William Harvey Research Institute

At twenty five and beyond

Queen Mary University of London
Barts and The London School of Medicine and Dentistry
Chronology

The development of the William Harvey Research Institute (WHRI)

1986
WHRI created with sponsorship from Glaxo Group Research

1991
Joins the Association of Medical Research Charities

1996
Becomes an integrated pharmacological research centre with incorporation of Clinical Pharmacology

1999
Transfer of Bone and Joint Unit from The Royal London

2000
Merger with Barts and The London Medical College, & thus with QM to becomes the Division of Pharmacology (WHRI = 140 people)

William Harvey Research Foundation takes over charity functions

2001
Transfer of Endocrinology from Barts growing WHRI to 180 people

2003
becomes one of six Institutes in the re-organised School of Medicine & Dentistry

2004
rated in top 20 pharmacological institutes in world by isicited.com

2006
Celebrates 20th anniversary

2007
Creation of Centres of Experimental Medicine & Rheumatology & Microvascular research and grows to 240 staff & students

2008
65% of research rated as World leading or internationally excellent by the UK Research Assessment Exercise.

Award of the National Institute for Health Research Cardiovascular Biomedical Research Unit.

2011
Opening of the 25m William Harvey Heart Centre

2012
Awarded a further National Institute for Health Cardiovascular Biomedical Research Unit and an Arthritis Research-UK Early Arthritis Centre
William Harvey Research Institute

At twenty five and beyond
Stained glass window of William Harvey by the artist Matthew Lloyd Winder installed in The William Harvey Heart Centre opened in July 2011
William Harvey (1578-1657)

William Harvey was educated at King’s School, Canterbury and Gonville and Caius College, Cambridge. He studied medicine in Padua, Italy (1600-1602), and then returned to England to practice. In 1607 he became a Fellow of the College of Physicians. Two years later he was appointed Physician to St Bartholomew’s Hospital, a position he held until c.1644. He was also Physician Extraordinary to King James I from 1618, and later Physician to King Charles I.

William Harvey’s training in Padua provided him with the most advanced medical knowledge of the time. At St Bartholomew’s Hospital he continued to study the function of the body’s organs. These investigations led to his discovery of the circulation of the blood, which he described in his classic work of 1628 *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (*The motion of the heart and blood in animals*). Almost four hundred years later, research into the regulation of the circulation still represents one of the most important efforts to identify new medicines to prevent heart disease, and to treat rheumatoid arthritis, renal disease or the many complications of diabetes.
This heart shaped arrangement of cells was spotted through a microscope by Dr Mathieu-Benoit Voisin, a fellow working with Prof Sussan Nourshargh of the WHRI. This image won the British Heart Foundation Art of Science Award in 2009-10.
Contents

Introductions
Vice Principal for Health-Richard Trembath 6
Principal Simon Gaskell 7
A farewell from the Warden-Nick Wright 8

25 years of the WHRI-Mark Caulfield 9

Current Research in the WHRI 14
Cardiovascular 14
• New Faculty in Focus 18
• Young Fellows in Focus 24

Endocrinology 28
• New Faculty in Focus 31
• Young Fellows in Focus 33

Inflammation 36
• Young Fellows in Focus 39

High Impact Papers since 2008 42

New initiatives in the last 5 years 44
Barts National Institute for Health Research 44
Cardiovascular Biomedical Research Unit 44
The William Harvey Heart Centre 45

Public Engagement at The WHRI 46

WHRI Alumni 48
Professor William Sessa – Cardiovascular 48
Professor Mike Thorner - Endocrinology 49

Teaching and Learning 50
Overview of the PhD programmes that WHRI offer 50
Graduate Entry Medicine 51
Masters at the WHRI 51

The William Harvey Research Foundation 52

William Harvey Ltd 53

Prizes 54
Welcome from the Vice-Principal for Health (2011 - current)

It is my great pleasure to write this welcome note to celebrate the Silver Jubilee of the William Harvey Research Institute (WHRI). I had just joined Barts and The London School of Medicine and Dentistry, last summer, when I was asked to present at the Annual Research Review of the Institute that was also celebrating 25 years of research successes. I was, and remain, truly impressed by the quality of the research undertaken within WHRI, a quality that is evident across all three of the main areas of research focus. In particular, I was gratified to see the WHRI’s investment in the future with exciting presentations by a number of high flying young fellows, supported by prestigious fellowships (NIHR, MRC, Wellcome, BHF and AR-UK, to name just a few). Whilst important to recognise past-achievements, as new head of the School I am looking to build upon past success through investment in early career researchers.

The near completion of our new Hospitals, through Barts Health Trust, presents us with a unique opportunity, particularly relevant to the WHRI, to further translate and extend the basic and clinical research, conducted within the Institute and the wider Medical School, into therapeutics that will benefit our local community and beyond. I am fully committed to the vision of translating our research excellence into benefit for patients, through the identification of new biomarkers for disease stratification, or new therapeutic opportunities and devices, to be developed within our School or through our strategic alliances, such as the recent relationship established with UCL Partners.

Our location, in East London, gives us access to a large patient population, a significant burden of diseases typically associated with multiple comorbidities. The distinct ethnic backgrounds, represents a further ‘unique’ opportunity to contribute to fundamental discoveries, related to disease pathogenesis and patient stratification based on new targets and biomarkers. The WHRI, with its new Clinical Trial Unit within the Heart Centre, its vibrant basic and clinical research in areas that map to major complex disorders, represents a fundamental component of the School’s plan to push this imperative forward, assuring not only the Institute’s development but also growth of the School of Medicine and Dentistry.

Well done to all and my personal thanks for the excellence that you are renowned for:

Richard Trembath FMedSci
Vice-Principal for Health,
Queen Mary University of London and Executive Dean of Barts and The London School of Medicine
I am delighted to write this brief introduction to the new brochure celebrating the silver jubilee of the William Harvey Research Institute. The great research institutes of the world typically combine a distinguished history and a great sense of ambition. The WHRI has both in abundance. The foresight of the late Sir John Vane in establishing a pioneering pharmacological research institute has been followed by a broadening and deepening of the original vision, so that the Institute is now recognised to be amongst the top tier of such research establishments. The realisation of the ambition to set up a Heart Research Institute at Charterhouse Square represents the latest milestone in the WHRI’s development. No such ambitions are achieved alone and the support in this venture of the Medical College of St Bartholomew’s Hospital Trust, of Quintiles Transnational Corporation, the National Institute for Health Research, the Charles Wolfson Charitable Trust and the Wolfson Foundation has been critical. New academic appointments will ensure the success of the new Centre.

Medical research of the highest quality depends also on broad and effective intellectual interactions, and on a facility for translation of discovery into clinical practice. Thus, the location of the WHRI within the Barts and The London School of Medicine and Dentistry, and within Queen Mary University of London provides a stimulating intellectual environment, while the close interaction with the Barts and The London NHS Trust and healthcare partners across East London ensures a continuing connection between discovery and practice.

Twenty five years represents a substantial period of success for the WHRI, but is short in the context of a medical institution that includes the work of William Harvey within its heritage. I have no doubt that much of the history of the WHRI is yet to come, but if the first twenty five years come to be viewed as no more than its adolescence, what a precocious youngster it will appear to have been!

Simon J Gaskell
Principal
A farewell from the Warden (2001-2011)

2011 was a great year for the William Harvey Research Institute – not only did they celebrate their Silver Jubilee, but they also opened the new William Harvey Heart Centre on Charterhouse Square – an event we had been looking forward to for some time.

Twenty-five years is a comparatively short time in which to establish a reputation and brand name as strong as the William Harvey Research Institute has done over this period – although I am sure such success was engrained in Sir John Vane’s vision when, in 1986 he established the Institute at St. Bartholomew’s Hospital Medical College. Over this period the Institute has become internationally-renowned for its seminal contributions to clinical pharmacology in its widest sense, and has become a beacon for attracting talent in the fields of cardiovascular medicine, endocrinology and rheumatology under the inspirational leadership of Professor Mark Caulfield.

I suppose, in a way, the success of the William Harvey Research Institute reflects in microcosm the research success we have enjoyed right across the School: it is very difficult indeed to find a sphere where Barts and the London clinical academics and scientists have not made a major contribution in recent years, and I do not think it is an exaggeration to say that this is reflected in the general acclaim for the standing which our research has reached over the last 10 years.

It is usually said that the possession of fine buildings do not necessarily presage research success for the future: however, we should reflect on the success of the Blizard Institute, possibly engendered by that fine building; in which case we shall be looking for even greater things from the William Harvey Research Institute over the next 25 years!

It only remains for me to express our heartfelt thanks to the late Mr Clive Priestley and the members of the Medical College of St Bartholomew’s Hospital Trust for making our Heart Centre a reality, and for me to wish the William Harvey Research Institute the very best of luck for the future. It has been a privilege to be associated with your success.

Sir Nicholas Wright
Warden, Barts and the London School of Medicine and Dentistry
25 years of the William Harvey Research Institute (WHRI)

In 1986 the Nobel Laureate, Professor Sir John Vane FRS established the William Harvey Research Institute at the Medical College of St Bartholomew’s Hospital together with friends and co-founders Derek Willoughby, Gus Born FRS, Erik Angaard, Iain MacIntyre FRS and Rod Flower FRS. I doubt they could have imagined that it would become the largest Pharmacological Centre in the UK and one of the premier Pharmacological Institutes in the World.

Our alumni from the past 25 years are now spread across the globe running major research groups in the world’s leading universities such as Yale, St Louis, Singapore, Milan and leading Pharmaceutical companies and Biotechnology industries.

The William Harvey at Queen Mary University of London.
Since 2000, as part of Barts and The London Medical School and Queen Mary, University of London, the WHRI and the Medical School have gone from strength to strength. In the 2008 Research Assessment Exercise the Medical and Dental School was ranked overall 5th in the UK for World Leading or Internationally Excellent research. Over this same period the Medical School’s research spend increased from £18.7m to over £60m.

As we move into our 26th year it is a genuine delight to be able to share some of our real successes with you and, in particular; the growth in depth and quality of our programmes in cardiovascular, inflammation and endocrine research. Our goal is to combine talents from different disciplines, such as, genomics, cell biology, pharmacology, with translational bench to patient studies and large-scale clinical trials, all with the ambition of therapeutic innovation. The very nature of pharmacological research endeavour requires thinking outside the confines of research silos that might be limited to organ-based or very specific disease processes.

Research success at the WHRI - the UK’s largest Pharmacology Research Institute.
Under the stewardship of Prof Mark Caulfield as the Institute Director, the WHRI has now become the largest pharmacological research institute in the United Kingdom University Sector and larger than most in Europe. We have grown from 140 people, in 2002, to number; in 2012, over 330 clinicians and scientists, including 93 graduate students with multiple new Chairs, Groups and talented young researchers. Even since our 20th anniversary we have enlarged substantially with 28% growth in staff and graduate students. This period of growth has been accompanied by a transformation of our research quality; in the 2008 UK Research Assessment Exercise 65% of our research was rated as world leading or internationally excellent. In 2006 we were ranked position 17 amongst the top twenty pharmacological centres in the World by Thomson Reuters (ISI cited 2006).

Taking our research at the WHRI and Queen Mary to the next level.
Further evidence of success is showcased herein through the work of our younger scientists who will become the leaders of tomorrow. Their success can be measured with over 45 publications in the highest impact journals since 2008 (Nature Journals, New England, Journal of Clinical Investigation, Journal of Experimental Medicine). Together with the research endeavour of our senior faculty in just two years we have increased our Programme Grants from 6 to 10, and in addition we hold two major EU Framework 7 awards on stem cell research. Most recently one of our very talented new recruits has won a Bill and Melinda Gates Foundation Award of $1m. The research quality of our arthritis
Sir John Vane (1927-2004)
Founder of the William Harvey Research Institute
programme has been recognised by award of a further Oliver Bird PhD Programme by the Nuffield Foundation and a National Institutes of Health Research (NIHR) Experimental Medicines Evaluation Programme in stratified arthritis care. In 2007 our hypertension research was recognised by award of European Society of Hypertension Excellence Centre status. Capitalising upon our strong portfolio of experimental models and wealth of experience in integrative physiology and pharmacology our Endocrine theme led a successful Medical Research Council application for an in-vivo MRes/PhD programme which has just been renewed as an MRes programme for the next 3 years.

| The upward trajectory of the William Harvey Research Institute 2001-2012. |
|-------------------|-------------------|-------------------|
| Clinicians and Scientists | 140 grew to 240 | 240 grew to 330 |
| Top papers       | 25 over 7 years   | 35 over 4 years   |
| Programme Grants held | 6 (1 MRC, Wellcome, 1 National Multiple Sclerosis Society (USA) & 1 EU) | 12 (1 MRC and 1 NIHR Stratified Medicine Award, 5 Wellcome, 3 BHF, 1 Gates Award, 1 Wellcome Investigator Award) |
| RAE rating       | 65% outputs 3* or 4* |
| Infrastructure   | John Vane Refurbishment commenced | Heart Centre opened |
|                  | John Vane refit finished |

The William Harvey Translational Research Philosophy

A real advantage of the WHRI model for therapeutic innovation is that it fosters a two-way flow of hypothesis generation from the scientist at the bench, through the clinician, to our patients and then back again in the form of clinical data, samples, and experience. This means any scientist can develop a new diagnostic or validate their therapeutic target and then use genomics or proteomics to explain variation in patient response and disease outcomes. In the following pages we describe some of our research programmes and talented individuals that contribute to this translational programme.

Our National Institute for Health Cardiovascular Biomedical Research Unit at Barts.

