



# National Institute for Health Research

## NIHR BIOMEDICAL RESEARCH UNITS

### FULL APPLICATION FORM

**Note:** The accompanying *NIHR Biomedical Research Units - Invitation to Submit Full Application* contains essential guidance on the information you need to provide when completing this proforma.

Please complete the form using a font size no smaller than 10 point (Arial).

#### 1. AREA OF RESEARCH

Indicate the specific priority area in which the partnership wishes to be considered for an NIHR Biomedical Research Unit:

Cardiovascular disease

#### 2. DETAILS OF THE PARTNERSHIP AND FORMAL AUTHORISATION

**Name and address of the NHS Organisation:**

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**Signature:** ..... **Date:** .....

**Name, job title and address of the individual who is authorising this application on behalf of the NHS Organisation (eg Chief Executive):**

Mr Julian Nettel, Chief Executive, Barts and The London NHS Trust.

**Signature:** ..... **Date:** .....

**Name and address of the University:**

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**Name, job title and address of the individual who is authorising this application on behalf of the University (eg Vice Chancellor or Dean):**

**Prof Sir Nicholas Wright FMedSci** Warden, Barts and The London School of Medicine and Dentistry,  
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**Signature:** ..... **Date:** .....

### 3. EXCELLENT BASIC BIOMEDICAL RESEARCH

#### **Internationally excellent pharmacology at Barts and The London: the engine for translation.**

At **Barts and The London NHS Trust [BTL]** and the **BTL School of Medicine and Dentistry**, our internationally excellent strengths in basic cardiovascular science are co-located within the William Harvey Research Institute (WHRI), so that together, they can generate translate concepts into clinical care within the adjacent St Bartholomew's Hospital Cardiovascular Centre and our ethnically diverse East London Community. WHRI is ranked in the top 20 Pharmacological Institutes worldwide (*isicited.com* 2006). Our strategy has been to create a translational hub where 240 clinicians and scientists integrate cardiovascular genetics, stem cell biology, pharmacology, inflammation research, epidemiology and large-scale trials to create a flow of concepts from the bench into the clinic ([www.whri.qmul.ac.uk](http://www.whri.qmul.ac.uk)). Since 2001 WHRI has spent £38.5M on research and in the past 3 years our staff have published over 22 papers in Nature Journals, Science, the New England Journal of Medicine and the Lancet which have led to changes in National and International guidelines for CV clinical care. This presents an excellent environment for creating and testing novel therapies which could apply across the UK population and the international community.

#### **BTL pharmacological strengths- the research engine for translation**

In this partnership, we have created a unique CV pharmacology environment that provides the basic science research engine that with NIHR funding will drive translational step change. As a partnership we have taken steps to accelerate translation of CV therapies by attracting new translational faculty and establishing state of the art, core facilities in genomics, proteomics, biological services and flow cytometry. Additionally, we have invested in small animal in-vivo imaging and microscopy with intravital microscopy, spinning disc confocal microscopy and 2- photon microscopy which offers high resolution tissue characterisation of molecular targets. This is complemented by small animal echocardiography, microPET/CT and NanoSPECT/CT where we have in house radiochemistry/radiopharmacy expertise to allow molecular and functional imaging of new therapies and tracking of engraftment of stem cells in experimental models. To ensure that the generation of new chemical entities will not limit our translational ambition we have initiated collaboration with Advinus (Tata Pharmaceuticals, India) that offers access to high quality molecular modelling, medicinal chemistry and toxicology.

