

Grant Awards 2005/2006



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Introduction

In the year April 2005 to March 2006, the BHF spent over £55 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 Fellowships, Programme Grants, Special Projects, Infrastructure Grants and Project Grants.

A summary of research from BHF chairholders

Listed by town

UNIVERSITY OF BIRMINGHAM

The Chair of Cardiovascular Medicine

Held by: Professor M P Frenneaux MBBS (Hon) MD FRCP FRACP FACC FESC

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 toward 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 further 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 that 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 BIRMINGHAM

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 BIRMINGHAM

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 also implicated 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

The Chair of Cardiovascular Sciences

Held by: Professor M R Bennett MBChB 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 re-narrowing 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 either to halt or to reverse this process.

UNIVERSITY OF CAMBRIDGE

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 EDINBURGH

The Duke of Edinburgh Chair of Cardiology

Held by: Professor K A A Fox MBChB 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 investigate 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. Our 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

The Walton Chair of Medical Cardiology

Held by: Professor S M Cobbe MA MD FRCP FMedSci

Electrophysiological and intracellular Ca²⁺ changes in heart failure. We have demonstrated regional variability in changes in cellular electrophysiology and Ca²⁺ 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. In the area of nuclear cardiology, a number of projects 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

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. Furthermore, we shall 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 nitric oxide and the superoxide anion. We have 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

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 pre-operatively to see whether the inflammatory 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 this may interfere with recovery. We are investigating this in the isolated perfused heart. 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

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 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

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 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 commonest 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 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 have 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 recently we have 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 for looking at the development of coronary heart disease.

UNIVERSITY OF LONDON
Imperial College (Hammersmith)

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
Imperial College (Hammersmith)

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. 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 cardiopulmonary bypass as safe as possible.

Our current research focuses on the following areas:

- 1 **Systemic 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 cardiopulmonary bypass 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 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 between all the countries of Europe. All these registries are based in the Cardiac Surgical Unit at Hammersmith.

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 Ca²⁺-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 Ca²⁺-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.

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 Ca²⁺ 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 Ca²⁺ 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

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. Areas of research include: 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; and cardiac myocyte cell cycle regulation in development of heart failure.

Homograft valve research and tissue engineering. Research aims 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 carrying out research 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. Our research is looking at viral infections in transplantation and cardiovascular disease.

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

Organ preservation, metabolic research and gene therapy. Areas of research include: improving the performance of donor organs; and the mechanism of myocardial injury during transplantation and other clinical conditions of ischaemia.

Circulatory support. We are carrying out research into the 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; care and investigation of patients for transplant and post-operatively.

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 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

St George's

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 also carrying out research into 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; 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: 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 there are studies on: 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.

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

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 habit, smoking, stress and exercise).

We have developed high-speed, accurate and cheap methods to examine genes from either 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, so that we can carry out powerful genetic analyses.

We have continued to study patients with the disorder familial hypercholesterolaemia, and since this 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 UK middle-aged men 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 it 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 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 altering that process might limit the damage that occurs during ageing.

Heart attacks are caused by a clot forming in the coronary artery. This clot is initiated by little cells called platelets clumping together. Platelets are produced from bone marrow cells called megakaryocytes, and we have discovered that changes in these cells may lead to increased platelet reactivity and clotting. How platelets are made from megakaryocytes is therefore being studied in the test tube in the laboratory.

UNIVERSITY OF LONDON
University College London

The Chair of Psychology

Held by: Professor A P A 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, the impairment in quality of life is not directly related to the clinical severity of heart disease in many cases. We are studying the way in which emotional factors and patients' understanding of their illness contribute to later quality of life.

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 deficiencies in the partitions dividing the four major cardiac chambers, and hearts 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 so as to establish those factors which may have contributed to death.

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

University College London (Institute of Child Health)

The Chair of Developmental Cardiology

Held by: Professor S G Haworth MD FRCPATH FRCP FACC FMedSci – retired 30.9.05

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.

UNIVERSITY OF MANCHESTER

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 through 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

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 – the Clinical Trial Service Unit (CTSU) – 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 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 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 (30-40 thousand 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 carried out. 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

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

The Chair of Cardiovascular Science

Held by: Professor M A Hanson MA DPhil CertEd FRCOG

Developmental Origins of Adult Disease Centre. The research strategy of the 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 2005 – 31 March 2006

Fellowships

Senior Research Fellowships

FS/05/089/19373

Dr P Kohl PhD MD
University of Oxford
Cardiac mechano-electric feedback and arrhythmias: from pipette to patient
5 years £294,761

FS/05/125/19379

Dr A D Hingorani MBBS MRCP PhD
University College London
RENEWAL: A research framework for Mendelian randomisation studies of biomarkers relevant to cardiovascular disease
5 years £559,430

Basic Science Fellowships

BS/05/001/18360

Dr C Emanuelli PhD
University of Bristol
Pathways and therapeutic potential of neurotrophins in neovascularisation and healing of the ischaemic and diabetic heart
5 years £296,459

BS/05/003/19552

Dr D J Henderson BSc PhD
University of Newcastle
RENEWAL: Neural crest cell interactions in outflow tract development and congenital heart defects
5 years £286,455

BS/05/002/18361

Dr A Zhou PhD
University of Cambridge
Structural mechanisms in the control of fibrinolysis
5 years £271,750

Intermediate Research Fellowships

FS/06/004/20404

Dr K B Abbitt BMedSc PhD
University of Sheffield
The effects of disturbed flow on ULVWF and platelet and leukocyte recruitment
3 years £127,697

FS/05/094/19935

Dr N Ahmed BSc PhD
University of Essex
Hotspot glycation of apolipoprotein B100 by dicarbonyls at LDL receptor recognition domains – importance in dyslipidaemia and atherosclerosis in diabetes
3 years £133,714

FS/05/063/19521

Dr R A Bass BSc MSc PhD
University of East Anglia
Regulation of vascular cell behaviour by maspin, a non-inhibitory serpin
3 years £147,275

FS/05/064/19525

Dr G C Burdge BSc PhD
University of Southampton
Nutrient restriction before birth, and regulation of gene expression and maintenance of lipid homeostasis in later life
3 years £173,365

FS/06/006/20413

Dr A Cheong PhD
University of Leeds
The control of REST expression in vascular smooth muscle cells: transcriptional regulation and vascular proliferation
3 years £142,374

FS/06/002/20395

Dr J T B Crawley BSc PhD
Imperial College, London
Proteolytic specificity of the ADAMTS13 metalloprotease domain
3 years £156,706

FS/05/065/19497

Dr T R Gaunt BSc PhD
University of Southampton
The growth hormone gene cluster: relationship with early growth and adult cardiovascular disease
3 years £134,869

FS/05/027/18932

Dr M T Ghorbel MSc PhD
University of Bristol
The identification of the molecular processes underlying reoxygenation injury in children undergoing repair of cyanotic congenital heart disease
3 years £157,417

FS/05/093/19934

Dr S Jiang PhD
King's College London
Preclinical study of CD4+CD25+ regulatory T cells with indirect allospecificity as cell therapy to induce donor-specific cardiac transplantation tolerance
3 years £164,231

FS/06/003/20402

Dr G A Knock PhD
King's College London
Functional and molecular investigations into the role of pp60^{C-Src} in the responses of the pulmonary vasculature to hypoxia and agonists
3 years £167,907

FS/06/005/20411

Dr C M McEniery BHMS PhD
University of Cambridge
Mechanisms underlying hypertension in young adults
3 years £177,566

FS/05/059/18390

Dr J T C Murray PhD
University of Dundee
Functional and biochemical analysis of hVps34 and hVps15 in insulin-regulated glucose homeostasis: a major predisposing factor for atherosclerotic complications
3 years £144,087

FS/05/095/19937

Dr S Padmanabhan MBBS MD PhD
University of Glasgow
Hypertension pharmacogenetics – discovering genetic determinants of blood pressure response
3 years £256,205

FS/05/062/19516

Dr M Ponticos PhD
University College London
The role of the homeobox transcription factor Nkx2.5 in atherosclerosis
3 years £184,046

FS/05/092/19519

Dr J J Rochford BSc PhD
University of Cambridge
Early molecular events in the control of fat cell development
3 years £161,804

FS/05/024/18923

Dr J Selvanayagam BSc MBBS FRACP
University of Oxford
Imaging of myocardial oxygenation with blood-level dependent magnetic resonance imaging
3 years £232,423

FS/05/060/18921

Dr S E Stringer BSc PhD
University of Manchester
Investigation of the role of heparan sulphate proteoglycans in angiogenesis
3 years £203,883

FS/06/001/19932

Dr J O Turner MBBS MRCP DPhil
Imperial College, London
Regulation of inflammatory signalling by adiponectin in obesity and the metabolic syndrome
3 years £321,061