The strength of our programmes in cardiovascular disease have been recognised by the award in 2008 of a Cardiovascular Biomedical Research Unit to Barts Health of £5.45m. This success reflects the partnership between the WHRI and clinicians in our allied NHS Trust from which we have transformed our cardiovascular research and created an advanced cardiac imaging centre. Perhaps the strongest endorsement of our research programme is that the progress made has been rewarded with award of a further NIHR Cardiovascular Biomedical Research Unit (£6.55m) for a further 5 years (2012-2017).

Our Arthritis Research-UK Early Arthritis Centre and NIHR Translational Research Partnership.

Our musculoskeletal programmes have secured in open competition an NIHR Translational Research Partnership to enhance academic/industrial collaboration to develop early molecules to translation. This has paved the way for award of an Arthritis Research UK Early Arthritis Treatment Centre led by Prof Cos Pitzalis which will accelerate concepts into the clinic and disseminate our national leading expertise in ultrasound directed synovial biopsy of the joint in rheumatoid arthritis.

Our Child Health Research Centre appeal for Paediatric Endocrinology.

Endocrinology is now a major theme at the WHRI and with many successful clinical and scientific training fellowships for young researchers. Part of the success of this research strand relates to the paediatric to adulthood approach which we take to endocrine disease. Recently, Adrian Clark led a successful fundraising appeal for £700k toward a Paediatric Endocrine Chair which has led to the appointment of Prof Leo Dunkel, an international leader in the field of paediatric endocrine research, to the Chair of Paediatric Endocrinology.

The unique Charterhouse Square Campus of Barts and The London/Queen Mary

A specific strength of the WHRI is the environment with state of the art facilities in the John Vane Science Centre, on the picturesque and historic Charterhouse Square campus of Barts and The London completely refurbished between 2000 and 2010. This campus also offers a superb collaborative environment with the first Cancer Research UK Clinical Centre known as the Barts Cancer Institute within the same building and providing important collaborative links in inflammation,
25 years of the William Harvey Research Institute (WHRI)

angiogenesis and signalling. The world renowned Wolfson Institute of Preventive Medicine adjacent where research has led to folic acid supplementation of staple food in 40 countries to prevent spina bifida and to improve the treatment and prevention of breast and cervical cancer.

Investing in faculty for the new William Harvey Heart Centre at Queen Mary.

In a major partnership with the Medical College of St Bartholomew’s Hospital Trust we have completed a £25m investment in cardiovascular research by opening in 2011 the new William Harvey Heart Centre. Our distinctive strategy for this Heart Centre combines new basic science strengths in the study of how genes raise blood pressure, and how disorders of heart rhythm are triggered, alongside high-calibre stem cell biology and biomarkers research. These new basic science strengths will generate novel concepts, which combined with extant top-class pharmacology will help realise our ambition of translating discoveries into cardiovascular clinical care at the new Barts hospital and elsewhere. We are also extremely grateful for funding from the National Institute for Health Research, Quintiles Transnational, Charles Wolfson Charitable Trust, the Wolfson Foundation and the Barts Foundation for Research.

To deliver this mission we have appointed 3 new cardiovascular chairs and groups:

• Prof Andrew Tinker FMedSci who holds Wellcome and British Heart Foundation Programmes and leads a major new group investigating disorders of heart rhythm. His work will functionally characterise and investigate novel therapeutic targets generated from these genetic studies working alongside our strong clinical electrophysiology group at Barts Health NHS Trust.

• Prof Adrian Hobbs who holds a Wellcome Trust Programme and BHF and BBSRC funds. His group focuses on the guanylate cyclase family of enzymes and the interaction between nitric oxide and natriuretic peptides in the cardiovascular system. He will develop new therapies for heart disease prevention and has brought translational research in pulmonary hypertension to WHRI.

• Prof Federica Marelli-Berg holds a British Heart Foundation Programme to investigate cardiovascular immunology and has just won the College’s first Bill and Melinda Gates Foundation Award.

The William Harvey Heart Centre has been built to complement the tremendous opportunities arising from the concentration of cardiovascular clinical care at the adjacent newly rebuilt St Bartholomew’s Hospital which will open in 2014. To really capitalise upon this platform we are embarked on a further phase of expansion with more new cardiovascular faculty joining us here at WHRI and Queen Mary.

Success in commercialising intellectual property.

The WHRI is committed to fully exploit the commercial potential of our research pipeline and have progressed partnerships by licensing two patents to Unigene Corporation (Fairfield, NJ) to generate lead candidates for annexin. As part of this deal, we have worked together with this US Biotech to attain a therapeutic benefit from the synergism between calcitonin and glucocorticoids for the treatment of rheumatoid arthritis and other forms of arthritis. In addition, we aim to capitalise on Unigene Corp. proprietary know-how on peptide production and peptide oral delivery to give impulse to the development of novel fragments of the anti-inflammatory protein Annexin A1 (patented June 2012) for the treatment of post-ischaemic pathological conditions.

In a separate programme with MRC Technology we have high throughput screening for drug targets for the melanocortin 3 receptor and formyl peptide receptor. In a distinct programme scientists won the National Innovation of the Year Award for their work on an inhaled nitric oxide delivery system for use in ventilated patients and possibly in chronic obstructive pulmonary disease. Recently members of the WHRI have been more engaged in device development with a novel approach to prevention of venous thrombosis know as Gekko being brought to market.

Converting WHRI research into benefits for patients

The new Heart Centre has offered the opportunity to completely modernise our Clinical Research Facility whilst retaining it within the midst of our faculty. This is a deliberate commitment to generate a high cadre of researchers who are focussed on basic science with translational potential to clinical development. The work of Amrita Ahluwalia on the potential of beetroot as a source of dietary nitrate is a BHF funded translational programme which looks very promising as a disruptive approach to blood pressure lowering. In distinctive
translational work on renal denervation for resistant hypertension which was showcased in the 2011 statement by the Prime Minister on Life Sciences we have not only been lead recruiter to the study but have led creation of a Joint Societies statement on renal denervation to support safe adoption into healthcare.

Our work is not confined to translation of bench to small numbers of patients but we have also made substantial contributions to later phase studies such as 1157 patients as the largest patient contribution to the ASCOT study. This continues to change clinical practice, with new International Guidance for cholesterol lowering and blood pressure reduction. Indeed our faculty co-led revision of the National Institute of Health and Clinical Excellence Guidance for hypertension changing the approach to blood pressure diagnosis and therapy which was launched in the press with members of our expert patient group.

Since 2008 we have a major partnership with Quintiles Transnational which is the world’s largest clinical research organisation. This has led to establishment of a large-scale clinical research hub (Prime Site) where we manage over 44 clinical trials across multiple therapeutic areas. This has created enormous opportunities for our patients who suffer some of the most appalling rates of disease in Western Europe. In addition, the ethnic diversity of the community we serve provides a major opportunity to investigate new therapies which may have implications for emergent countries in South Asia and Africa. Based upon our primary care partnership 120 practices serving 500,000 people in East London we have engaged patients in advising, structuring and developing our research programmes here at WHRI.

Training the talent of the future
We lead safe prescribing training for all medical students and have established a unique computer-based safe prescribing assessment for final-year medical students. We contribute to the National Safe Prescribing Assessment which will commence across all UK Medical Schools next year and oversee year 1 of the Graduate Entry Programme (4 year medicine course for those with a degree) and offer 1 year Batchelor of Medical Science degrees. In addition we have a large number of PhD and post-doctoral students training, alongside a number of highly successful Masters programmes, including an MRC MRes in Integrative Physiology and in the Mechanisms of Vascular Disease.

The WHRI future strategy beyond 2012
The WHRI has been transformed since 2002 but this upward trajectory has simply fuelled our desire to pursue our goal of becoming the premier Pharmacological Institute for therapeutic innovation. This is greatly facilitated by our international strategic links to Harvard and other European and US centres for genomics and also to major industrial partners which together presents tremendous platforms for collaborative science which will characterise the successful centres of tomorrow. In addition, our focus for the future has been distilled further by our new Vice Principal for Health, Richard Trembath, by the demarcation of our Medical School key priority research themes of:

1) Discovery Science
2) Experimental Medicine
3) Populations and The Public.

The ethos of the WHRI coupled with our record in development of novel drug targets and device development and our recent expansion of our capabilities to translate our basic science discoveries into the clinic arena place the Institute within the heart of the Medical School aspirations.

Above: Opening of the Clinical Research Facility of The William Harvey Heart Centre in July 2011. From left to right Simon Gaskell (Principal of QMUL), Mark Caulfield (Director of WHRI) and Dennis Gillings (Founder and Executive Chairman of the Board of Quintiles Transnational).
Current Research in the WHRI
Cardiovascular

Research in Cardiovascular Health and Disease

Advancing our understanding of the physiology of the cardiovascular system and teasing apart mechanisms of disease progression within this system has been at the heart of our research aims since the inception of the William Harvey Research Institute by Sir John Vane in 1986. The early years focused on pre-clinical assessment of, amongst other factors, components of the pathways for both nitric oxide and prostacyclin generation. The more recent years have seen an expansion of our range of interests resulting in further advance in our pre-clinical work but under the leadership of Prof Mark Caulfield an additional move to effect translation of our many basic findings into the clinical arena with the setting up and effective running of a clinical trials unit. The award of an NIH Cardiovascular Biomedical Research Unit in 2008 and the establishment by Prof Caulfield of our new William Harvey Heart Centre, opened last summer, has placed our institute in prime position to take the discovery of new targets for cardiovascular therapeutics through to pre-clinical investigation and finally translation into the clinical setting. Our current research interests reflect the broad expertise available in our institute, the highlights of which are described below.

Genetics and complex cardiovascular disease

Genome-wide association studies (GWAS) in the last few years have identified a number of genomic loci underlying inter-individual differences in genetic susceptibility to cardiovascular disease particularly coronary heart disease and hypertension and/or related traits such as blood lipid levels and blood pressure. The WHRI over the past few years has made major contributions to these fields collaborating with and leading international consortia that have identified a number of novel targets for therapeutics or biomarkers. In particular Prof Shu Ye and his group have identified genetic variants at chromosome 9p21 and chromosome 10q11 locus that influence the development and progression of atherosclerosis and contributed to a large scale association study which led to the identification of a number of novel genomic loci for coronary heart disease.

Separately Professors Mark Caulfield (FMedSci) and Patricia Munroe have led GWAS in very large resources identifying the first common genetic variants associated with blood pressure and hypertension (Nature Genetics, 2009, Nature and Nature Genetics 2011) Top 5 paper in worldwide cardiovascular research 2011. More recently in 2011, Caulfield and Munroe have led the discovery of a further 16 loci. Interestingly, they have shown that all of the genetic variants discovered thus far have small effects (±1mmHg for systolic blood pressure and ±0.5 mmHg for diastolic blood pressure), and most of the variants are in genomic regions with no prior candidate blood pressure genes. Thus the results from GWAS are providing a wealth of information on new genes/pathways associated with blood pressure. The impact of targeting of these identified pathways within the newly established clinical translational facilities at the WHRI offer exciting opportunities for the coming years.

Association of SNP rs1333049 on chromosome 9p21 with a cumulative risk of cardiovascular disease in a population-based prospective study
Ischaemia-reperfusion injury and vascular inflammation

During the last decade, Prof Christoph Thiemermann (FMedSci) and his team have discovered a number of molecules that reduce the tissue injury caused by shock and ischaemia-reperfusion. These molecules include inhibitors of poly-ADP ribose polymerase (PARP), radical scavengers, ligands of peroxisome proliferator activated receptors (PPAR), especially PPAR-γ. In particular, Prof Thiemermann has shown more recently the potential of erythropoietin in tissue injury by demonstrating that it reduces the tissue injury caused by ischaemia-reperfusion (heart, kidney, liver), septic shock, arthritis and trauma-haemorrhage. To date, a number of clinical trials are being conducted to test whether erythropoietin, a drug which is currently on the market for the treatment of anaemia, also improves the outcome in adult patients with trauma and myocardial ischaemia as well as in premature babies with brain ischaemia (EPOC-study, Japan).

Endothelial Derived Hyperpolarising Factor

Separately Prof Amrita Ahluwalia with Prof Adrian Hobbs (new faculty) have focused on enhancing understanding of the pathways underlying the protection of females from cardiovascular disease. Their research has identified that endothelium-derived hyperpolarizing factor (EDHF) is upregulated in females and underlies the protection of female mice, deficient in endothelial NO and prostacyclin, from hypertension unlike their male counterparts. More recently their research has demonstrated that this EDHF plays an important role in the suppressed acute inflammatory responses in females via suppression of inflammatory cell recruitment through the targeting of P-selectin. Their current research with the support of the translational facilities of the WHRI aims to determine whether similar relationships exists in humans and what impact such differences have on vascular function.

Platelet therapy in cardiovascular disease

Prof Tim Warner leads the WHRI efforts focused on understanding the processes involved in platelet activation in cardiovascular disease. Currently Prof Warner’s research focuses on prostanoids and the way in which they regulate platelet reactivity. In particular his research focuses on the effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in blood vessels and how aspirin and NSAIDs interact with anti-thrombotic medications. Prof Warner’s scientific papers from the WHRI have been highly cited (he has been listed by the ISI as among the top 0.5% of cited pharmacologists), and in recent years his published research has been used in deciding the therapeutic guidelines for NSAID and anti-thrombotic drug use both nationally and internationally. This is of importance as 100s of millions of people take these drugs each year, and is an example of the translational nature of the basic science research conducted at WHRI.