#### **Specific basic science programmes relevant to this BRU proposal:**

##### **1. Genetics of hypertension and coronary disease– Caulfield FMedSci with Munroe and Ye.**

Our cardiovascular genetics programme is geared to identification of novel genes, biomarkers and drug targets using large-scale hypertensive and coronary artery disease resources. **Local and National Partnerships:** Caulfield and Munroe lead the British Genetics of Hypertension (BRIGHT) study elucidating the genes causing high blood pressure and associated phenotypes for 5 other UK Universities (MRC, BHF, and Wellcome Trust funded, £3.8m). Our genomewide linkage and association scans (*Lancet*, 2003) as part of the Wellcome Trust Case Control Consortium (*Nature*, 2007) coupled with our candidate studies have identified potential cardiovascular drug targets for further investigation (Caulfield is Co-PI £16M 2005-2009). In a complementary coronary artery disease functional genomics programme Ye is studying matrix metalloproteinases in atherosclerosis (*Hum Mol Genetics*, 2007 and *Circ Research*, 2005). Ye, Caulfield and Munroe are part of a London wide collaborative (led by Hingorani at UCL) to replicate findings from genome scans and candidate studies. **International Partnerships:** Caulfield and Munroe lead a global meta-analysis of 33,000 blood pressure scans and have marshalled 65,000 subjects' DNA for replication of top signals placing the UK in a leading position in worldwide genetics of hypertension research. With Pfizer Pharmacogenomics Caulfield established a genetic repository from the ASCOT Trial and a genomewide scan of drug response to antihypertensives and statins is underway. In coronary disease Ye is collaborating with INSERM and the Karolinska Institute to understand functional effects of coronary disease genes. **Relevance to BRU proposal:** This will prime discovery of new biomarkers and targets for development within experimental models and if safe for translation into man.

##### **2. Cardiovascular stem cell therapy– Suzuki with Mathur, Rothman and Thiernemann FMedSci.**

At Barts and The London we implemented recommendations of the UK Stem Cell Research Initiative to establish centres where translational stem cell research is underpinned by strong basic science programmes and have appointed Suzuki, an MRC Senior Clinical Fellow, with an international reputation in this field (*Circulation* 2007 & 2004x2, *J Cell Biol* 2007, *Circ Res* 2007, *FASEB* 2006 & 2004, *PNAS* 2004). **Local and National Partnerships:** Suzuki holds an MRC Collaborative Grant to investigate insulin like growth factor 1 in heart failure and cell therapy (£600k with Rosenthal, Imperial College London/EMBL Rome). Our programme is focused upon the behaviour of grafted cells in a cardiac environment and the interaction between native cardiomyocytes and grafted adult and embryonic stem cells at genetic, molecular and cellular levels with the goal of improved graft quality and therapeutic efficiency. This group have developed several new cell-delivery methods that can be applied to clinical settings, including

retrograde intracoronary injection. This strongly complements the UK's largest clinical programme (800 cases in 5 years) led by Mathur (*Lancet 2004, PNAS 2004*) and permits rapid translation of basic science into humans. **International Partnerships:** We are testing cell sheet technology with Sawa and Okano at Osaka and Tokyo Women's Universities and this novel programme has enabled us to attract faculty committed to translation e.g. Yashiro (new Lecturer) who published on cardiac development in *Nature 2007 and Developmental Cell 2004 & 2006*. **Relevance to BRU proposal:** Our stem cell studies offer a key translational programme for this BRU (see section 1 in the research plan).

### **3. Vascular pharmacology – Ahluwalia with Webb and Hobbs.**

Our discovery that nitrite is protective in ischaemia-reperfusion injury demonstrated the cardiovascular potential of this alternative source of nitric oxide (*PNAS 2004, JASN 2007*). **Local and National Partnerships:** We have harnessed this potential by demonstrating that ingestion of nitrate in the form of beetroot results in a powerful hypotensive effect in humans that is due to bioconversion to nitrite (*Hypertension 2008*). In a separate Wellcome Trust Strategic Translational Programme (£750K) Ahluwalia and Hobbs are developing natriuretic peptide c-mimetics as medications that offer potent cardiovascular protective actions including prevention of clot formation, inhibition of the inflammatory processes associated with atherosclerosis and hypotensive actions (*PNAS 2003, Circulation 2004, PNAS 2004*). **Relevance to BRU:** Our studies on nitrite in cardiovascular disease will be a strong translational programme within this BRU (see section 2 and 3 in the research plan).