FS/05/061/19501

Dr C Wallace BSc MSc PhD
Queen Mary, London
The development of novel statistical genetic approaches for gene mapping and genome-wide association of hypertension in the BRIGHT study
3 years £128,203

FS/05/025/18925

Dr M I Wilson PhD
University of Cambridge
Turning NADPH oxidase and atherosclerosis off: structural studies of the P-Rex1, Rac GTPase and Gβregulatory complex
3 years £129,115

FS/06/007/20414

Dr L M Work BSc PhD
University of Glasgow
A combined approach to target reactive oxygen species
and neuronal death in stroke
3 years £149,954

Junior Research Fellowships**FS/06/008/20384**

Dr R M Dewberry BSc PhD
University of Sheffield
Notch and endothelial progenitor cells: death, division or
differentiation?
2 years £78,345

FS/05/032/18909

Dr T W R Doulton BSc MB BS MRCP
St George's, London
Does sodium affect endothelial function in individuals
with chronic kidney disease?
1 year 4 months £68,206

FS/05/030/18891

Dr J S Eason MBChB MRCP
University of Nottingham
The relationship between germline and somatic
mutations in congenital heart disease
2 years £113,482

FS/05/033/18911

Mr D M Espino BSc
University of Birmingham
Computational modelling of the mitral heart valve for
improved surgical repair of the chordae tendineae
2 years £69,004

FS/05/028/18423

Dr I J Gudmundsdottir MRCP
University of Edinburgh
The role of proteinase activated receptors in the human
vasculature
2 years £95,504

FS/05/029/18887

Dr J L Guy BSc PhD
University of Leeds
Regulation and function of angiotensin-converting
enzyme-2 (ACE2) expression in human cardiac fibroblasts
2 years £72,748

FS/05/034/18916

Dr N Hadjiloizou BSc MBBS MRCP
Imperial College, London
The effect of regional ventricular dysfunction on coronary
artery haemodynamics
2 years £92,539

FS/05/097/19941

Dr P Heck MRCP BMBCh
University of Cambridge
The effects of hyperinsulinaemia and hyperglycaemia
on myocardial performance in patients with coronary
artery disease
2 years £97,836

FS/05/066/18904

Dr S M Huq MBBS MRCP
Queen Mary, London
Metabolic phenotyping and pharmacogenetics of
patients with essential hypertension
2 years £109,171

FS/05/036/18920

Dr J P Kaski BSc MBBS MRCPCH
University College London
Idiopathic hypertrophic cardiomyopathy in pre-
adolescent children: development of a paediatric cardiac
symptom evaluation and sudden death risk stratification
algorithm
2 years £84,563

FS/06/009/20386

Dr M Marciniak MBBS
St George's, London
Effect of potassium bicarbonate and potassium chloride
on blood pressure, endothelial function and markers of
target organ damage in hypertensive patients
2 years £95,003

FS/05/067/19487

Dr M E Morley MRCP
University of Leeds
Mechanism of regulation of MMP-2 expression and
activity by chronic hypoxia – effects on human cardiac
fibroblast function
1 year 9 months £91,740

FS/05/031/18906

Dr T L Mwambingu MBChB
University of Leeds
Fibrin structure/function in pre-menopausal women with polycystic ovary syndrome: the effect of insulin resistance independent of glycaemia, and the role of post translational modifications to fibrinogen
2 years £91,032

FS/05/035/18917

Dr S P Page BMedSci MBBS MRCP
University College London
Prevalence and significance of disease in relation to age in patients with hypertrophic cardiomyopathy caused by MyBPC3 mutations
2 years £87,395

FS/05/070/19496

Dr M Paspaspyridonos BSc PhD
University of Oxford
Functional characterisation of inflammatory mediators in unstable human atherosclerotic plaques
2 years £72,362

FS/06/010/20397

Mr S D Patel MRCS MBChB
King's College London
The role of vascular progenitor cells in restenosis following arterial injury
2 years £100,848

FS/05/069/19495

Mr N Roberts MBChB
St George's, London
Characterisation of endothelial progenitor cells in patients undergoing coronary artery bypass surgery. From pathogenesis to therapy
2 years £116,384

FS/05/098/19942

Dr D Sharkey MMedSci MB BS MRCPCH
University of Nottingham
Programmed to fat dysfunction – the early origins of cardiovascular and metabolic disease?
2 years £96,578

FS/05/096/19933

Mr J Watt MBChB MRCP
University of Strathclyde
Coronary stent deployment, oxidative stress, endothelial regeneration and risk of thrombosis
2 years £89,376

FS/05/068/19492

Dr Z I Whinnett MRCP BM BS BMedSci
Imperial College, London
Investigation of a new non-invasive method for haemodynamic optimisation of biventricular pacemakers: validity on exercise, immediate and medium-term effect on exercise capacity
1 year 6 months £85,041

Clinical PhD Studentships**FS/05/102/19951**

Dr Z Astroulakis MB BS MRCP
King's College London
Endothelial progenitor cell reserve and response to exercise and cardiac rehabilitation
3 years £183,329

FS/05/100/19945

Dr V Bills MBChB
University of Bristol
Vascular permeability in pre-eclampsia
3 years £134,956

FS/05/038/18937

Miss A Burdess BSc MBChB MRCS
University of Edinburgh
Role of inflammation and platelet activation in the adverse cardiovascular outcomes of patients with critical limb ischaemia: a double-blind randomised controlled trial of clopidogrel
3 years £143,039

FS/06/012/20424

Dr S Daga MBChB
University of Edinburgh
Platelet activation in the pathogenesis of infective endocarditis
3 years £146,196

FS/05/037/18438

Dr H B Fallouh MRCS
King's College London
Protection of the ischaemic myocardium: calcium desensitisation and polarisation as alternatives to hyperkalaemia
3 years £162,787

FS/05/072/19480

Dr E Fernandes MD MBChB
Imperial College, London
Transplantation tolerance induction via genetic
modification of naive T cells with Foxp3 and allograft
specific TCR genes
3 years £158,633

FS/05/099/19944

Dr S Hamdulay BSc MBBS MRCP
Imperial College, London
Statins and rapamycin – therapeutic synergy in vascular
cytoprotection
3 years £174,309

FS/05/071/18437

Dr S Leaver BMedSci MB BS MRCP
Imperial College, London
Redox regulation of cytokine biosynthesis in sepsis:
in vivo and *in vitro* investigation of a role for thioredoxin
3 years £165,351

FS/05/101/19950

Dr R Ray MA MBBS MRCP
King's College London
The role of the NADPH oxidase isoform NOX4 in
endothelial cells *in vivo*
3 years £164,357

FS/05/105/18944

Mr M Saha MBBS MRCP
King's College London
Collateral myocardial blood flow. The relative roles of
stenosis severity and circulating endothelial progenitors
3 years £206,035

FS/05/104/18941

Dr R Sarwar BSc MBBS MRCP
Imperial College, London
Genetic determinants of left ventricular mass
3 years £166,344

FS/06/011/20420

Mr A Wadoodi MBChB BMSc MRCS
King's College London
The role of bone marrow in thrombus resolution
3 years £163,442

PhD Studentships**FS/05/049/18877**

Mr F Ali BSc
University of Nottingham
Ion channel characterisation in the human
fetoplacental unit
3 years £71,426

FS/06/022/20373

Mr P Andrikopoulos BSc
Imperial College, London
A novel mechanism controlling calcium signalling in
human endothelial cells: voltage-gated sodium channel
activity and its functional consequences
3 years £83,623

FS/05/056/18907

Ms K Baeten BPharm MPharm
University of Aberdeen
Thrombospondin as a modulator of thrombus lysis
3 years £75,350

FS/05/057/18908

Mr R Bailey BSc
Queen Mary, London
Skeletal versus cardiac isoform effects on muscle regulation
3 years £79,710

FS/05/042/18866

Ms S Bent BSc
University of Manchester
The role of calmodulin in decoding the calcium signal in
muscle excitation-contraction coupling
3 years £73,668

FS/05/118/19971

Mr M Black BSc
Liverpool John Moores University
The effects of exercise training on endothelial and
smooth muscle function in older men and women
3 years £72,907

FS/06/020/20372

Mrs J Brewin BSc MSc
University College London
Adoptive immunotherapy with EBV-specific CTL for
lymphoproliferative disease post-solid organ
transplantations
3 years £85,368

FS/05/050/18883

Mr P Calcraft BSc
University of St Andrews
Differential activation of Ca²⁺-sensitive ion channels in the plasma membrane of arterial smooth muscle: spatial co-ordination of Ca²⁺ signalling by IP₃ cADPR and NAADP
3 years £74,758