Dietary approaches to cardiovascular disease

Cardiovascular disease now sits as the biggest killer worldwide and with projections that by 2030 30% of the population worldwide will be hypertensive there is an urgent need to identify preventative strategies that might slow and even halt this impending epidemic. Lifestyle factors have been proposed as an essential component of the clinical armamentarium against the battle with cardiovascular disease and harnessing the beneficial effects of a healthy diet is thought to represent an important stategy with substantial potential. Prof Roger Corder has produced some

Within the new clinical facility in The William Harvey Heart Centre we measure a parameter called called pulse wave velocity. This measures how healthy the blood vessels are by determining the speed at which the blood is pushed through the circulation by the heart.
of the seminal studies identifying the procyanidins as important beneficial micronutrients that can be found in red wines and cocoa products.

**Nitrate in cardiovascular disease**

Prof Amrita Ahluwalia has led another active but distinct area of research funded by the British Heart Foundation to elucidate the potential role of inorganic nitrate in the diet on cardiovascular disease. Fruit and vegetable-rich diets reduce blood pressure and risk of ischaemic stroke and ischaemic heart disease. Whilst these cardioprotective effects are unequivocal, the exact mechanisms underlying the benefits of a fruit and vegetable rich diet remain uncertain. Recent evidence has highlighted the possibility that dietary nitrate, an inorganic anion found in large quantities in vegetables (particularly green leafy vegetables and beetroot), may have a role to play. This beneficial activity lies in the processing in vivo of nitrate to nitrite and thence to the pleiotropic molecule nitric oxide. Prof Ahluwalia’s lab have led research demonstrating the blood pressure lowering, anti-platelet and endothelium protective effect of dietary nitrate in healthy volunteers. Current research focuses on capitalizing on the recent advances in translational opportunities created at the WHRI that will allow determination of the potential beneficial effects of dietary nitrate in patients with cardiovascular disease.

Prof Suzuki has focussed his research efforts on identifying novel approaches to heart failure based upon stem/progenitor cell therapy and regenerative medicine. A particular highlight of his ongoing projects include the development of a novel “cell-sheet” therapy to the heart using temperature-responsive culture dishes, thus providing an intact sheet of cardiac cells that can be placed in situ following infarction. Currently Prof Suzuki is investigating strategies that might improve stem/progenitor cell survival following intracoronary injection and particular targets include a novel TLR signalling pathway that protects cardiomyocytes via regulating their energy status as well as other approaches that might enhance the maturation of cardiomyocytes.

At the clinical end of the translational spectrum Prof Mathur has established one of the largest clinical trials for autologous cell therapy in the treatment of patients with cardiovascular disease who despite medical therapy are still symptomatic or have room for improvement. This has led to several important collaborations not only within the UK but also throughout Europe and to the recent award to Prof Mathur (who is the co-ordinator) and his 18 collaborating partners by the European Commission to design, and conduct, the definitive trial to answer the question of potential benefit of cell based therapy in acute infarction patients. Prof Mathur also led the group that drafted the only consensus document that has been published to date regarding the future of clinical trials of stem cell therapy (European Heart Journal, 2008) and continues to coordinate this important area of research through the various European centres. Prof Mathur’s prominent role has led to considerable media interest with appearances regarding the consent process and stem cell therapy for patients on the BBC Horizon programme and BBC Superdocs that was presented by Lord Winston. Prof Mathur’s leading position is recognized by his role as an expert adviser to the NHS on the future of regenerative medicine and cardiovascular disease.

**Stem cell research in cardiac disease**

The WHRI over the past 5 years has established itself as an important centre for stem cell research in cardiovascular disease. This initiative is led dually by Prof Ken Suzuki and Prof Anthony Mathur providing a continuum of basic science and clinically-oriented interests and expertise respectively that represents a truly translational approach to this field of research.

**Figure:** A dietary nitrate load in the form of beetroot juice lowers blood pressure in healthy volunteers.

**Stem cell research in cardiac disease**

The WHRI over the past 5 years has established itself as an important centre for stem cell research in cardiovascular disease. This initiative is led dually by Prof Ken Suzuki and Prof Anthony Mathur providing a continuum of basic science and clinically-oriented interests and expertise respectively that represents a truly translational approach to this field of research.
Mechanisms of renal disease
Prof Magdi Yaqoob’s work focuses on uraemia and in particular the molecular mechanisms that underlie uraemia-induced cardiovascular disease. Recent work includes the discovery that 11βHSD1 plays an important role in uraemia-induced insulin and erythropoietin resistance and the investigation of the effect of the galactoside binding proteins (galectins) upon the microcirculation in experimental uraemia. At a clinical level Prof Yaqoob’s group have shown a therapeutic effect of dietary bicarbonate supplementation to diminish the requirement for dialysis in patients with chronic kidney failure as well as the identification of two complement polymorphisms (C3) in 1147 patients that revealing that allograft outcome was not improved when matching donor and recipient for C3 sub-types in renal transplantation. Prof Yaqoob’s group have a major interest in the role of Ischaemia-reperfusion injury in acute renal injury, in particular the possible therapeutic utility of ischaemic pre and post-conditioning (IPC) in the setting of chronic uraemia. Their pre-clinical models have shown exceptional utility of these techniques and future research of course will focus on clinical translation.

Cardiac rhythms and atrial fibrillation
Prof Richard Schilling leads a group investigating the mechanisms and treatment of complex rhythm problems from the bench top to the clinical setting. Basic science projects include an investigation of the association of telomere biology and risk of sudden arrhythmic death (in collaboration with Ken Suzuki). In contrast one of their studies with immediate clinical impact is a London wide trial investigating the safety and feasibility of a novel strategy for paramedics to treat and discharge patients with cardiac rhythm problems without transfer to hospital.

The main interest of the group is translational research into atrial fibrillation, the commonest heart rhythm problem. Some of the clinical strategies developed by Prof Schilling’s research have been adopted world-wide. For this reason Prof Schilling is part of the NICE atrial fibrillation guidelines development group and is invited to meetings around the world to teach and operate. This is an area of research that the WHRI hopes to grow substantially due to significant unmet clinical need by combining Prof Schilling’s extensive clinical expertise with the basic science expertise of one of the recent Heart Centre recruits whose research likewise focuses on pathways that underlie atrial fibrillation, Prof Andy Tinker.

Advanced Cardiovascular Imaging
With NIHR support we have made a step change in translational CV research. We have done this by adding deeper cardiovascular phenotyping of patients across our translational programmes of novel therapies derived from the WHRI assisted greatly by our dedicated 1.5 Tesla cardiac MRI scanner and from access to a state-of-the-art 3 Tesla scanner. In October 2009, we performed the first non-invasive coronary angiogram on the NIHR funded state of the art and first of its kind in the UK cardiac CT scanner (dual source, dual energy). An additional NIHR Capital grant supported the setting up of a cutting edge cardiovascular imaging core lab, that allows quantification of (almost) all vascular and cardiac measurements required in our research studies. Our new advanced cardiovascular imaging centre is also an excellent educational facility for our clinical Cardiology and Radiology Registrars training in non-invasive cardiac imaging and our clinical research fellows. The London Deanery supports 6 London Advanced Cardiac CT Fellowships to be trained in our centre in partnership with two other London hospitals. We also train international Cardiology and Radiology Consultants interested in setting up a clinical CMR stress imaging service. We host two intensive courses annually which provide hands-on experience in image acquisition and image analysis and interpretation.
New Faculty in Focus
Cardiovascular

Adrian Hobbs, Professor of Cardiovascular Pharmacology

Adrian completed his B.Sc. in Pharmacology, obtaining First Class Honours, at King’s College London in 1989 and remained at the same institution to undertake a Ph.D. with Dr. Alan Gibson in the Pharmacology Department. During his Ph.D. research he made a significant contribution to the understanding of the role of nitric oxide (NO) as a neurotransmitter in non-adrenergic, non-cholinergic (NANC) nerves, using the rodent anococcygeus as a classical model of nitrergic innervation. He was also the first to demonstrate the importance of NO-mediated NANC transmission in regulating airway smooth muscle tone.

Having completed his Ph.D. in the autumn of 1992, he took up a post-doctoral position in the laboratory of Nobel Laureate, Prof. L.J. Ignarro, in the Department of Pharmacology at the University of California, Los Angeles. Adrian’s first two years at UCLA were supported by a Fulbright-Hays Research Fellowship and subsequently he was awarded a Fellowship by the American Heart Association to remain in Prof. Ignarro’s lab for a further two years. During this time, his attention turned to NO synthase itself and the biochemical mechanisms regulating enzyme activity. In particular, he focused on the bioactivity of nitroxyl (HNO) and provided the first convincing evidence that this molecule can be generated endogenously (by NO synthase). The significance of HNO to human physiology and pathophysiology is now at the very cutting edge of NO research, as it relates to host defence & cardiac function. At the end of 1996, he returned to the UK to take up a post-doctoral position at the Wolfson Institute for Biomedical Research, University College London, under the mentorship of Sir Salvador Moncada. Since that time he has established his own independent research group with extensive peer reviewed support from the Wellcome Trust, BHF and BBSRC; as well as securing his own personal funding, initially being awarded a Wellcome Trust Career Development Fellowship followed by a Wellcome Trust Senior Fellowship.

Since returning from the US, Adrian’s group has focused on the guanylate cyclase family of enzymes and the interaction between NO and natriuretic peptides in the cardiovascular system. This area of interest has taken his research into the realm of pulmonary hypertension and potentially new therapeutic approaches for this debilitating disease (Figure 2). More recently, he has initiated a programme of work that has culminated in the identification of C-type natriuretic peptide as an important endothelium-derived vasoactive peptide; in addition, he has discovered and characterised a novel signalling pathway in the blood vessel wall, triggered by CNP, involving activation of natriuretic peptide receptor-C (NPR-C) and G-protein gated inwardly-rectifying K+ channels (GIRKs) that regulating vascular tone, local blood flow and systemic blood pressure (Figure 1).

Selected publications

Figure 1: Schematic representation of the novel CNP-NPR-C signalling pathway that my group have characterised in the cardiovascular system.
Adrian has joined the Heart Centre at the WHRI as Professor of Cardiovascular Pharmacology to harness the translational potential of the environment, exploiting the exceptional links between pre-clinical and clinical research, with the goal of developing and evaluating novel treatments for cardiovascular disease stemming from his academic research findings; this will centre on ischaemic disorders (myocardial infarction, stroke) and pulmonary hypertension/heart failure.

Current research interests
The focus of his research is the physiological and pathological actions and interactions of a family of homologous enzymes, the guanylate cyclases (GC), with emphasis on the cardiovascular system. These proteins act as receptors for nitric oxide (NO) and natriuretic peptides and exert complementary cytoprotective, anti-atherosclerotic effects on the heart and vasculature. In accord, loss of these signalling pathways precipitates cardiovascular disease.

Major research areas include:
• Pharmacological and biochemical characterization of the mechanism of sGC activation by NO-donor drugs, non NO-based enzyme activators, nitroxyl (HNO), carbon monoxide (CO) and hydrogen sulphide (H2S)

• Evaluation of cellular redox status on sGC expression and activity

• Pharmacological assessment of the interaction between soluble and particulate isoforms of GC in the vasculature, in the context of pulmonary hypertension, heart failure and stroke; development of a novel combination therapy for pulmonary hypertension

• Evaluation of the (patho)physiological roles of CNP as a mammalian endothelium-derived hyperpolarising factor (EDHF) in regulating vascular tone and blood flow

• Investigation of the biological roles of the natriuretic peptide receptor (NPR)-C in regulating vascular smooth muscle, leukocyte and platelet reactivity; design & development of small molecule NPR-C agonists for the treatment of cardiovascular disease.

Prof Hobbs’s work is funded by The Wellcome Trust, BHF, MRC and The British Lung Foundation.
Medical School Themes: Discovery Science, Experimental Medicine

Current Research in the WHRI
Cardiovascular

New Faculty in Focus
Cardiovascular
Federica Marelli-Berg, Professor of Cardiovascular Immunology

Federica Marelli-Berg graduated in Medicine in 1989 at the University of Milan, obtained her Certified Board in Haematology at the University of Pavia (Italy) in 1993 and completed her PhD studies in 1997 (University of London) under the supervision of Professor Robert Lechler. In 2000 she was awarded a Governors’ Lectureship from Imperial College London, where she continued her career as a Senior Lecturer (2004), Reader (2006) and Professor of Immunology (August 2011). In November 2011 she joined the WHRI to develop the theme of Cardiovascular Immunology within the newly built Heart Centre.

Her research is supported by the British Heart Foundation (including a Programme Grant), the Medical Research Council of the UK and the Gates Foundation.

**T cell trafficking in inflammation and immunoregulation.**

The regulation of T lymphocyte motility and homing is the main focus of our laboratory. We were the first to describe that primed T cells are induced to cross endothelial cell barriers following recognition of cognate antigen expressed on the endothelium itself. This is now recognised as a key mechanism by which specific T cells ‘find’ antigen-rich tissue where they exert their effector functions. Based on this work, we have identified molecular mediators which can be targeted pharmacologically to control T cell-mediated inflammation.

For example, we have shown that the p110delta catalytic subunit of PI3K plays a key role in mediating antigen-dependent T cell trafficking. The activity of this intracellular mediator can be modulated pharmacologically with specific Inhibitors (Provided as a collaboration with ICOS Co, US) resulting in the inhibition of T cell-mediated inflammation and the development of chronic heart allograft rejection in vivo. Similarly, we have recently shown that Vav1, a GTPase activator which is recruited by TCR signalling, plays a key role in the retention of memory effector cells into target tissue. Importantly, specific inhibitors of this molecule have been recently developed and we intend to assess their therapeutic potential.

