Grant Awards 2004/2005

British Heart Foundation

Contents

Introduction

In the year April 2004 to March 2005, the BHF spent over £50 million on research into the causes, prevention, diagnosis and treatment of diseases of the heart and circulation. This document gives a summary of research carried out by BHF chairholders, and details of all the awards made in the year including Basic Science Lectureships, Fellowships, Programme Grants, Special Projects and Project Grants.

A summary of research from BHF chairholders

Listed by town

UNIVERSITY OF BIRMINGHAM

Queen Elizabeth Hospital

The Chair of Cardiovascular Medicine

Held by: Professor M P Frenneaux MBBS(Hon) MD FRCP FRACP FACC FESC – from 1 May 2004

Studies are being carried out in three main areas.

Heart failure

- Potential therapeutic role of agents which alter the fuel the heart uses (from fatty acids towards glucose)
- Factors responsible for the control of venous function in heart failure
- Epidemiology and pathophysiology of heart failure with normal left ventricular ejection fraction
- Studies assessing the mechanism by which biventricular pacing reduces symptoms in patients with heart failure and aiming to better select those likely to benefit from this form of therapy.

Hypertrophic cardiomyopathy (HCM)

- The role of inappropriate vasodilation as a cause of episodic hypotension and syncope
- The effects of drug interventions on abnormal vascular responses (including abnormal exercise blood pressure responses) in HCM
- The potential role of biventricular and left ventricular pacing as a therapeutic strategy in HCM.

Depression

- Studies on the mechanisms responsible for increased cardiovascular risk in patients with a history of depression.

UNIVERSITY OF BIRMINGHAM

The Chair of Cardiovascular Sciences and Cellular Pharmacology

Held by: Professor S P Watson PhD FMedSci

The work of the laboratory is concerned with the molecular mechanisms underlying platelet activation in health and disease.

Megakaryocyte studies. Platelets are made from megakaryocytes in the bone marrow. Because platelets do not have a nucleus, they cannot be modified by gene targeting techniques. We are therefore targeting megakaryocytes in order to produce mutant platelets. We are also investigating the ability of platelet stimulatory agents to activate megakaryocytes as a model system to study platelet-based signalling cascades.

Platelet collagen receptors. Collagen is the most thrombogenic component of the subendothelial matrix. We are investigating the proteins on the platelet surface that underlie activation by collagen through the use of molecular and cell biology techniques. This includes determination of the structure-function relationships of the cytosolic tail of the major activating receptor for collagen, GPVI. Adhesion receptors represent important targets for development of anti-thrombotic agents.

Platelet-endothelial cell interactions. Endothelial cells form a thin layer of cells that separate the blood from the body tissues. We are investigating the ability of platelets to bind to healthy and diseased endothelial cells and the implications for thrombus formation in intact vessels.

Platelets and immune disorders. Platelet activation by collagen shares a number of key similarities with the mechanism of activation of B- and T-lymphocytes. We have shown that individuals with the X-linked immunodeficiency, XLA, have impaired platelet activation. We have shown that this is due to a deficiency in the tyrosine kinase Btk in platelets. We have also shown that the level of this impairment is reduced by the presence of a second member of the Btk family of tyrosine kinases in platelets, namely Tec.

Platelet proteomics. Proteomics is a new way to identify the protein composition of cells. We have mapped the platelet proteome identifying the presence of several hundred proteins, many of which have not been previously described in platelets.

Platelet signalling cascades. We are using biochemical approaches and genetic means to investigate the way in which receptors for collagen and other adhesion molecules stimulate platelet activation. We have demonstrated that immunoglobulin and integrin receptors stimulate a common protein, named phospholipase C, through distinct signalling cascades. We are investigating the ability of the cyclic nucleotide cGMP to modify platelet function.

Platelet studies in the clinic. We are measuring the levels of key receptors for platelet adhesion molecules in healthy individuals and patients with platelet-based bleeding problems of unknown cause. A focus of this work is on individuals who have bleeding problems caused by an impairment in platelet activation by collagen.

Snake venom toxins. Snake venom toxins represent a rich source of bioactive materials that act on platelets and the coagulation system. A large number of snake venom toxins are used in clinical medicine. We are characterising the toxins from a number of rare, poisonous snakes from Asia and South America. We have isolated a novel toxin that generates thrombin formation and a second toxin that stimulates platelet activation through a novel receptor.

Thrombus formation under arterial flow. We are using an *in vitro* flow-based system to monitor the events that give rise to thrombus formation under arterial rates of flow. The experiments are performed on different adhesion proteins including von Willebrand factor and collagen. The experiments permit a much greater insight into the molecular mechanisms that underlie thrombus formation.

UNIVERSITY OF BRISTOL

Royal Infirmary

The Chair of Cardiac Surgery
Held by: Professor G D Angelini MD MCh FRCS FETCS

Improving the patency of saphenous vein grafts. We have discovered that supporting coronary artery bypass grafts with an external porous loose-fitting mesh prevents wall thickening that can lead to failure. A clinical trial is ongoing to test the impact of this modification to the basic surgical procedure.

We have demonstrated that thapsigargin, a drug that depletes calcium stores, also inhibits narrowing of vein grafts and may therefore be a pharmacological alternative to external supports.

We have also shown that gene therapy can be used to prevent narrowing of vein grafts.

Myocardial protection during open-heart surgery

- **Adult.** We continue to investigate the effectiveness of different techniques of myocardial protection in patients. At present we are comparing warm versus cold blood cardioplegia in aortic valve replacement surgery.

- **Paediatric.** We have recently shown that the use of cold crystalloid cardioplegia to protect the heart during paediatric surgery confers better protection to children's compared to infants' hearts.

Coronary revascularisation without cardiopulmonary bypass

A randomised study comparing conventional coronary artery bypass surgery versus operating on the beating heart has been completed. The study showed that patients undergoing beating heart operations suffer fewer complications in surgery.

UNIVERSITY OF BRISTOL

Royal Infirmary

The Chair of Vascular Cell Biology
Held by: Professor A C Newby MA PhD

Vessel wall matrix turnover and smooth muscle cell proliferation. Excessive amounts of extracellular matrix and increased numbers of vascular smooth muscle cells cause coronary arterial blockages. We have proposed a connection between these events, in that increased activity of enzymes that digest matrix (metalloproteinases) is required for smooth muscle cell proliferation. We continue to produce direct evidence for this in models of atherosclerosis and also in other situations where blocked veins and arteries are a clinical problem, for example in vein grafts and after angioplasty.

Atherosclerotic plaque rupture in heart attacks. Increased protease activity is implicated also in making atherosclerotic plaques unstable, which leads to life-threatening events such as unstable angina and heart attacks. We are investigating the underlying mechanisms of increased protease activity in the hope of developing new treatments.

Gene therapy for vascular disease. Since coronary artery disease only occurs in discrete locations, it has been suggested that local treatment with highly effective agents might circumvent the poor efficiency and side-effects of whole body treatments. In this context, transfer of normal human genes may be a viable alternative to conventional drugs. We have succeeded in showing that transfer of genes for inhibitors of metalloproteinases provides beneficial effects in models of vein grafting.

Surgical improvement of vein-graft occlusion. Veins are used frequently for coronary artery bypass grafting, although their wall is poorly adapted to arterial blood pressure. To correct for this we (in collaboration with the Chair of Cardiac Surgery) have used veins surrounded by an external support with highly encouraging initial results.

Mechanisms of adenosine formation. Adenosine is a chemical messenger that improves blood flow in the heart. We have recently succeeded for the first time in isolating the gene that is responsible for adenosine formation. This breakthrough will aid future research and could lead to new treatments.

UNIVERSITY OF CAMBRIDGE

Addenbrooke's Hospital

The Chair of Cardiovascular Sciences

Held by: Professor M R Bennett MB ChB PhD MRCP

Vascular smooth muscle cells and inflammatory cells comprise the atherosclerotic plaque, whose rupture causes artery occlusion and heart attacks. Excessive accumulation of vascular smooth muscle cells also promotes renarrowing of arteries after revascularisation, such as intracoronary stenting (restenosis) and bypass grafts. The proliferation of these cells is therefore critical to understanding these processes. A major focus of work performed by the research group has been to identify the important regulatory molecules that control cell proliferation in atherosclerosis and restenosis, using a variety of cell and molecular biology techniques. We have characterised why cells in advanced human atherosclerotic plaques proliferate poorly, and are therefore unable to repair minor damage in plaques. We have also determined how cells from in-stent narrowings bypass conventional cell cycle control, and how novel therapies such as brachytherapy (radiation therapy) affect human cells. These studies have led to the design of anti-proliferative agents that are disease-specific, and are currently being tested. In addition, genetic profiling has identified novel markers of disease, a prelude to rational drug design to target disease tissue.

Vascular smooth muscle cell death also promotes instability of atherosclerotic plaques, and we continue to study the regulation of this process. We have determined that smooth muscle cells from advanced plaques have lost the ability to protect themselves from cell death, and are also killed by local inflammatory cells. These studies have elucidated mechanisms of cell death in atherosclerosis, and will also examine the beneficial effect of cholesterol-lowering drugs on cell death. Finally, new studies have recently been funded to study the processes of cell ageing in atherosclerosis, and to identify mechanisms to either halt or reverse this process.

UNIVERSITY OF CAMBRIDGE

Papworth Hospital

The Chair of Cardiac Surgery

Held by: Professor B R Rosengard MD FRCS FACS

Mechanisms of immune responses triggered by endothelium. Although novel immunosuppressant drugs have virtually eliminated the risk of acute rejection of heart transplants, the risk of chronic rejection in the form of accelerated arteriosclerosis remains unchanged. It has previously been held that graft rejection is triggered by 'passenger leukocytes', donor white blood cells present in the graft, which migrate to the recipient's secondary lymphoid organ and activate host T cells that attack the graft and lead to rejection. We have hypothesised that graft endothelial cells are capable of directly activating host T cells, which would explain why chronic rejection occurs long after the clearance of passenger leukocytes. So far, we have demonstrated a difference between subsets of T cells ($CD4^+$ and $CD8^+$) in their ability to be activated by endothelium. Our ongoing work is focused on defining the molecular basis of this difference to develop target molecules for therapeutic intervention.

Myocardial stem cell biology. Until recently, the heart was believed to lack regenerative capacity. However, there is mounting evidence that a population of progenitor cells within the heart is capable of proliferation and differentiation into mature cardiac myocytes in response to injury. The challenge is to understand why this process is so limited, which results in inadequate healing after large myocardial infarcts or global insults to the heart (eg, viral infection). Our work is trying to define the molecular basis of differentiation of adult cardiac myocytes from embryonic stem cells, hopefully to identify those processes which inhibit complete myocardial regeneration. In addition, we are exploring several approaches to myocardial tissue engineering as potential therapeutic strategies for both congenital and acquired cardiac disease.

Tissue engineered vascular conduits. Both coronary artery and peripheral artery bypass procedures depend on the ready availability of adequate arteries or veins. Many patients lack suitable blood vessels for grafting, which limits their ability to benefit from surgical revascularisation. In collaboration with a biotechnology company, we will begin clinical trials of utilising wholly autologous, engineered vascular conduits. Engineered vessels will have no foreign proteins and will be 'grown' from a small skin and vein biopsy from a patient. If successful, this will revolutionise vascular surgery and will provide proof of principle for other tissue engineering approaches.

***Ex vivo* donor organ resuscitation.** Heart transplantation is limited by the availability of suitable donors. Papworth Hospital has pioneered approaches to *in vivo* donor organ resuscitation and evaluation, which have become the 'standard of care' both in the UK and North America. In collaboration with a biotechnology company, we will test a device which will perfuse explanted hearts with substrate enhanced, warm, oxygenated blood and thereby resuscitate the organs outside of the inflammatory milieu of the brain-dead donor. Moreover, the resuscitation device will permit hearts to be fully evaluated anatomically, physiologically and biochemically, which will allow us to develop an evidence-based assessment of organ suitability, which will undoubtedly increase organ utilisation.

UNIVERSITY OF CAMBRIDGE

Addenbrooke's Hospital

The Chair of Cardiovascular Medicine

Held by: Professor P L Weissberg MD FRCP FESC FMedSci – resigned 30 November 2004

Vascular smooth muscle cell gene expression. We have identified and sequenced an entirely novel gene which is expressed in both smooth muscle and cardiac muscle. We have also identified its chromosomal location and anticipate that this may turn out to be an important molecule in the regulation of contractile function. We have also identified a family of genes, containing some novel members, that regulate the transcription of smooth muscle specific genes. Our most recent studies have allowed us to propose a model for the regulation of expression of smooth muscle specific proteins by members of the transforming growth factor beta super family.

Vascular calcification. We have now established that vascular calcification is a regulated process involving both inhibitory and facilitative gene products. We have also established that apoptotic cell death, under certain circumstances, may lead to the precipitation of calcium salts and the initiation of soft tissue calcification. In addition, we have found potentially important genetic variability in the gene coding for matrix Gla protein, an important inhibitory protein, which may predispose some individuals to develop either earlier or more pronounced calcification.

Vascular smooth muscle cell death. Our continuing studies into the causes and consequences of vascular smooth muscle cell death by apoptosis have allowed us to characterise important intercellular interactions that might lead to instability of atherosclerotic plaques and, therefore, the development of heart attacks and strokes.

Vascular imaging. By adopting a novel approach to imaging of atherosclerosis, we have obtained promising pilot data in patients with symptomatic vascular disease which suggest that, with further development, non-invasive imaging of atherosclerotic inflammatory activity may become feasible.

CARDIFF UNIVERSITY

University of Wales College of Medicine

The Sir Thomas Lewis Chair of Cardiology

Held by: Professor M P Frenneaux MBBS(Hon) MD FRCP FRACP FACC FESC – resigned 30 April 2004

Heart failure

- We are investigating novel therapies for heart failure including new drug therapies and pacing.
- We are investigating the mechanisms responsible for malfunction of baroreceptors in heart failure. These special pressure-sensitive receptors are crucially important in the control of the circulation, and malfunction is associated with a higher mortality rate. We have also been evaluating therapies to improve this malfunction.
- We have also been evaluating the factors responsible for control of veins. This is an unexplored area which may be very important in heart failure.

Arterial stiffness. Increased arterial stiffness is a marker of cardiovascular risk. We have been using a non-invasive technique to assess arterial stiffness, examining the impact of risk factor intervention.