### **4. Protecting organs against ischemia-reperfusion (IR) injury and leukocyte transmigration – Perretti, Flower FRS, Nourshargh and Thiemermann FMedSci.**

We have three complimentary but distinct strategies for protecting against vascular inflammation and IR injury that offer strong translational potential within this BRU.

**4.1 Annexin biology - Local and National Partnerships:** With Wellcome Programme and Principal Fellowship funding Perretti and Flower identified and patented annexin 1, and its specific G-protein coupled receptor, termed ALX, as major effectors of endogenous anti-inflammation (*Nature Med 1996; 2002*). These discoveries enabled development of short annexin 1-derived peptides with therapeutic potential (*J Leukoc Biol, 2004*) in experimental systems of IR injury (*Faseb J 2001; 2005, 2007, Blood 2003*). **International Partnerships:** Following limitation of infarct size in the heart and brain in experimental models we commercialised our work with Unigene Corp. (\$1.2M) and are developing annexin 1 mimetics (short ≤ 24 amino acid peptide) to control ischaemia-reperfusion injury.

**4.2 EPO analogues - Local and National Partnerships:** Our aim is to discover novel drug targets to treat the injury caused by ischaemia-reperfusion (heart, kidney, brain) and we recently demonstrated (*JASN, 2004; Kidney Int., 2004*) that erythropoietin (EPO) protects the kidney against ischaemia and reperfusion injury. These effects were not related to an increase in haematocrit, but secondary to tissue protection. Most notably, EPO causes a 50% reduction in mortality in critically ill patients with trauma and haemorrhage but the clinical utility of EPO is limited by increased haematocrit. **International Partnerships:** To address these limitations Thiemermann is collaborating with the Warren Institute in New York (Cerami & Brines) to develop novel EPO analogues with tissue-protective effects in the heart, Kidney and brain.

### **4.3 Mechanisms of leukocyte transmigration-Nourshargh**

**Local and National Partnerships:** This Wellcome Trust funded programme (900K) dissects the molecular interactions mediating leukocyte emigration through vessel walls with the aim of identifying new anti-inflammatory targets. Our work investigates novel approaches to anti-inflammatory therapeutics based upon inhibiting leukocyte migration through endothelial and post-endothelial cell barriers (*Nature Rev Immunology, 2007, Trends in Immunol. 2005*). We have demonstrated functional roles for certain endothelial cell junctional molecules, eg PECAM-1, ICAM-2 and JAM-A, in regulation of leukocyte emigration into inflamed tissues including in response to ischaemia reperfusion injury (*J Exp Med., 2002 & 2006; Blood 2006 & 2007*). **International Partnerships:** Following our discovery of a key role for the endothelial cell junctional molecule JAM-C in leukocyte transmigration (*J Immunol., 2005 and ATVB, 2007*) and in the function of peripheral nerves (*Science, 2007*), we are investigating these factors as a source of novel drug targets for ischaemia reperfusion injury with Imhof (University of Geneva).

**Relevance to BRU proposal:** This programmes offer molecules at advanced pre-clinical development or ready to enter phase 1 (annexin and EPO analogue) and in leukocyte transmigration a programme at an early discovery level which offers new concepts for translation within this BRU (section 2 of research plan).

These programmes will fuel translational research in this proposed BRU with the goal of patient benefit.