Additionally, we discovered the influence of co-stimulatory signals in determining the anatomy of T cell immunity and tolerance. These data have obvious relevance to therapeutic strategies based on co-stimulation blockade (autoimmunity transplantation and cancer). As these observation bear relevance to the disastrous outcome of the TGN1214 clinical trial in Northwick Park, following their publication we attracted a great interest in our research from both national and international press (for further information please visit the web using Marelli-Berg TGN1214 as keywords).

**Recent Publications**


Finally, we have recently investigated the role of the adhesion molecule CD31 in the regulation of antigen-dependent T cell-mediated inflammation. We focussed on this molecule as it is capable to regulate TCR signalling and it is trans-homophilically engaged during antigen presentation and lymphocyte migration. In brief, we have confirmed the key contribution of this molecule to both naïve and memory T cell trafficking, and unveiled previously unknown immunomodulatory effect of this molecule on T cell activation and tolerance. Lack of CD31-mediated interactions (which can be targeted by antibodies) leads to amplified T cell responses, which, for example, favour tumour clearance. In addition, our study has revealed a key function of CD31-mediated interactions in cytoprotection of both T cells and the endothelium. Given that a CD31 polymorphism affecting its signalling domains has been identified in humans, we aim to correlate the expression of polymorphic alleles of this molecule with the predisposition to cardiovascular diseases.

Research funded by a BHF programme grant will aim at programming the homing properties of naturally occurring CD4+ CD25+ regulatory T cells. We will apply a number of mechanisms (such as TCR- and co-stimulation-induced T cell recruitment and the induction of tissue-specific homing receptors by tissue-derived factors, see below) to programme antigen-specific Tregs, which can be selectively targeted to specific antigenic sites and organs, particularly to the heart. These studies will contribute to the application of Treg-based immunotherapy by targeting T reg localisation to specific lymphoid and non-lymphoid tissue, thus diminishing the number of Treg cells required to achieve operational immune suppression.

**Programming organ-specific T cell homing in vaccination.**

A prominent feature of protective immune surveillance - as it should be achieved by vaccination - relies upon the ability of memory T cells to patrol and efficiently access the tissue where antigen re-challenge is likely to re-occur. Based on preliminary in vitro and in vivo observations (unpublished) we have proposed that immunization with antigen together with tissue-derived factors induces the development of memory T cells with homing selectivity for the tissue (both lymphoid and non-lymphoid) where the factor is produced, thus targeting and enhancing protective recall responses, irrespective of the immunization route.

We are currently validating these findings in preclinical models of infection.
New Faculty in Focus
Cardiovascular

Andrew Tinker, Professor of Cardiac Electrophysiology

Andrew Tinker studied Medicine at Oxford University and the Royal Free Hospital Medical School, London. He then undertook a number of clinical jobs and further postgraduate training. His interest in cardiovascular research began following the award of an MRC Clinical Training fellowship to work with Alan Williams at the National Heart and Lung Institute. During his PhD he studied the basic mechanisms by which the heart contracts and specifically how calcium passes through an intracellular ion channel. At around this time great progress was being made in the molecular cloning of ion channels and particularly potassium channels. He thus took advantage of an award by the Wellcome Trust to perform postdoctoral studies in this area with Lily Jan at UCSF: one of the pioneering laboratories in this field. He returned to the UK in 1996 to UCL as a Wellcome Trust Senior Clinical Research Fellow and subsequently a Chair in Molecular Medicine in 2004. His interests in potassium channel biology in the cardiovascular system continue to this day. In recognition of his work in this area he was made a fellow of the Academy of Medical Sciences in 2006. In the last few years he has become increasingly interested the potential for translational studies and he is joining the Heart Centre in the hope of exploiting the unique environment offered by the WHRI and Barts and the London NHS Trust.

Scientific Interests
Potassium channels influence the electrical excitability of cells. For example, the orchestrated increase of activity of these during the cardiac action potential results in membrane potential repolarisation. In addition to direct regulation by membrane voltage their activity can also be modulated by protein kinases, directly by G-proteins, cellular phospholipids and ATP for example. Specifically we are working in three areas

• ATP-sensitive K+ channels are activated by declining ATP levels and thus couple cellular metabolism to membrane excitability. In heart muscle they are involved in adaptation to stress and cellular protection and in smooth muscle they influence vascular tone. There are important questions as to the role that KATP channels in different tissues play in cardiovascular physiology and pathology To address this we have generated unique murine models in which it is possible to conditionally delete component subunits in specific tissues. Combining this approach with various in-vivo physiological techniques we aim to examine the role of the channel in the action of vasodilators, vasoconstrictors and the response of smooth muscle to metabolic challenge. Secondly, the absence of the channel may significantly worsen the outcome in pathological conditions such as cardiac ischaemia and sepsis. We aim to address this question and determine the pathophysiological mechanisms for the poor outcomes.

Recent Publications
• K+ currents activated through muscarinic receptors are present in nodal and atrial tissues and are carried by G-protein-gated inwardly rectifying K+ channels. Acetylcholine released from vagal nerve afferents binds to muscarinic receptors and activates GIRK channels via inhibitory heterotrimeric G-proteins. Physiologically this results in heart rate slowing and constitutive activation of these channels is also implicated as a driver for atrial fibrillation. We have been interested in the basic signalling properties of this pathway but more recently we have focused on the (patho)physiological function of G-proteins and channel regulation in determining cardiac arrhythmia. For example, in mice with global genetic deletion of the inhibitory G-protein subunit Gi2, we were able to show they were predisposed to ventricular tachyarrhythmias (Figure 1). We are extending these studies using conditional genetic approaches in mice to understand the role that these and other related proteins have in the precipitation of abnormal heart rhythm via the autonomic nervous systems and the intrinsic myocyte response.

• Sudden arrhythmic death (SAD) is a substantial health burden and can occur in the absence of structural heart disease. One such recognised group of diseases causing SAD are the hereditary long QT syndromes and underlying this are mutations in a number of ion channel genes and associated proteins. Our studies here have focused on the K+ channel complex constituted of KCNQ1 and KCNE1. We have suggested that in the majority of cases the pathogenic mechanism involves the failure of trafficking of the channel complex to the plasma membrane (Figure 2). We are trying to understand the mechanisms and auxiliary proteins involved in this process and also how we might ameliorate the abnormal trafficking of disease causing mutant K+ channels.

Prof. Tinker’s work is supported by the British Heart Foundation, Wellcome Trust, MRC and Heart Research UK.

Intracellular retention of KCNQ1 mutants causing the long QT syndrome (labelled with a green fluorescent protein) in the endoplasmic reticulum (marked with a red fluorescent protein) syndrome.
Young Fellows in Focus
Claudio Mauro - British Heart Foundation Intermediate Fellow

Dr. Claudio Mauro obtained an MSc in 2002 and a PhD in Molecular Oncology and Endocrinology in 2007 from the University of Naples “Federico II”, Italy. During his training at the Department of Cellular and Molecular Biology and Pathology in Naples he studied the molecular mechanisms of NF-KB/Rel transcription factors regulation downstream of TNF-receptors and endoplasmic reticulum stress, and on theo Incogenic role of NF-KB in thyroid tumourigenesis. In 2007 he worked at the Ben May Institute, University of Chicago (USA), as a research fellow funded by the Italian Association for Cancer Research before joining in 2008 the Department of Medicine at Imperial College London until 2011. During his time as a post-doctoral fellow, he identified a fundamental new role for NF-KB in the control of the cellular circuitries governing energy homeostasis and metabolic adaptation, and causally linked this metabolic function of NF-KB to tumourogenesis, opening new opportunities for therapeutic intervention in cancer. The knowledge and expertise he gained prompted him to start his independent investigation of the implications of alterations of the metabolic machinery in T lymphocytes in the pathogenesis of inflammation-driven metabolic diseases such as atherosclerosis, hypertension, obesity and type 2 diabetes. He has chosen the William Harvey Research Institute for the development of his future studies because of the opportunity to join a cardiovascular and immunology-oriented environment that fits with his current scientific interests.

Whilst it’s known that the metabolic status of T cells determines anergy and differentiation toward effector versus regulatory or memory subsets, and regulate T-cell growth, whether the metabolic machinery controls trafficking in T cells is unknown. In the next few years Dr Mauro plans to investigate the mechanisms of metabolic control of trafficking in T cells to gain a better understanding of the physiology of T cell trafficking but also likely enhancing our understanding of why and how T cells selectively infiltrate atherosclerotic plaques, obese adipose tissue, and the perivascular fat and kidneys in hypertensive individuals, where they are not cleared and perpetuate the chronic inflammation that drives the progression of the disease. At the same time we would gain knowledge of the mechanisms of T cell infiltration in autoimmune diseases with a strong inflammatory component such as rheumatoid arthritis.

Key publications

* Mauro C is joint first author

Metabolic pathways determining T lymphocyte-mediated immune response
(modified from Jones, RG & Thompson, CB. Immunity 27: 173-178, 2007)
Young Fellows in Focus
Dr Qingzhong Xiao - British Heart Foundation Intermediate Research Fellow

Dr Qingzhong Xiao studied Medicine at the Chongqing University of Medical Sciences, China, where he obtained his BMed in 1994. However, a career in research beckoned and during his tenure as a Lecturer in Clinical Microbiology and Immunology at Sun Yat-Sen Medical College, Sun Yat-Sen University, Guangzhou, China he acquired his research credentials by completing his Master Degree in Medical Immunology and Doctoral Degree (PhD) in Pathology and Pathophysiology which were awarded in 1999 and 2003, respectively. With his research credentials Dr Xiao travelled to the UK to begin life as a jobbing researcher where he joined Professor Qingbo Xu’s group at St Georges Hospital (2003-2006), eventually moving with Professor Xu to King’s College London in 2006. With Prof Xu Dr Xiao established novel approaches to successfully induce embryonic stem cell differentiation toward vascular endothelial cells and smooth muscle cells. In addition he investigated the therapeutic effects of stem cell-derived vascular cells in cardiovascular diseases, such as damaged/injured vessels. He identified several molecules (Nox4, HDAC3, HDAC7 and Nrf3) that are involved in vascular endothelial and smooth muscle cell differentiation during his studies. These molecules represent novel targets for influencing stem cell fate, and could therefore provide new strategies for therapeutic intervention in atherosclerosis and angioplasty-induced restenosis, as well as utility in constructing engineered vessels for in vivo vascular grafting to repair diseased/damaged vessels.

Current research interests focus on investigating the underlying molecular mechanisms involved in stem/progenitor cell migration into atherosclerotic lesion and it’s relevance in the development of vascular diseases. With Professor Shu Ye, Dr Xiao’s has shown that atherosclerotic lesions in MMP8 deficient mice contain less stem/progenitor cells than MMP8 wild type mice, and MMP8 enhances stem/progenitor cell migration in vitro. These findings formed the basis for his British Heart Foundation Intermediate Basic Science Research Fellowship that was awarded in 2009.

Selected Publications:
Young Fellows in Focus
Abigail Woodfin - British Heart Foundation Intermediate Fellow

Abigail Woodfin studied Molecular and Cellular Biology (BSc) at the University of Bath from 1997-2001, and on completion of these studies started a PhD with Dr Paul Fraser at Kings College London, where she began working in the field of in vivo imaging of vascular inflammation. Her research at Kings focussed on the mechanisms controlling cerebral microvascular permeability, and how these may contribute to the formation of oedema following ischaemic stroke.

Following this Abigail took a position with Professor Sussan Nourshargh at Imperial College within the Cardiovascular Medicine Unit of the National Heart and Lung Institute. Her research focussed on microvascular inflammation and the migration of white blood cells (leukocytes) through vessel walls into the surrounding tissues at sites of injury and inflammation, and during this time she continued to develop her interest in various models of in vivo imaging. In 2007 Abigail assisted Professor Nourshargh in setting up the new Centre for Microvascular Research at the WHRI. Here, Abigail has worked with Professor Nourshargh on developing methods for visualising leukocyte/vessel wall interactions combining the real time imaging of living tissues with high resolution confocal microscopy. These methodologies enable the construction of sequential high resolution 3D models of inflammatory processes in living tissues.

In 2011 Abigail was awarded a BHF Intermediate Basic Science Research Fellowship to continue to utilise her imaging expertise to study inflammatory processes within newly formed, or angiogenic, blood vessels. Abigail will test the hypothesis that differences in the structure and morphology of newly formed microvessels in chronic inflammatory conditions result in differences in the profile, dynamics and mechanisms of inflammatory responses within angiogenic microvessels, with a view to identifying novel targets for therapeutic intervention.

Key publications

Shows leukocytes (green) migrating through a blood vessel wall (red) and into the surrounding tissues. A protein specific to blood vessel walls (PECAM-1) was labelled with a red fluorescent antibody. Genetically modified mice with a green fluorescent protein expressed in their leukocytes were used, enabling the emigration of leukocytes from the blood into the surrounding tissues to be observed.

Angiogenic blood vessels: The growth of new blood vessels was stimulated by reducing blood flow, and hence oxygen levels in a small area of tissue. The structure of these vessels was then visualised using fluorescent antibodies against different proteins - PECAM-1 (green), smooth muscle actin (red) and collagen IV (blue). Vessel sprouts which have not yet connected to other vessels can be seen.
Current Research in the WHRI Endocrinology

Research in Endocrinology

For over half a century, Endocrinology at Barts and the London has become globally regarded as the centre of excellence in clinical endocrinology. It trained many of the world’s leading clinical and academic endocrinologists, and receives referrals of the most complex endocrine cases from around the world. Endocrinology played a key role in the development and clinical application of radioimmunoassays for many peptide hormones that are used today. Ground-breaking clinical research was performed on hypothalamic releasing peptides and the use of dopamine and somatostatin agonists or growth hormone antagonists in treatment of pituitary adenomas.