Endothelial function. The thin layer of cells which lines blood vessels is crucially important in normal blood vessel function. Dysfunction is believed to be a key factor in atherosclerosis. We are investigating mechanisms and evaluating therapies aimed at restoring endothelial function.

Echocardiographic research. We are evaluating the role of new echocardiographic techniques. In particular, we are investigating the role of a technique known as Tissue Doppler Imaging to non-invasively identify patients with coronary artery disease.

Health service delivery. We are co-ordinating a large NHS R&D-funded programme evaluating cardiac rehabilitation following heart attacks.

Intracellular calcium signalling. An intensive programme of research is underway investigating the structure and function of the calcium release channel, the protein that controls calcium-mediated heart muscle contraction.

Electron paramagnetic resonance spectroscopy. This technique is being used to measure tissue oxygen, nitric oxide and ultimately reactive oxygen species and will provide very important information to aid our understanding of cardiovascular disease and sepsis.

UNIVERSITY OF EDINBURGH

New Royal Infirmary

The Duke of Edinburgh Chair of Cardiology

Held by: Professor K A A Fox MB ChB FRCP FESC FMedSci

The mechanisms and consequences of arterial vessel wall injury. Our research investigates the mechanisms that underlie early atheroma development in the arterial wall, including the impact of key genetic, inflammatory and dietary factors. The latter include the role of partially oxidised lipids and essential fatty acids. These early mechanisms are linked with abnormalities in the function of vascular endothelial cells and with activation of fibrin and platelets triggering thrombotic complications. Our clinically related studies demonstrate that it is possible to identify patients with threatened myocardial infarction, to inhibit the thrombin and platelet aggregation mechanisms and to diminish the risks of major cardiovascular complications. This work has included more accurate assessment of the frequency and clinical significance of acute coronary syndromes (myocardial infarction and unstable angina).

Characterisation of the vessel wall and myocardium. Our group has characterised the major structural components of atheroma (lipid deposits, fibrous material and calcified deposits) using high resolution ultrasound, and we have demonstrated the ability to differentiate clots of varying composition. This experimental work has the potential for clinical application and current studies are investigating the characteristics of atheromatous plaques in patients with arterial disease. The work employs novel techniques (developed in Edinburgh) to resolve the kinetics of vessel wall and myocardial contraction and relaxation. These techniques also have the potential to differentiate forms of heart muscle and skeletal muscle dysfunction including those seen in heart failure.

Cardiac specific gene targeting. The group is examining the molecular genetics of key factors involved in the risks of vessel wall injury and hypertension. These include the identification of important steps in the regulation of the renin-angiotensin system (blood pressure and vessel wall tone), glucocorticoid metabolism (susceptibility to atheroma) and accelerated phase hypertension. The group has recently succeeded in genetically marking renal juxtaglomerular cells, critically involved in blood pressure regulation.

Cardiac arrest studies. This group now has the largest single-centre experience in Europe of survivors of out-of-hospital cardiac arrest. We have determined that specific brain enzyme markers predict the risk of death and cognitive impairment among those surviving initial resuscitation, and further work has examined deficits in memory and mental function among those suffering prolonged out-of-hospital cardiac arrest. Using magnetic resonance imaging, the anatomical substrate for such defects has been defined, and related work examines the risks of further arrhythmias. This work allows specific rehabilitation measures to be targeted at survivors of cardiac arrest.

UNIVERSITY OF GLASGOW

Royal Infirmary

The Walton Chair of Medical Cardiology
Held by: Professor S M Cobbe MA MD FRCP FMedSci

Electrophysiological and intracellular Ca^{2+} changes in heart failure. We have demonstrated regional variability in changes in cellular electrophysiology and Ca^{2+} handling, suggestive of down-regulation of the sarcoplasmic reticulum in the outer and middle layers of the left ventricular wall, but up-regulation in the area closest to the left ventricular cavity. This area of up-regulation is a potential site of origin of cardiac arrhythmias in the failing heart.

Electrophysiological effects of left ventricular dilatation. We have observed that the electrical properties of the cells adjacent to an area of myocardial infarction are heterogeneous. Heterogeneity is even more marked when the left ventricle is distended. The increase in heterogeneity may predispose to an increased risk of developing ventricular fibrillation.

Prediction of survival in heart failure. We have completed a follow-up study in 199 patients with stable congestive heart failure. During a three-year follow-up, there were 47 cardiac deaths. The most reliable marker proved to be the level of brain natriuretic peptide in the blood. This offers the opportunity of improved risk prediction in heart failure, with the opportunity to select patients for more intensive treatment.

Effects of adenosine on the atrioventricular node. We have extended our studies into the mechanisms of action of adenosine, which may be used to terminate cardiac arrhythmias. Adenosine activates a potassium current which reduces excitability of the atrioventricular nodal cell. However, its main effect is due to slowing of recovery of the inward calcium current.

Nuclear cardiology. A number of projects in the area of nuclear cardiology continue to evaluate the effects on non-invasive markers of myocardial ischaemia and left ventricular function in coronary disease.

Electrocardiology computing group. Further refinements in the techniques for computer analysis of electrocardiograms have included enhancements to arrhythmia interpretation and further assessment of paediatric ECG interpretation by computer.

Out-of-hospital cardiac arrest. Analysis of the database from the Scottish Ambulance Service has continued. We have demonstrated lower rates of successful resuscitation among women, principally attributable to the lower likelihood of the cardiac arrest being witnessed. Seasonal variations have been demonstrated, with poorer success rates in the winter.

UNIVERSITY OF GLASGOW
Western Infirmary
The Chair of Cardiovascular Medicine
Held by: Professor A F Dominiczak MD FRCP FMedSci

Molecular genetic strategies in cardiovascular and cerebrovascular disease. These strategies are designed to unravel the susceptibility and severity genes for blood pressure regulation, left ventricular hypertrophy and the sensitivity to cerebrovascular ischaemia in a stroke-prone spontaneously hypertensive model. We shall also use the quantitative trait loci identified in experimental studies to guide the genetic analysis of human cardiovascular and cerebrovascular disease.

Endothelial function in vessels. These studies focus on a hypothesis that one of the major modifiable determinants of endothelial dysfunction is an imbalance between the nitric oxide and the superoxide anion. We demonstrated that the nitric oxide-dependent endothelial dysfunction in vessels is due to excess of superoxide anion generated by the endothelium. These studies are currently being translated from bench to bedside with the use of a non-invasive vascular ultrasound technique.

Vascular gene transfer strategies. Targeted gene transfer strategies have been designed to restore the nitric oxide/superoxide balance in experimental models *in vivo* and in human saphenous veins *ex vivo*. We developed viral vectors based on recombinant adenoviruses encoding bovine and human endothelial nitric oxide synthase genes and demonstrated high levels of foreign gene expression associated with a significant improvement of endothelial nitric oxide bioavailability in functional studies. Further work in this area will address similar strategies in human veins as well as new viral vectors and new cDNA constructs to address more thoroughly the issue of local molecular therapeutic strategies.

UNIVERSITY OF GLASGOW
Royal Infirmary
The Chair of Cardiac Surgery
Supported by the Isidore and David Walton Charitable Trust
Held by: Professor D J Wheatley MD ChM FRCSEd FRCS(Glasg) FRCPEd FMedSci

Research on replacement heart valves. We are developing a new polyurethane valve using polyurethane materials which are more resistant to being degraded by biological processes and, therefore, suitable for long-term use. A new polyurethane heart valve has been implanted into an experimental model, with a mechanical and a porcine valve as controls for comparison. The function of these valves has been measured after six months' implantation and the results obtained compared with laboratory-based tests. Chemical changes to the surface of polyurethane heart valves can be used to improve the blood compatibility, but may have unpredictable effects on valve durability. We have made several chemical changes to valve leaflets, and investigated the effects of these on the durability of valves in laboratory tests.

Studies of the effect of heparin (anticoagulant) and the heart-lung machine on blood cells. We have found that heparin causes clumping and loss of blood platelets but a beneficial effect is that heparin blocks the effects of white blood cells which can cause damage. We have modified and simplified the detection of circulating platelet clumps in humans so that the effects of heparinisation for cardiopulmonary bypass can readily be seen. We are investigating the effect of adding fish oil to the diet preoperatively to see whether the inflammation-type response of the white cells from the heart-lung machine can be decreased after heart surgery.

Studies of aspects of techniques for protecting the heart during cardiac surgery. An unwanted effect of solutions used to preserve the heart during operations is that small blood vessels can shut down and may interfere with recovery. We are investigating this in the isolated heart which, uniquely in Britain, is perfused with blood. We are making casts of the blood vessels to determine which solution is least damaging. We are also studying the effect of adding an amino acid nutrient to the heart before restoring the blood supply during operations in order to improve function.

UNIVERSITY OF LEEDS

General Infirmary

The Chair of Cardiology

Held by: Professor S G Ball PhD FRCP

- We are undertaking a large-scale collaborative search of the DNA from individuals with premature heart disease to find the genes responsible for the early onset of heart attacks.

- We are studying how abnormalities in receptors (which convey messages from the outside to the inside of cells) alter their usual function and so cause heart disease or make it worse.

- We are studying how the heart repairs itself after it has been damaged by lack of blood caused by disease in the coronary arteries using magnetic resonance (MR) imaging, which avoids X-rays and ‘invasive’ tests.

- We are undertaking trials to find new drugs to treat patients with hearts damaged after a heart attack and to prevent heart attacks in the first place.

- We are also studying how blood pressure and heart rate are controlled and why this goes wrong in some patients, causing them to faint easily.

- We are finding out how lack of oxygen is sensed by the heart.

UNIVERSITY OF LEICESTER
Glenfield Hospital
The Chair of Cardiology
Held by: Professor N J Samani BSc MD FRCP FACC FMedSci

Many common cardiovascular diseases have a significant genetic contribution. Elucidation of the nature of the genes involved and how they interact with acquired risk factors may have important benefits in formulating both better preventative as well as therapeutic strategies in the future. The main interests of the group are elucidating the molecular genetic basis of two of the most common cardiovascular problems: high blood pressure (hypertension) and coronary artery disease.

Hypertension and blood pressure regulation. Using experimental models and human cohorts, we have identified several genetic loci that influence blood pressure and we are currently using genomic and bioinformatics approaches to identify the causal genes. At the same time, we have investigated the role of several candidate genes in hypertension and shown, for example, that some gene variants influence risk only in obese subjects – findings that may have implications for choice of drug therapy. From a population perspective and for developing preventative strategies, it is important to know the interaction of genes and environment in determining blood pressure values in the normal population and we have recently started a detailed investigation of this.

Coronary artery disease. Together with colleagues in Leeds, we have assembled one of the largest family-based cohorts in the world to identify genetic determinants of premature coronary artery disease and heart attacks. Currently, the genome-wide scan to systematically locate the chromosomal regions that harbour such genes is being undertaken. At the same time, we have investigated the role of candidate genes in risk of premature heart attacks using a case-control design and a novel approach that allows a large number of gene variants to be screened simultaneously, and we have detected several associations that we are pursuing further.

Genetic abnormalities in platelets and susceptibility to heart attacks. Platelet aggregation is an important part of the development of the clot in the coronary artery, the immediate cause of a heart attack. We have shown that healthy adult children of subjects with a premature heart attack have platelets that are more ‘sticky’ than those of controls without such a family history. This points to a possible genetic abnormality in platelets which increases susceptibility to heart attacks and we are currently investigating relevant genes.

Biological ageing and risk of coronary heart disease. Heart disease is an age-related disease, but why is there such a variation in its onset even in subjects with similar risk factor profiles? Using a cellular marker of biological age, we have recently found evidence that subjects with coronary heart disease may be biologically much older than chronologically matched healthy subjects. If this is corroborated in further studies, it may provide a new paradigm to looking at the development of coronary heart disease.

UNIVERSITY OF LONDON
University College London (Institute of Child Health)
The Joseph Levy Chair of Paediatric Cardiac Morphology
Held by: Professor R H Anderson BSc MD FRCPath

The unit is involved with research into the structure of the normal and congenitally malformed heart, with particular reference to the arrangement of the system of fibres which co-ordinates electrical activity within the heart.

The developing heart. There is now great interest in the location of genes within the tissues of the developing heart. Our particular interest is in how hearts develop with major deficiencies in the partitions dividing the four major cardiac chambers, and with abnormal connections of the great veins.

Echocardiographic correlation. There is still much to be learnt about the accurate echocardiographic diagnosis of congenitally malformed hearts. We continue to study the structure of the malformations as seen in autopsied hearts. This provides us with the information to check the accuracy of diagnosis during life, and to improve the techniques of recognition, particularly for the fetal echocardiographer. We are also checking the accuracy of three-dimensional reconstruction.

Understanding the nature of abnormal conduction. The techniques for curing abnormal rhythms within the heart are increasing all the time, and with this increase in experience doctors are requiring greater knowledge of the abnormal pathways for conduction. Our current interest is in exploring the pathways responsible for atrial flutter and fibrillation and combining this with knowledge of conduction through the atrioventricular node.

The long-term effect of treatment of congenital heart disease. It is now increasingly recognised that, although surgical treatment has greatly improved the outlook for patients born with diseased hearts, problems still remain in the long term. We continue our study of those patients who die a long time after their initially successful treatment in order to establish those factors which may have contributed to death.

UNIVERSITY OF LONDON
St George's Hospital Medical School
The Prudential Chair of Clinical Cardiology
Held by: Professor A J Camm QHP MD BSc FRCP FESC FACC FCGC C.St.J

Atrial fibrillation is a common rhythm disorder which is being investigated in a long series of studies. Examples include: design and testing of pacemaker algorithms for control of atrial fibrillation, and the development of implantable defibrillators.

We are investigating: new medications and medical regimens for paroxysmal, persistent and permanent atrial fibrillation; mapping of atrial fibrillation at surgery to identify areas which can be destroyed in order to eliminate the rhythm disturbance; and use of digital recordings in order to evaluate the mechanisms initiating atrial fibrillation.

Heart muscle disorders, such as hypertrophic cardiomyopathy and dilated cardiomyopathy generally occur in families. These disorders and other genetic cardiac conditions which may cause sudden unexpected cardiac death, are under investigation. We are looking at the genetic basis and phenotype/genotype correlations in hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic dysplasia, Marfan syndrome, Long QT syndrome,

Brugada syndrome, sudden infant death syndrome and the conditions responsible for sudden death in professional athletes.

