agents which we will investigate for their potential in angiogenic gene therapy, aiming to undertake clinical trials in patients with peripheral vascular disease and critical limb ischemia.

In large animal models, we will continue to investigate the feasibility of GLP-1 encapsulated eluting stem cells as a treatment for left ventricular dysfunction following MI, following our recent proof-of-concept work. We are also investigating the properties of graphene, a University of Manchester discovery, as a coating for stents to reduce complications following percutaneous coronary intervention.

Chapter 7

Stroke Research

Aim

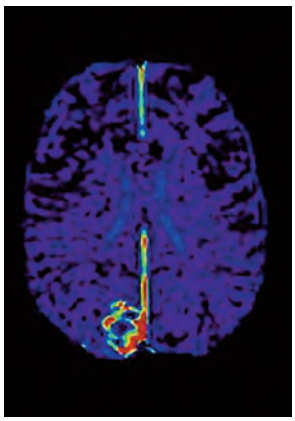
To become the leading UK centre for comprehensive stroke research (i.e. covering the spectrum from basic life sciences right across the clinical stroke pathway addressing both knowledge translation gaps: bench to bedside and implementation into clinical services) with corresponding external core funding and ultimately one of the top three international comprehensive stroke research centres.

Our priorities:

Stroke is a devastating condition affecting people of all ages, causing death and long term disability, and is an NHS research priority area and research strength of this University. Almost uniquely our research combines life sciences and inter-disciplinary clinical research, covers all clinical subtypes of stroke (including ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage) and all stages of clinical care.

We will:

- Build our research portfolio to achieve internationally recognised excellence advancing the bi- directional translation between 'basic science' and medical/surgical research, repair/recovery, acute/chronic rehabilitation, long-term support, and implementation into clinical practice.
- Develop relationships across the relevant academic and clinical disciplines: medicine, surgery, psychology, nursing, physiotherapy, occupational therapy, speech and language therapy, pharmacy, life sciences, social sciences, biostatistics, health economics, primary care, public health.
- Become 'the model of best practice' for involvement of stroke survivors and their care-givers across the research pathway to ensure our research continues to impact on clinical care, improving service delivery and outcomes for people with stroke in collaboration with commissioners and providers.
- Develop collaborations with leading international stroke centres, organisations and industry, and increase commercial/ clinical partnerships.



Dynamic contrast enhanced MR imaging demonstrates increased blood-brain barrier permeability surrounding the haematoma

Our strengths:

High calibre inter-disciplinary research team - With a proven track record of taking discoveries from basic science into clinic via funded clinical trials in subarachnoid haemorrhage and ischemic stroke, and rehabilitation of communication and mobility, with affiliates from the Faculties of Life Sciences (FLS), Medical and Human Sciences (FMHS) and Manchester Business School (MBS), and NHS centres. Our ICVS substantitve PIs are Professor Pippa Tyrrell, and Drs Adrian Parry-Jones (NIHR Clinical Lecturer in Stroke) and Mr James Galea (NIHR Clinical Lecturer in Neurosurgery). Key NHS colleagues include Andrew King, Professor of Neurosurgery.

Substantial research grant income (2008-13) - Stuart Allan, Nancy Rothwell and colleagues (Pinteaux, Brough, Lawrence) in the Faculty of Life Sciences bring expertise in experimental models of stroke (£5.2 million from the MRC, EU, BHF, Wellcome Trust). Stroke dysphagia studies are led by Shaheen Hamdy (Wellcome Trust, BBSRC) and evidence our commercial success (Phagenesis – http://www.phagenesis.com). Matt Lambon-Ralph is internationally recognised for his functional imaging studies in neuroscience (MRC, NIHR). Sarah Tyson leads a research programme into physical rehabilitation following stroke and the organisation of rehabilitation services (NIHR, ESRC, charities £2.7 million). Audrey Bowen leads on neuropsychological rehabilitation studies (cognition, communication) and user involvement (NIHR, EU £3.5 million). Ruth Boaden, Pippa Tyrrell and Sarah Tyson lead on NIHR funded implementation research including the CLAHRC 2, HS&DR and KTPs respectively.

Impact – Our stroke research has resulted in two REF 2014 impact case studies: Bowen, Tyrrell, Vail, Lambon-Ralph (UoA 4) and Boaden, Tyrrell (UoA19). All eligible members have been returned to REF2014. Highly cited papers have been published in journals such as: Stroke, BMJ, Health Technology Assessment, Cochrane, PNAS, Blood, Neuron, Journal of Neuroscience. Members collaborate with senior NHS policy makers engaged in improving regional and national service delivery e.g. through the (new) Strategic Clinical Networks (Tyrrell, Tyson) and Intercollegiate Stroke Working Party (Tyrrell, Bowen) respectively.