#### 4. STRATEGY FOR TRANSLATING BASIC BIOMEDICAL RESEARCH INTO EXCELLENT CLINICAL RESEARCH FOR THE BENEFIT OF PATIENTS

##### The BTL Cardiovascular (CV) Translational Research Partnership.

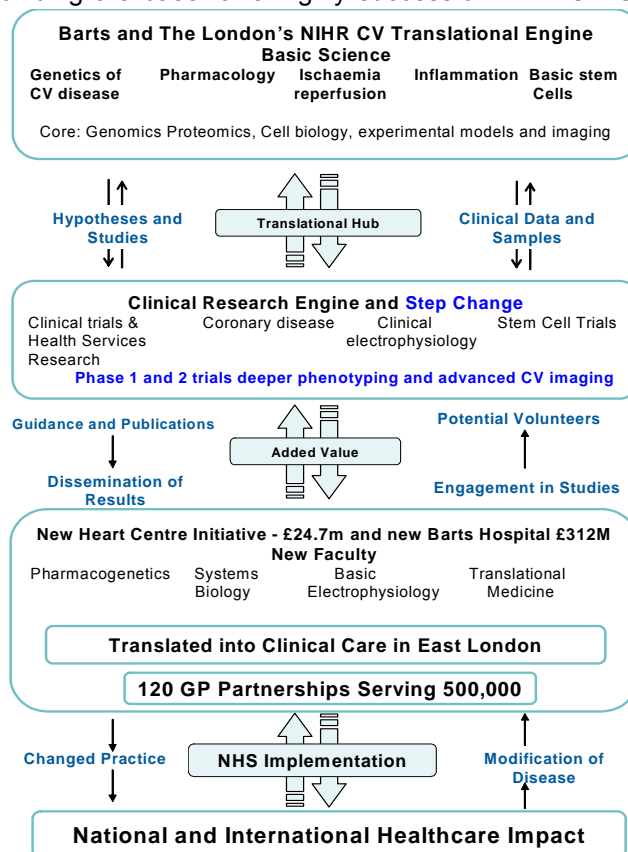
The strategic translational research partnership which underpins this proposal is based on clinical and academic excellence at BTL. The **BTL NHS Trust** has been consistently rated among the top teaching hospital trusts in the UK for clinical excellence ([www.bartsandthelondon.nhs.uk](http://www.bartsandthelondon.nhs.uk)). Our mission statement is “bringing excellence to life” delivered by providing care for a richly diverse, East London Community of 1.56M people, set to grow by 350K by 2016, and who suffer some of the worst rates of CV disease in the UK ([www.heartstats.org.uk](http://www.heartstats.org.uk)). The unique racial and ethnic diversity of our local population means that our research findings can be generalised to the UK as a whole, and beyond. Our translational research programme will benefit from the stellar facilities being created through a £1bn PFI scheme to rebuild St Bartholomew’s and The Royal London Hospitals, where our 6800 staff deliver care in 99K inpatient episodes and 518K outpatient episodes per year. Our university partner, **BTL School of Medicine and Dentistry**, trains 300 doctors and 75 dentists each year and has transformed its research performance with income rising from £18.7M in 2002-03 to £42M projected in 2007-08, exceeding some Russell Group Medical Schools. Since 2002 we have focused joint investment upon **strengthening CV therapeutic innovation** as a key translational research theme across the University/NHS partnership.

##### BTL create the governance framework for a successful NIHR CV Biomedical Research Unit (BRU).

We have made significant progress toward providing the base for a highly successful NIHR CV Centre.

We have created an Academic Health Sciences Centre and established a CV Clinical Academic Unit and applied for Foundation Trust status. This offers a unified management and governance framework across the University and NHS Trust partnership which is vital to the success of this NIHR proposal.

The CV clinical service at BTL delivers the largest number of revascularisations in the UK (2700 percutaneous and 1500 surgical revascularisations), thus providing an excellent patient base for translational research. This has been greatly enhanced by investment in the BTL Trust’s 24/7 Heart Attack Centre (NHS service), which is now revascularising 755 ST elevation (STEMI) and non- STEMI patients per year adding depth to our research platform. In addition, with the assistance of the Barts and The London Charity the NHS Trust has installed a £2M Cardiac 1.5T MRI suite next to the Heart Attack Centre and have funded an NHS CV Imaging consultant to lead service delivery. These significant service developments greatly enhance the environment for our translational research.