Over the last decade the Endocrine centre has developed its basic science research under the leadership of Professor Adrian Clark, while maintaining an excellent international reputation for its clinical endocrinology practice. Endocrinology became incorporated into the WHRI in 2003 with the relocation to state-of-the-art laboratories in the John Vane Science Centre. In addition to the longstanding strengths in adult endocrinology, Prof Martin Savage’s work developed a world-wide reputation in Paediatric Endocrinology, and recent discoveries and developments, together with the recruitment of Professor Leo Dunkel from Kuopio, Finland, currently positions the Department as the leading centre for Paediatric Endocrinology research in the UK.

Genetic basis of endocrine disease

Endocrinology has a long-standing interest in identifying the genetic causes of endocrine diseases. Our international referral base for both paediatric and adult endocrinology patients provides an unrivalled environment to study unique patients and families and to understand the molecular and pathophysiological mechanisms underlying these diseases. Our success is exemplified by the identification of six novel genes causing familial glucocorticoid deficiency published in Nature Genetics in 2012 (Prof Adrian Clark (FMedSci) and Dr Lou Metherell), identification and characterisation of genes involved in the growth hormone axis (Dr Metherell), assessment of gene mutations in familial pituitary adenoma patients published in the New England Journal of Medicine in 2012 (Prof Marta Korbonits), the study of novel genes underlying hyperlipidaemia (Prof Carol Shoulders) and the identification of a novel gene for a rare bone disease (Prof William Drake). As well as studying the gene function and consequences of clinically relevant mutations using in vivo and in vitro models, the genetic studies of endocrine diseases have proved instrumental in the characterization of novel clinical syndromes and the determination of genotype-phenotype correlations. This has enabled new clinical guidelines to be set-up, ultimately directly benefitting patient screening and management.

Adrenal development and function

The centre has an academic focus on adrenal cell biology. Research over the last few years led by Professor Clark and more recently by Dr Li Chan has concentrated on the interaction of the ACTH receptor (MC2R) and its accessory protein MRAP.MRAP was discovered in the centre and shown to be vital for MC2R cell surface trafficking and signalling. Current research focuses on the expression and function of MRAP and its homologue MRAP2 in the developing foetal adrenal and in the adult gland. Dr Peter King has led studies on the mechanisms controlling adrenal gland development, demonstrating that sonic hedgehog is
required for the growth of the adrenal primordium in rodent models. Cells receiving sonic hedgehog signals have the properties of stem or progenitor cells both during development and in the adult gland (Figure 1). The interplay between hedgehog, BMP and FGF signalling appears to be essential for adrenal gland development and differentiation, as well as in the pathogenesis of adrenal cancer. Dr Metherell’s focus is on research into the cell biology of genes discovered in her analyses of families with familial glucocorticoid deficiency. Recently identified genes (NNT and GPX-1) have been shown to influence susceptibility to oxidative stress and play a role in adrenal steroidogenesis, whilst MCM4 is involved in adrenal cell division and turnover. Dr Storr leads on the investigation of another gene, encoding the nuclear pore protein ALADIN (mutations in which cause Triple A syndrome), which protects adrenal cells against oxidative stress.

**Hormones and metabolism**

A long-term interest group has been the study of mechanisms underlying the fetal origins of adult disease. Studies funded by the MRC, BHF and Diabetes UK have identified important epigenetic changes of key genes, such as the adrenocortical angiotensin receptor, following fetal in-utero insult. More recent studies exploiting new technological advances in high throughput sequencing reveal that extensive DNA methylation and histone modification disturbances are associated with these phenomena.

Knowledge of the causes of inherited lipid disorders is important for understanding atherosclerosis, steroid metabolism and energy homeostasis. Prof Carol Shoulders’ group, funded by the MRC and BHF, has gained insight into the cellular mechanisms that regulate lipid transport at both the cellular and whole-body level. For their studies the group continues to exploit the power of genome-wide genetic analyses recently published in Genome Research.

One of the prominent examples of the interaction of endocrine system and the regulation of metabolism is via the metabolic enzyme AMPK. This kinase not only regulates the energy level of the cell, influencing ATP generating and consuming processes, but also has profound effects on muscle, heart, liver function as well as appetite regulation. Prof Korbonits’ interest in growth hormone secretagogues, including the stomach-derived endogenous counterpart ghrelin, led to the study of ghrelin’s effects on AMPK and its interaction with other appetite-modulating compounds such as endocannabinoids. These novel observations of the hormonal regulation of AMPK by growth hormone, IGF-I and glucocorticoids led to a clinical study to elucidate the effects of this in humans.

**Cell biology and models of disease**

Dr Paul Chapple researches cellular systems responsible for the biogenesis, trafficking and quality control of proteins. Disruption of these systems is associated with multiple human disease states e.g. obesity, neurodegeneration and ageing. Current interests include understanding the role of molecular chaperones in the life cycle of G-protein coupled receptors and defining a novel chaperone system involved in mitochondrial dynamics. Dr Tristan MacKay is developing novel stem cell platforms to study endocrine disease by deriving induced pluripotent stem (iPS) cells from patient cohorts. This includes establishing methodologies to differentiate such iPS cells along endocrine lineages in order to study complex biochemistry in disease-affected cell types. These cell biology themes are closely interconnected with other research programs in endocrinology particularly in the areas of intracellular trafficking and lipid disease.

**Figure:** The rat adrenal cortex is built from several layers and data from Dr Leonardo Guasti, a lecturer in the Department, suggest that cells in the inner undifferentiated zone (between the white markers) are already committed towards a zona fasciculata phenotype (corticosteroid production). The steroidogenic enzyme SCC (cholesterol side chain cleavage enzyme, stained with red) is highly expressed in this inner undifferentiated zone while it is coexpressed (as shown in yellow) with 11betahydroxylase (CYP11B1, green) in the proper zona fasciculata. The outer undifferentiated zone is rich in Preadipocyte factor-1 (Pref-1, purple), which, along with Sonic Hedgehog, regulates the fate of adrenal stem/progenitor cells. ‘Cap’ is showing the capsule of the adrenal gland.
**Clinical Research**

The adult endocrine unit has a high throughput of conditions that are rarely seen elsewhere, such as complex pituitary tumours, adrenal disease, hyperparathyroidism, differentiated thyroid tumours, endocrine malignancies and genetically-determined tumour-prone syndromes. The primary goal of the department for these patients is meticulous assessment and optimal clinical care. In addition, research into the natural history, pathophysiology and outcomes of therapy are undertaken. Work is ongoing in patients with conditions including Conn’s syndrome and hyperparathyroidism and pituitary disease, phaeochromocytoma & paraganglioma and neuroendocrine tumours. These projects are carried out and overseen by Prof Will Drake, Dr Scott Akker, Dr Maralyn Druce in collaboration with colleagues in biochemistry and radiology. The unit is also engaged in commercially organised clinical studies.

![Prof Korbonits and a patient with gigantism who shares the disease causing mutation in the AIP gene with the famous Irish giant in the Hunterian Museum in London.](image)

**Funding**

The Centre for Endocrinology has an outstanding track-record of winning funding for Clinical Training Fellowships and Clinician Scientist Fellowships in paediatric and adult endocrinology from the MRC and Wellcome Trust schemes, as well as the Barts and the London Charity. Project grants from MRC, Wellcome, BBSRC, BHF, BTLC, EU, NIHR as well as via collaboration with industrial partners ensures that our research can continue in the future.
New Faculty in Focus
Endocrinology
Leo Dunkel, Professor of Paediatric Endocrinology

Leo Dunkel joined the Centre for Endocrinology in February 2011 to advance his translational research and benefit from the molecular endocrinology environment of the Centre. Leo has a long-standing interest in growth and reproductive biology. He aims to translate knowledge of genetics and the molecular regulation of physiological processes to further the understanding of related pathology and ultimately the development of novel targeted therapies.

Before moving to the UK he held a Chair of Paediatrics, at the University of Kuopio, Finland. He studied medicine and also completed his residency in paediatrics and paediatric endocrinology at the University of Helsinki. After his residency, he undertook postdoctoral training at the Division of Reproductive Biology, Stanford University. In 1994 he won the Hallman Prize for a Young Distinguished Scientist, and in 2008 the European Society for Paediatric Endocrinology (ESPE) Research Award. In the past 10 years his work has focused on the role of oestrogen in the regulation of linear growth. These studies have examined the evidence for therapies that inhibit the biological action of oestrogen in the treatment of various growth disorders. They culminated in the first two placebo controlled clinical trials using a third generation aromatase inhibitor to promote growth (Figure 1). Below is the image of one page of a document, as well as some raw textual content that was previously extracted for it. Just return the plain text representation of this document as if you were reading it naturally. Do not hallucinate.
Current Research in the WHRI
Endocrinology

Current focus in his group is in utilising novel cell models to interrogate the genetic factors underlying the regulation of growth and the timing of sexual maturation through the GnRH neuronal network. These studies use induced pluripotent stem cell (iPSC) lines for the ramification of neuronal differentiation to GnRH neurons in patient cohorts with disorders of sexual maturation (constitutional delay in growth and puberty and hypogonadotropic hypogonadism). This platform will act as a basis to study changes in neuronal maturation whilst genetically manipulating candidate gene expression in patient generated iPSC versus controls. Simultaneously, exome sequencing in a large, well-characterized population of patients with constitutional delay of growth and puberty is also underway. Ultimately this work aims at unravelling the cellular biochemistry underlying the neuroendocrine control of sexual maturation.

Figure 2: Panel A. Genetics of puberty. The precise genetic basis of the extreme tails of normal puberty is unclear. Whether genetic variation in these genes plays a role in modulating pubertal timing in the general population (outside of families with GnRH deficiency or constitutional delay of puberty, CDGP) is not currently clear. Panel B. Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effects (odds ratio).
Young Fellows in Focus
Lou Metherell- MRC New Investigator Award Reader in Endocrine Genetics

Lou Metherell graduated from the University of Manchester with BSc (Hons) Biology in 1985. During her undergraduate studies she developed an interest in genetics which led her to undertake a postgraduate diploma in Human Genetics at the University of Aberdeen. After a brief period in industry she returned to science and was awarded her PhD from the University of Greenwich in 1999 for her work on rapid PCR methods for the identification of bacterial pathogens. She joined the Endocrinology department in 1998 and her research has focussed on the genetics of endocrine disease with particular emphasis on the genetics of growth disorders and ACTH insensitivity. She was appointed Lecturer in Endocrine Genetics in 2009.

Lou maintains an interest in childhood growth disorders, particularly in defects of the growth hormone – IGF1 pathway. In conjunction with Professor Martin Savage she has described many novel defects in the growth hormone receptor (GHR), the most significant of which was the identification of pseudoexon inclusion in GHR as a novel disease mechanism in growth failure. The recognition that mutations in other genes in the pathway, such as STAT5B and the acid labile subunit, IGFALS, also cause GH insensitivity expanded the genotypic spectrum of primary IGF1 deficiency.

Following on from the work of Professor Adrian Clark in identifying the melanocortin 2 receptor (MC2R) as the first cause of Familial Glucocorticoid Deficiency (FGD), Dr Metherell has also discovered mutations in its accessory protein (MRAP) are also implicated in the disease. In 2008 she was awarded a New Investigator Research Grant from the Medical Research Council which has enabled her to continue her research into the causes of Familial Glucocorticoid Deficiency (FGD) by both genetic and proteomic approaches. This funding has resulted in 3 novel genes being linked to FGD. A mutation in the gene MCM4 (mini chromosome maintenance-deficient 4 homologue) is associated with a unique form of adrenal failure found in the Irish Traveller community. The syndrome also involves natural killer cell deficiency and increased chromosome fragility. Interestingly mutations in GPX1 and NNT, two genes intimately involved in antioxidant defence, cause a phenotype that is indistinguishable from FGD caused by MC2R/MRAP defects. Current work is concentrated on discovering the pathogenetic mechanisms underlying these new aetiologies in FGD.

Selected publications

MRAP is essential for trafficking of MC2R to the cell surface. The cell on the left has been transfected with both MC2R (in green) and MRAP (in red) whereas the cell on the right only has MC2R. Only the cell with both MRAP and MC2R is expressing MC2R at the cell surface.
Dr Li Chan studied Medicine at Cambridge before undertaking her basic paediatric training at Barts and the London Hospitals. During this time she undertook research studying the insulin-like growth factor-1 and growth hormone receptor gene in small for gestational age infants in Prof. Martin Savage and Prof. Adrian Clark’s team and worked as a member of the NESTEGG (Northern European Study of Genes in Growth) team. In 2005 she was awarded a clinical training fellowship funded by the Barts and the London Charity and subsequently she gained an MRC clinical research training fellowship, which enabled her to complete her PhD investigating a novel receptor trafficking protein MRAP2 (melanocortin receptor accessory protein two). Her work on melanocortin receptor accessory proteins, MRAP and MRAP2, as regulators of the melanocortin receptor family has revealed important novel aspects of melanocortin receptor biology. She was awarded the Society for Endocrinology Young Investigator prize in 2008 based on this work, and is recipient of a Novo-Nordisk educational award as well as a Clinician-Scientist in Training prize in Endocrinology. During this time she was also involved with two other areas of research: the mutational analysis of patients with Familial Glucocorticoid Deficiency, and the long-term follow-up of paediatric Cushing’s disease patients.