Several techniques to assess the cardiac electrical risk of patients with heart disease are being developed and assessed, using several large databases stemming from multi-centre clinical trials. These include: heart rate variability – frequency, time and non-linear methods; a new technique known as heart rate turbulence; and spatial and temporal variability of the QT interval (QT dispersion).

In the field of coronary artery disease we are carrying out many studies into the infective basis of coronary atheroma, particularly involving chlamydia pneumoniae; the inflammatory nature of coronary artery disease; and syndrome X – angina with 'normal' coronary arteries.

Many other studies in the field of cardiac transplantation, the measurement of endogenous and exogenous cardiac analytes, and peri-operative risk statistics are also being undertaken.

UNIVERSITY OF LONDON

University College London (Institute of Child Health)
The Vandervell Chair of Congenital Heart Disease
Held by: Professor J E Deanfield BA BChir MB FRCP FMedSci

Non-invasive study of endothelial function in pre-clinical atherosclerosis. This enables an understanding of the mechanisms by which the endothelium regulates vascular biology relevant to the development of atherosclerosis.

Genetic and environmental interaction on vascular function in the young. A large cohort of children (more than 8,000) are undergoing vascular phenotyping including measures of endothelium dependent and independent vascular function at the age of 10 years. These children have had blood taken for genetic characterisation as well as annual follow-ups during which a detailed profile of lifestyle and cardiovascular risk factors has been established. This is by far the largest such study being undertaken.

Study of the role of endothelial progenitor cells in vascular development and vascular biology in the young. These bone marrow derived cells may be an important protection mechanism relevant to the initiation and progression of early vascular disease.

UNIVERSITY OF LONDON
Imperial College (Hammersmith Hospital)
The Sir John McMichael Chair of Cardiovascular Medicine
Held by: Professor D O Haskard DM FRCP FMedSci

The research interest of the unit is the cellular and molecular mechanisms of inflammation within the cardiovascular system.

Mechanisms of vascular endothelial cell activation. Work on endothelial cell biology *in vitro* has concentrated on investigating the control of expression of adhesion molecules and complement regulatory proteins in response to cytokines and growth factors. We are particularly interested in the role of protein kinase C in signalling endothelial cell activation and in the inhibitory effects of high density lipoproteins. We have cloned and characterised the mouse ICAM-1 promoter with a view to exploring ICAM-1 promoter function with *in vivo* models.

Vascular endothelial activation *in vivo*. We have identified and generated reagents to adhesion molecules for use in models of inflammation and have made monoclonal antibodies to P-selectin and ICAM-1. We have now scaled down the technique of intravenous targeting of radiolabelled monoclonal antibodies, and are using the technique to understand changes in endothelial cell function in chronic models of inflammation. One clinical application of this approach is the imaging of activated endothelium in patients with cardiovascular inflammation and we are developing an sFv anti-E-selectin monoclonal antibody for this purpose.

Mechanisms of leukocyte transmigration through endothelium. We are investigating the molecular interactions that mediate leukocyte extravasation through endothelium *in vivo*, using intra-vital microscopy. Ongoing projects include the dissection of the role of PECAM-1, and the role of leukocyte-derived proteases. We are examining the effects on leukocyte transendothelial migration of the proteinase inhibitor aprotinin, which is in routine clinical use for the prevention of bleeding following cardiopulmonary bypass.

Mechanisms of monocyte and macrophage adhesion and migration. We are performing *in vitro* experiments to explore the changes in adhesion mechanisms that accompany the differentiation of a monocyte into a macrophage once the monocyte has migrated into arterial tissue during atherogenesis.

UNIVERSITY OF LONDON
University College London (Institute of Child Health)
The Chair of Developmental Cardiology
Held by: Professor S G Haworth MD FRCPath FRCP FACC FMedSci

High pressure in the blood circulating through the lung (pulmonary hypertension) is a frequent cause of death and disease in childhood. The only curative form of treatment is lung transplantation. The problem usually arises at birth, when the blood vessels of the lung fail to adapt normally to extrauterine life. Our research programme is designed to find out how adaptation occurs in normal babies, and what happens to the blood vessels when it does not. This knowledge is essential in the search for effective treatment.

We are studying the formation of blood vessels in the lung from four to five weeks' gestation, working out how the wall of the blood vessel is developed in the primitive lung bud of the embryo.

We have shown that the pressure in the circulation falls after birth because the contractile framework of the smooth muscle cells in the arterial wall normally breaks down immediately after birth to allow the vessel to distend. Once this has taken place, the framework reforms, but into a different pattern. In newborn babies with pulmonary hypertension, this process fails.

We know that the pulmonary arteries of the newborn constrict easily when stimulated, and virtually close down. This prevents blood circulating through the lung. Using new videomicroscopic techniques, we can now track the movement of cells on the vessel wall and learn how to control the degree of constriction.

Receptors receive and transmit signals reaching the surface of cells within the vessel wall. We are studying changes in the distribution and density of those receptors known to influence blood flow.

We have found that the pulmonary arteries produce little nitric oxide before birth. Birth normally switches the synthesis on, but pulmonary hypertension is associated with a reduced output. We are studying the regulation of nitric oxide production during the newborn period.

Newborn pulmonary arteries and veins at first do not respond to drugs like adult vessels. Therefore we are studying the pharmacological properties of the newborn pulmonary vasculature and the rate and manner in which normal vessels mature.

In children with congenital heart disease who have too much blood flowing to the lungs through the holes in their heart, the pressure in the blood vessels within the lung increases and the arteries become damaged and blocked. Eventually these changes are irreversible and prevent the heart being repaired, and the only ‘curative’ form of treatment is heart-lung transplantation.

UNIVERSITY OF LONDON

University College London

The Chair of Cardiovascular Genetics

Held by: Professor S E Humphries BSc PhD MRCPath

In any individual, premature coronary artery disease is caused by a mixture of genetic factors and environmental factors. For both of these, factors that predispose or that protect have been identified. We aim to characterise and to understand how the genetic make-up of an individual interacts with the environment (such as eating habits, smoking, stress and exercise).

We have developed high-speed, accurate and cheap methods to examine genes either from a small blood sample or from the cells in a simple mouthwash. This allows us to analyse samples from several thousand patients or healthy people a week. We are now carrying out some powerful genetic analyses.

We have continued to study patients with familial hypercholesterolaemia. Since this disorder is associated with risk of early heart disease but is treatable once discovered, we have established a diagnostic service for the estimated 110,000 such patients in the UK and their relatives.

We have detected two mutations in the gene for lipoprotein lipase, an enzyme that breaks down triglycerides in the blood, and have found that 6-10% of the population carries one of these mutations. Studies in several thousand middle-aged men in the UK have shown that carriers of these mutations are at greatly elevated risk of developing early heart disease but only if they are smokers. If confirmed in other studies, this suggests that the estimated 550,000 men over the age of 16 in the UK who carry this mutation, of whom a third are likely to be smokers, would greatly reduce their risk of heart disease if they stopped smoking.

We have continued to identify mutations in genes that control the levels of proteins that cause the blood to clot. Chemical messengers called cytokines are involved and studies are underway to look at the genes coding for one of these cytokines called IL-6. Early evidence suggests that this may explain why some people who smoke develop extremely high levels of certain clotting factors such as fibrinogen.

We are examining genes that code for the proteins that regulate the structural components of the vessel wall. The incorrect expression of these proteins may be crucial in the development of heart disease.

A genetic explanation for the differences in risk of cardiovascular disease may eventually lead to the development of new therapeutic strategies.

UNIVERSITY OF LONDON

University College London

The Chair of Cardiovascular Science

Held by: Professor J F Martin MD FRCP FESC FMedSci

We are undertaking studies to be able to put a gene into human arteries that will allow them to be protected against the wear and tear of daily life. This gene will first be tested at surgery, where we hope it will protect against blockage of arteries after surgery.

An associated area is looking at how this gene, which is called Vascular Endothelial Growth Factor, has its beneficial effect in arteries. To do this we are examining, in cells in the laboratory, how it signals within cells to make them switch on protective mechanisms.

We are also studying how arteries age. This is an important problem that affects us all. In particular we are examining how changes in the genetic message within the nucleus of a cell in the heart or artery might make it grow old, and how by altering that process we might limit the damage that occurs during ageing.

A heart attack is usually caused by a clot forming in a coronary artery. This clot is initiated by small cells in the blood called platelets clumping together. We have discovered that changes in the properties of cells in the bone marrow, where platelets are made, might lead to increased clotting. How platelets are generated is therefore being studied in isolated bone marrow cells.

UNIVERSITY OF LONDON
Imperial College (NHLI)
The Simon Marks Chair of Cardiology
Held by: Professor P A Poole-Wilson MD FRCP FACC FESC FMedSci

The work of the department is focused on understanding the underlying abnormalities of heart muscle and vascular smooth muscle in relation to diseases of the cardiovascular system.

The sarcoplasmic reticulum Ca^{2+}-release channel (ryanodine receptor-RyR). This intracellular membrane channel plays a pivotal role in the control of cardiac muscle contraction. We are studying its structure using cryo-electron microscopy and the mechanisms governing its function using biophysical, molecular biological and biochemical approaches.

Ryanodine receptor function. The ryanodine receptor controls Ca^{2+}-release during excitation-contraction coupling in the heart and we are investigating how this channel can be regulated physiologically and pharmacologically and how conditions such as ischaemia affect its function.

Cardiac cell ionic regulation. We are investigating the cellular mechanisms that underlie cardiac arrhythmias, the cellular responses to cardiac hypertrophy and the existence of a mechanism in the heart that imitates contraction in a similar way to skeletal muscle.

Cardiovascular cell interactions. We are investigating how direct contacts (junctions) between adjoining cells and between cells and their surroundings enable co-ordination of function in the healthy heart and blood vessels, and the contribution of alterations in these interactions to dysfunction in disease.

The effects of steroid hormones on the cardiovascular system. We are studying the effects of ovarian and related hormones on arterial vasoreactivity both *in vitro* in animal and human tissue, and in the clinical setting in humans with coronary heart disease. The results of these studies will increase our understanding of the effects of these hormones on cardiovascular physiology and pathophysiology, and may lead to new treatment options.

Intracellular signalling pathways in heart disease. The mechanisms that lead to increased growth of the heart muscle cells (myocardial hypertrophy) and the subsequent death of those cells (myocardial necrosis and failure) involve a variety of protein kinase enzymes that are now being more fully characterised in this department.

Signalling in myocyte growth and hypertrophy. We are using molecular and pharmacological approaches to understand the mechanisms through which hormones and growth factors stimulate the growth of cardiac muscle cells.

Adenovirally-mediated gene transfer into cardiac myocytes. Using adenoviral vectors, levels of key proteins in the excitation contraction process are modified in adult human and animal myocytes. Functional consequences of overexpression or down-regulation using antisense strategies are then observed.

Troponin function in failing human hearts and familial hypertrophic cardiomyopathy. We are studying troponin and tropomyosin from normal adult, fetal and end-stage failure hearts using an *in vitro* motility assay. There is a clear abnormality of troponin function leading to slower filament movement and higher Ca^{2+} sensitivity. This seems to be due to altered levels of troponin phosphorylation. We are also studying abnormalities in troponin function due to hypertrophic cardiomyopathy.

Smooth muscle thin filaments. We are investigating the structure and function of smooth muscle tropomyosin, caldesmon and Ca^{2+} binding proteins in the regulation of vascular smooth muscle thin filament activity and hence contractility.

Integrated physiology and pathology in heart failure. A large group is undertaking work to apply laboratory advances in the understanding of heart failure to patients with a variety of the clinical manifestations of heart failure. At present the major interests are in cachexia, the origins of symptoms and the processes perpetuating the syndrome of heart failure.

Cardiac magnetic resonance. A substantial group is using cardiac magnetic resonance (CMR) to delineate coronary blood flow, heart muscle function and anatomy in patients.

Epidemiology. A section of the department is devoted to studies on the epidemiology and prevention of coronary heart disease.

UNIVERSITY OF LONDON

King's College London

The Chair of Cardiology

Held by: Professor A M Shah MD FRCP FESC

Role of endothelial dysfunction in left ventricular hypertrophy. We are studying the contribution of endothelial dysfunction to the myocardial contractile dysfunction characteristic of cardiac hypertrophy and to its progression to heart failure. This includes investigation of changes in expression and activity of nitric oxide synthase and of endothelial proteins that generate reactive oxygen species (ROS), as well as assessing mechanisms of cellular dysfunction in isolated cardiac myocytes. We are also assessing the role of tumour necrosis factor (TNF) in ROS generation and in the progression of hypertrophy.

Mechanisms of endothelial cell dysfunction. Endothelial dysfunction is implicated in the genesis of numerous cardiovascular disorders. Generation of ROS by endothelial cells is a major mechanism for endothelial dysfunction. We are investigating the molecular structure and biochemical regulation of a novel ROS-generating protein complex, endothelial cell NADPH oxidase. This involves molecular and cell biological approaches as well as gene knockout studies.

Characterisation of cardiodepressant factor released by endothelial cells. We are attempting to define the chemical nature of a potent endothelial cell-derived factor released during hypoxia that is capable of down-regulating cardiac contraction.

Mechanisms of myocardial dysfunction in sepsis. We have found that abnormalities of muscle myofilament proteins may be involved and are investigating the underlying mechanisms.

Cardiac effects of nitric oxide in humans. The effects of nitric oxide on cardiac contractile function are being studied in normal subjects, and in patients with cardiac hypertrophy and heart failure.

Mechanisms underlying endothelial dysfunction in insulin resistant subjects. Insulin resistance, a kind of pre-diabetic state, is a risk factor for atherosclerosis. We are addressing how it may lead to endothelial dysfunction.

Transcriptional regulation of cardiac myocyte growth and development. Cardiac myocyte differentiation and growth are subject to regulation by certain transcriptional factors that determine gene expression. We are studying the role of GATA factors. This work is potentially relevant to normal and disease settings where myocardial remodelling occurs, eg, heart development *in utero* and post-myocardial infarction respectively.

UNIVERSITY OF LONDON

University College London

The Chair of Psychology

Held by: Professor A P Steptoe MA DPhil FBPsS Acss

Emotional stress and vascular processes. It has been known for many years that emotional stress influences blood pressure, heart rate and blood flow. We are studying the effects of stress on biological responses that are directly implicated in coronary artery disease, including inflammatory cytokine release, blood platelet activation, vascular endothelial dysfunction and haemostatic responses.