FS/06/013/19962

Miss P Campagnolo BSc MSc
University of Bristol
Vascular progenitor cells contribute to angiogenesis from adult human vessels in organ culture and to neovascularisation of ischaemic limbs
3 years £74,643

FS/05/113/19965

Miss A Caporali BSc
University of Bristol
Effect of nerve growth factor (NGF) on diabetes-induced apoptosis of cardiomyocytes and endothelial cells and intra-myocardial NGF gene transfer to combat diabetic cardiomyopathy in mice
3 years £78,173

FS/05/043/18867

Mr E W Carter BSc
University of Kent
Mechanisms and specificity in targeting plasma membrane Ca²⁺-ATPase 2 to intercalated discs
3 years £74,418

FS/05/055/18905

Mr A Chadburn BSc
University of Leicester
Molecular characterisation of the unique properties of the vascular ATP-sensitive potassium channel
3 years £74,418

FS/05/082/19426

Miss A Chase BSc
University of Bristol
Characteristics, vulnerability to ischaemia and protection of hearts and myocytes isolated from mice with ischaemic disease
1 year 9 months £42,903

FS/05/048/18876

Mr D Colombo BSc
University of Birmingham
Regulation of platelet collagen receptor GPVI signalling by tetraspanin superfamily proteins
3 years £74,898

FS/05/117/19967

Ms M Connolly BSc
King's College London
The role of small heat shock proteins in p38 MAP kinase-mediated suppression of nitric oxide-induced vasorelaxation
3 years £84,073

FS/05/087/19466

Miss R D Davies BSc
University of Cardiff
Role of complement regulators in the pathogenesis of atherosclerosis in ApoE-deficient mice
3 years £82,875

FS/05/053/18902

Miss L C Duffley BSc MRes
University of Manchester
Role and regulation of the sarcoplasmic reticulum in the ageing myocardium
2 years 6 months £60,930

FS/05/106/19409

Mr R Dixon BSc
University College London
Leptin: a cardioprotective adipocytokine?
3 years £79,710

FS/05/085/19460

Mr S Ellison BSc
University of Birmingham
Regulation of platelet ITAM and integrin receptor signalling by transmembrane protein tyrosine phosphatases
3 years £74,898

FS/05/041/18865

Mr D Elsey BSc MSc
Royal Veterinary College, London
Roles and mechanisms of action of the L-cysteine/cystathionine- γ -lyase/hydrogen sulphide pathway in the heart
3 years £78,850

FS/05/077/19404

Miss M Gardner BSc
Imperial College, London
Essential role of calcium in ADAMTS13 function
3 years £79,710

FS/05/112/19957

Ms J A Greig
University of Glasgow
Design and evaluation of *in vivo* targeted
antioxidant peptides
3 years

£78,883

FS/05/078/19406

Ms G Leoni BSc
Queen Mary, London
Melanocortin receptor deficiency and the control of
leukocyte / endothelium interactions
3 years

£80,880

FS/05/111/19956

Mr J A Hansell BA
University of Cambridge
Developmental programming of cardiovascular disease
by hypoxia and oxidative stress
3 years

£84,646

FS/05/073/18868

Miss R M MacKenzie MSci
University of Glasgow
Gene silencing by small interfering RNAs to dissect
function of the glutathione S-transferase mu type 1
3 years

£75,353

FS/05/076/19402

Mr M Harrison BSc
University of Nottingham
Nutritional programming of hypertension and renal
disease: intergenerational effects
3 years

£74,713

FS/05/115/19963

Miss C Major BSc
University of Nottingham
The role of stearyl coenzyme A desaturase in regulating
lipid and lipoprotein metabolism
3 years

£78,643

FS/05/047/18875

Mr R Hunter BSc
University of Bristol
Identification and characterisation of protein kinase B
substrates in human platelets
3 years

£74,737

FS/05/045/18872

Ms P Matthews BSc
King's College London
Developmental programming of cardiovascular disease
by maternal dietary fat: a mechanistic study using a
murine model
3 years

£79,710

FS/05/054/18903

Ms A Ioannidou BSc
University of Aston
Activation and pharmacology of CGRP and ADM
receptors: studies with chimeric receptors and
other techniques
3 years

£74,658

FS/06/019/20371

Mrs C Matute MSc
University College London
Mechanisms mediating functions of neuropilins 1 and 2
in endothelial cells
3 years

£83,848

FS/05/052/18901

Ms A Kalyva BSc MSc
University of Kent
The role of tropomyosin hetero-dimers in cardiac muscle
regulation and cardiomyopathy
3 years

£71,418

FS/05/079/19407

Mrs F Meng MSc
University of Birmingham
Role of metabolite sensitive ion channels in HPV and
response of PASMC to chronic hypoxia
3 years

£74,238

FS/05/051/18897

Mr M Khan MSc
Imperial College, London
Would inhibitors of the asparaginyl hydroxylase FIH
(factor inhibiting HIF) be useful in ischaemic disease?
3 years

£80,170

FS/05/080/19415

Mr C Nelson BSc
University of Leicester
The application and development of relative survival
methods in coronary heart disease
3 years

£54,399

FS/06/014/19964

Miss S New BSc
Imperial College, London
Factors influencing mesenchymal stem cell differentiation and function in tissue engineering heart valves
3 years £84,555

FS/05/083/19457

Mrs M Omonkowska BSc
University of York
Identification of the residues involved in the non-covalent interactions of fibrin and fibronectin in haemostasis, wound healing and thrombosis
3 years £74,420

FS/05/075/19397

Mr P Penson MPharm
University of Cardiff
 β -adrenoceptor subtypes and transduction pathways involved in myocardial pre- and post-conditioning
3 years £74,919

FS/05/110/19954

Mr A G Pinder BSc
University of Cardiff
Nitrite uptake and metabolism in human erythrocytes – a source of vascular nitric oxide?
3 years £78,454

FS/06/017/20366

Miss S Pitkin BA
University of Cambridge
In vitro characterisation of the function of the apelin family of peptides in man and their role in cardiovascular disease
3 years £84,955

FS/05/044/18870

Mr G Pomeroy BSc
University of Cardiff
Learning the rules of heart morphogenesis in the xenopus embryo model
3 years £74,164

FS/05/040/18863

Ms L Satchell BSc
University of Reading
The mechanisms of low density lipoprotein oxidation by iron at acidic pH
3 years £75,793

FS/05/039/18409

Miss S Schievano MSc
University College London
Computational structural analysis as a tool to develop valved stent applications and technology
3 years £78,961

FS/05/108/19949

Mrs S Shakya Shrestha BSc MPhil
University of Cambridge
A prospective population study of dietary and plasma carotenoids and coronary heart disease
3 years £84,949

FS/05/103/18006

Mr S J Shelton BSc
University of Nottingham
A role for serum response factor (SRF) in the survival of cardiomyocytes following hypoxia
3 years £74,410

FS/05/088/19467

Ms A Sidibe BSc
St George's, London
Proteomic and metabolomic analysis of smooth muscle cells derived from ApoE^{-/-} mice
3 years £80,890

FS/05/107/19948

Ms K E Skene BSc
Robert Gordon University, Aberdeen
Studies on the role of the endocannabinoid anandamide as a possible modulator of events during neointimal formation
3 years £76,901

FS/05/074/18884

Miss K Stanfield MSc
London School of Hygiene & Tropical Medicine, London
Are there ethnic differences in adiposity at birth between Indians and Europeans in the UK?
3 years £73,921

FS/05/116/19966

Ms A Tatham BSc
University of Oxford
Identifying key regulators of tetrahydrobiopterin synthesis
3 years £88,653

FS/05/084/19458

Ms V S Thomson BSc
University of Glasgow
Cyclic AMP/EPAC- induced 'suppressor of cytokine signalling-3' (SOCS-3) gene transcription and the control of insulin sensitivity in vascular endothelial cells
3 years £70,403

FS/05/046/18874

Mr D C Waithe BSc
University College London
Trafficking of cardiac and sympathetic neurone voltage-gated calcium channel subunits
3 years £79,710

FS/06/018/20368

Miss H R Watson
University of Southampton
Identifying the motifs responsible for maintaining cardiac calcium pumps in the sarcoplasmic reticulum: a search for targeting and retrieval signals
3 years £75,129

FS/05/081/19423

Mr P West MBiolSci
University of Sheffield
Toll-like receptors and MIF: an investigation of a molecular and cellular cooperative network central to cardiovascular disease
3 years £74,645

FS/05/086/19462

Mr C Zervides BEng MSc
University of Sheffield
Understanding venous valve operation in the normal state: influence of respiratory and gravitational loads
2 years £38,932