Patient, public and user involvement - Members actively engage in outreach activities to promote our research on stroke (Allan, Rothwell, Lawrence). We have an exemplary record of research user involvement e.g. the Manchester-led ACT NoW research was chosen as a case study of best practice by the NIHR Stroke Research Network (Bowen, Tyrrell, Vail, Lambon-Ralph).

Research networks - Our members play key national and local roles in the Stroke Research Network and Stroke Association (Tyrrell, Bowen, Vail, Tyson). Our members are co-applicants on two EU COST Actions to develop international research networks in pre-clinical stroke (Allan) and aphasia (Bowen).

The stroke research group based at Salford Royal NHS Foundation Trust

Translational research – Almost uniquely our research covers the spectrum from basic life sciences right across the clinical stroke pathway addressing both knowledge translation gaps: bench to bedside (taking a treatment from laboratory studies into phase 2 studies of ischemic stroke and subarachnoid haemorrhage) and implementation into clinical services (rehabilitation and service improvement studies).

Clinical links – Strong clinical and academic collaborations have developed from working alongside the neurosurgeons (Andy King, Hiren Patel, James Galea) and stroke physicians (Pippa Tyrrell, Craig Smith, Adrian Parry-Jones) at our clinical base, the Neurosciences Centre at Salford Royal Foundation Trust, Greater Manchester's site for all neurosurgery, interventional neuroradiology and inpatient neurology and the GM Comprehensive Stroke Centre, one of the UK's largest, admitting over 1000 acute strokes each year and hosting an NIHR Hyperacute Stroke Research.

Salford Royal NHS Foundation Trust

Our opportunities:

Rehabilitation is a newly co-ordinated area of activity in the group with enormous potential for interdisciplinary collaborations within Manchester and increasing international reach. Leadership could be provided by two affiliated members Tyson (School of Nursing) and Bowen (School of Psychology).

International collaborations - We are establishing collaborations with Berlin (Charite), Melbourne (Florey Institute of Neuroscience), Brisbane (University of Queensland) and Auckland University of Technology from basic science through to rehabilitation that will enhance our research capability and international profile, enabling us to attract the highest calibre stroke researchers.

Horizon 2020 - Health and systems medicine is a key strategic area for Horizon 2020. Our two current EU funded COST Actions (Allan, Bowen) will increase our network of international collaborators and deliver opportunities to secure Horizon 2020 funding in preclinical and rehabilitation research.

Industry - Current investment by the pharmaceutical sector in stroke is limited; however, this would quickly change if significant new research areas were identified and potential therapeutic breakthroughs identified. New developments in regenerative medicine, more predictive preclinical research and our own clinical trials of an anti- inflammatory agent, if positive, would see a step change in attitude and a return of investment. Working closely with Business Development in FLS and FMHS as well as UMIP, we will place ourselves in prime position to take full advantage of any move back by industry.

Chapter 8

Education and Training

The Institute of Cardiovascular Sciences has an outstanding track record in developing early-career researchers. Our vision is to continue developing high quality, world class and innovative programmes for the training of the next generation of academic and clinician cardiovascular scientists.

We aim to:

- Build upon on our current activities by continuously improving the quality of teaching, engaging with students at all levels of education, fostering and inspiring an interest in academic training in Cardiovascular Sciences.
- Encourage the pursuit of postgraduate training for outstanding individuals seeking to develop their skills within the fields of cardiovascular health, disease and therapy.
- Continue to offer and develop outstanding opportunities in postgraduate training and career development in clinical and non-clinical Cardiovascular Sciences.

Undergraduate Training

Undergraduate teaching (UGT) in the Institute is overseen and coordinated by Professor Ann Canfield. In recognition of its importance, greater than 10% of all academic staff time is contributed to undergraduate medical education. Several academic staff have leadership roles within the medical undergraduate programme; Ann Canfield is Cross-Faculty Lead for Undergraduate Medical Education (FLS/FMHS; Phase 1), Cathy Holt is the Deputy Director for the Student Experience and leads the Manchester Medical School Communities (MMSC) project, Elizabeth Cartwright leads the Cardiorespiratory Fitness module (Phase 1) and International Relations for Manchester Medical School, Paul Kingston is the new Lead for the Heart, Lungs and Blood Module (phase 2) and Vasken Ohanian is non-clinical co-lead of Heart, Lungs & Blood module (Phase 2), Mamas Mamas is Deputy Lead of European Options.
Clinical academics play an important role in teaching medical students on ward rounds, clinics and in operating theatres.
All eligible clinical academics in the Institute are Clinical Academic Advisors; non-clinical academics act as Tutors for Personal and Professional Development, PBL tutors and MMSC Champions.
Members of the Institute deliver lectures on the cardiovascular system to undergraduate medical students, serve on mitigating circumstances, progress and Health and Conduct committees, and interview prospective medical students. The Institute recognises the importance of inspiring the next generation of clinicians into cardiovascular research and so staff supervise dissertations (PEPs) and research projects undertaken by 4th year medical students and those undertaking intercalated BSc and MRes degrees.