Psychological factors in acute coronary syndromes. We are seeking to understand whether psychological factors trigger acute symptoms in some patients with advanced coronary heart disease. Patients are being interviewed soon after admission to coronary care, and provide information about stresses in their lives, and about the hours leading up to the onset of chest pain. The associations between these reports and biological processes are being evaluated.

Quality of life and coronary heart disease. Acute coronary heart disease can have severe effects on subsequent quality of life. However, in many cases the impairment in quality of life is not directly related to the clinical severity of heart disease. We are studying the way in which emotional factors and patients' understanding of their illness contribute to later quality of life.

UNIVERSITY OF LONDON

Imperial College (Hammersmith Hospital)

The Chair of Cardiothoracic Surgery

Held by: Professor K M Taylor MD FRCS FRCSE FESC FSA

Pathophysiology of cardiopulmonary bypass. During open-heart surgery the patient's heart and lung functions are taken over by the heart-lung machine. This technique is known as cardiopulmonary bypass (CPB). Although greatly improved and refined since the earliest days of cardiac surgery in the 1950s, major challenges still exist for researchers, in order to make CPB as safe as possible.

Our current research focuses on the following areas:

1 **Systematic Inflammatory Response Syndrome (SIRS)** – the end result of the interaction between activated white blood cells (neutrophils) and the endothelial cells which form the inner lining of all blood vessels.

2 **Protease inhibitor drugs** (eg, aprotinin) which have been shown to have beneficial effects in the inflammatory and bleeding consequences of CPB in cardiac surgery patients.

Programmes 1 and 2 involve close collaboration with Professor Dorian Haskard's unit (q.v.) – the BHF Department of Cardiovascular Medicine at Hammersmith Hospital.

3 **Effects of cardiopulmonary bypass surgery and cardiac surgery on the brain** – including structural changes imaged by magnetic resonance imaging (MRI) and cognitive testing of patients' brain function.

Audit and outcome analysis of cardiac surgery. The UK Heart Valve Registry is a prospective database of all UK patients having a heart valve replacement operation since 1 January 1986. (There are now over 60,000 patients on the database.) The Central Cardiac Audit Database is a major project designed to introduce a standard dataset for cardiology and cardiac surgery procedures, to be used throughout cardiac centres in the UK. The European Cardiac Surgery Registry is a pan-European project, funded by the European Union, to compare the quantity and quality of cardiac surgery operations in all the countries of Europe. All these registries are based in the Cardiac Surgical Unit at Hammersmith Hospital.

UNIVERSITY OF LONDON

Imperial College (NHLI)

The Chair of Cardiothoracic Surgery

Held by: Professor Sir Magdi Yacoub FRCS FMedSci FRS

Clinical programme. Clinical procedures undergoing development and assessment of results include total heart replacement (domino) and cardiac transplantation in children. Lung transplantation techniques being studied include pulmonary hypertension and large donors, paced linkage, direct bronchial revascularisation using internal mammary artery and lung lobe transplantation from live donors.

Acute and chronic rejection of transplanted organs. Research is aimed at understanding the processes underlying both acute and chronic rejection in transplantation. We are preparing for xenotransplantation by studying the role of T cells and coagulation factors.

Obliterative bronchiolitis. We have a wide range of clinical studies, both diagnostic and therapeutic, and a programme of basic scientific research.

Biochemistry of heart failure. Research aims to understand the changes in protein expression in the heart during the disease process and after transplantation. Other studies include the development of a non-invasive method for detecting acute rejection after solid organ transplantation, the role of anti-cardiac myosin antibodies in the diseased and transplanted heart, and anti-endothelial antibodies and transplant-associated coronary artery disease.

Molecular studies of the heart. We are carrying out research into the development, organisation and function of the heart at a molecular level. This includes analysis of human cardiac troponin gene promoter and gene organisation; expression of the NF-kappa-B transcription factor complex in heart development; gene expression in heart failure in brain-dead donors; and cardiac myocyte cell cycle regulation in the development of heart failure.

Homograft valve research and tissue engineering. We are aiming to characterise the mechanisms of lipoprotein induced adhesion molecule expression in human endothelial cells; to define the anti-atherogenic reactions of HDL in human heart-derived endothelial cells; and to produce a tissue engineered aortic heart valve.

Accelerated coronary sclerosis. We are attempting to understand the mechanisms of vessel tone and the regulation of vascular smooth muscle cell growth; and to understand atherosclerosis in coronary arteries and bypass grafts.

Molecular analysis of infection. We are investigating viral infections in transplantation and cardiovascular disease.

Molecular connective tissue research. This includes clinical and molecular studies in Marfan syndrome.

Organ preservation, metabolic research and gene therapy. We are looking at: ways of improving the performance of donor organs; the mechanism of myocardial injury during transplantation and other clinical conditions of ischaemia.

Circulatory support. We are investigating development of left ventricular assist devices (VAD) as a bridge to transplantation and possibly a bridge to recovery.

Transplant research. We are carrying out studies in: immunosuppressive therapy; coronary disease in transplant patients and other pathologies; and care and investigation of patients for transplant and post-operatively.

UNIVERSITY OF MANCHESTER

The Cardiac Physiology Unit

The Chair of Cardiac Physiology
Held by: Professor D A Eisner MA DPhil

How is calcium release regulated in the heart? Most of the calcium (Ca) that activates contraction comes from an intracellular store, the sarcoplasmic reticulum (SR). Release occurs throughout a specialised channel, the ryanodine receptor (RyR) that is opened by an increase of cytoplasmic Ca concentration. This results in the process known as calcium-induced calcium release (CICR), in which the entry of calcium into the cell (via the L-type Ca channel) causes the release of much more from the SR. We are interested in the steps that regulate this mechanism, in particular: the effects of altering Ca entry into the cell; the properties of the RyR; and the Ca content of the SR.

Spontaneous Ca release and arrhythmias. When the Ca content of the cell increases beyond a certain limit, Ca is released spontaneously from the SR. The release activates depolarising membrane currents, resulting in spontaneous action potentials and cardiac arrhythmias. This occurs during reperfusion following ischaemia. Of particular interest is the question of whether it is possible to interfere with this spontaneous release without also depressing normal release. In other words, is it possible pharmacologically to abolish arrhythmogenic Ca release without affecting normal contraction?

Ischaemia and metabolic inhibition. Ischaemia decreases or abolishes cardiac contraction. On reperfusion spontaneous Ca release often occurs, resulting in arrhythmias and cell death. This reperfusion damage can be a major problem following cardiac surgery. We are investigating the changes of calcium handling which occur during and following simulated ischaemia. As part of this project, we are looking at the effects of the individual metabolic changes that occur in ischaemia (for example pH, ATP etc).

Cardiac hypertrophy and failure. If the workload of the heart increases, it hypertrophies. Hypertrophy can increase the incidence of cardiac arrhythmias and, if excessive, can lead to heart failure. We are investigating the changes in cellular Ca handling which occur in hypertrophy and failure.

The effects of polyunsaturated fatty acids. Much epidemiological evidence suggests that a diet rich in polyunsaturated fatty acids (PUFAs) protects against heart disease. We are studying the effects of PUFAs on Ca handling and contraction.

UNIVERSITY OF OXFORD

Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU)

The Chair of Medicine and Epidemiology

Held by: Professor R E Collins MBBS LMSSA BSc MSc

When important causes of vascular disease are to be assessed, their effects are sometimes so extreme that they can be reliably inferred from **observational studies** of sufficiently large size (as for smoking and heart attacks). Treatments may, however, produce only moderate improvements in outcome (which might still save thousands of lives each year in a disease as common as heart disease), and the best way to detect such effects is by getting large-scale **randomised trial** evidence. Our unit aims to assess the causes and treatment of vascular disease reliably.

Meta-analyses. As one way of achieving such evidence, CTSU has established the use of collaborative systematic combinations ('meta-analyses') of all the randomised trials that have addressed the same treatment question. Regular updates of these meta-analyses, as well as new collaborations (such as one for cholesterol-lowering trials), ensure that the results become increasingly relevant to patient care.

Mega-trials. CTSU has also established the use of very large, simple randomised 'mega-trials' to assess reliably the effects on survival of widely practicable treatments. For example, it conducted the four International Studies of Infarct Survival (ISIS-1 to ISIS-4, randomising 140,000 patients) whose results substantially improved the emergency treatment of heart attacks. In the current Heart Protection Studies among a total of 30,000 patients at high risk of heart attacks, CTSU is assessing several years of treatment with certain vitamins and with various doses of cholesterol-lowering drugs. Other major CTSU vascular trials include: the PEP trial showing that aspirin reduces pulmonary embolism (15,000 patients); the CAST trial showing that aspirin is beneficial in the emergency treatment of stroke (20,000 patients); and the Chinese Cardiac Studies of the emergency treatment of heart attacks (30,000-40,000 patients).

Observational epidemiology. CTSU also conducts large-scale studies of the causes of disease. In large part due to CTSU there is recognition of how great the future worldwide epidemic of deaths due to tobacco will be. CTSU has helped to establish several large observational studies of smoking in various populations to monitor, and help control, this epidemic.

Blood-based epidemiology. The establishment in CTSU of a specialised epidemiological laboratory is allowing some uniquely large studies of blood-based risk factors for heart disease to be conducted. For example, questionnaires and blood samples from tens of thousands of patients in the ISIS trials have already been used to quantify the effects of smoking on heart attack risks and are now being used to assess the contribution of various biochemical and genetic factors. A study involving hundreds of thousands of individuals in Mexico City will also help to investigate the causes of heart attacks, strokes and other chronic diseases.

UNIVERSITY OF OXFORD

Laboratory of Physiology

Burdon Sanderson Professor of Cardiovascular Physiology

Held by: Professor D Noble CBE FRS FRCP(Hon) FMedSci – retired 30 September 2004

Ischaemia. Detailed models of the biochemical changes occurring during and after interruption of the blood supply have been developed. When coupled to previously developed models of the electrical and mechanical properties of cardiac cells, these new models reconstruct the mechanisms of arrhythmogenesis during ischaemia and reperfusion and allow the successful reconstruction of the actions of drugs that protect against such arrhythmias.

Mechano-electric feedback. The mechanical properties of the heart play a large role in the initiation of some forms of arrhythmia. A new laboratory has been set up during the course of the past year to specifically target the mechanisms of this feedback via experimental investigations and by computer modelling.

Role of sodium ions. We have completed a project to investigate a paradox in the effect of sodium removal on the heart. The project succeeded in showing that this is attributable to a previously unknown indirect action of sodium ions on the potassium channels responsible for determining the resting potential of cardiac cells.

Cell volume. Large changes in cell volume occur in a variety of pathological states. We have determined the ways in which changes in cell volume generate changes in electrical and mechanical properties. In particular, we have concluded a study into the effects of swelling on pacemaker activity and have shown that, in contrast to previous expectation, this causes a slowing of heart rhythm brought about primarily by the reduction in cytosolic potassium concentration during swelling.

Whole organ modelling. We have succeeded in incorporating our cell models of cardiac electrophysiology and biochemistry into the whole ventricular anatomical and mechanical models created by our collaborators in Auckland, New Zealand. This link-up has created the first organ-level model of the heart that includes detailed descriptions of the transporter proteins, and can thus be used to investigate a large number of drug actions on membrane receptors, the effects of mutations of channel proteins, and changes in expression levels of cell proteins.

UNIVERSITY OF OXFORD

John Radcliffe Hospital

The Field Marshal Earl Alexander Chair of Cardiovascular Medicine
Held by: Professor H C Watkins MD PhD FRCP FMedSci

Molecular genetics of heart muscle disease. We are generating an understanding of the way in which mutant contractile proteins cause hypertrophic cardiomyopathy, thereby increasing knowledge about the basic regulation of cardiac muscle contractility.

Genetic susceptibility to heart diseases inherited as complex traits. One of the largest studies worldwide is being developed to identify susceptibility genes for early coronary artery disease. Genetic susceptibility to hypertension and other markers of cardiovascular risk in an extended family collection is being analysed. A candidate gene approach has been developed in areas of particular biological interest, for example the contribution of variants in metalloproteinase genes and their inhibitors.

Endothelial function and adenoviral gene transfer. Adenoviral gene transfer is being used to investigate the role of nitric oxide synthesis and degradation in vascular pathology. Studies in cell culture, in model systems and in *ex-vivo* human tissue are exploring the value of gene transfer as an investigational tool and, potentially, as a therapeutic strategy.

The transcriptional response to hypoxia. The way cells adapt themselves to hypoxia is being investigated. This work involves molecular and cell biology approaches centred around the cloning of novel proteins that interact with the transcriptional apparatus. Gene knockout studies have also been initiated.

The role of nitric oxide in controlling heart rate and myocardial excitability. We are studying a novel pathway whereby nitric oxide acts to increase the cardiac pacemaker current. Importantly, this current is also expressed in ventricular tissue during myocardial hypertrophy, suggesting that nitric oxide may have an important detrimental effect on the risk of arrhythmia in cardiac hypertrophy.

UNIVERSITY OF SOUTHAMPTON

Princess Anne Hospital

The Chair of Cardiovascular Science
Held by: Professor M A Hanson MA DPhil CertEd FRCOG

Developmental Origins of Adult Disease Centre. The Centre, established in January 2000, plays a key role in the training and career development of basic and clinical scientists and, in a wider context, in raising the awareness of the importance of the DOAD (developmental origins of adult disease) hypothesis. Its long-term research goal is to inform future public health policy. It is organised into five major sub-divisions: Maternal and Fetal Physiology; Population Studies; Human Nutrition; Endocrinology and Metabolism; and Bone and Joint.

The research strategy of the DOAD Centre focuses on understanding further the mechanisms by which a range of adult conditions including coronary heart disease, stroke, type 2 diabetes and osteoporosis may originate through fetal adaptations to under-nutrition (fetal programming). The Centre's two principal objectives are: a) to understand the processes which underlie programming in terms of integrative biology, and b) to develop novel strategies to prevent cardiovascular disease, type 2 diabetes and osteoporosis by optimising fetal nutrition and improving childhood growth.