FS/06/016/20362

Student to be appointed
University College London
Impact of alpha-1 antitrypsin on coronary heart disease: *in vivo* and *in vitro* studies
3 years £83,848

FS/05/114/19959

Student to be appointed
University of Bristol
Capillary permeability and ultrastructure in microalbuminuria
3 years £78,881

FS/05/109/19952

Student to be appointed
University of Cardiff
Mechanisms of vascular dysfunction in rheumatoid arthritis
3 years £85,971

FS/06/015/20361

Student to be appointed
University of Manchester
The myogenic response and predisposition to hypertension-induced cerebral haemorrhage
3 years £77,676

FS/06/021/20380

Student to be appointed
NIBSC, Herts
Modelling the kinetics of plasminogen activation in fibrin clots
3 years £81,623

4-Year PhD Studentships**FS/05/121/19570**

Dr D R Greaves BSc PhD
University of Oxford
Second intake 2005/2006 4-year PhD Studentship Scheme: Mr Tom Collins; Miss Jenna Cash; Miss Anna Michell
4 years £314,166

FS/05/119/19568

Prof J J Mullins PhD
University of Edinburgh
Second intake 2005/2006 4-year PhD Studentship Scheme: Miss Caroline Tabor; Ms Agnieszka Kozak; Mr Stylianos Bournazos
4 years £293,337

FS/05/120/19485

Prof J D Pearson PhD
King's College London
Second intake 2005/2006 4-year PhD Studentship Scheme: Miss Sara Alom Ruiz; Mr Andrew Hall; Miss Negin Sarafraz-Shekary
4 years £311,286

International Fellowships

FS/05/090/19371

Dr C Berry MBChB MRCP PhD
University of Glasgow
Endothelial repair: relationships with human coronary
atheroma *in vivo*
1 year £51,352

FS/05/123/19970

Dr M L Penichet MD PhD
From: University of California, Los Angeles
To: University of Surrey
The use of antibody-cytokine fusion proteins to
reprogram the immune system in atherosclerosis
10 days £1,350

FS/05/091/19369

Dr M D O'Neill MB BCh BAO DPhil
Imperial College, London
Role of non pulmonary vein sources in maintenance of
atrial fibrillation
1 year £43,255

Overseas Visiting Fellowship

FS/05/122/19920

Dr I Lorenzen-Schmidt MS PhD
From: University of California, San Diego
To: University of Oxford
Subcellular signalling mechanisms in cardiac
mechanoelectric feedback
2 years £65,394

Travelling Fellowships

FS/05/124/19972

Mr H S Leong MSc
From: St Paul's Hospital, Vancouver
To: Imperial College, London
The role of polymeric vitronectin and endothelial
vimentin in the generation of vimentin antibodies and
transplant graft vasculopathy
3 months £3,000

FS/05/058/18949

Dr A Nicolaou BSc PhD
From: University of Bradford
To: Harvard Medical School
Lipidomic analysis and profiling of novel omega-3 fatty
acid-derived anti-inflammatory mediators and their
aspirin-triggered epimers
3 weeks £2,177

Programme Grant renewals

RG/05/014/20064

Prof S E Humphries PhD FRCPath MRCP
University College London
Functional genetic variants and DNA-based tests for
coronary heart disease risk
3 years £675,873

Progress report

The importance of gene to environment interaction in the development of coronary heart disease risk has been demonstrated in several studies with smoking as the environmental insult, and extended to other challenges such as exercise, thus confirming the importance of environmental context when undertaking genetic studies. The progress from the study of single gene variants to haplotype analysis has highlighted the complexity of genetic variation within a single gene and in a gene cluster. The feasibility of using genetic risk information together with conventional risk factors in risk algorithms is under scrutiny. Genotyping has been aided by the development of high throughput methodologies as well as the development of several methods for mutation detection which have been applied to familial hypercholesterolaemia both for research purposes and in the setting of a diagnostic service. Progress on *in vitro* functional assays of both promoter and protein variants has been very successful as has been the genotype-specific testing *in vivo*. This body of work has taken forward our understanding of the genetic basis of coronary heart disease and the importance of gene to gene and gene to environment interactions in risk determination.

RG/05/005/18583

Prof S Neubauer MD FRCP
University of Oxford
Energy metabolism in heart failure – role of high-energy-phosphate storage and delivery via the creatine kinase/phosphocreatine system
5 years £1,074,252

Progress report

Over the past five years, this programme has made a number of key observations, all related to the central hypothesis that energy metabolism is deranged in the failing heart, contributes to pump failure and can be a specific target for therapy. For example, we demonstrated that energetic derangement precedes the development of pump failure. Using hearts depleted of the energy storage compound phosphocreatine, we showed that an intact energy metabolism is essential during an acute myocardial infarction. We demonstrated that ablation of creatine

kinase isoenzymes and of an enzyme essential for creatine synthesis, guanidinoacetate methyl transferase, leads to a marked cardiac phenotype with left ventricular hypertrophy and dilatation, loss of pumping reserve and increased susceptibility to ischaemia. We also uncovered some of the main mechanisms responsible for regulation of the myocardial creatine transporter, which regulates myocardial creatine content. Overall, we found strong evidence of a pathophysiologic role of cardiac energetics in heart failure. In the subsequent programme we are now exploring, among other hypotheses, whether energetic changes can specifically be corrected and whether this will prevent heart failure from occurring.

RG/05/009/19136

Prof N S Peters MD FRCP
Imperial College, London
Remodelling of conduction and gap-junctional coupling
in myocardial arrhythmogenesis
5 years £1,096,342

Progress report

Heart rhythm disturbances occur when there is disruption of the normal electrical impulses that pass through the heart. We have been examining the changes in the pattern of the electrical connections of the heart, and what it is about heart disease that causes these changes. On the background of having demonstrated for the first time a direct relationship between disturbances of these electrical connections and life-threatening heart rhythm disturbances, we went on to demonstrate for the first time that modifying the behaviour of these electrical connections alters the speed of spread of electrical activity in the heart of conscious patients, and more so in those with heart diseases prone to rhythm disturbances. We will now investigate the mechanism by which interventions that we have previously shown to modify the electrical connections may not only modify electrical activity and tendency to rhythm disturbances, but may also directly modify the underlying disease process to reveal novel interventions for prevention and treatment of heart rhythm disturbances.

RG/05/013/20037

Prof P J Scambler MRCPATH
 University College London
 Developmental genetics of DiGeorge (22q11 deletion) syndrome: investigation of pathways controlled by the transcription factor Tbx1
 5 years £1,005,552

Progress report

The aims of the work were to identify genes that are mutated in human congenital heart defects and to work out how they control heart development. We have used DNA 'chip' technology to unravel how one of these genes (Tbx1, pronounced 'tea box one') works to switch other genes on and off. A major finding from this work was that the production and destruction of vitamin A in the embryo is affected in the absence of Tbx1, and this is likely to exacerbate the heart defects seen. We discovered another gene, Nkx2.6, which is required to form a wall between the main arteries that leave the heart for the body and lungs respectively.

RG/05/006/19256

Prof A P A Steptoe MA DPhil DSc FBPSS AcSS
 University College London
 The psychophysiology of coronary heart disease
 5 years £1,229,792

Progress report

Over the last five years, we have investigated psychological influences on the long-term development of coronary heart disease, and emotional factors in the triggering of heart attacks. We have discovered that psychological and social factors may accelerate the development of disease through activating hormonal and inflammatory processes involved in coronary atherosclerosis, and that these effects are more prominent in people of lower socioeconomic status. Our work with patients who have suffered a heart attack has found that stress and intense emotion act as triggers of symptom onset in a proportion of patients. These emotional triggers are underpinned by heightened biological reactions, including the activation of processes contributing to thrombus formation. People vary in their response to admission to hospital with a heart attack, and feelings in the first few days after the acute event can have a lasting influence on adaptation and quality of life.

RG/05/012/19636

Prof R Trembath MB FRCP FMedSci
 King's College London
 The molecular genetics of pulmonary arterial hypertension
 2 years 5 months £476,011

Progress report

Primary pulmonary hypertension has recently been renamed at least in part due to advances contributed by our programme to identify and understand the role of variation in genes that lead to abnormal structure and function of the blood vessels passing from the heart to the lungs. The new term pulmonary arterial hypertension better explains which vessels show disease and emphasises the consequences, namely high pressure in the system placing a considerable burden upon the right side of the heart, which eventually fails. The term primary has been dropped as we and others have now identified a further gene that, when altered, can lead to the development of pulmonary arterial hypertension and its appearance in families. Both genes form part of a complex signal relay pathway allowing cells to receive messages from the exterior and respond accordingly. The programme has successfully characterised many of the DNA changes that may contribute to this process and has produced a detailed picture of the manner by which they alter the signalling processes necessary for normal function of pulmonary blood vessel cells. Detailed analysis has also started to identify other components of the pathway that may impact upon disease development. These studies have become particularly important as we look at the ways these new findings can be developed to help patients and their relatives with this worrying and life-threatening disorder, including the introduction of predictive tests. There can be little doubt that the discoveries emanating from this and related work now challenge the research community in pulmonary vascular disease to integrate their own findings together with defects in TGF-beta signalling pathway.