After her PhD she succeeded in obtaining the only national GRID training post in Paediatric Endocrinology in 2008. The following year she was awarded a 5 year tenure-track MRC/Academy of Medical Sciences clinician scientist fellowship (£1,056,610) to build on existing work and study the effects of melanocortin receptor accessory proteins in energy homeostasis and adrenal function. In 2012 she won the Journal of Endocrinology prize for outstanding young researcher who has made a significant contribution to research in basic endocrinology.

Selected publications:

Figure: Adrenal expression of MRAPs and MC2R. The figure shows the expression of Mrap and Mrap2 in the developing rat adrenal gland and the expression of MC2R (red) in the undifferentiated zone (ZU) of the adult adrenal gland.

Current Research in the WHRI
Endocrinology
William Harvey Research Institute
Age beyond five and beyond
Experimental arthritis research
Why some people are more prone than others to inflammatory disease is one of the fundamental questions addressed by Prof Cos Pitzalis. Can tissue biomarkers be identified that can be used to categorise patients presenting with early arthritic symptoms into groups that drug treatment can be specifically tailored to their need? This notion is under active scrutiny using such cutting edge techniques as ultrasound guided synovial biopsies from small joints with the aim of building a comprehensive data base which can be related to (for example) the success of biologics in these patients he has just been awarded NIHR Experimental Medicine and MRC Stratified Medicine Programmes amounting to £5.9m.

The spectrum of arthritic disease is huge and includes such conditions as Sjögren’s Syndrome, where inflammation and the excessive presence of lymphocytes and IgG in the secretory ducts of the lacrimal and salivary glands blocks normal gland function leading to ‘dry eye’ and ‘dry mouth’. Dr Michele Bombardieri leads a team investigating this phenomenon by monitoring the profile of cytokines released in affected glands, and the presence of auto-antibodies in Sjögren’s patients.

Cartilage biology
When the inflammatory response has proceeded unchecked it may cause significant tissue damage. This is what is seen in many cases of (for example) rheumatoid arthritis. The aim of ‘regenerative medicine’ is to restore function to the tissue often by employing a tissue engineering approach. Such a strategy has been adopted by Dr Francesco Dell’Accia’s group who have been using mesenchymal stem cells taken from human synovial membranes and periostium to produce cell-based preparations for joint repair and to attempt to identify the molecular signals that stimulate growth and repair (Journal of Cell Biology 2010).

Underpinning much research in this group has been the development of a chimeric SCID mouse model. By implanting human tissue in these mice, it has been possible to evaluate the effect of drugs on human tissues under conditions where the inflammatory response can be tightly controlled and manipulated, conferring a huge experimental advantage (PLoS Medicine in 2009).

Resolution of inflammation
It was the 18th Century British surgeon John Hunter who first observed that inflammation was not just a ‘disease’ but that it played a crucial role in healing and remodelling of tissues following injury. This notion was largely overlooked until comparatively recently when researchers realised that inflammation was not only regulated by pro-inflammatory mediators but that the body also deployed a considerable palette of anti-inflammatory mediators as well. This concept is now referred to as the study of the Resolution of Inflammation. Profs Mauro Perretti and Rod Flower FRS both have been pursuing this idea for a number of years and have particularly focussed upon the role played by endogenous glucocorticoids and their second messenger molecules such as the protein Annexin 1. This not only plays a significant part in the...
acute anti-inflammatory effect of glucocorticoids but is also crucial in the action of some anti-allergic drugs such as the cromones. In addition, more recently the group have identified a novel role for Annexin I in the anti-inflammatory effects of oestrogen and suggest that such an effect may underlie sex-differences in inflammatory responses (see Figure). The G-protein coupled cell surface receptor for annexin-1 was identified by members of the group as the formyl peptide receptor FPR2 and this initiated a study into the role of this receptor in the regulation of inflammation and the potential exploitation for drug discovery programmes (peptides and small molecules).

Unexpectedly, Annexin I also appears to regulate adaptive immunity too, a finding that has given rise to a new branch of research. Indeed, the recent discovery by Dr Fulvio D’Acquisto’s group that anti-Annexin 1 antibodies can have dramatic actions in alleviating T cell-mediated experimental autoimmunity, providing another impetus to commercialisation of this concept.

Many other endogenous anti-inflammatory molecules are also of interest to the group including the melanocortin peptides, lipoxins and resolvins and galectins. The latter are complex glycoproteins that exert anti-inflammatory effects through cell surface receptors and their biology is another topic of active investigation by Dr Dianne Cooper’s group. Lipoxins and resolvins are anti-inflammatory lipids, sometimes acting through the same receptor as annexin I and on other occasions utilising the receptor for chemerin, ChemR23. The role of all these mediators and their receptors are under active study with the clear objective of producing better and safer anti-inflammatory agents as well as understanding the complexities of the innate immune system.

**Cytokines and B-cells**

Using anti-inflammatory molecules to quench the inflammatory response is a notion that is also actively pursued by Prof Yuti Chernajovsky where improving current treatments and developing new therapeutic strategies through molecular design and stem cell engineering utilising gene delivery is a major focus.

The unit has developed two methods of targeting biologicals to disease sites: Firstly, scFv, derived from human antibody phage display libraries, is used to target reactive oxygen species-modified cartilage protein in arthritic joints and to deliver anti-inflammatory cytokines or cytokine receptors. Secondly, the unit has designed ‘latent cytokines’ by making fusion proteins with the latency associated peptide of transforming growth factor beta that upon dimerisation forms a ‘shell’ around pharmaceutically active peptides linked using a matrix metalloproteinase cleavable site. The active compounds cannot therefore interact with their receptors unless released from the shell at sites of inflammation or tissue remodelling. This strategy increases half-life, reduces toxicity and ensures that the drug is released only where needed and is applicable to many inflammation-related scenarios including autoimmunity and cancer.
Degenerative chronic inflammatory conditions are characterised by tissue destruction caused by immune cells and local cells such as synoviocytes (in arthritis) and glia cells (in multiple sclerosis). Whilst immunosuppressive therapies slow down disease progression little repair occurs because of lack of differentiation factors, the inability of endogenous stem cells to survive (or function) in the inflammatory milieu, or the ensuing scar tissue. The unit is engineering stem cells using lentiviral vectors that confer survival. The lack of trophic and differentiation factors can be rectified using latent cytokines. Engineered chimeric receptors with extracellular domains comprising scFV that binds cell surface molecules or extracellular matrix fused to the transmembrane and signalling domains of receptors known to facilitate survival or differentiation, is a further strategy.

Another important strand of our work is to understand the pathology of systemic lupus erythematous (Prof Rizgar Mageed) and the specific contribution of deficient B cell-signalling pathways; the role of differentially spliced isoforms of the ARTS-I gene in shedding of cytokine receptors in ankylosing spondylitis and the immune link between type I diabetes and rheumatoid arthritis.

**The microcirculation**

‘Without vessels there is no inflammation’ wrote the pioneering pathologist, Julius Cohnheim. **Prof Sussan Nourshargh (FMedSci)**, a Wellcome Trust Senior Investigator, and her colleagues focus upon molecular and cellular events within the microvasculature. Key areas of interest are mechanisms of leukocyte trafficking, vascular permeability, flow and maintenance of vascular integrity in inflammation. The group has a strong expertise in the application of specialised imaging methods, such as confocal intravital microscopy, that allows in vivo observation of events within the microcirculation, such as leukocyte vessel wall interactions, in real-time in 3D and 4D. They have applied this technique to investigate the molecular pathways that mediate and regulate leukocyte transmigration through venular walls in inflamed tissues. Recent findings in this area have identified the adhesion molecule JAM-C as a key regulator of polarised movement of neutrophils through venular walls in a luminal to abluminal direction. Furthermore, ‘reverse neutrophil transmigration’ was noted under conditions of ischaemia/reperfusion (I/R) injury during which the expression of JAM-C from endothelial cell junctions was reduced. These findings provide insight into the fundamental question of how neutrophil motility is regulated in vivo and suggest that neutrophil reverse transmigration can contribute to dissemination of systemic inflammation. The role of JAM-C is also under investigation in numerous other disease models such as a model of ovarian cancer in collaboration with Professor Fran Balkwill (Barts Cancer Institute). The group have also identified distinct roles for certain chemokines in recruitment of monocytes and a novel role for pericytes as a key regulator of neutrophil sub-endothelial cell motility.

**Current Research in the WHRI**

*Inflammation*

The latent cytokine delivery system (Prothyx®) is a fusion protein between the latency associated peptide of TGFβ that confers a shell structure by dimerisation and a peptide or cytokine with pharmacological properties linked via a metalloproteinase cleavage site. This delivery system provides longer half-life, disease specific delivery and latency i.e. no side effects. Applications in: autoimmunity, inflammation, cancer, atherosclerosis, infection and regeneration.
Young Fellows in Focus
Dr Lucy Norling - Arthritis Research UK Career Development Fellowship

After completing a BSc in Human Biology at Aston University, attracted by the opportunity to study pharmacology at the top level, Lucy joined the WHRI enrolling in a Masters degree course on the ‘Mechanisms of vascular diseases’ funded by Barts & The London Research Advisory Board. Following this Lucy felt fully equipped to begin her PhD studies investigating the anti-inflammatory effects of the endogenous protein, Galectin-I, with Prof Mauro Perretti and Dr Dianne Cooper. This PhD provided Dr Norling with the determination to build a career in science, and with bridging support of a Wellcome Trust Value-In-People award she was able to generate preliminary data for an Arthritis Research UK Foundation Fellowship that she was awarded in 2008.

Dr Norling’s current work focuses on investigating the pathways for generation and bioactivity of novel lipid mediators derived from omega-3 fatty acids during the resolution phase of inflammation, in particular – the DHA derived Resolvins. These endogenous mediators have anti-inflammatory and pro-resolving properties and may explain the protective effects seen in RA patients taking fish oil supplements. In particular Dr Norling’s research focuses on the molecular mechanisms by which Resolvins limit leukocyte recruitment to inflammatory sites, a hallmark of the inflammatory response.

With support from Arthritis Research UK, Dr Norling spent the past two years training at Harvard Medical School, Boston, with the mentorship of Professor Charles Serhan, who pioneered this field and whose expertise lies in lipid mediator lipidomics. This rewarding experience exposed her to a highly stimulating work environment and provided her with a strong technical basis in lipidomic analyses that will facilitate her future research. Dr Norling’s future research plans are to investigate whether dysfunctional pathways in the generation of these lipid mediators exist in chronic inflammatory pathologies such as RA and vasculitis.

Selected Publications:

![Resolvin D2 reduces leukocyte adhesion (↓) and emigration (*) in the inflamed mouse cremaster.](image)
William Harvey Research Institute
At twenty five and beyond

Current Research in the WHRI

Inflammation

Young Fellows in Focus
Michele Bombardieri- HEFCE “new blood” Clinical Senior Lectureship.

Dr Bombardieri has been recently appointed as Clinical Senior Lecturer and Consultant Rheumatologist at the Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute. He graduated in 1999 in Medicine and Surgery at Catholic University of Rome and worked until 2002 in the group of Prof Valesini at the University of Rome La Sapienza where he completed his clinical training. Since 2004 he worked with Prof Pitzalis’ group at King’s College London as a PhD student in Experimental Medicine and Rheumatology. In 2005 Dr Bombardieri was awarded a Clinical Research Fellowship from the Arthritis Research UK. Following completion of his PhD in 2007 he relocated to the William Harvey Research Institute at Queen Mary University of London as part of the new Centre for Experimental Medicine and Rheumatology. He was awarded an Arthritis Research UK Clinician Scientist Fellowship in 2008 and in June 2010 an HEFCE “new blood” Clinical Senior Lectureship.

Dr Bombardieri has a long standing research interest in the pathogenesis of chronic inflammatory/autimmune disorders, with particular focus on the role of inflammatory cytokines and chemokines and of new autoantibody specificities in rheumatoid arthritis (RA), and Sjögren’s syndrome (SS). He is currently working on two main projects: 1) identification of novel cytokines and their pathogenic relevance in patients with and animal models of SS and RA and 2) dissecting the mechanisms regulating autoreactive B lymphocytes recruitment, activation, proliferation and differentiation in the salivary glands of patients with SS and in the synovium of RA. In addition, Dr Bombardieri is currently investigating the cellular and molecular mechanisms involved in the response/relapse/resistance to B cell depleting agents in SS and RA.

Key publications


The WHRI hosts the British Microcirculation Society in April 2011
High Impact Papers since 2008
LETTERS

Resolvins D2 is a potent regulator of leukocytes and controls microbial sepsis

Michelle Younghui, Ehui W. M. Nweke, Ina V. Verma, Yan Yang, Chunmei Gu, Huyi Wu, Attilio M. Mezzano, David Bonilla, and Thomas J. Roberts

Pericytes support neutrophil subendothelial cell crawling and breaching of venular walls in vivo

Cheon Sook Jeong, Matthew R. Bock, Venita A. Kemler, James Wieland, Jennifer L. DeVinney, Douglas P. Hayden, and Teresa M. Moon

WNT-3A modulates articular chondrocyte phenotype by activating both canonical and noncanonical pathways

Michael Schulte, Susan Shimer, Jacob Barnard, Thomas Piehl, Mansi Sharma, Tzoukla V. Tsoukla, and Christopher H. Teitelbaum

C3 Polymorphonuclears and Allograft Outcome in Renal Transplantation

John Appelgren, M.D., and Ahmed M. Yagoub, M.D., and André Phan, M.D.