##### Investment in a new Translational Heart Research Centre.

A major strength of this proposal is the commitment by our University partner to deliver an internationally competitive CV translational research programme, confirmed by recent investment of £2.4M to appoint leading faculty (Suzuki and Nourshargh) and in a new **£24.7M Heart Research Centre** (£18.7M in building and £6M in new faculty) with the ambition of developing novel cardiovascular therapies. This 3172m<sup>2</sup> Heart Research Centre provides a joint NHS/University clinical research facility at ground level with extensive translational laboratory space over 3 floors. The new Chairs e.g. basic electrophysiology, vascular pharmacogenetics, cardiovascular systems biology and translational medicine (not shown in the figure) provide distinct basic strengths matched to clinical priorities and offer new translational depth to research. The Heart Research Centre will open in 2009 in juxtaposition to the new St Bartholomew’s Hospital Cardiac Centre (£312M) providing the shared physical environment for our proposed CV BRU translational programme.

### **Proposed step change in Translational Research arising from this BRU initiative.**

We have focused our shared objectives for this revised BRU bid upon making a major step change in translation from our unique pharmacological research engine into CV care by developing novel approaches and infrastructure to intensively phenotype patients in early phase studies;

1. By creating an **innovative advanced CV imaging programme** aimed at developing and optimising strategies for imaging in early phase translational research;
2. By enabling deeper phenotyping in early phase translation through a **new CV clinical research facility**;
3. By creating state of the art **integrated bioinformatics infrastructure** with NHS information systems.

This will transform our ability to create novel approaches to **high fidelity, intensive phenotyping in early phase translation of novel CV therapies** by developing and optimising advanced imaging approaches. The enhanced information capture from these early studies could significantly accelerate translation and add value to our programmes in stem cell therapy, ischaemia reperfusion injury and nitrites in CV prevention. This will combine excellence within the WHRI with our high cadre NHS CV specialists in a translational programme which can fully capitalise upon our clinical base for broader patient benefit. This will create a unique pharmacological training environment from which to train a new cadre of translational CV clinicians and scientists and increase much needed UK capacity in CV imaging for patient benefit.

**1. Advanced CV imaging.** The major focus of this proposal is the creation of an advanced CV imaging centre (high cadre imaging team, training posts and imaging hardware) to enable step change in deeper phenotyping of patients across our translational programmes of novel therapies e.g. molecular localisation and CV functional effects of novel compounds in the prevention of ischaemia reperfusion injury and stem cell therapeutic trials. Our goal is that the application of deeper phenotyping will serve as a platform for advanced imaging research to develop innovative molecular and functional imaging approaches using our new 1.5T CV MRI, 64-slice time-of flight PET/CT (both exist but need academic capacity to be developed alongside a translational programme) and the 256-CT scanner requested herein. This will add value to our existing strengths in functional and molecular SPECT/CT and PET/CT imaging led by Avril (new co-applicant) and Mather (molecular imaging plus radiopharmaceutical expertise- collaborator).

**Human capacity:** We propose to use the BRU to create a high cadre integrated CV imaging team led by an international researcher at Chair level supported by a senior lecturer (both honorary consultants). To accelerate translation we propose to use this initiative to build the essential depth of a multidisciplinary imaging team including; a research physicist (skilled in kinetic modelling of contrast and tracer agents) research radiographer (expertise in MR/CT), an imaging administrator, 2 academic clinical fellows in imaging funded for one full year to capture pilot data for substantive fellowships from MRC, NIHR or charities (6 x one year fellowships for junior doctors at ST3 level), and a secretary/receptionist to both meet and greet patients and support the academic posts. This integrated team will be expected to lead and develop national and international multidisciplinary imaging research and training capacity through educational and training initiatives. The team will closely interact with existing resources in Radiology, Nuclear Medicine, and Radiochemistry/Radiopharmacy to optimise the research and clinical applications of cardiovascular CT, MRI, SPECT/CT and PET/CT.