Awards made during the year 1 April 2004 - 31 March 2005

Basic Science Lectureships

BS/04/002/16787
Dr C H George BSc PhD
Cardiff University
Molecular mechanisms underlying ryanodine receptor dysfunction in stress-induced ventricular tachycardia
5 years £243,736

BS/04/001/16790
Dr S E Ozanne BSc PhD
Addenbooke's Hospital, Cambridge
Molecular mechanisms by which poor early growth links coronary artery disease, insulin resistance and type 2 diabetes
5 years £277,198

Fellowships

Senior Research Fellowships

FS/04/079/17545
Dr D P Francis MRCP
Imperial College (St Mary's Hospital), London
Optimisation, regulation and stabilisation of cardiopulmonary physiology in chronic heart failure: maximising current pacemaker therapies, and potential for new dynamic therapies
5 years £467,223

FS/04/080/17549
Dr C M Shanahan BSc PhD
Addenbrooke's Hospital, Cambridge
The role of nesprins in cardiovascular cell function
5 years £300,820

Intermediate Research Fellowships

FS/04/082/17531
Dr K Bradley BSc PhD
University of Glasgow
Regulation of the calcium-dependent transcription factor NFAT in native vascular smooth muscle
3 years £127,368

FS/04/027/17070
Dr I Hers BSc MSc PhD
University of Bristol
Insulin regulation of platelet signalling: molecular mechanisms underlying platelet hyperactivity in diabetic heart disease
3 years £159,190

FS/04/026/16663
Dr P A Kingston MBChB
University of Manchester
Studies of gene therapy for in-stent (re)stenosis: i) modification of extracellular matrix deposition; and ii) non-viral gene transfer in stented coronaries
3 years £192,372

FS/04/054/17538
Dr M Mayr MD PhD
St George's Hospital Medical School, London
Proteomic analysis of smooth muscle cells in response to mechanical stress
3 years £158,861

FS/04/052/17065
Dr V Pucovsky MSc PhD
St George's Hospital Medical School, London
Investigation of non-contractile cells with filopodia resembling interstitial cells of Cajal, freshly isolated from the wall of resistance arteries
3 years £166,398

FS/04/025/15868
Dr T L Shaw BSc PhD
Middlesex Hospital (UCL)
Molecular characterisation of novel plakoglobin interactions in arrythmogenic right ventricular cardiomyopathy and their role in cardiomyocyte survival
3 years £153,382

FS/04/053/17529
Dr A Snabaitis BSc PhD
King's College London
Novel regulation of the Na+/H+ exchanger by protein kinase B in the adult myocardium
3 years £170,226

FS/04/083/17979
Dr Y Sun PhD
King's College London
Molecular mechanism of cardiac muscle regulation: role of changes in the conformation of troponin C *in situ*
3 years £184,079

FS/04/081/17523
Dr S Wildman BSc PhD
Royal Free Hospital (UCL)
Extracellular ATP, renal P2 receptors and the epithelial sodium channel: implications for renal Na+ excretion and blood pressure control
3 years £153,001

Junior Research Fellowships

FS/04/084/17987
Dr R G Assomull MA MBBChir MRCP
Imperial College (Royal Brompton Hospital), London
Accuracy and cost-effectiveness of cardiovascular magnetic resonance versus X-ray coronary angiography to determine the aetiology of heart failure
2 years £105,345

FS/05/002/18412
Dr A Bermudez-Fajardo DDS PhD
University of Surrey
Immunomodulation of atherosclerosis using dendritic cells
2 years £87,045

FS/04/060/17507
Dr W M Bradlow BMed Sci BM BS
Imperial College (Royal Brompton Hospital), London
Assessment of structure and function of the right ventricle and central pulmonary arteries in pulmonary hypertension using cardiovascular magnetic resonance
2 years £97,743

FS/04/028/16327
Dr J G Burniston BSc PhD
Liverpool John Moores University
Integration of the cellular and functional adaptations of the heart and skeletal muscles to the administration of a ß2-adrenergic receptor agonist
2 years £72,717

FS/05/007/18428
Mr N Cartwright MA MB BS MRCSEd
Imperial College (NHLI), London
Gram negative bacterial sensing in human vessels: relevance to human sepsis
2 years £106,778

FS/05/006/18425
Dr J E R Davies MRCP MBBS BSc
Imperial College (St Mary's Hospital), London
Coronary haemodynamics in hypertension and left ventricular hypertrophy
2 years £107,183

FS/05/005/18420
Dr P De Winter MSc
King's College London
Effects of selective oestrogen receptor modulators (SERMs) on endothelial antioxidant gene expression in oestrogen receptor knockout mice
2 years £89,883

FS/05/004/18416
Dr O S Dhillon BSc MB ChB MRCP
Leicester Royal Infirmary
Urotensin-like peptides and prognosis after acute coronary syndromes
2 years £93,331

FS/05/001/17986
Dr A Gatt MD MRCP MRCPath
Royal Hallamshire Hospital, Sheffield
The value of the endogenous thrombin potential in the mangement of anticoagulated patients
2 years £94,785

FS/04/029/17075
Dr A Gill MBChB LRCP LRCPS
Bristol Royal Infirmary
Mechanisms underlying up-regulation of basement membrane degrading metalloproteinases in reponse to vascular injury
2 years £84,101

FS/04/085/17989
Dr A J Hogarth MBChB
St James's University Hospital, Leeds
Differences in sympathetic neural activation between men and women following acute myocardial infarction
2 years £86,844

FS/04/057/17496
Dr L Howard MB BChir MA DPhil MRCP
Addenbrooke's Hospital, Cambridge
Mechanisms of pulmonary artery smooth muscle cell proliferation and survival in hypoxia: a key role for the phosphoinositide 3-kinase/Akt pathway
2 years £109,454

FS/04/061/17513
Dr L E Hudsmith MA BM BCH MRCP
John Radcliffe Hospital, Oxford
Hypertrophic cardiomyopathy and the myocardial energy depletion paradigm - a cardiac magnetic resonance study in patients with genotyped HCM
2 years £97,443

FS/04/056/17537
Dr B J McHugh BA PhD
University of Edinburgh
Investigating novel modulators of integrin affinity
2 years £77,617

FS/04/059/17504
Dr S M Munir BSc MB ChB MRCP
King's College London
Effects of exercise on pressure wave reflection
2 years £106,549

FS/04/058/17501
Dr S Muzaffar BSc PhD
Bristol Royal Infirmary
The pathobiology of reactive oxygen species in vein graft disease
2 years £ 66,953

FS/04/055/17080
Dr T C Pakrashi BA BM BCh MRCP
St George's Hospital Medical School, London
Electrocardiographic assessment of response to cardiac resynchronisation therapy
2 years £95,522

FS/05/003/18415
Dr E J Shepherd MBChB
Freeman Hospital, Newcastle upon Tyne
The anatomy and physiology of the pulmonary vein-left atrial junction in subjects with and without paroxysmal atrial fibrillation. The role of pressure and anatomical substrates in the development of atrial fibrillation
2 years £101,862

Clinical PhD Studentships

FS/04/032/17090
Dr N S MacCallum MBBS MRCP FRCA
Imperial College (NHLI), London
Impaired caeruloplasmin-mediated antioxidant protection against myeloperoxidase activity: implications for patients with sepsis and its sequelae
3 years £178,472

FS/05/008/18433
Dr M M Mahmoudi BSc MB BS MRCP
Addenbrooke's Hospital, Cambridge
Regulation of vascular smooth muscle cell senescence by DNA damage checkpoint kinases
3 years £156,933

FS/04/087/17994
Dr G E Marshall BSc MB ChB MRCP
Glasgow Royal Infirmary
Pharmacological remodelling in human atrium: electrophysiological and molecular mechanisms of action potential prolongation ß-adrenoceptor by antagonist therapy
3 years £136,523

FS/05/010/18435
Dr A Muir BSc MBChB MRCP
University of Glasgow
Atrioventricular nodal function in a rabbit model of chronic heart failure
3 years £139,610

FS/04/030/16696
Mr J Niehueser-Saran BSc MBBS
King's College London
Nrf2-mediated antioxidant stress gene expression in human fetal vascular endothelial and smooth muscle cells
3 years £126,953

FS/04/063/17521
Dr G Pieles MD
University of Oxford
Genetic mechanisms in heart development
3 years £112,570

FS/04/031/17089
Dr C Skene MB ChB MRCP
University College London
Mechanisms and consequences of vascular smooth muscle cell senescence: the role of nitric oxide
3 years £159,092

FS/05/011/18440
Ms N Summerfield BSc BVM&S MRCVS
Imperial College (NHLI), London
Cellular changes during the progression of myocardial hypertrophy to failure
3 years £140,621

FS/04/086/17998
Mr M B Will MBChB MRCS
Glasgow Royal Infirmary
Generation of cardiomyocytes from mesenchymal stem cells derived from adult human sternal bone marrow
3 years £149,478

FS/04/062/17518
Dr M J Zaman BSc MBBS MRCP
University College London
Prognosis of coronary disease in different South Asian populations in Britain
3 years £155,624

PhD Studentships

FS/04/076/17592
Miss A Asimaki BSc
University College London
Arrythmogenic right ventricular cardiomyopathy – a disease of the demosome: genetic and functional studies
3 years £73,500

FS/04/034/15975
Miss E Bovill BSc MBBS
University College London
The role of the aryl-hydrocarbon receptor in cardiomyocyte apoptosis and doxazosin mediated gene expression in heart failure
3 years £73,500

FS/04/040/17100
Miss T Brenner Dipl.-Ing
Addenbrooke's Hospital, Cambridge
The role of TASK channels in aldosterone secretion by human adrenal glomerulosa cells
3 years £79,860

FS/05/013/18393
Mr J Burgoyne BSc
King's College London
Oxidative stress in the ageing human heart: examining the roles of cardiac protein cysteine oxidation
3 years £79,500

FS/04/092/18009
Mr A F Catchpole MA
University of Oxford
Cardiac inflammation and insulin resistance in the chronically infarcted rat heart
3 years £78,273

FS/05/012/18005
Miss A Cook
King's College London
Role of the 90 kDa ribosomal S6 kinase RSK2 in the regulation of sarcolemmal Na+/H+ exchange
3 years £80,168

FS/04/065/17564
Miss R David BSc MSc
Imperial College (Hammersmith Hospital), London
The role of Vav1 in the regulation of T cell recruitment in inflammatory sites
3 years £73,500

FS/04/042/17105
Mr G Evans BSc
Queen's Medical Centre, Nottingham
An investigation of the role and mechanism of regulation of phospholipase Cδ1 activity in vascular smooth muscle
3 years £68,893

FS/04/071/17586
Mr P F A D C Ferreira BSc
Imperial College (Royal Brompton Hospital), London
Investigating imaging artefacts and improving MRI measurement of myocardial perfusion
3 years £63,653

FS/04/089/18007
Miss F Govani BSc
Imperial College (Hammersmith Hospital), London
Identification of a further gene for hereditary haemorrhagic telangiectasia
3 years £84,533

FS/04/088/18013
Ms H Jundi BSc
Cardiff University
Elucidating ryanodine receptor domain interaction in sudden cardiac death (SCD): towards the development of novel therapeutic strategies
3 years £74,418

FS/04/072/17590
Miss K A King BSc
University of Oxford
Determination of the functional role of individual domains of cardiac myosin binding protein-C and the effects of cardiomyopathy-causing mutations
3 years £80,933

FS/04/043/17108
Ms A Leung BSc
University of Bristol
Is the adenine nucleotide translocase a critical component of the mitochondrial permeability transition pore and ATP-dependent potassium channel?
3 years £68,758

FS/04/049/17115
Miss Y T Y Li BSc
Barts and the London NHS Trust
The farnesoid X receptor (FXR) as a regulator of vascular inflammation
3 years £73,530

FS/04/036/17093
Ms K Lisiak BSc
University of Aberdeen
Leucocyte synthesis of TAFI1 and its role in thrombus stability
3 years £69,133

FS/04/067/17577
Mr D Martindill BSc
Institute of Child Health (UCL)
Investigating nucleolar sequestering of Hand1 as a novel mechanism of negatively regulating Hand1 activity in the developing heart
3 years £74,214

FS/04/064/17120
Miss R Masson BSc
Western Infirmary, Glasgow
Targeted gene delivery *in vivo* using a novel adeno-associated virus-2 (AAV-2) virus library
3 years £68,208

FS/04/045/17110
Miss A McGuckin BSc
University of Glasgow
Interaction between serotonin and TASK-1 potassium channels in the pulmonary artery
3 years £67,846

FS/04/037/17095
Mrs E McManus BSc
University of Bristol
Role of small G-proteins of the ARF family in platelet function
3 years £68,736

FS/04/035/17092
Miss L Methven BSc
University of Glasgow
Endothelial α_{1b}-adrenoceptors
2 years £44,632

FS/04/073/17581
Miss H Mikolajek BSc
University of Southampton
Structural basis of complement activation by C-reactive protein in atherothrombotic disease
3 years £68,208

FS/04/070/17583
Mr C Mitchell MSc
University of Strathclyde, Glasgow
Signalling mechanisms underlying P2Y receptor-mediated vasoconstriction in pulmonary arteries
3 years £68,208

FS/05/020/18408
Mr J D Mitchell BA
Addenbrooke's Hospital, Cambridge
Neuromedin U: a novel transmitter in the human cardiovascular system with an emerging role in disease
3 years £81,778

FS/04/090/18014
Mr D G Nowak MSc
University of Bristol
Regulation of angiogenic and anti-angiogenic isoforms of VEGF
3 years £75,351

FS/04/069/17578
Mr E Osman BSc
Royal Free Hospital (UCL)
Expression of ApoAI-Milano and analogues: towards effective HDL therapy for acute treatment of atherosclerosis
3 years £77,710

FS/04/091/18008
Ms J Paynter MNeurosci
University of Oxford
A structural and functional analysis of heteromeric inwardly rectifying (Kir) potassium channels
3 years £78,933

FS/05/021/18410
Miss S Petit MSc
Imperial College London
Molecular characterisation of the chemokine CXCL16/SR-PSOX and its receptor CXCR6: a potential axis for the therapeutic treatment of atherosclerosis
3 years £80,130

FS/04/044/17109
Mr J Polke BSc
Western Infirmary, Glasgow
Functional genomic analysis of the glutathione-S-transferase mu type 1, positional candidate gene for hypertension
3 years £68,208

FS/04/068/17575
Ms G Pourmahram BSc
King's College London
Modulation of hypoxic pulmonary vasoconstriction by luminal flow
3 years £74,736