Circulation

Ischaemic Conditioning Protects the Uterine Heart in a Robust Model of Myocardial Infarction

Cevdet Y. Bayram, Karen McCaffrey, Aymen Naaman, Peter A. Zuckerman, Martin Kalmar, Gheorghe Thanoumenou, and Mohammad M. Yagoub

Genome-wide association study identifies eight loci associated with blood pressure

Joao Souza, Natalie Clough, Fabian R. Kepple, Eric Giner-Llatas, Maria Calzado, Luisa de Miguel, Monica Soler, Luisa Caire, John Luke, and John Elliott

AIP Mutation in Human Adenomas in the 18th Century and Today

Catherine J. L. Douglas, Michael J. Marthaler, John C. Goodwin, and John S. Elston

SLC2A9 is a High-Capacity Urate Transporter in Humans

Mark L. Epstein, David J. Goeckeler, Peter P. Glynn, Jesse D. O'Donnell, Joel Williams, Paul J. St. John, and Paul W. Shockley

William Harvey Research Institute
At twenty five and beyond
In 2008, and again in 2012, the excellence of our cardiovascular research was recognised by the award of our National Institute of Health Research (NIHR) Cardiovascular Biomedical Research Unit (£12m). Our Translational research programme integrates cardiovascular genetics, stem cell biology, inflammation science, pharmacology, electrophysiology, advanced CV Imaging, experimental medicine and large-scale trials to create a flow of concepts from the bench into the clinic.

The NIHR via our CVBRU funded during the first award the establishment of the advanced imaging centre, our clinical research centre and established our new bioinformatics and biorepository facility. Our current NIHR BRU award funds accelerating genomics into healthcare, vascular inflammation, electrophysiology and advanced imaging. We have used the platform of the NIHR BRU at Barts to be the UK leading recruiter to an innovative trial of Renal Denervation. Our role in this trial was showcased in the Prime Minister’s statement on UK Life Sciences in 2011. This funding has allowed us to have a multidisciplinary approach to support many areas of translational research, including drug discovery, stratified medicine and clinical informatics. We are working in close partnership with clinicians working across all the disease areas at the WHRI, including Cardiovascular, Inflammatory and Endocrine diseases. In addition have built linked clinical databases to a Cardiovascular Bio-repository which will help prime scientific bench to bedside research, rapid recruitment of patients and analysis of clinical trial cohorts by genotype or phenotype.

One example of the success of our BRU has been our involvement in a landmark randomised clinical trial, published in the Lancet in collaboration with the medical device company Ardian, to demonstrate the effectiveness of their new catheter-based treatment for therapy-resistant hypertension. The Simplicity Cather System is used to perform a procedure termed renal denervation.

Once in place within the renal artery, the device delivers low power radio frequency energy to deactivate the surrounding renal sympathetic nerves. This, in turn, reduces activity of the sympathetic nervous system, which reduces blood pressure. The trial demonstrated the potential of this device to impact significantly on the standard care for a large number of patients who are suffering from hypertension but who do not respond to current pharmaceutical therapies.

The William Harvey Clinical Research Centre.
To complement our bench to bedside discovery and experimental medicine programmes we have a state-of-the-art Translational Clinical Research Centre. Our dedicated professional clinical research team are managing over 33 concurrent trials, many with first patient enrolled within 70 days. The facility has enabled multiple partnerships with the Pharmaceutical Industry and a major strategic Prime Site partnership with Quintiles Transnational. This offers us the opportunity to participate in all Quintiles trials placed in the UK but also gives us complete freedom to work with any other Pharma or biotechnology sponsor. In 2011 we recruited over 225 patients to Quintiles Trials and were 3rd best performing Prime Site Worldwide.
The William Harvey Heart Centre

The William Harvey Heart Centre, dedicated to tackling the growing burden of heart disease and stroke world-wide was opened by Sir William Castell; LVO on the 7th July 2011.

The new Heart Centre – based at Queen Mary’s Charterhouse Square campus - represents a significant £25m investment and will provide a flow of innovative new therapies from the laboratory to the patient suffering from heart disease across north-east London and beyond. The Centre is unique in its ability to encompass laboratory work with patient engagement through its internal Clinical Trials Unit which can call upon a broad range of clinical experts from Queen Mary, University of London and Barts and The London NHS Trust to run clinical studies in multiple therapeutic areas specialising in but not limited to: cardiovascular, respiratory, endocrinology, addiction and rheumatology. The Heart Centre forms part of Barts and The London Cardiovascular Biomedical Research Unit and is specifically designed to provide the cardiovascular research hub for the £312m rebuild of St Bartholomew’s Hospital which will open in 2014.

Heart disease and stroke are the leading cause of death world-wide, causing 17 million deaths per annum, and there remains serious un-met need for new therapies. The distinctive approach of the William Harvey Heart Centre will be to combine new basic science strengths in pharmacology with study of how genes raise blood pressure and how disorders of heart rhythm are triggered, alongside high calibre stem cell biology and biomarkers research so generating novel approaches to these common causes of premature death and disability. Set alongside the unique diversity of the east London community the William Harvey Heart Centre offers the potential for discoveries made here to have impact upon the growing global burden of cardiovascular disease.

Professor Mark Caulfield, Director of the William Harvey Research Institute, said: “We are indebted to Mr Clive Priestley CB for his tireless devotion to create this Centre for our ethnically diverse east London community suffer appalling rates of heart disease, possibly due to undiscovered risk factors that may offer the basis for new treatments. Our strategic focus on translational therapeutic innovation will ensure that the William Harvey Heart Centre competes with the best in the world, addressing areas of important unmet need with global healthcare implications.”

Donors and supporters:
St Bartholomew’s Hospital Medical College Trust
Medical College of St Bartholomew’s Trust
Quintiles
National Institute for Health Research
The Department of Health
The Charles Wolfson Charitable Trust
The Wolfson Foundation
Barts & The London Charity

Opening of The William Harvey Heart Centre, from left to right, the late Clive Priestley, Sir William Castell and Prof Mark Caulfield.

The front of the new William Harvey Heart Centre
Public Engagement at The WHRI

Since 2008 the WHRI has substantially expanded its public and patient engagement activities as we recognise the importance of taking our science to the general public. A few examples are given below.

Lead by the NIHR funded Centre for Advanced Cardiovascular Imaging we have been reaching out to our patients and the local community in the East End with our ‘Let’s talk hearts’ seminar series. This is a new series of talks generously supported by Barts and The London Charity which is open to all, providing a forum to learn about heart conditions, how (and why) you keep your heart healthy and the latest research. The first seminar on “keeping fit keeps your heart fit” was held in March 2011 in the Whitechapel library with over 70 people who engaged in a lively discussion. Several seminars have followed covering topics such as heart failure, heart muscle disease and stem cell therapy in heart disease.

A further example of our success in bringing our science to the general public is our recent contribution to The Royal Society Summer Festival 2012 where in addition to members of the public scientists present to students and teachers, other scientists, policymakers and the media. Dr Fulvio D’Acquisto won a highly prestigious place to exhibit our research at the Festival. The exhibit, created and manned by Dr D’Acquisto and a team of ~30 WHRI students and scientists, was entitled ‘Inflammation: The Fire of Life’ and run over an entire week in early July. Over 12,000 high school students, teachers, members of the public attended the exhibit which was therefore a great success not only for the WHRI but also the SMD and the College (see http://sse.royalsociety.org/2012/exhibits/fire-of-life/).

Thanks to the support of the Royal Society we now have 3 social media web sites (Tumbler, Facebook and Twitter) showing key events and information about the research on inflammation carried out at the WHRI (http://swelling-pains.tumblr.com/; http://www.facebook.com/SwellingPains; https://twitter.com/QMUL_WHRI).

We recognise that to ensure the security of the future biomedical science base in the UK we must reach out and enthuse the scientists of the future. To this end the WHRI staff have focussed on showing school kids that the science we do has relevance and can be fun. In 2011 and 2012, WHRI staff have held an annual event ‘The Barts and The London Science Festival’ at Charterhouse Square supported by our NIHR CVBRU and the Wellcome Trust. The Science Festival is aimed at anyone interested in science from teenagers to adults (and big kids!) of any age and features a Science Market, a Science Competition, acting, lecturetes and much more and over two years has been attended by over 350 school students and some have exhibited their own inventions (http://www.youtube.com/watch?v=-LmE7QtDxAg).

Dr Fulvio D’Acquisto speaking to the general public at the Royal Society Summer Festival 2012.
Bringing science to school kids, the Barts and The London Science festival is an annual event launched in 2011 organised by WHRI staff.
Cardiovascular

Professor William Sessa, Yale University

After completing my PhD in Pharmacology in December 1989 at New York Medical College, the Chairman, Dr. Jack McGiff, recommended me to continue my training at the WHRI. Jack was a friend and colleague of Sir John’s and worked with him during his time at Wellcome. Realizing this would be a fantastic opportunity to work in a world-class laboratory with a stellar history of training scientific icons in the field of autacoid pharmacology, I quickly adjusted my thinking of doing a post-doc in the US and enthusiastically came to the WHRI in January of 1990. I had a wonderful time in the lab, working with an international group of fantastic scientists on the regulation of endothelial derived releasing factor EDRF release as well the biosynthesis of endothelin. I think I was a bit of a novelty in the lab, being an irreverent American, but I established very dear friends during my time in London; friendships that I still cherish today. Scientifically, I worked very closely with Markus Hecker and Jane Mitchell on arginine metabolism and EDRF release from cultured endothelial cells and the pathway we dissected in 1990 is the presently well established citrulline-arginine cycle that is important for regenerating arginine during sustained NO synthesis. I really enjoyed the camaraderie of the lab during this time, especially, the late night scientific discussions in the pub! My wife and I still look very fondly on our brief but very rich time spent at the WHRI.

After returning to the US in September 1991, I took up a second post-doctoral position at the University of Virginia School of Medicine (UVa), one of the major US institutions where molecular biology was being applied to research problems in the cardiovascular system. Due to the incredibly productive experience at the WHRI, I went to UVa feeling little pressure to publish. So, I immersed myself in the burgeoning field of molecular biology and took on an ambitious project to isolate the cDNA that encoded eNOS. I had no experience in cloning and the lab I worked in used to joke with me saying that “I didn’t know DNA from a french frie!” They were right of course, but I tried anyway with the help and mentoring of several people and was successful in the race to clone this gene. Cloning eNOS was directly related to my wonderful training in pharmacology and biochemistry at WHRI which allowed me to capitalize on the details of how eNOS generates NO. Fortunately, I landed a position in Pharmacology at Yale in 1993, one of the best Pharmacology Departments in the US and I decided that I should really focus on understanding the regulation and cell biology of eNOS, in order to separate myself from others in the field. This tactical decision allowed us to identify the lipid modifications determining the cellular trafficking of eNOS, characterize its regulation through protein-protein interactions and phosphorylation sites, all levels of regulation way beyond the initial description of the calcium-calmodulin dependency of this important enzyme. Interestingly, Sir John’s first faculty post was at Yale in 1954 and in 1995, I hosted his visit to the Department of Pharmacology where he had a chance to rekindle old friendships. In addition to eNOS, our lab broadened its interests into three additional areas of vascular biology, namely, understanding the role of Nogo-B in inflammation and angiogenesis, microRNA regulation of endothelial and smooth muscle function and the regulation of caveolae in endothelial cells.

My time at WHRI was intellectually stimulating, personally rewarding and overall a wonderful experience. Congratulations on your silver jubilee celebration and the opening of the Heart Centre.

William C. Sessa, Ph.D.
Alfred Gilman Professor of Pharmacology
Director; Vascular Biology & Therapeutics Program
Yale University School of Medicine
Endocrinology

Prof Mike Thorner, University of Virginia

I was a member of the Bart’s Hospital Endocrinology Unit from 1972 until 1977. It provided me with the foundation for my career. First the incredible talent that we had including Professors Besser, Landon, Chard, Rees, Doniach, Jones, Lowry and Scowen to mention just a few. Each week we had research meetings and metabolic ward rounds where everything was up for discussion and however junior each person was, he or she had a voice and was heard. Thus it was an environment for real scientific and clinical exchange. The pillars the experience gave me was the value of collaboration whether local or at other institutions both at home and abroad, the skills in experimental design and implementation, knowledge and hands on experience of developing immunoassays and the experience of working with new compounds whether they were drugs, or peptides – I had the good fortune to be able to work with bromocriptine and with hypothalamic hormones which were rapidly being discovered at that time. One patient sticks in my mind to this day, as she had acromegaly and a metastatic carcinoid tumor – we could never understand the relationship. I am sure that the experience with her led to my being able to identify my patient in Charlottesville with acromegaly and somatotroph hyperplasia which led me to CT scan her to find the tumor in the tail of the pancreas from which the last hypothalamic hormone was isolated, sequenced and cloned. Thus my experiences at Bart’s gave me the foundation for my career in neuroendocrinology and specialization in hypothalamic pituitary disease.

In 1977 I joined the faculty in the Department of Medicine at University of Virginia and rose through the ranks as Program Director of the General Clinical Research Center, Chief of the Division of Endocrinology and Metabolism and Chair of the Department of Medicine. Under my leadership the Department rose in NIH ranking for research support from 43 to 28, and research income increased by 400%. I have been NIH funded from 1978 and currently hold a grant on Ghrelin Regulation and I am co-director of the Neuroendocrinology Training grant.

My most important contributions to endocrinology have been the recognition of a GHRH-secreting adenoma as mentioned before and the demonstration that prolactin secreting pituitary tumors can be effectively treated with dopamine agonist drugs which not only lower prolactin levels to normal and restoring gonadal function but also lead to shrinkage of the tumors to allow visual field defects to recover and resolution of headaches and other mass effects. My current primary research interest has been the decline of growth hormone secretion during aging and its reversibility with growth hormone secretagogues.