RG/05/008/19114

Prof B R Walker MRCP MD FRCPed

University of Edinburgh

Tissue-specific disruption of glucocorticoid signalling:
new mechanisms and therapies for cardiovascular risk

5 years

£808,824

Progress report

This programme (2001-2006), and an associated Senior Fellowship to Professor Brian Walker (1996-2006), addressed the hypothesis that increased activity of the steroid hormone cortisol contributes to the association between multiple cardiovascular risk factors.

Abnormalities were identified both in the secretion of cortisol and in tissue sensitivity to cortisol in people with essential hypertension and obesity. In particular, the enzyme 11 β -HSD1 was shown to generate excess cortisol within adipose tissue in obese patients. In prospective studies, exposure to exogenous steroid hormones was shown to induce increased cardiovascular disease event rates. In 2006-2011, the focus is on dissecting the genetic and functional basis for dysregulation of 11 β -HSD1 in obesity, and testing the value of reducing cortisol action as a preventive strategy for cardiovascular disease.

Programme Grants

RG/05/004/18607

Prof S G Ball PhD FRCP
University of Leeds
Cardiac magnetic resonance imaging in coronary heart disease: from research to clinical practice
5 years £1,290,448

RG/06/001/20057

Dr B Casadei MD MRCP
University of Oxford
The role of myocardial nNOS in the regulation of cardiac function and calcium handling in normal and failing hearts
5 years £642,879

RG/05/007/18585

Dr J M Gibbins BSc PhD
University of Reading
The inhibition of platelet function through immunoreceptor-like signalling
5 years £673,569

RG/05/011/19634

Dr D R Greaves BSc PhD
University of Oxford
Chemokines as a therapeutic target in atherosclerosis
5 years £678,844

RG/05/015/20041

Dr A W Poole MA PhD VetMB
University of Bristol
Role of PKC isoforms in platelet function
5 years £836,191

RG/05/010/19613

Prof A Tinker MRCP PhD
University College London
The regulation and function of ATP sensitive K⁺ channels in the cardiovascular system
5 years £752,277

Special Projects

SP/05/001/18616

Dr J P Bourke MRCP FRCPI FRCP
University of Newcastle
The Duchenne muscular dystrophy heart protection study – a randomised trial of ACE-inhibitor and beta-blocker therapy in preventing cardiomyopathy
5 years £379,794

SP/06/001/19637

Dr G D Kitas PhD MRCP
University of Manchester
Trial of atorvastatin for the primary prevention of cardiovascular events in rheumatoid arthritis (TRACE RA) (Jointly funded by BHF and the Arthritis Research Campaign)
5 years £547,465

Infrastructure Grants

IG/06/001/21011

Prof J G P Sissons MD FRCP FRCPath
University of Cambridge
Imaging and phenotyping centre with cardiovascular research facilities
£500,000

Project Grants

PG/06/034/20637

Dr M D Bootman BSc PhD
Babraham Institute, Cambridge
The role of inositol 1,4,5-trisphosphate receptors in regulating cardiac function
3 years £207,368

PG/05/116/19386

Dr N J Brand BSc PhD
Imperial College, London
Cloning and characterisation of cardiac determinants of glucose transporter 4 (GLUT4) expression in myocardium
3 years £147,766

PG/05/096/19021

Prof N Chaturvedi MBBS MSc MRCP MFPHM MD
Imperial College, London
Explanations for the elevated risk of stroke in South Asians
3 years £199,940

PG/05/111/19746

Dr E Dupont PhD
Imperial College, London
Mechanism of action potential generation and propagation investigated in a genetically engineered cell model
3 years £265,961

PG/05/102/19683

Prof S E Harding BSc PhD
Imperial College, London
Mechanisms of cardiac depression by the β 2-adrenoceptor
2 years £105,639

PG/06/008/20252

Prof S E Harding BSc PhD
Imperial College, London
Sarcoplasmic reticulum Ca^{2+} - release channel phosphorylation state and function in the failing heart
2 years £103,514

PG/06/010/20256

Dr P K Luther BSc PhD
Imperial College, London
Electron tomography of the sarcomere in cardiac muscle: 3D organisation of myosin binding protein C and role in cardiac disease
2 years £205,461

PG/05/136/19997

Dr F M Marelli-Berg MD PhD
Imperial College, London
The role of CD31 (PECAM-1)-mediated interactions in antigen-driven T cell-mediated inflammation and transplant rejection
3 years £179,068

PG/06/025/20396

Prof S B Marston DPhil MA
Imperial College, London
Development and functional investigation of transgenic mouse models of dilated and hypertrophic cardiomyopathy
3 years £267,921

PG/06/027/20425

Prof S B Marston DPhil MA
Imperial College, London
Contractile protein phosphorylation and dephosphorylation in HOCM and end-stage failing human heart
3 years £136,976

PG/06/026/20419

Dr J C Mason PhD MRCP
Imperial College, London
The role of heme oxygenase-1 in the cytoprotective and anti-inflammatory effects of statins on the vascular endothelium
3 years £175,152

PG/05/105/19692

Dr C Monaco MD PhD
Imperial College, London
Toll-like receptor signalling in atherosclerosis
2 years £97,882

PG/05/132/19890

Dr A M Randi MD PhD
Imperial College, London
Regulation of angiogenesis by the adhesion molecule ICAM-2
2 years £163,609

PG/05/092/19515

Dr S M Rankin BSc PhD
Imperial College, London
Defining the role of chemokines in the mobilisation of endothelial progenitor cells from the bone marrow
3 years £158,928

PG/05/120/19838	Dr C M N Terracciano MD PhD Imperial College, London Regulation of Na ⁺ /Ca ²⁺ - exchanger activity by the β 2-adrenoceptor in the normal and failing heart 2 years	£130,781	PG/05/089/19443	Dr A Smith BSc PhD King's College London The <i>in vitro</i> behaviour of lymphatic endothelial cells isolated from patients with primary lymphoedema 2 years	£116,312
PG/06/041/20699	Dr P D Weinberg MA MSc DIC PhD Imperial College, London Re-assessment of the role of blood flow in arterial disease 1 year 6 months	£77,852	PG/06/002/20704	Prof S B J Ebrahim MFPHM MD London School of Hygiene & Tropical Medicine, London British Women's Heart and Health Study: the causes and consequences of cardiovascular disease in older women (Jointly funded by the BHF and the Department of Health) 1 year	£84,805
PG/05/074/19101	Prof M R Wilkins MD FRCP Imperial College, London Erythropoietin and pulmonary hypertension 1 year 6 months	£110,509	PG/05/072/19092	Prof T W Meade CBE DM FRCP London School of Hygiene & Tropical Medicine, London The role of the haemostatic system in coronary heart disease 2 years	£71,147
PG/05/067/19012	Dr K S Authi BSc PhD King's College London Biochemical characterisation of the role and activation of TRPC1 and TRPC6 in megakaryocytic cells 3 years	£150,607	PG/05/071/19091	Prof A J L Clark MB BS MRCP Queen Mary, London Do glucocorticoid response elements direct the extent of DNA methylation in responsive genes during fetal programming events? 3 years	£183,653
PG/06/030/20579	Prof S D Brain BSc PhD King's College London Mechanisms involved in TRPV1 receptor-dependent vascular reactivity 3 years	£157,287	PG/06/048/20813	Dr R J Schilling MBBS MRCP Queen Mary, London Comparison of conventional with minimal catheter approaches for the mapping and ablation of cardiac arrhythmias: a randomised control trial 2 years	£93,364
PG/06/013/20291	Dr A C Brewer BSc PhD King's College London Transcriptional regulation of NADPH oxidase isoforms in the vasculature 2 years	£92,091	PG/05/093/19531	Dr S S Ye MB MD PhD Queen Mary, London Functional analyses of the MMP3 gene 5T/6T polymorphism that is associated with progression and complications of atherosclerosis 3 years	£142,751
PG/06/032/20349	Prof P J Chowienczyk BSc FRCP King's College London Arterial calcification, stiffening and bone mass density in female twins 2 years	£129,193	PG/05/114/19802	Dr C F Lawson BSc PhD Royal Veterinary College, London Role of anti-ICAM-1 antibodies in cardiovascular disease 2 years	£99,563
PG/05/138/20014	Prof A M Shah MD FRCP FESC FMedSci King's College London Investigation of the effects of neuronal nitric oxide synthase on human cardiac function <i>in vivo</i> 2 years	£126,719			