FS/05/018/18403
Ms A Power BSc
University of Manchester
Characterisation of the cardiac L-type voltage-gated calcium channel: the sum of its parts
3 years £74,061

FS/05/014/18396
Ms M Reilly BSc
University of Strathclyde, Glasgow
The regulation and cellular effects of proteinase-activated receptor-4 in human endothelial cells
3 years £75,120

FS/04/046/17111
Miss E Robinson MPharm
University of Strathclyde, Glasgow
Interactions between the effects of cannabinoids on ischaemia-induced arrhythmias, leukocyte function and coronary artery reactivity in the rat
3 years £68,893

FS/04/041/17102
Mr S C Rogers BSc MSc
Cardiff University
Red blood cell mediated vasodilatation: significance during hypoxia and effect on venous tone
2 years £56,110

FS/04/047/17112
Miss S Samsuddin BSc MSc
Barts and the London NHS Trust
The metabolic actions of ghrelin in the heart
3 years £73,290

FS/04/048/17114
Mr C Scheiermann Dipl Biochem
Imperial College (Hammersmith Hospital), London
Role of JAM-C in leukocyte migration and activation *in vivo*
3 years £88,570

FS/04/050/17116
Mr C Sigalas BSc
University of Bristol
Elucidation of the role of calmodulin in the regulation of cardiac ryanodine receptor function
3 years £68,737

FS/05/016/18398
Miss A Sowerby
University of Leicester
Modulation of arterial Ca^{2+}-activated K^+ (BK_{Ca}) channels by angiotensin II
3 years £71,308

FS/05/019/18407
Student to be appointed
Imperial College London
Electron tomography of the I-band in mammalian cardiac muscle
3 years £79,991

FS/05/017/18400
Student to be appointed
University of Bristol
Cross-talk between $P2Y_1$ and $P2Y_{12}$ receptors for ADP in platelets
3 years £74,737

FS/05/015/18397
Student to be appointed
University of Leicester
Interrelationship between K_{ATP} channels, adenosine and protein kinases in protection of isolated cardiac myocytes
3 years £73,818

FS/04/039/17099
Mr S R Thompson BSc
University College London
Identification and investigation of variants within IL18 system genes and their effect on risk of atherosclerosis
3 years £77,500

FS/04/038/17096
Miss S Wallace BA
Addenbrooke's Hospital, Cambridge
Inflammation, vascular stiffness and endothelial dysfunction: investigation of mechanisms and clinical implications
3 years £74,718

FS/04/033/16707
Miss E Williams BSc
University College London
A study of psychosocial factors related to cardiovascular disease risk in UK Indian Asian men and women
3 years £70,065

FS/04/074/17587
Miss H Woolson BSc
University of Glasgow
Suppressor of cytokine signalling-3 (SOCS3) induction as a novel mechanism of A2A adenosine receptor-mediated inhibition of pro-inflammatory cytokine signalling in endothelial cells
3 years £68,508

FS/04/075/17589
Miss J A Wray BSc
Barts and the London NHS Trust
Cytochrome P450 2J2 as an endogenous source of PPAR-alpha ligands
3 years £73,530

4-Year PhD Studentships

FS/05/022/18785
Prof J J Mullins PhD
University of Edinburgh
First intake 2004/2005 4-year PhD Studentships Scheme: Mr Sanjay Thakar; Mr Mathieu Blanc; Miss Malgorzata Wamil
4 years £299,832

FS/05/023/18789
Prof J D Pearson PhD
King's College London
First intake 2004/2005 4-year PhD Studentships Scheme: Miss Nadia Caro-Goldrine; Miss Catherine Stables; Mr Colin Murdoch
4 years £310,116

Travelling Fellowships

FS/04/051/17250
Dr M Sekine MD PhD
From: Toyama Medical and Pharmaceutical University, Sugitani Toyama, Japan
To: University College London
Policy implications of social inequalities in cardiovascular diseases among British and Japanese civil servants
6 months £9,180

FS/04/077/17597
Dr S Thomas BSc PhD
From: National Institute for Biological Standards and Control, Hertfordshire
To: Monash University, Prahran, Victoria, Australia
Real-time studies of platelet aggregation, thrombus formation and coagulation under flow conditions using confocal technology and thrombin generation
6 months £6,000

FS/04/093/18015
Dr A V Vorotnikov PhD
Cardiology Research Center, Moscow
Imperial College (NHLI), London
Caldesmon control by MAP-kinase
3 months £10,160

International Fellowship

FS/04/078/17551
Dr J H F Rudd PhD MRCP MB BCh
From: Addenbrooke's Hospital, Cambridge
To: Mount Sinai Medical Center, New York
An evaluation of multi-modality imaging (FDG-PET/CT/HRMR) to detect and characterise atheroma in the carotid artery thoracic aorta and coronary arteries
1 year £45,688

Programme Grant Renewals

RG/04/006/16797
Dr R W Farndale MA PhD
University of Cambridge
Platelet receptors for collagen; activatory pathways, their control and inhibition
5 years £821,815

Progress report
The platelet expresses two collagen receptors, integrin $\alpha_2\beta_1$ and Glycoprotein (Gp) VI, both important in securing the adhesion and activation of platelets during coronary thrombosis that leads to an occlusive clot. We have identified novel sequences in the blood vessel wall collagens that bind both integrin and GpVI, and have located the collagen-binding surface of GpVI. We have shown that cross-talk between the two receptors is important to support platelet adhesion and thrombus deposition under arterial flow conditions. With Dr Willem Ouwehand, I have investigated the genetics of GpVI and found that the rarest of the common forms is less reactive to collagen, which may be valuable in predicting coronary thrombosis and, most importantly, we have jointly developed an antibody to block GpVI which may provide a novel anti-thrombotic therapy.

RG/04/010/18148
Prof W J McKenna FESC FACC
The Heart Hospital (UCL)
Arrhythmogenic right ventricular cardiomyopathy – a disease of the desmosome: gene identification studies to provide the basis for improved clinical diagnosis and the development of genetic diagnosis
5 years £1,261,038

Progress report
The work involved mutation analysis in 250 patients of eight genes which cause hypertrophic cardiomyopathy. These genes accounted for 60% of disease. Particular genes were associated with particular disease expression. Troponin T mutations caused premature sudden death in the absence of severe disease manifestation. Myosin binding protein C mutations caused late onset (5^{th}/6^{th} decade) disease which was nonetheless severe and associated with disease complications. The logistics and indications for mutation analysis in hypertrophic cardiomyopathy will be formally evaluated from the available dataset.

RG/04/009/17747
Prof A C Newby MA PhD
Bristol Royal Infirmary
Mechanisms of neointima formation and role of extracellular proteolysis
5 years £843,592

Progress report
A heart attack happens when a blood clot forms on top of a blockage in the coronary arteries, a so-called 'vulnerable plaque'. Plaques become vulnerable when the vascular smooth muscle cells in the artery wall give up growing and producing strength-giving collagens but instead make enzymes that actually destroy collagen. We found a gene called Skp-2 that regulates smooth muscle growth and another called NF-kappaB that switches on production of digestive enzymes. To progress these findings towards the clinic, we have established a new mouse model and used new imaging methods to study vulnerable plaques in patients.

RG/05/001/18608
Dr C M Shanahan BSc PhD
Addenbrooke's Hospital, Cambridge
The role of vascular smooth muscle cells in the development and progression of vascular disease
5 years £986,195

Progress report
Our studies focus on the mechanisms that lead to dysfunction of vascular smooth muscle cells, the major cell type in the vessel wall. Our aim is to identify ways to maintain vascular smooth muscle cell health and thus limit diseases that cause heart attack and stroke such as atherosclerosis (often called 'hardening of the arteries'). Specifically we have demonstrated that calcification, the cause of vessel wall hardening, is a cell-mediated process and therefore a potential target for therapeutic modification. Calcification results from vascular smooth muscle cell damage and death leading to the release of microparticles that initiate calcium crystal growth in the vessel wall. In association with this, vascular smooth muscle cells change from contractile cells that maintain normal vascular function, to cells with properties similar to bone cells that are able to orchestrate calcification. We have identified some of the complex signalling pathways that initiate and maintain these disease-associated cellular changes and this is a key step in ultimately identifying ways to inhibit these processes. In addition, we have characterised a novel family of proteins, called nesprins, which may be important in age-related vessel wall dysfunction.

RG/04/007/17334
Prof G L Smith BSc PhD
University of Glasgow
A longitudinal study of myocardial remodelling following infarction in the rabbit heart
5 years £1,005,488

Progress report
Increasing the expression of a SR Ca^{2+} pump protein using adenoviral transfection increased contractility of heart muscle. However, excessive Ca^{2+} pump expression had a negative inotropic effect. Improvements in contractility could also be achieved by modulating the activity of the SRCa^{2+} channel controlling Ca^{2+} leak from the SR. Examination of the expression of the Ca^{2+} handling proteins in different layers of myocardium showed that, in general, myocardial infarction caused a uniform change in protein expression throughout. Of the proteins examined, only the SR Ca^{2+} release channel showed regionally distinct changes. We showed that regions adjacent to a myocardial infarct developed the greatest degree of electrical heterogeneity and were therefore likely areas for the generation of arrhythmias. In parallel with this work, optically imaging the electrical activity of the epicardial surface revealed that the large infarct scar was capable of supporting the electrical activity.

RG/05/002/18611
Prof P J T Vallance BSC MBBS FRCP FMedSci
University College London
ADMA and DDAH signalling in vascular disease
5 years £1,302,907

Progress report
Nitric oxide is a gas produced by the lining of blood vessels that acts to keep blood vessels patent and prevent atherosclerosis. We identified a substance in blood called ADMA that blocks the formation of nitric oxide. Over the past five years ADMA has emerged as a novel risk marker for cardiovascular disease and we have undertaken a series of studies to identify where ADMA comes from, how it is handled by the body, and how it exerts detrimental effects. Our work has mapped this novel biochemical pathway, identified new opportunities for drug treatments and provided the basis for using ADMA as a risk marker. ADMA is formed when certain proteins are broken down and so the idea that it may also act as a signalling model raises the possibility that molecules sometimes thought of as 'waste products' are used as signals to alter the behaviour of cells.

Programme Grants

RG/04/005/14168
Prof M P Frenneaux FRACP FACC
Queen Elizabeth Hospital, Birmingham
Mechanisms controlling venous tone and preload in CHF
5 years £626,902

RG/05/003/18612
Dr D E Newby BM MRCP
University of Edinburgh
Atherothrombotic effects of air pollution
5 years £1,178,407

RG/04/008/17733
Prof Q Xu MD PhD
St George's Hospital Medical School, London
Impact of progenitor cells in the pathogenesis of arteriosclerosis
5 years £993,292

Special Projects

SP/04/003/18586
Dr J R Bradley DM MRCP
Addenbrooke's Hospital, Cambridge
Cambridge-Yale collaborative programme in cardiovascular research
3 years £50,000

SP/04/004/18146
Prof D Field MBBS DM
Leicester Royal Infirmary
Randomised trial to assess the neuroprotective effect of mild cooling in neonates receiving extra corporeal membrane oxygenation (ECMO)
5 years 6 months £383,321

SP/04/002/17335
Prof J Scott FRCP FRS
Imperial College, London
Human genetic variation underlying risk of insulin resistance and type 2 diabetes in Indian Asian and Northern European men
4 years £1,593,681

SP/04/005/18626
National Prevention Research Initiative
5 years £1,250,000

Project Grants

Listed by BHF fundraising regions

Region 1
Northumberland, Durham, Tyne and Wear, Cleveland, Yorkshire *(excluding South Yorkshire)*, Cumbria

PG/05/019/18486
Dr T F C Batten BSc PhD
University of Leeds
Does oestrogen maintain cardiovascular health via actions on receptors expressed by brainstem neurones?
3 years £113,864

PG/04/125/17971
Dr S A Deuchars BSc PhD
University of Leeds
Properties and connections of a novel group of spinal interneurones influencing sympathetic neuronal activity
3 years £181,724

PG/05/041/18673
Dr D J Henderson BSc PhD
University of Newcastle
Regulation of outflow tract remodelling by non-canonical Wnt signalling
3 years £206,994

PG/05/012/18279
Dr K M Naseem BSc PhD
University of Bradford
The molecular regulation of integrin $\alpha_2\beta_1$-mediated platelet adhesion and spreading by nitric oxide
3 years £136,853

PG/04/102/17686
Ms A J Orrell BSc
University of York
Validation of a brief questionnaire to measure activity levels in people with heart disease
1 year £20,240

PG/04/122/17912
Dr R J Pease BA PhD
Leeds General Infirmary
The role of arylactamide deacetylase in mobilising hepatic lipids for secretion and its cellular distribution in the adrenal gland
3 years £152,007

PG/04/059/17165
Prof C S Peers BSc PhD
University of Leeds
Is testosterone an endogenous Ca^{2+} channel antagonist?
2 years £79,494

Region 2
Essex, Norfolk, Suffolk, Cambridgeshire, Hertfordshire, Buckinghamshire, Bedfordshire, Northamptonshire and London North of Thames

PG/05/024/18513
Dr A Ahluwalia BSc PhD
Barts and the London NHS Trust
Investigation of the mechanisms involved in kinin-B1 receptor-induced leukocyte recruitment
2 years £82,955

PG/05/023/18509
Dr H A A Al-Khayat BSc PhD
Imperial College London
Myosin filament ultrastructure in health and disease
2 years £103,487

PG/04/107/17742
Prof M R Bennett BSc MA MBChB PhD MRCP
Addenbrooke's Hospital, Cambridge
Control of human atherosclerotic plaque vascular smooth muscle cell senescence
3 years £151,316

PG/05/011/18278
Dr J R Bradley DM MRCP
Addenbrooke's Hospital, Cambridge
Regulation of TNFα converting enzyme (TACE) in human vascular endothelial cells
2 years £98,362

PG/05/025/17839
Prof P G Camici MD FRCP
Imperial College (Hammersmith Hospital), London
Development and implementation of ultra-short TE-MRI for the assessment of myocardial fibrosis in mice and patients with myocardial infarction
2 years £129,981

PG/05/033/18647
Prof P G Camici MD FRCP
Imperial College (Hammersmith Hospital), London
Myocardial insulin resistance: molecular mechanisms and their contribution to heart failure
2 years £120,278