I am proud that many of my trainees who are now leaders in their field such as Dr. Mary Lee Vance, Professor of Medicine at UVA; Dr. Ken Ho, Professor of Medicine, University of Queensland and, Director of Translational Research Institute (TRI), Australia; Dr. Peter Clayton, Professor of Pediatrics, University of Manchester; Dr. Mark Hartman, Director of Endocrinology, Eli Lilly and Co, Indianapolis and Dr. Ian Chapman, Professor, University of Adelaide, Australia, while I am grateful for my training and fond memories of my time at Bart’s and the friendships that endure to this day.
Teaching and Learning

Overview of the PhD programmes that WHRI offer

WHRI is committed to delivering an internationally-acknowledged, high quality, comprehensive research training programme leading to the award of PhD and MD(Res). This is underpinned by a rigorous monitoring system involving regular submission of reports and oral assessments and a mentoring program for all our research students. The purpose of this is twofold; firstly to provide an independent and transparent assessment of the progress of all research students and hence to ensure timely and successful completion of their PhD or MD(Res). Secondly it provides confidential pastoral care for the student and an independent source of advice on both academic and non-academic issues. In this way the majority of our students complete their degree within 4 years. In addition, students have access to a wide programme of transferable skills training and career advice. A strong emphasis is also placed on the presentation of the student’s work at both national and international meetings as well as publishing in high impact journals. Opportunities exist across all the Institute’s research themes. These are usually fully funded places offered by the Medical School and other grant awarding bodies including the MRC, BHF, Wellcome, the ARC and most recently 1 year NIHR fellowships via our recent successful NIHR CV BRU that enable clinicians to familiarise themselves with the research world and make submissions for PhD funding. The success of this scheme has recently been realized with the award of a BHF Clinical Fellowship to Shanti Velmurugan and an NIHR Clinical fellowship to Dan Jones. Funding can also be available through our excellent links with Industry. Typically we have more than 30 new students enrolled each year. We also run an MRC funded MRes in inflammation: cellular and vascular aspects. This MRes often forms the basis of four year MRes/Phd courses that are also available within our institute. More recently we were awarded a 4 year MRes/PhD course funded by the British Heart Foundation worth £2.4m that will begin in September 2013.

NIHR CV BRU Clinical research fellows. From left to right: Dr Filip Zemrak, Dr Dan Jones, Dr Shanti Velmurugan and Dr Ian Stone
Graduate Entry Medicine

The School of Medicine and Dentistry recruits between 40 and 50 science graduates each year onto its accelerated medical degree course. This enables students to graduate MB BS within 4 years. Many of these students are ideally suited to careers in academic medicine. In a major new education initiative, the William Harvey Research Institute is planning to greatly expand its teaching portfolio within this programme. Particular foci of development will be to increase the basic science content in key areas of pharmacology and immunology and to provide an expert-led problem-based learning environment. Students will be encouraged to develop their research skills and practice of evidence-based medicine through a novel mentoring scheme. Each student will be provided with a ‘home’ in a research centre within the Institute where they can experience medical research at first hand and receive specialist tutorial assistance with their medical studies. We are confident that this new initiative will enhance the student learning experience within an environment of research excellence.

Masters programmes at the WHRI

Well known for its strategic commitment to the highest quality of research, WHRI also offers the best possible educational, cultural and social experience for students thanks to its rich educational heritage. In recent years postgraduate education has become an essential part of higher education at WHRI. Alongside Professor Atholl Johnston, Dr Nina Ravic (Academic Manager for Postgraduate Studies) has helped develop and is successfully managing a broad portfolio of Masters level postgraduate courses. Moreover, the significant increase in numbers of students recruited into our Masters courses over the past three years (85 students enrolled into 2010/11 WHRI MSc programmes) suggest popularity as well as the quality of service our institute offers.

Masters in Clinical Drug Development and Healthcare Research Methods

Professor Atholl Johnston (Clinical Pharmacology) has developed modular postgraduate programmes in Healthcare Research and in Clinical Drug Development. These courses give individuals the necessary academic background and specialist skills needed to carry out clinical drug development or healthcare research in a contract research organization, pharmaceutical industry or Health Service environments.

Masters in Forensic Medical Sciences course

In 2006, with the appointment of Professor Peter Vanezis as Professor of Forensic Medical Sciences, the MSc in Forensic Medical Science was established. This course fulfils the national and international need for scientific and medical professionals who can apply a critical and scientific approach to their forensic practice, and who wish to have a broad understanding of the various interrelated disciplines of forensic medicine and science.

Masters course in Analytical Toxicology

Professor Robert Flanagan developed the Analytical Toxicology programme primarily for those practicing in the clinical field, but is useful and relevant to students who wish to follow a career in forensic, pharmaceutical, or environmental toxicology as the skills and knowledge base needed for those disciplines is complementary and overlapping.

Masters course in Critical Care

The MSc in Critical Care Medicine is intended to provide participants with a thorough grounding in the discipline, together with the tools to maintain their knowledge base, through a course of advanced, specialist instruction from a faculty of World leading intensivists.

Masters course/ Postgraduate diploma in Endocrinology and Diabetes

This distance learning MSc/PGDip course in Endocrinology and Diabetes was developed by Dr Maralyn Druce. It provides clinicians with theoretical and clinically applied aspects of their discipline, and incorporates elements of the UK specialty training curriculum for endocrinology and diabetes mellitus.
The William Harvey Research Foundation

The William Harvey Research Foundation (WHRF) has been a member of the Association of Medical Research Charities since 1990. Its activities are directed by a Board of Trustees currently formed by Professor Jeremy Pearson (chairman), Mr Michael Draper, Mr Peter Marshall, Professor Stephen DeCherney, Mrs Ann Hacker, Dr Robert Naismith, Mr Michael Webster and Professor Richard Trembath (Vice Principal for Health of the Medical School).

The Foundation supports research primarily in the WHRI on the following areas:
• inflammatory diseases, rheumatism and arthritis
• high blood pressure, heart disease and myocardial infarction
• diet and vascular health
• kidney disease
• septic shock and organ failure
• diabetes and endocrine disorders

For the non-scientist this may seem a wide spectrum of different illnesses. In reality, several common themes link these diseases. In keeping with the historical context of the work of William Harvey, the most important shared interest is the circulation. Our emphasis is mainly on the local control of blood vessels and the interactions that occur with circulating blood cells. The prominence of this in these areas of research is due to the key role of the vascular endothelium in different diseases mechanisms. The endothelium is a single layer of cells lining all blood vessels. It confers many beneficial effects that help maintain a healthy circulation. The endothelium also controls the local response to inflammation, which frequently plays a key part in these diseases. Hence, research on the vascular endothelium and the mechanisms that control inflammation will lead to new ways of preventing and treating these common and disabling diseases.

Because new insights from one of these diseases are often relevant in other areas, the shared interests and cross-fertilisation of ideas in the William Harvey Research Institute adds value to the research and benefits the whole organisation.

The William Harvey Research Foundation continues to play a key role in funding the training of young medical researchers through PhD Studentships. It also acts as a catalyst for new directions in research by funding strategically relevant projects with small grants to obtain proof of concept results.

Visit us (also for donations) at: www.whrf.org.uk
William Harvey Research® Limited
Tailor made solutions for drug discovery

Professor Chris Thiemermann, 
CEO, WHRL

William Harvey Research Limited (WHRL) is internationally recognized as a leading provider of preclinical contract research for the Biotech and Pharmaceutical industry. Founded in 1990, we have been supplying a broad range of high quality studies for global pharma, specializing in models of cardiovascular and inflammatory diseases. Our aim is to offer a professional service to our clients; a major strength is the development of bespoke study design and advice, alongside high quality reporting and academic input.

From preclinical contract research and bespoke study design, to long-term collaboration with strategic partners, we provide our research services internationally to the biotechnology and pharmaceutical industry through our team of experts based at the world-renowned William Harvey Research Institute (WHRI), London, the largest pharmacological research institute in the UK with 65% staff rated world-class or internationally leading in RAE 2008. Because of this, we can offer expertise across a broad range of therapeutic areas and currently have more than 120 in vivo and in vitro disease models available in our catalogue. A primary aim is to co-ordinate contract research as an Efficacy, Verification and Interpretation service (EVIS) and to deliver excellent standards of research.

We offer disease models in the following areas:

Models of Inflammation
Paw oedema, pleurisy and peritonitis, acute joint inflammation, intravital microscopy, skin oedema, thermal nociception and acute lung injury.

Models of Cardiovascular Disease
Acute myocardial infarction, stroke, acute and chronic kidney failure, organ transplantation, shock and multiple organ failure, atherosclerosis, hypertension and diabetes.

Cell Based Assays
Primary human leukocytes (e.g. neutrophils, T-cells), endothelial cells, cell to cell interaction under flow, cardiomyocytes, platelets, mesangial cells, proximal tubule cells.

Proof-of-concept Disease Models
Arthritis, multiple sclerosis, colitis, chronic heart failure, chimaeric models, trauma – haemorrhage, metabolic syndrome and obesity.

William Harvey Conferences®

Since its creation, WHRL has established a reputation for organizing prestigious scientific conferences and is especially proud of its series of annual symposia, the John Vane Memorial Symposium on Prostacyclin and Pulmonary Vascular Disease (JVMS) which has been held in London since 2006. The JVMS has proved to be an essential international meeting, bringing together over 200 world-class speakers and specialists in the field of Pulmonary Vascular Disease from across the globe each year.

WHRL is the trading company of the William Harvey Research Foundation www.whrf.org.uk, a registered charity whose funds support research projects, new state-of-the-art equipment, or fellowships and training programmes.

Further information about our company and available services can be found on our website: www.williamharvey.co.uk. You can also reach us by phone on +44 (0)207 882 8808 and by email: whrl@qmul.ac.uk.
## Prizes

### Previous Prize Winners

#### Outstanding Contribution to Science Medal

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Dame Nancy Rothwell</td>
</tr>
<tr>
<td>2005</td>
<td>Jonathan Seckl</td>
</tr>
<tr>
<td>2006 (20th WHRI anniversary)</td>
<td>Garret Fitzgerald</td>
</tr>
<tr>
<td>2007</td>
<td>Elisabetta Dejana</td>
</tr>
<tr>
<td>2008</td>
<td>Paul Stewart</td>
</tr>
<tr>
<td>2009</td>
<td>Alberto Mantovani</td>
</tr>
<tr>
<td>2011 (25th anniversary)</td>
<td>John L. Wallace</td>
</tr>
</tbody>
</table>

#### John Vane Medal

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Sir William Castell</td>
</tr>
<tr>
<td>2006 (20th WHRI anniversary)</td>
<td>Gustav Born</td>
</tr>
<tr>
<td>2007</td>
<td>Carlo Patrono</td>
</tr>
<tr>
<td>2008</td>
<td>Charles Serhan</td>
</tr>
<tr>
<td>2009</td>
<td>Bill Sessa</td>
</tr>
<tr>
<td>2011 (25th WHRI anniversary)</td>
<td>Rod Flower</td>
</tr>
</tbody>
</table>

#### Iain Macintyre Award for Endocrinology

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 (25th WHRI Anniversary)</td>
<td>Richard Eastell</td>
</tr>
<tr>
<td>2012</td>
<td>Adrian Clark</td>
</tr>
</tbody>
</table>

#### Derek Willoughby Medal

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 (20th WHRI anniversary)</td>
<td>Dan Simmons</td>
</tr>
<tr>
<td>2007</td>
<td>Anthony Cerami</td>
</tr>
<tr>
<td>2008</td>
<td>Mark Walport</td>
</tr>
<tr>
<td>2011 (25th WHRI anniversary)</td>
<td>Tim Williams</td>
</tr>
</tbody>
</table>

#### Young Investigator Award

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Felicity Gavins Chris Wallace</td>
</tr>
<tr>
<td>2005</td>
<td>Nimesh Patel Frankie Swords</td>
</tr>
<tr>
<td>2006 (20th WHRI anniversary)</td>
<td>Sadani Cooray Blerina Kola</td>
</tr>
<tr>
<td>2007</td>
<td>Frances Humby Hetal Patel</td>
</tr>
<tr>
<td>2008</td>
<td>Renuka Dias Doris Proebstl</td>
</tr>
<tr>
<td>2009</td>
<td>Jesmond Dalli</td>
</tr>
<tr>
<td>2011</td>
<td>Jenna Cash</td>
</tr>
<tr>
<td>2012</td>
<td>Martina Beyrau Lorenzo Rattazzi Andrew Leinster</td>
</tr>
</tbody>
</table>
Harvey demonstrates his Theory of Circulation to King Charles I
The William Harvey Medal is awarded annually to an outstanding scientist. Recent winners have been Nancy Rothwell FRS, Jonathan Seckl and Garrett FitzGerald.

Similarly we recognise annually outstanding young investigators. Recent winners have been Doris Proebstl, Jesmond Dalli, Jenna Cash, Martina Beyrau, Lorenza Rattazzi and Andrew Leinster.
William Harvey Research Institute – at a glance

- Top 20 Pharmacology Institutes in the world
- 330 scientists from more than 44 nations
- More than 80 PhD students in 2011
- £50 million spent on research since 2001
- More than 35 publications in top journals (Nature, Nature Genetics and Medicine, Science, New England, Lancet) in the past four years
- Over £9 million spent on lab refurbishment since 2003
- Twenty-first-century Heart Centre (£25 million) opened in 2011