PG/05/117/19690

Dr A Afzal MD PhD
St George's, London
Study of stress genes and their effects on vascular inflammatory markers in a large twin cohort
2 years £202,365

PG/05/129/19885

Dr T F K Antonios MBChB MSc MD MRCP
St George's, London
The role of capillary rarefaction in the pathogenesis of essential hypertension and pre-eclampsia: insights from studies in pre-eclamptic women
2 years £111,595

PG/05/109/19699

Prof A J Camm MD FRCP FMedSci FESC FACC FCGC
St George's, London
Assessment of heart rhythm irregularity and haemodynamic status in patients with atrial fibrillation
2 years £134,859

PG/05/126/19870

Dr J E Cartwright BSc PhD
St George's, London
The role of soluble HLA-G in induction of endothelial apoptosis and uterine vascular remodelling in early pregnancy
3 years £199,833

PG/06/009/20255

Miss M Jahangiri MBBS FRCS
St George's, London
Ventricular function in valve disease – when does the ventricle fail irreversibly, and can this be detected by non-invasive imaging using strain rate echocardiography?
2 years £73,924

PG/05/101/19680

Prof W A Large PhD BPharm
St George's, London
Investigation into the expression, modulation and pharmacology of cGMP-dependent chloride channels in vascular myocytes
3 years £176,815

PG/06/036/20648

Prof M Malik MD PhD DSc
St George's, London
Quantitative evaluation of ventricular repolarisation abnormalities in standard resting electrocardiogram for prediction of long-term prognosis in the general population
2 years 6 months £235,504

PG/06/003/19604

Prof P H Whincup MB MSc PhD
St George's, London
Contributions of physical activity and fitness to emerging ethnic differences in cardiovascular disease risk: a study in children
2 years 6 months £70,722

PG/05/090/19444

Dr J L McGregor PhD DrBH
Thrombosis Research Institute, London
Functional genomics and cellular biology of CD36
2 years £117,446

PG/05/108/19695

Dr M Burch MB BChir MD FRCP
University College London
The relationship of endothelial damage and dysfunction to development of coronary allograft vasculopathy after cardiac transplant in children
2 years £147,510

PG/05/062/18991

Prof D F Cutler BSc PhD
University College London
Lysosome related organelles and vascular inflammation
3 years £141,916

PG/05/135/19913

Dr P M Elliott MBBS MRCP
University College London
Prevalence of sarcomeric protein gene mutations in children with unexplained left ventricular hypertrophy
2 years £126,252

PG/06/022/20348

Dr M Falasca BSc PhD
University College London
Role of class II phosphoinositide 3-kinase in endothelial cell functions
3 years £216,063

PG/05/049/18027

Dr S M Hall PhD
University College London
Association between regional differences in pulmonary arterial smooth muscle cell phenotype and force generation: cause and effect
2 years £74,493

PG/05/112/19747

Dr P D Lambiase MRCP
University College London
Electrophysiological characterisation of arrhythmogenic right ventricular cardiomyopathy in genetically affected probands and asymptomatic relatives using non-contact endocardial mapping
2 years £147,121

PG/05/080/19232

Dr R J MacAllister MBBS MD MRCP
University College London
Selective modulation of natriuretic peptide-mediated dilatation in the pulmonary vasculature: mechanism and therapeutic potential
3 years £150,623

PG/06/015/20305

Prof J S Owen BSc PhD
University College London
Low-toxicity oligonucleotides and delivery vehicles to optimise gene editing technology and create the natural atheroprotective phenotype, ApoAI-Milano
2 years £97,524

PG/05/118/19834

Dr A Stephanou MSc PhD
University College London
Role of autophagy in the ischaemic myocardium
2 years £106,904

PG/05/131/19887

Prof A Tinker MRCP PhD
University College London
The mechanism of abnormal trafficking of potassium channels in the pathogenesis of the hereditary Long QT syndromes
3 years £143,410

PG/06/019/20328

Dr B J Wojciak-Stothard MSc PhD
University College London
Role of Rho GTPases in nitric oxide-mediated cytoskeletal remodelling and barrier function in pulmonary endothelial cells *in vitro*
3 years £196,750

PG/05/054/18791

Dr A B Mackenzie BSc PhD
University of Bath
The role of ATP gated P2X7 receptors in endotoxin induced sepsis: pro-inflammatory signalling between the endothelium and monocytes
3 years £143,124

PG/06/014/20304

Dr A B Mackenzie BSc PhD
University of Bath
The functional expression of N-methyl D-aspartate glutamate-type receptors by megakaryocytes
3 years £169,072

PG/05/084/19286

Dr D Thompson BA MSc PhD
University of Bath
Inflammation in cardiovascular disease: does physical activity improve pro- and anti-atherogenic inflammation in newly diagnosed Type 2 diabetes?
2 years 6 months £117,440

PG/05/094/18735

Mr R S Bonser MRCP FRCS
University of Birmingham
Identification of heart donors using biochemical probes
2 years 6 months £273,588

PG/05/125/19869

Mr R S Bonser MRCP FRCS
University of Birmingham
Application of remote ischaemic pre-conditioning to human coronary artery bypass surgery (CABG)
2 years 6 months £131,152

PG/06/039/20697

Dr S Egginton BSc PhD
University of Birmingham
Co-regulation of angiogenesis by flow-generated shear stress and growth factors
2 years £108,267

PG/05/052/18478

Prof M P Frenneaux MRCP FRACP MD FACC FRCP FESC
University of Birmingham
Mechanisms by which biventricular and left ventricular pacing improve cardiac performance in patients with heart failure
2 years £148,783

<p>PG/05/053/18782 Prof M P Frenneaux MRCP FRACP MD FACC FRCP FESC University of Birmingham Diastolic ventricular interaction and the effects of biventricular pacing in hypertrophic cardiomyopathy 2 years £127,925</p>	<p>PG/05/066/19010 Dr S J George BSc PhD University of Bristol An <i>in vivo</i> investigation into the regulation of smooth muscle cell proliferation by β-catenin signalling 3 years £135,580</p>
<p>PG/05/087/19436 Prof M P Frenneaux MRCP FRACP MD FACC FRCP FESC University of Birmingham Perhexiline therapy in patients with hypertrophic cardiomyopathy 3 years £230,565</p>	<p>PG/05/103/19684 Dr S J George BSc PhD University of Bristol Regulation of vascular smooth muscle cell apoptosis by a C-terminal fragment of N-cadherin 2 years £76,193</p>
<p>PG/06/007/20246 Dr D Hauton BSc PhD University of Birmingham Metabolism and the hypertrophied heart: the role of fatty acids and triacylglycerol in cardiac metabolism and dysfunction 3 years £135,367</p>	<p>PG/06/042/20700 Prof J C Hancox BSc PhD University of Bristol Investigation of the molecular basis of HERG potassium channel blockade by amiodarone and its relatives 3 years £147,808</p>
<p>PG/06/044/20703 Mr D Pagano MD FRCS University of Birmingham Metabolic support with perhexilene to protect myocardium undergoing coronary surgery 3 years £185,855</p>	<p>PG/05/143/20104 Dr A F James BSc DPhil University of Bristol Atrial remodelling in spontaneously hypertensive rats: effects of angiotensin receptor blockade 3 years £187,394</p>
<p>PG/06/040/20698 Dr C M Ring MA PhD University of Birmingham Cognitive function in hypertension 3 years £148,346</p>	<p>PG/06/033/20633 Dr A F James BSc DPhil University of Bristol Atrial remodelling in rats with increased afterload due to banding of the ascending aorta 2 years £108,726</p>
<p>PG/05/134/19908 Prof S P Watson BSc PhD FMedSci University of Birmingham Studies on three novel platelet membrane signalling proteins 3 years £152,258</p>	<p>PG/06/035/20641 Prof P Madeddu MD University of Bristol New insights into the mechanisms of kallikrein-induced neovascularisation: role of metalloproteinases and PI3K-Akt pathway 3 years £165,587</p>
<p>PG/06/038/20658 Prof S P Watson BSc PhD FMedSci University of Birmingham Contribution of the P2Y₁₂ ADP receptor to mild bleeding disorders 2 years £79,706</p>	<p>PG/05/098/19595 Dr H Mellor BSc PhD University of Bristol Control of pro-angiogenic signals through the regulation of VEGF receptor-2 trafficking 3 years £131,520</p>