Postgraduate Training

The Institute of Cardiovascular Sciences runs two successful Master of Research programmes, which aim to equip students with broad based biomedical research skills with an emphasis on application to cardiovascular science. It is now widely recognised by employers and research councils that unravelling the basis of cardiovascular disease and the development of new therapies are high priority areas for investment, especially since the economic burden of cardiovascular disease is increasing. It is also recognised that a gap has opened up between the skills possessed by new graduates and the skills normally expected on entry to a research degree or an industrial research career. The MRes in Cardiovascular Health and Disease (CVHD, Programme Directors, Elizabeth Cartwright and Ashraf Kitmitto) has been specifically designed to fill this gap for those who wish to pursue a research career in cardiovascular sciences. The MRes CVHD consists of taught modules providing specialist knowledge of the principles of the cardiovascular system in health and disease, with an emphasis on emerging technologies, and two research projects consisting of a literature review and grant / fellowship proposal and a laboratory / clinical based project, which is written up as a research paper and presented as a short talk. The programme attracts students from a variety of different backgrounds (intercalating medical students, qualified clinicians and basic science students) and is designed to support and develop a diverse student population. The MRes CVHD has been running for four years, has a 100% pass rate and has trained over 35 students, of which 13 were clinicians or intercalating medical students. Students graduating from this MRes take a variety of career paths, which include PhD, clinical academia and specialty training.

Our second programme - the MRes in Cardiovascular Science (directed by Elizabeth Cartwright) - forms year one of our four year British Heart Foundation PhD Programme. This MRes provides opportunities to develop skills in a wide range of experimental techniques and gain an appreciation of the major challenges of cardiovascular research. It incorporates seminars, master-classes, tutorials and three laboratory rotations. To ensure broad training, students select each of the three mini projects they undertake from groups of supervisors who have differing research interests and, additionally, employ different experimental techniques. Successful students are awarded an MRes in Cardiovascular Sciences at the end of year one; all students completing this MRes go on to study for a PhD.

Postgraduate Research and Training

Programmes

Postgraduate research (PGR) education within the Institute is supported and developed by Jaqui Ohanian (PGR Director). Currently, there are over 70 postgraduate research students in the Institute studying the mechanisms and treatment of cardiovascular disease. Our student body is diverse with home, EU and overseas students from clinical and non-clinical backgrounds. In the past five years 60 PhD, 56 MD, 11 MPhil and 1 DSc have been awarded to students studying cardiovascular science. Currently, 90% of our postgraduate research students successfully complete their degree

programmes within the stipulated programme deadlines. In the 2014 national Postgraduate Research Experience Survey (PRES) students within our Institute scored their overall satisfaction with their degree programme as 84%, placing the Institute within the top quartile for student experience. In addition to our standard PhD/MD/MPhil programs we have a four year British Heart Foundation (BHF) PhD (Programme Director, Elizabeth Cartwright). This prestigious programme was originally awarded in 2009 and recently renewed in 2013. The award is valued at >£5.5 million and provides four fully funded studentships per year until 2018, with one matching studentship provided by FMHS. The four-year BHF PhD delivers an innovative new approach to doctoral training. Via a combination of taught and research modules students develop the necessary skill-sets to become future research leaders in cardiovascular sciences. Training is structured to encourage students to take novel, interdisciplinary approaches to key research questions. Many of our clinical students have BHF Clinical Fellowships to support their PhD. We also receive studentships from the MRC and BBSRC Doctoral Training Programs, and have held MRC CASE studentships with industry partners. Recently we have been awarded two President's Doctoral Scholarship awards.

All our postgraduate research students are taught and supervised by nationally and internationally recognised leaders, both clinical and basic scientists, in the fields of human genetics, cardiac and vascular biology, heart failure and stroke. We have excellent research facilities in both hospital and university buildings, offering state-of the-art laboratories, open write up areas and bioscience start-ups - an unrivalled environment for postgraduates to learn, network and advance their careers. Training support is extensive with the Institute playing host to a network of world-leading cardiovascular scientists and clinicians. Interdisciplinary research projects are encouraged and supported through the Institute's links with academics across the University and within the NHS hospital trusts. Weekly seminars, Masterclasses and the annual Postgraduate Showcase give our students the opportunity to meet, interact with and present their work to academics and fellow students in the Institute and the wider research community. Our recently launched student blog and newsletter (http://blogs.mhs.manchester.ac.uk/cvpostgrad/) ensures that all of our students are kept informed and in touch with relevant events.