PG/05/004/18158
Dr A H Chester PhD BSc
Imperial College (Harefield Hospital), Middlesex
Role of cross-talk between the scaffold and mesenchymal stem cells in tissue engineering a heart valve
3 years £155,685

PG/04/089/17456
Mr T C Clayton BSc MSc
London School of Hygiene and Tropical Medicine
Recent respiratory infection and risk of heart attacks and strokes
1 year 6 months £38,371

PG/05/021/18493
Dr P M Elliott MBBS MRCP
The Heart Hospital (UCL)
Restrictive cardiomyopathy (RCM) in children: prevalence of familial disease and sarcomeric protein gene mutations
1 year £67,694

PG/04/098/17487
Dr M C P Glyn MSc PhD
Imperial College, London
Examining the cellular events regulating endothelial cell responses to hypoxia, ischaemia and reperfusion in the heart
3 years £175,498

PG/05/017/18482
Dr R P Gray MRCP MD PhD
Whittington Hospital (UCL)
Mechanisms underlying the increase of intracellular sodium in left ventricular hypertrophy
2 years £111,190

PG/04/081/17384
Dr J P J Halcox BA MB BChir MA MRCP
Institute of Child Health (UCL)
Endothelial progenitor cells and endothelial dysfunction in early life
2 years £171,786

PG/05/018/18485
Prof A D Hughes BSc MBBS PhD
Imperial College (St Mary's Hospital), London
Regulation of expression of functional L-type calcium channels ($Ca_v1.2$) in human vascular smooth muscle cells
2 years £96,434

PG/04/114/17841
Dr J A Huntington BSc PhD
University of Cambridge
Molecular recognition determining the pro- and anti-thrombotic activities of thrombin
3 years £135,849

PG/04/115/17842
Dr J A Huntington BSc PhD
University of Cambridge
How antithrombin selectively inhibits thrombosis
3 years £145,305

PG/04/123/17935
Prof D Jordan BSc PhD DSc
Royal Free Hospital (UCL)
Investigation into the role of 5-HT_7 receptors in cardiovascular afferent integration
3 years £135,266

PG/04/074/17269
Dr P R Kemp BSc DPhil
University of Cambridge
Regulation of expression of the smooth muscle-restricted gene Nov by transcription factors
2 years £64,051

PG/04/082/17389
Prof D A Lane BA PhD
Imperial College (Hammersmith Hospital), London
Molecular recognition of activated protein C by its endothelial cell receptor and by protein S
2 years £110,074

PG/04/099/17287
Prof D S Latchman PhD DSc
Institute of Child Health (UCL)
Role of specific serine residues in CBP and p300 in cardiac development and hypertrophy
3 years £120,521

PG/05/008/18268
Dr E A Lidington BSc PhD
Imperial College (Hammersmith Hospital), London
The role of protease activated receptor-2 in human endothelial cell cytoprotection during inflammation
2 years £124,932

PG/04/061/17173
Dr K T MacLeod BSc PhD
Imperial College (NHLI), London
The effect of oestrogen-related compounds on L-type Ca current in the heart
2 years £104,297

PG/05/014/18298
Dr M P Mahaut-Smith BSc PhD MA
University of Cambridge
Interactions between P2 receptor signals in the platelet
3 years £130,372

PG/04/065/17244
Prof K P Moore BSc MBBS FRCP
Imperial College (Hammersmith Hospital), London
Anandamide and cardiac dysfunction in cirrhosis
3 years £166,290

PG/04/116/17845
Dr P Nihoyannopoulos DM MD FRCP
Imperial College (Hammersmith Hospital), London
Molecular imaging of inflammation in myocarditis using targeted microbubble contrast enhanced echocardiography
3 years £250,379

PG/04/120/17871
Dr K M O'Shaughnessy MRCP
Addenbrooke's Hospital, Cambridge
The use of Xenopus Oocyte expression to investigate the effects of WNK kinases on expression and trafficking of ion transporters and channels
3 years £139,548

PG/04/060/17166
Prof M Perretti MSc PhD
Barts and the London NHS Trust
Investigation into the protective role of carbon monoxide (CO) in vascular inflammation using new CO-releasing molecules (CO-RMs)
2 years £96,513

PG/04/126/17974
Prof N S Peters MD FRCP
Imperial College (St Mary's Hospital), London
Pre-emptive ablation of myocardium prone to the development of functional conduction block in the infarcted heart to prevent defibrillator therapy
3 years £145,603

PG/05/027/18592
Dr D Proudfoot BSc PhD
Addenbrooke's Hospital, Cambridge
Regulation of vascular calcification by matrix Gla protein (MGP)
3 years £135,971

PG/05/047/18736
Dr M S Sandhu BSc MSc PhD
University of Cambridge
Insulin-like growth factors and risk of coronary heart disease: genetic and molecular epidemiology
3 years £168,645

PG/05/003/18157
Prof N J Severs PhD DSc
Imperial College (Royal Brompton Hospital), London
Cellular mechanisms of gap junction remodelling in heart disease
3 years £143,809

PG/04/113/17840
Dr C M Shanahan BSc PhD
Addenbrooke's Hospital, Cambridge
A role for nesprin-1 in vascular smooth muscle cell function and atherosclerosis
2 years £81,948

PG/05/035/18655
Dr C C Shoulders DPhil
Imperial College (Hammersmith Hospital), London
Cloning of the genes within the chromosome 11p14.1-q12.1 interval conferring susceptibility to the lipid abnormalities of familial combined hyperlipidaemia
3 years £231,358

PG/04/085/17409
Prof A K Soutar BSc PhD
Imperial College (Hammersmith Hospital), London
Investigation of the role of normal and mutant forms of NARC-1 in the regulation of plasma LDL-cholesterol concentration
3 years £161,940

PG/04/077/17362
Dr A Stephanou MSc PhD
Institute of Child Health (UCL)
Role of STAT-1 interaction with p53 family members during ischaemia/reperfusion injury in the myocardium
3 years £139,166

PG/04/092/17463
Dr P Syrris BSc PhD
Middlesex Hospital (UCL)
Do mutations in PTPN11 cause hypertrophic cardiomyopathy in the absence of Noonan syndrome?
1 year £50,289

PG/04/110/17827
Prof P J Talmud PhD DSc FRCPath
University College London
In vivo and *in vitro* studies of Apolipoprotein AV and its relation to other genes in the APOA5-A4-C3-A1 gene cluster
3 years £150,199

PG/05/005/18163
Dr C M N Terracciano MD PhD
Imperial College (Harefield Hospital), Middlesex
Cellular, molecular and functional effects of unloading in normal and diseased hearts
3 years £197,253

PG/04/078/17370
Dr S A M Thom MBBS MRCP
Imperial College (St Mary's Hospital), London
Image-based analysis of coronary artery flow patterns and shear stress using MR and computational fluid dynamics
2 years £149,664

PG/05/009/18270
Dr J R Tippins PhD
Imperial College London
Thromboxane receptor function at the subcellular level in oxidative stress
3 years £150,198

PG/04/055/17036
Dr L Zhao PhD
Imperial College (Hammersmith Hospital), London
The role of tetrahydrobiopterin in the pulmonary circulation
2 years £88,578

Region 3
Scotland

PG/05/006/18224
Dr A H Baker BSc PhD
Western Infirmary, Glasgow
In vivo targeting of atherosclerotic plaques: potential for therapeutics and diagnosis
3 years £116,526

PG/04/100/17637
Dr J Brittenden MD FRCS
University of Aberdeen
A randomised controlled trial of omega-3 fatty acid on platelet and endothelial function in patients with peripheral arterial disease
2 years £96,281

PG/04/112/17838
Dr K E Chapman BSc PhD
Western General Hospital, Edinburgh
Adipocyte glucocorticoid receptors in the development of hypertension and the metabolic syndrome
3 years £176,789

PG/04/066/17251
Dr S Currie BSc PhD
University of Strathclyde, Glasgow
An integrated biochemical and physiological study of the cardiac ryanodine receptor complex and its regulation by calcium/calmodulin dependent protein kinase II
3 years £171,586

PG/04/049/16226
Dr B H Cuthbertson MD MBChB FRCA
University of Aberdeen
The use of BNP as a predictor of outcome in coronary artery bypass surgery
3 years £127,534

PG/04/127/18022
Dr E Davies BSc PhD
Western Infirmary, Glasgow
Functional analysis of mutations / polymorphisms in steroidogenic genes and their implications for human cardiovascular homeostasis
2 years £88,508

PG/04/101/17652
Prof A F Dominiczak MD FRCP FMedSci
Western Infirmary, Glasgow
Functional characterisation of the Gstm1 deficiency in the stroke-prone spontaneously hypertensive rat: *in vitro* and *in vivo* studies
3 years £153,686

PG/04/063/17186
Dr A Graham BSc PhD MA
Glasgow Caledonian University
Mitochondrial sterol 27-hydroxylase and regulation of macrophage cholesterol efflux pathways
2 years £80,297

PG/04/071/17177
Dr G S Hillis MBChB
Aberdeen Royal Infirmary
Prediction of functional recovery following acute myocardial infarction: a comparison of echocardiography and cardiac magnetic resonance imaging
2 years £72,885

PG/04/086/17410
Dr A J Jovanovic MD PhD
Ninewells Hospital, Dundee
Diadenosine tetraphosphate-mediated regulation of sarcolemmal KATP channels in the heart
3 years £119,305

PG/04/096/17627
Dr A J Jovanovic MD PhD
Ninewells Hospital, Dundee
A link between sarcolemmal ATP-sensitive $K^+(K_{ATP})$ channels and AMP-activated protein kinase (AMPK) in mediating cardioprotective signalling
3 years £127,035

PG/05/007/18240
Dr Y V Kotelevtsev BSc PhD
University of Edinburgh
Mechanisms of acclerated atherogenesis and sudden death in an $ApoE^{-/-}$ / $11HSD2^{-/-}$ double knockout mouse
3 years £184,858

PG/04/054/17033
Prof M R MacLean BSc PhD
University of Glasgow
Interactions between serotonin transport inhibitors and 5-HT_{1B} receptors in pulmonary arteries
3 years £139,442

PG/04/131/18118
Dr D E Newby BM MRCP
Edinburgh Royal Infirmary
Development of a clinical model of thrombosis and endogenous fibrinolysis
3 years £155,877

PG/05/002/17467
Dr K G Oldroyd MBChB FRCP MD
Western Infirmary, Glasgow
Validation of myocardial perfusion magnetic resonance imaging using combined assessment of coronary and fractional flow reserve
2 years £146,829

PG/05/026/18159
Dr T M Palmer BSc PhD
University of Glasgow
Suppressor of cytokine signalling-3 (SOCS3) induction: a new physiological role for the cyclic AMP sensor 'EPAC' in limiting endothelial dysfunction
3 years £162,924

PG/04/084/17400
Dr D Pau BSc PhD
Royal Infirmary, Glasgow
Human atrial cellular calcium handling, arrhythmogenic mechanisms of 5-hydroxytryptamine, and their modulation by atrial fibrillation
3 years £181,619

PG/04/051/17026
Dr I P Salt BSc PhD
University of Glasgow
Regulation of endothelial nitric oxide synthesis by the AMP-activated protein kinase cascade
3 years £119,703

PG/05/001/17696
Dr N Sattar PhD MRCPath
Glasgow Royal Infirmary
Insulin sensitisation as a novel mechanism to lessen ischaemic burden in non-diabetic patients with chronic stable angina: a pilot study
2 years 6 months £143,649

PG/04/058/17157
Prof G L Smith BSc PhD
University of Glasgow
A study of the subcellular actions of sorcin in ventricular cardiac muscle
3 years £130,251

PG/05/032/18645
Prof G L Smith BSc PhD
University of Glasgow
Electrophysiology of ventricular myofibroblasts within myocardial infarction scars of rabbit hearts
1 year £43,044

PG/04/062/17181
Prof A D Struthers MD FRCP
Ninewells Hospital, Dundee
Does aldosterone blockade improve endothelial dysfunction in patients with coronary artery disease but without heart failure?
2 years 6 months £104,071

Region 5
Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire, South Yorkshire

PG/05/028/18599
Dr N P J Brindle BSc PhD
University of Leicester
Regulation of endothelial function by Tie1 RIP signalling
3 years £134,336

PG/04/129/18095
Dr J Emsley BSc PhD
University of Nottingham
Coagulation factor XI structure, activation and receptor binding
3 years £119,312

PG/04/050/16888
Prof M Galinanes PhD FRCS FECTS
Glenfield Hospital, Leicester
Efficacy of mode of delivery of autologous bone marrow cells into heart scar muscle for the recovery of contractile function
3 years £157,540

PG/04/076/17361
Prof A J Knox MBChB FRCP MD
City Hospital, Nottingham
Cytokines and mediators impair cyclic AMP accumulation in response to prostacyclin analogues in human pulmonary artery smooth muscle
2 years £92,877

PG/04/073/17255
Dr S A Lewis MSc PhD
City Hospital, Nottingham
Cluster randomised, controlled trial of pro-actively identifying smokers and offering evidence-based support to stop smoking
2 years £183,653

PG/04/093/17615
Prof L L Ng MA MD FRCP
Leicester Royal Infirmary
Kinase activation of NADPH oxidase in pre-eclampsia
2 years £83,028

PG/05/034/18654
Dr J M Saxton PhD
Sheffield Hallam University
Effect of upper- and lower-limb exercise training on biomarkers of atherosclerosis and cardiovascular risk in intermittent claudication
6 weeks £15,819

PG/04/103/17690
Prof R C Trembath MB FRCP FMedSci
University of Leicester
Investigating the role of SREBP1 in familial partial lipodystrophy using a knock-in mouse model
3 years £169,243

Region 6
Wales

PG/04/091/17461
Dr D J Bowen BSc PhD
Cardiff University
The von Willebrand factor (VWF) tyrosine/cysteine 1584 polymorphism: determination of its frequency and effect on VWF levels in a normal population
2 years £77,612

Region 7
Lancashire, Merseyside

PG/04/105/17734
Prof J Adgey MD FRCP
Royal Victoria Hospital, Belfast
Identification of posterior AMI with non-diagnostic ECGs using body surface mapping and radionuclide imaging
2 years £80,777

PG/04/088/17423
Prof P N Durrington MD FRCP
Manchester Royal Infirmary
Investigation of the potential of glycation of lipoproteins as an atherogenic modification
2 years £132,732