PG/05/121/19842		PG/06/028/20552	
Prof C H Orchard BSc PhD		Dr M P Mahaut-Smith BSc PhD MA	
University of Bristol		University of Cambridge	
Cardiac t-tubule function in health and disease		Molecular identification and activation mechanisms of	
3 years	£181,528	cation-permeable channels in the platelet and	
		megakaryocyte	
		3 years	£125,001
PG/05/142/20101		PG/06/023/20353	
Dr R M A Sitsapesan MSc PhD		Prof G Murphy BSc PhD	
University of Bristol		University of Cambridge	
Investigating the impact of SR load and phosphorylation		Post-ischaemic endothelial repair: the roles of	
on ryanodine receptor mutations associated with		aminopeptidase N and membrane type 1 (MT1) MMP and	
arrhythmias and sudden death		their interactions in angiogenesis	
3 years	£149,243	3 years	£145,724
PG/05/070/19090		PG/05/139/20026	
Prof A R Wolf MA MB BChir MD FRCA		Dr K M O'Shaughnessy BM BCh DPhil MRCP FRCP	
University of Bristol		University of Cambridge	
Is perinatally programmed hypertension a consequence of		Investigation into the molecular genetics of large artery	
autonomic nervous system dysfunction?		stiffening: a candidate gene based approach	
3 years	£153,226	2 years	£135,156
PG/06/024/20354		PG/05/122/19843	
Prof M R Bennett BSc MA MBChB PhD FRCP		Dr D A Slatter MA PhD	
University of Cambridge		University of Cambridge	
Selective vascular smooth muscle cell death in		Characterisation of platelet binding to collagen IV using	
atherosclerosis		synthetic peptides	
3 years	£160,383	2 years	£125,041
PG/05/127/19872		PG/06/004/19848	
Dr A P Davenport BSc PhD		Dr A Zhou PhD	
University of Cambridge		University of Cambridge	
Characterisation and function of the novel trace amine		Vitronectin and the regulation of fibrinolysis and	
receptor, TA1 and its ligand tyramine in the human		coagulation	
cardiovascular system		2 years	£91,021
3 years	£189,994	PG/05/051/18422	
PG/05/083/19261		Prof W H Evans PhD	
Dr D P Dutka MD MRCP		University of Cardiff	
University of Cambridge		A stem cell approach to cardiac repair	
The effects of insulin on ischaemic left ventricular		2 years	£82,507
dysfunction in patients with coronary artery disease with			
and without Type 2 diabetes mellitus		PG/05/133/19892	
2 years	£103,481	Prof T M Griffith MA MRCP	
PG/05/081/19235		University of Cardiff	
Dr J L Griffin BA DPhil		Analysis of the inhibitory effects of nitric oxide and cGMP	
University of Cambridge		on gap junctional communication and the EDHF	
Defining the influence of peroxisome proliferator-		phenomenon	
activated receptors (PPARs) on the metabolome of the		3 years	£161,598
mouse heart			
3 years	£168,970		

<p>PG/05/110/19743 Dr J E Hall MBChB FRCA MD University of Cardiff Novel haemostatic assays to predict bleeding in cardiac surgery 2 years £13,808</p>	<p>PG/05/091/19511 Prof D J Webb MBBS MD FRCP University of Edinburgh Endothelin receptor antagonism as a therapeutic target in chronic kidney disease 2 years £151,085</p>
<p>PG/05/063/18995 Prof F A Lai BSc PhD University of Cardiff Human cardiac ryanodine receptor mutations associated with arrhythmogenesis and sudden cardiac death – the role of the redox status 3 years £145,709</p>	<p>PG/06/031/20581 Prof D J Webb MBBS MD FRCP University of Edinburgh Investigation of endothelin-1-mediated regulation of blood pressure and renal haemodynamics through cell type-specific knockout of endothelin B receptors 3 years £182,261</p>
<p>PG/05/077/19210 Prof F A Lai BSc PhD University of Cardiff Structure-function of the human cardiac calcium release channel interaction with immunophilin 3 years £138,089</p>	<p>PG/05/097/19593 Prof A H Baker BSc PhD University of Glasgow Evaluation of sustained efficacy of venous bypass graft gene therapy 2 years £59,787</p>
<p>PG/05/055/18794 Dr B Latinkic BSc PhD University of Cardiff Characterisation of cardiac differentiation in <i>Xenopus</i> explants 2 years £118,489</p>	<p>PG/05/075/19122 Dr R Lindsay MBChB MRCP PhD University of Glasgow Programming of later adiposity, glucose tolerance and cardiovascular risk in offspring of mothers with Type 1 diabetes 3 years £139,749</p>
<p>PG/05/123/19851 Dr D P Ramji BSc PhD University of Cardiff Intracellular signalling pathways activated by agonists of liver-X-receptors in macrophages 3 years £130,426</p>	<p>PG/05/130/19886 Dr C Loughrey BVMS PhD MRCVS University of Glasgow Cellular basis for arrhythmias: the inter-relationship between calcium transients and calcium waves in cardiac muscle 3 years £173,954</p>
<p>PG/05/069/19089 Prof A D Struthers MD FRCP FESC University of Dundee Exploring the therapeutic potential of xanthine oxidase inhibitors in coronary artery disease 2 years 6 months £183,839</p>	<p>PG/06/029/20577 Dr X Y Luo BEng MSc PhD University of Glasgow Towards a better understanding and design of mitral bioprosthesis 2 years £63,001</p>
<p>PG/06/005/20233 Dr M E Diaz BVSc MSc PhD University of Edinburgh Characterisation of the effects of myocardial iron toxicity at the cellular level 3 years £139,896</p>	<p>PG/06/016/20312 Dr J G McCarron BSc PhD University of Glasgow Ca²⁺ store organisation, luminal regulation and IP₃ receptor-evoked Ca²⁺ release in vascular smooth muscle 2 years £107,077</p>

PG/05/140/20094 Prof J C McGrath BSc PhD University of Glasgow Isolation and analysis of each of the three vascular α 1-adrenoceptor subtypes using double α 1-adrenoceptor knockout mice 3 years £156,660	PG/06/006/20236 Dr L A Tskhovrebova PhD University of Leeds Structure of titin molecule – spatial conformation of the eleven-domain super-repeat 3 years £150,786
PG/05/050/18155 Dr C M Wright MSc MD University of Glasgow What determines leanness and fatness in childhood and how do they track over time? 1 year 6 months £88,873	PG/06/012/20287 Dr N A Turner BSc PhD University of Leeds Expression, regulation and function of p38 MAP kinase subtypes in human cardiac myofibroblasts 3 years £133,155
PG/06/043/20702 Prof J G F Cleland FRCP FESC University of Hull Metformin against gliclazide in patients with diabetes and heart failure 2 years £129,289	PG/06/011/20283 Dr I C Wood BSc PhD University of Leeds Regulation of gene expression and smooth muscle function by repressor element 1-silencing transcription factor 2 years £115,903
PG/05/060/18984 Dr J F X Ainscough BSc PhD University of Leeds Conditional over-expression of human AT1 receptors in the adult mouse heart 2 years 6 months £158,022	PG/06/017/20320 Dr R J Evans BSc DPhil University of Leicester The contribution of lipid rafts to the regulation of P2Y receptors in the cardiovascular system 2 years £75,922
PG/06/047/20812 Dr S C Calaghan BSc PhD University of Leeds The role of caveolae in mechanotransduction in the adult heart: location, translocation, interaction and functional significance of stretch-activated signalling components 3 years £193,729	PG/05/099/19600 Dr M Hussain BSc PhD University of Liverpool Mechanisms responsible for the increased functional reserve in compensated hypertrophy 2 years £90,298
PG/05/124/19868 Dr S Ponnambalam BSc PhD University of Leeds The role of VEGF receptor 2/KDR trafficking, recycling and proteolysis in the regulation of VEGF-A signalling and endothelial function 3 years £130,903	PG/05/065/18997 Dr M Y Alexander BSc PhD University of Manchester A study to understand the structural and functional aspects of C15, a novel gene involved in vascular calcification 1 year £41,223
PG/05/059/18980 Dr D S Steele BSc PhD University of Leeds Properties of sub-cellular Ca^{2+} release sites contributing to nuclear Ca^{2+} regulation in myocardial cells 3 years £192,765	PG/05/088/19439 Dr C E Austin BSc PhD University of Manchester Extravascular pressure as a modulator of human resistance artery tone: modulation in normal and compromised pregnancy 2 years £77,228