The Clinical Specialist Training Programme in Cardiology in the North Western region provides training in all aspects of cardiology and cardiovascular medicine and is designed to offer comprehensive exposure to all specialties in order to allow Specialist Registrars to pursue career aspirations in Academic Cardiology as well as sub-specialties such as electrophysiology, non-invasive imaging, coronary intervention, adult / paediatric cardiology and congenital heart disease, as well as newer areas, such as maternity and genetics. The programme offers opportunities for doctors who wish to train flexibly, which can be readily adapted to provide protected time for academic training and research. The introduction of the NIHR programme for academic clinical fellows in 2006 has been highly successful and almost every Fellow appointed to date has gone on to either a PhD programme, a higher research Fellowship or Clinical Lectureship. Professor Anthony Heagerty is the academic lead for the NIHR programme and Professor Bernard Clarke provides mentoring of clinical academic cardiologists at all stages as a member of the Deanery specialist training committee. Both Professsor Anthony Heagerty and Professor Bernard Clarke are former training programme directors of the North West Deanery programme.

Support

It is recognised that undertaking a postgraduate degree can be challenging and that students need support throughout their studies. In addition to their supervisory team, each student has an academic adviser who acts as a mentor and guides and advises them. The Institute also has a postgraduate administrator (Joy Stewart), tutors (Cathy Holt and Andrew Trafford), a trainer (Katherine Dibb), director (Jacqueline Ohanian) and student representatives to support our students. Students' views and concerns are fed back into the Institute Senior Management Team through the Institute's Director for Postgraduate Research Education (Jacqueline Ohanian) and prompt action is taken to address them. Our students are spread across many sites in Manchester and student led meetings of the Manchester Academic Cardiology Group ensure that those based away from the main site have a forum for communication and support. Additionally, our students organise informal 'Hungry for Science' meetings to encourage interaction with the Institutes of Human Development and Inflammation and Repair. The Graduate Society provides a forum for interaction with postgraduate research students across the Faculty. Additionally, the Institute PGR Director (Jaqui Ohanian), assures that the Institute is strongly aligned with Faculty postgraduate strategy.

Career Development

Support for career development is facilitated by the postgraduate trainer (Katherine Dibb) through career training events held within the Institute and the Faculty. Additionally, the Faculty Fellowship Academy is promoted to help final year PhD students with a strong CV plan an early career postdoctoral fellowship.

Our NIHR academic clinical programme also appoints at least one new NIHR academic clinical lecturer per year. Currently the Institute hosts three NIHR clinical Lecturers. All the previous Clinical Lecturers (funded by the BHF, MRC, NHS and The University of Manchester) have gone on to obtain other NHS Consultant Posts, Intermediate Fellowships or Senior Lecturer posts. Close academic mentoring of clinical academics is provided by Professor Anthony Heagerty. Professor Bernard Clarke provides clinical mentoring to ensure clinical training is appropriate and academic time is protected

Social Responsibility and Public Engagement

MAKING A **DIFFERENCE**

We take our role in society very seriously within the Institute of Cardiovascular Sciences. Most of our research income comes from the **British Heart Foundation (BHF),** whose funds are derived entirely from public support. Therefore, we consider it particularly important to ensure that we listen to local people and provide as much exposure to our research for them as we can. We are keenly aware that it is a privilege to contribute to the improvement of the cardiovascular health of the people in the Northwest of England and beyond. Greater Manchester has the worst cardiovascular health in England; while attempting to make world-leading research discoveries, it is also important for us to make every effort to ameliorate the epidemic on our own doorstep.

The strategic aim of the Institute's social responsibility and public engagement strand is to use our position within The University of Manchester to **facilitate and promote local initiatives** which are likely to improve the cardiovascular health of people of Greater Manchester. In order to achieve this aim, we support a number of initiatives:

1. Educational outreach days

Ann Canfield has organised a series of successful hands-on interactive educational events at museums throughout Manchester. These events are staffed by members of the Institute and exhibit our cutting edge research and clinical practice.