PG/05/010/18272
Dr G Edwards BSc MSc PhD
University of Manchester
Calcium-sensing receptors in the control of vascular tone
3 years £123,316

PG/04/111/17832
Prof D A Eisner MA DPhil
University of Manchester
Integrative analysis of Ca^{2+} cycling in cardiac myocytes in response to TNFα: the role of SERCA
3 years £82,473

PG/05/042/18679
Dr I M Fearon BSc PhD
University of Manchester
Hypoxic regulation of cardiac sodium channels
2 years £129,357

PG/05/045/18729
Prof D F Goldspink PhD DSc
Liverpool John Moores University
Gender differences and exercise thresholds in improving aerobic capacity, cardiovascular risk factors, peripheral and cardiac adaptations in endurance-trained older people
3 years £137,742

PG/05/020/18487
Dr M Hussain BSc PhD
University of Liverpool
Subcellular signalling in type-2 diabetic cardiomyopathy
3 years £163,000

PG/05/044/18715
Dr P A Kalra MA MB BChir FRCP MD
Hope Hospital, Salford
The effect of renal revascularisation on cardiac structure and function in atherosclerotic renovascular disease (ARVD)
3 years £64,014

PG/04/052/17027
Prof C M Kielty BSc PhD
University of Manchester
Marfan syndrome: fibrillin-1 mutations and disease severity correlations
3 years £205,584

PG/05/015/18479
Prof C N McCollum MD FRCS
Wythenshawe Hospital, Manchester
The detection of venous-to-arterial circulation shunts (v-aCS): an evaluation of available techniques
1 year 6 months £135,787

PG/05/016/18480
Dr J Ohanian BSc PhD
Manchester Royal Infirmary
Regulation of phospholipase Cδ1 by noradrenaline in vascular smooth muscle
3 years £142,246

PG/04/130/18114
Dr J M Quayle BSc PhD
University of Liverpool
Regulation of P_2Y receptor-mediated Ca^{2+} transients by membrane potential in arterial smooth muscle cells
2 years £96,384

PG/04/095/17625
Dr A W Trafford BVS PhD
University of Manchester
Late calcium sparks (larks) and dysfunctional calcium signalling in heart failure
3 years £149,641

Region 8
Oxfordshire, Gloucestershire *(excluding South Gloucestershire)*, West Midlands, Warwickshire, Staffordshire *(North and South)*, Shropshire, Herefordshire, Worcestershire

PG/05/013/18296
Dr J M Armitage BSc MBBS MRCP
Radcliffe Infirmary, Oxford
Addition of baseline blood and urine sampling to the BHF ASCEND study (a study of cardiovascular events in diabetes)
2 years £143,044

PG/04/132/18123
Mr W J Brawn FRCS FRACS
Birmingham Children's Hospital
The impact of pulmonary artery banding on ventricular function in patients with a morphologic right ventricle in the systemic circulation
3 years £33,923

PG/05/040/18671
Prof K M Channon MD MRCP
John Radcliffe Hospital, Oxford
Pre-operative, non-invasive ultrasound assessment of radial artery endothelial function to predict early graft failure and outcome from coronary bypass surgery
3 years £136,704

PG/05/036/18656
Dr P S Gill MRCGP
University of Birmingham
Heart failure among the ethnic minority communities in Birmingham: E-ECHOES (Ethnic - Echocardiographic Heart Of England Screening) study
3 years £324,438

PG/04/087/17414
Dr P Kohl PhD MD
University of Oxford
Characterisation of regional cardiomyocyte properties using single-cell 'work-loop' investigations
3 years £153,271

PG/04/121/17880
Dr P Kohl PhD MD
University of Oxford
Stretch effects on the ATP dose-response curve of the ventricular ATP-dependent potassium channel (K_{ATP})
1 year £46,734

PG/04/108/17760
Prof L M Machesky BSc PhD
University of Birmingham
Signalling to platelet actin assembly via integrins: the role of Rac, Scar/WAVE and Arp2/3 complex
3 years £127,199

PG/04/083/17399
Prof J M Marshall BSc PhD
University of Birmingham
The inhibitory effect of nitric oxide on mitochondrial respiration, adenosine accumulation and vasodilatation
3 years £150,661

PG/05/022/18506
Prof G B Nash BSc PhD
University of Birmingham
Regulation of leukocyte recruitment by the basement membrane deposited by vascular endothelial cells
3 years £136,314

PG/04/075/17280
Prof C O S Savage MD PhD FRCP
Queen Elizabeth Hospital, Birmingham
Molecular basis of the vascular damage induced by anti-neutrophil cytoplasm antibodies in a murine model of vasculitis
2 years £90,220

PG/04/068/16764
Prof J W Sear BSc MBBS PhD
John Radcliffe Hospital, Oxford
Perioperative ischaemic evaluation study (POISE): evaluation of protection against peri-operative cardiac events offered by acute beta-blockade
1 year £134,704

PG/04/117/17846
Dr J C St John PhD BSc
University of Birmingham
The characterisation of mitochondrial DNA differentiation in cardiomyocytes derived from embryonic stem cells
3 years £159,179

PG/05/029/18602
Dr S R Stedman MB ChB FRCA
Birmingham Heartlands Hospital
Magnesium sulphate for the prevention of superventricular dysrhythmias following non-cardiac thoracic surgery
2 years £35,506

PG/04/070/16955
Dr S Stoilova-McPhie BSc PhD
University of Warwick
Structure determination of membrane-bound human factor VIII and its active form factor VIIIa by cryo-electron microscopy and crystallography
3 years £118,606

PG/05/037/18663
Prof D P Taggart PhD MD FRCS
John Radcliffe Hospital, Oxford
A randomised trial of on-pump beating heart surgery and blood cardioplegia in patients with impaired left ventricular function using cardiac magnetic resonance imaging and biochemical markers
2 years £143,125

PG/04/109/17796
Dr J N Townend BSc MD FRCP FESC
Queen Elizabeth Hospital, Birmingham
Is spironolactone safe and effective in the treatment of cardiovascular disease in mild chronic renal failure?
2 years £189,622

Region 9
Hampshire, East and West Sussex, Surrey, Berkshire, Kent, London South of Thames, Isle of Wight

PG/04/094/17616
Prof S D Brain BSc PhD
Guy's Hospital, London
Characterisation of the receptor-mediated mechanisms that underlie the protective effects of endogenous adrenomedullin in cardiovascular hypertrophy
3 years £148,212

PG/04/053/17031
Prof G Brooks B Pharm PhD
University of Reading
The role of myostatin as a cell cycle regulator of cardiomyocyte growth
3 years £155,452

PG/04/119/17870
Prof P J Chowienczyk BSc FRCP
St Thomas' Hospital, London
Modulation of vascular function through the beta-2-adrenoreceptor: role of beta-2-adrenoreceptor responses in hypertension
2 years £97,658

PG/04/057/17152
Dr J M East BSc PhD
University of Southampton
Targeting the cardiac calcium pump modulator phospholamban to the sarcoplasmic reticulum: identifying targeting motifs and characterisation of the retention apparatus
3 years £126,463

PG/04/118/17847
Dr P Eaton BSc PhD
St Thomas' Hospital, London
An investigation of how small heat shock proteins protect the heart from ischaemia
3 years £151,362

PG/05/046/18730
Dr C H D Fall BSc MBChB FRCP
Southampton General Hospital
Relationship of growth in infancy and childhood to adult endothelial function and body composition: the New Delhi birth cohort
3 years £184,538

PG/05/038/18664
Dr I A Greenwood BSc PhD
St George's Hospital Medical School, London
Regulation of calcium-activated chloride currents in vascular smooth muscle cells by dephosphorylatory mechanisms
3 years £182,225

PG/05/043/18709
Dr R S Haworth BSc PhD
St Thomas' Hospital, London
A novel regulatory role for protein kinase D in myofibrillogenesis?
3 years £197,475

PG/04/080/17377
Prof H S Markus MRCP MD
St George's Hospital Medical School, London
Variation in the phosphodiesterase 4D gene and carotid atherosclerosis
1 year £66,837

PG/04/104/17705
Prof H S Markus MRCP MD
St George's Hospital Medical School, London
Investigating cognitive function in hypertension using diffusion tensor imaging
2 years £83,820

PG/04/064/17241
Prof J D Pearson MA PhD
Guy's Hospital, London
Polymorphonuclear leucocytes, vascular damage and systemic inflammation
3 years £99,356

PG/04/056/17038
Prof V R Preedy BSc PhD DSc
King's College London
A proteomic investigation into post-translationally formed protein adducts in alcoholic cardiomyopathy
3 years £153,429

PG/04/048/16631
Prof M J Shattock BSc PhD
St Thomas' Hospital, London
Electrophysiological characterisation of sodium-potassium pump regulation by phospholemman
3 years £160,994

PG/04/067/17252
Dr R C M Siow BSc PhD
Guy's Hospital, London
Effects of TGFß1 on Nrf2 mediated heme oxygenase-1 expression in vascular smooth muscle cells
2 years £100,691

PG/04/072/17197
Prof P H Whincup MB MSc PhD
St George's Hospital Medical School, London
Early life exposures and coronary heart disease risk: building a systematic framework of observational evidence
3 years £153,163

PG/05/039/18669
Dr S S Ye MB MD PhD
Southampton General Hospital
Molecular genetic and functional analysis of TLR4 gene variants
3 years £138,263

Region 10
Wiltshire, Dorset, Somerset, Devon, Cornwall, Channel Islands, South Gloucestershire

PG/04/079/17372
Prof G D Angelini MD MCh FRCS FETCS
Bristol Royal Infirmary
BHACAS-1 and -2: multiple slice computed tomographic angiography for non-invasive assessment of graft patency and five-year clinical follow-up
1 year 6 months £159,564

PG/04/069/17189
Prof C J Garland BSc PhD
University of Bath
Mechanisms underlying contact-mediated myoendothelial vasodilator activity in the resistance vasculature
3 years £178,149

PG/04/090/17460
Dr J C Hancox BSc PhD
University of Bristol
HERG pharmacology in relation to the short QT syndrome
2 years £71,946

PG/05/030/18634
Dr N King BSc PhD
University of Bristol
An investigation into the expression and activity of cysteine transporters in heart: relationship to glutathione synthesis and cardioprotection
2 years £142,251

PG/05/031/18642
Prof C H Orchard BSc PhD
Bristol Royal Infirmary
Effect of acidosis on the cardiac atrio-ventricular node
3 years £204,326

PG/04/097/17620
Dr A W Poole MA PhD VetMB
University of Bristol
Genetic and biochemical analysis of the role of novel protein kinase C isoforms, PKCδ and PKCθ, in platelet function and thrombosis
2 years £104,004

PG/04/106/17736
Dr R M A Sitsapesan MSc PhD
University of Bristol
Role of the cardiac ryanodine receptor carboxyl-terminal tail region in subunit assembly and single-channel function
3 years £163,880

PG/04/128/18094
Dr R M A Sitsapesan MSc PhD
University of Bristol
Investigation of the molecular mechanisms underlying adenine nucleotide interactions with the cardiac ryanodine receptor
3 years £158,412

PG/04/124/17944
Dr D Thompson BA MSc PhD
University of Bath
A role for T lymphocyte and monocyte haem oxygenase-1 (HO-1) in the atheroprotective effect of regular physical activity
2 years £117,736

Analysis of the distribution of Project Grants, 2000/2001 – 2004/2005 inclusive

The following table shows the distribution of Project Grants in the various disciplines. The figures are approximate as some grants may involve more than one discipline, in which case the major subject is recorded. The figures in brackets indicate the number of awards made. This table does not include funds used to endow and maintain Chairs, Programme Grants or Fellowships.

SPECIALTY	2000/2001	2001/2002	2002/2003	2003/2004	2004/2005	Total (5 years)	%
Biochemistry	£3,612,332 (31)	£3,984,862 (30)	£4,006,692 (34)	£2,866,735 (26)	£3,405,687 (25)	£17,876,308 (146)	18.84
Clinical cardiology and diagnosis	£835,862 (6)	£1,620,282 (15)	£377,378 (4)	£348,901 (3)	£884,332 (7)	£4,066,755 (35)	4.29
Epidemiology	£654,549 (5)	£1,764,524 (16)	£2,906,241 (27)	£3,139,913 (24)	£2,494,365 (19)	£10,959,592 (91)	11.55
Genetics	£1,739,059 (15)	£1,529,512 (13)	£763,988 (4)	£795,549 (6)	£858,451 (7)	£5,686,559 (45)	5.99
Hypertension	£380,360 (4)	£901,674 (9)	£178,821 (2)	£902,817 (6)	£962,549 (8)	£3,326,221 (29)	3.51
Immunology	£609,831 (5)	£334,385 (3)	£254,268 (2)	£430,191 (3)	£195,869 (2)	£1,824,544 (15)	1.92
Paediatric cardiology	£849,779 (9)	£469,598 (4)	£588,217 (4)	£1,394,661 (10)	£33,923 (1)	£3,336,178 (28)	3.52
Pathology	£820,739 (7)	£1,906,572 (18)	£1,986,349 (15)	£1,132,606 (11)	£1,509,287 (11)	£7,355,553 (62)	7.75
Physiology, electrophysiology and anatomy	£2,414,834 (21)	£4,418,433 (41)	£6,345,518 (52)	£5,172,337 (39)	£4,010,487 (30)	£22,361,609 (183)	23.57
Surgery	£1,060,945 (11)	£89,582 (1)	£216,763 (2)	£300,690 (2)	£630,941 (5)	£2,298,921 (21)	2.42
Techniques and instrumentation	£503,258 (5)	£172,747 (1)	£123,250 (2)	£436,122 (5)	£149,664 (1)	£1,385,041 (14)	1.46
Thrombosis and atherosclerosis	£2,193,697 (21)	£1,607,501 (14)	£1,424,270 (13)	£1,942,121 (17)	£2,119,304 (16)	£9,286,893 (81)	9.79
Treatment and pharmacology	£1,431,095 (15)	£1,340,022 (10)	£1,161,638 (10)	£1,174,191 (8)	(0)	£5,106,946 (43)	5.38
TOTAL	**£17,106,340 (155)**	**£20,139,694 (175)**	**£20,333,393 (171)**	**£20,036,834 (160)**	**£17,254,859 (132)**	**£94,871,120 (793)**	**100**

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