PG/05/058/18979 Dr M P Burnham BSc PhD University of Manchester Redox-sensitivity of endothelial Ca ²⁺ -activated K ⁺ channels 3 years £143,905	PG/05/137/19999 Prof P M W Bath MB BS MRCP University of Nottingham Effect of an angiotensin receptor antagonist on cerebral blood flow, cerebral perfusion pressure and systemic and peripheral haemodynamics in patients with recent cerebrovascular disease 2 years 6 months £144,072
PG/05/079/19225 Dr I T Johnson BSc PhD University of Manchester Role and contribution of KCNK and K _v potassium channels in setting resting membrane potential in vascular myocytes 3 years £132,095	PG/05/104/19689 Prof S M Gardiner BSc PhD DSc University of Nottingham Cardiovascular function in endotoxaemia: influence of changing temporal and regional interactions between adrenomedullin, adenosine and ATP-sensitive potassium channels 3 years £114,440
PG/05/061/18990 Dr L C Kenny MBCh MRCOG University of Manchester Rational metabolome datamining for robust biomarkers of diagnostic and prognostic value in pre-eclampsia 3 years £164,333	PG/06/021/20345 Dr S Loughna BSc PhD University of Nottingham Rapid knockdown of developmentally important cardiac genes 3 years £188,935
PG/06/018/20326 Dr M I Mackness BSc PhD University of Manchester Antiatherogenic properties of paraoxonases 2 and 3 1 year 6 months £41,543	PG/05/141/20098 Dr N J Alp BSc MD FRCP University of Oxford Mechanisms of intracellular tetrahydrobiopterin generation and oxidation in the regulation of endothelial nitric oxide synthase activity 3 years £175,053
PG/05/119/19835 Dr D A Middleton DPhil BSc University of Manchester Further studies on the structure of sarcolipin, an atrial-specific regulator of calcium cycling in cardiac cells 1 year £47,093	PG/05/085/19330 Prof C C Ashley MA DSc PhD University of Oxford Understanding the mechanical defects in sarcomeric protein cardiomyopathies using force measurements on single cardiac myocytes 3 years £133,779
PG/05/082/19236 Prof L Neyses MD University of Manchester Generation and initial characterisation of a conditional cardiac specific gene deletion of the sarcolemmal calcium pump (PMCA1) 3 years £149,408	PG/05/064/18996 Dr B Casadei MD MRCP University of Oxford nNOS-mediated regulation of myocardial Ca ²⁺ fluxes and its relevance to the pathogenesis of heart failure 2 years 6 months £177,108
PG/05/056/18803 Dr H M Arthur BSc PhD University of Newcastle The role of TGF- β and TAK1 signalling in cardiac hypertrophy 3 years £147,713	
PG/06/046/20800 Prof M Walker MD FRCP University of Newcastle Investigation of the genetic basis of abdominal obesity 2 years £119,759	

PG/05/076/19124

Prof K M Channon MD MRCP
University of Oxford
Haemodynamic regulation by nitric oxide in exercise training: relative importance of nitric oxide synthase isoforms and enzymatic coupling
2 years £143,426

PG/05/113/19793

Dr R J Clarke MRCP
University of Oxford
Genetically-enriched case-control study of coronary heart disease
1 year £186,779

PG/05/073/19097

Prof P A Handford BSc PhD
University of Oxford
Analysis of normal FBN1 gene expression in control and Marfan syndrome patients – a potential marker of susceptibility to aortic disease
1 year £48,810

PG/06/045/20780

Prof R K Patient BSc PhD
University of Oxford
Genetic regulatory networks driving developmental induction of the myocardium
3 years £176,265

PG/05/115/19435

Dr J E Schneider PhD
University of Oxford
Development of proton magnetic resonance spectroscopy in human heart at 3 tesla
3 years £141,964

PG/06/020/20343

Dr J Selvanayagam BSc MBBS FRACP
University of Oxford
A comparison of myocardial perfusion imaging with cardiovascular magnetic resonance at 1.5T and 3T
2 years £147,363

PG/05/068/19057

Prof J R Stradling MD FRCP
University of Oxford
Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular study (MOSAIC)
3 years £151,653

PG/05/057/18975

Prof H W Watkins MD PhD FRCP FMedSci
University of Oxford
The role of altered cardiac energetics in conditions mimicking sarcomeric hypertrophic cardiomyopathy
1 year £63,749

PG/05/107/19694

Prof D C Crossman MD FRCP FACC FESC
University of Sheffield
Mechanisms regulating risk of myocardial infarction following infection
3 years £129,651

PG/05/100/19606

Dr E Kiss-Toth MSc PhD
University of Sheffield
Regulation of mitogen activated protein kinase signalling by the JIP family of scaffolding proteins in vascular smooth muscle cells
3 years £132,302

PG/05/095/19009

Dr R F Storey MSc MRCP
University of Sheffield
Studies of platelet P2Y₁₂ antagonism: receptor blockade with clopidogrel, inhibition of platelet-mediated inflammatory responses and interaction with $\alpha_{IIb}\beta_3$ receptor antagonists
2 years £126,320

PG/05/106/19693

Prof M A Hanson MA DPhil FRCOG
University of Southampton
A role for ER α in programming vascular dysfunction in offspring of rat dams fed a low protein diet during pregnancy
3 years £186,413

PG/05/078/19218

Prof D I Wilson MBBS MRCP
University of Southampton
Isolating a gene for hypoplastic left heart disrupted by a balanced chromosome translocation
3 years £139,932

PG/05/128/19884

Dr A M Evans BSc PhD

University of St Andrews

Nicotinic acid adenine dinucleotide phosphate and cyclic adenosine diphosphate-ribose: do these synergistic, convergent Ca²⁺ signalling pathways underpin hypoxic pulmonary vasoconstriction?

3 years

£142,856

PG/05/086/19382

Dr K A Matyka MD MRCP

University of Warwick

The role of reduced physical fitness in cardiovascular disease risk in South Asian children

3 years

£128,369

PG/06/001/19888

Prof V A Zammit MSc DPhil DSc

University of Warwick

Role of DGAT 1 and 2 expression in cardiac muscle triglyceride synthesis and secretion

3 years

£164,815

PG/05/048/17923

Dr G Furze BSc PhD RN

University of York

The development and evaluation of a lay-facilitated angina management programme (LAMP)

3 years

£152,460

Analysis of funding of Project Grants, 2001/2002 – 2005/2006 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	2001/2002	2002/2003	2003/2004	2004/2005	2005/2006	TOTAL (5 years)	% of total funding
Biochemistry	£3,984,862 (30)	£4,006,692 (34)	£2,866,735 (26)	£3,405,687 (25)	£4,197,106 (30)	£18,461,082 (145)	18.91
Clinical cardiology and diagnosis	£1,620,282 (15)	£377,378 (4)	£348,901 (3)	£884,332 (7)	£2,065,072 (13)	£5,295,965 (42)	5.43
Epidemiology	£1,764,524 (16)	£2,906,241 (27)	£3,139,913 (24)	£2,494,365 (19)	£2,458,646 (18)	£12,763,689 (104)	13.07
Genetics	£1,529,512 (13)	£763,988 (4)	£795,549 (6)	£858,451 (7)	£715,601 (6)	£4,663,101 (36)	4.78
Hypertension	£901,674 (9)	£178,821 (2)	£902,817 (6)	£962,549 (8)	£671,365 (5)	£3,617,226 (30)	3.71
Immunology	£334,385 (3)	£254,268 (2)	£430,191 (3)	£195,869 (2)	£308,719 (2)	£1,523,432 (12)	1.56
Paediatric cardiology	£469,598 (4)	£588,217 (4)	£1,394,661 (10)	£33,923 (1)	£631,633 (4)	£3,118,032 (23)	3.19
Pathology	£1,906,572 (18)	£1,986,349 (15)	£1,132,606 (11)	£1,509,287 (11)	£690,927 (6)	£7,225,741 (61)	7.40
Physiology, electrophysiology and anatomy	£4,418,433 (41)	£6,345,518 (52)	£5,172,337 (39)	£4,010,487 (30)	£6,470,879 (43)	£26,417,654 (205)	27.06
Surgery	£89,582 (1)	£216,763 (2)	£300,690 (2)	£630,941 (5)	£278,671 (4)	£1,516,647 (14)	1.55
Techniques and instrumentation	£172,747 (1)	£123,250 (2)	£436,122 (5)	£149,664 (1)	£63,001 (1)	£944,784 (10)	0.97
Thrombosis and atherosclerosis	£1,607,501 (14)	£1,424,270 (13)	£1,942,121 (17)	£2,119,304 (16)	£1,025,841 (9)	£8,119,037 (69)	8.32
Treatment and pharmacology	£1,340,022 (10)	£1,161,638 (10)	£1,174,191 (8)	(0)	£277,405 (2)	£3,953,256 (30)	4.05
TOTAL	£20,139,694 (175)	£20,333,393 (171)	£20,036,834 (160)	£17,254,859 (132)	£19,854,866 (143)	£97,619,646 (781)	100

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