- The Heart and Blood Vessels, The Body Experience, Manchester Museum 2013 and 2014
- The Heart as a Pump, The Body Experience, Manchester Museum, 2012
- Science Spectacular, Manchester Museum, 2012
- World Heart Day, Museum of Science and Industry 2012

Our public engagement activities are also partly supported by the major charities and funding agencies in the UK. An example of this was our Elevator Pitch events in 2013. This was a faculty wide project led by Clare Austin to inform and educate Year five (age ten to eleven) students about the research PhD students are doing across the Faculty. Our aim was to advertise the availability of postgraduate studies in Manchester and demonstrate a potential career path for budding scientists. Five schools were visited and we showed the students what a PhD is and what is involved in postgraduate study. Several postgraduate students from the Institute of Cardiovascular Sciences gave 'elevator pitches' about their projects. The project was supported by the Wellcome Trust Institutional Strategic Support Fund (Elevator Pitch: Selling our Science – £3000)

2. Bringing BHF volunteers to the Institute

We host three visits a year for BHF shop workers and volunteers. The visits typically last for three to four hours and the volunteers take a tour through our laboratories and meet with students, post-doctoral scientists and academic staff. We also organise lectures for the visitors for a more formal introduction to our science. In 2012, for example, we entertained 58 visitors over three visits. This programme, organised by Professors David Eisner and Bernard Clarke, provides both a means to support the efforts of the BHF volunteers whose commitment is the source of over 50% of the UK's cardiovascular research funding, and a way of thanking volunteers for their work on the BHF's behalf.

3. Using new media to keep up with our patients

The Grown-up Congenital Heart Disease (GUCH) service in Manchester has been a pioneer in embracing new technology to improve community services for patients. The online and mobile service has been developed by Linda Griffiths, a GUCH specialist nurse. The online transformation has been driven by ideas from the patients themselves; following a series of consultation events, and includes:

- A text messaging service so young people can access a health professional for themselves
- A website called www.hearts4teens.org.uk – now expanded to include a Facebook page so patients can contact each other for support.
- A youth forum called heart4teens that meets about three to five times a year. This has several purposes – being primarily social and educational but is also used by the team for ongoing consultation about the service.

In 2013, Linda and her colleagues Jane Hill and Mark Heyhoe were honoured for their work by the BHF with an 'Outstanding Achievement Award' presented at the annual Healthcare Achievement awards ceremony. Andrew Taylor, one of the patients treated by the team, spoke of the invaluable care he has received from Linda, his nurse: "Linda's dedication to her patients is nothing but remarkable. She set up a texting service for her patients to contact her whenever they have a life issue that conflicts with their conditions such as: sporting activities, leisure activities, alcohol, holiday travel, medication trouble, palpitations and many, many more. Her promptness to respond to our queries is always impeccable and Linda has helped so many of us carry out tasks we were afraid our conditions may not manage or dreams we deemed out of reach. She has given us the confidence to be more independent as we know help, from someone who fully understands our conditions, is just a text away"

4. Screening and treatment of vascular disease in disadvantaged communities

Professor Charles McCollum, lead for Vascular Surgery, has implemented practices which have changed the way that healthcare is delivered for patients. Funded by a major grant from the King Edward's Hospital Fund for London, Professor McCollum set up community clinics for the treatment of venous ulcers. The Community Leg Ulcer Services that were developed in Manchester became the national model for

treating patients with venous leg ulcers in the community using multilayer bandaging. Professor McCollum is also the director and co-founder of the Greater Manchester Abdominal Aortic Aneurysm Screening Programme, responsible for delivering screening for aneurysms in 65 year old men throughout the population of Greater Manchester. The screening programme is supported and improved by patient-driven events and publications, with a particular emphasis on disadvantaged communities.

5. In-reach at schools and community centres

Many of our faculty work is with sixth form students who are keen to pursue a career in science and medicine. We provide placements, both laboratory and clinical, in order to enhance their profiles, assist in the preparation of personal statements and arrange mock interviews. These are usually arranged through the Nuffield scheme, but we also accept applications directly from students on an informal basis. We lecture on the cardiovascular system both in schools and in wider forums, such as rotary clubs or radio. Ann Canfield is medical sciences editor of Biological Sciences Review, a magazine read by over 14,000 AS/A-level Biology students and their teachers each year. This magazine aims to convey, in a lively and readable way, the excitement of modern Biology and recent developments in research. Several members of the Institute have written articles on the cardiovascular system and heart disease for this magazine.

6. Science Stroke Art 2014

In May 2014 a unique collaboration between the Stroke Association and the University of Manchester was launched with Science Stroke Art 2014 www.sciencestrokeart.co.uk. This was a series of events that included a Stroke Story Event in the John Rylands Library, stroke poetry, a Pint of Science evening on stroke (Brains on Fire) and a Pi event at MOSI.

Notes

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