**Imaging infrastructure and consumables** – We have created an advanced imaging suite next to our Heart Attack Centre containing a new 1.5T MRI supported by 2 NHS consultants. Our present CT capability is greatly limited by an old 4 slice scanner and we have therefore costed a 256 slice scanner in to this proposal, to establish a state of the art translational research facility. With access to local cyclotron provision in London we can access radiotracers. We have therefore costed a contribution from this BRU toward a rhenium generator to generate agents to undertake CT/PET perfusion studies described later. We have also requested funds for scans on each modality to allow capture of pilot data to seed translational or imaging development grant applications and to deliver the imaging aspects of our proposed studies where this is unfunded from other sources.

**2. Integrated Bioinformatics** Our patient resource remains central to our translational ambitions and we will create a large, phenotypically rich, database linked and further integrated with key clinical, imaging and haematological/biochemical data captured from the Trust's new electronic clinical record service (CRS) and our digital imaging systems. To do this we will use HL7 messaging capturing numeric and textual data from the CRS in real time. For imaging data we would import the DICOM structure report which contains all values recorded on the source equipment (echo, cath lab, MRI etc). This will capture raw imaging data (usually discarded) to allow future application of novel image analysis approaches and we propose to use a modular storage system starting with 2 terabyte MAS servers with image management software (designed for medical imaging application) plus digital tape back-up. The data presentation will be as user friendly web-based applications will be applied for viewing of numeric, textual, waveform and image data. This will provide translational researchers with a highly phenotyped electronic patient resource to generate cohorts and populate research protocols. Following advice from commercial healthcare IT providers and

NHS IT developers we have included the costs of building key components of the database system. These include a bioinformatician, a data entry post, a consent nurse together with necessary software and hardware with digital tape back up and high level security. We will also seek collaboration with other UK centres developing similar systems to ensure compatible database structures to facilitate collaboration,.

**3. A new translational CV Clinical Research Facility.** Within our Heart Research Centre we have planned a 1200 m<sup>2</sup> General Clinical Research Facility adjacent to 3 floors of translational CV laboratories. This will serve as the translational research hub of this CV BRU. We have estimated that 25% of the CRF activity (300 m<sup>2</sup>) will be dedicated to extensive phenotyping of patients engaged in CV translational clinical research at any time and have requested infrastructure funding toward fit-out of this vital element of the proposed BRU. We will derive revenue and staff costs from our research activity.

#### **National strategic partnerships as a platform for success**

- **National Institute of Clinical Outcomes Research (NICOR).** Timmis chairs the academic group, charged with developing the research potential of the Myocardial Infarction National Audit Project.
- **NHS Innovations London (NHSIL)** Our interventional cardiology programme (Rothman) has won recent NHSIL awards for patenting and development of novel interventional devices, including the Ascending Thoracic Aorta Graft for emergency percutaneous treatment of dissection, a device for reopening chronic coronary occlusions, a device for closing patent foramen ovale and a percutaneous cardiac support device. Collectively this has generated 7 patent filings and £750K.
- **UK Stem Cell Foundation £1.2M, Charles Wolfson Foundation £600K and Barts and The London Charity** have funded the implementation of the translational stem cell programme of Mathur.

#### **International and industrial partnerships.**

- **Quintiles Transnational:** donated £1M toward fit out of our Heart Centre clinical research facility (CRF) within the new Heart Centre. Our vision for this joint NHS/University clinical research facility fitted with the aspirations of Quintiles to see an international network of academically led translational clinical research facilities with access to large patient bases. We retain complete academic freedom to work with any sponsor and Quintiles are advising on establishing this CRF as a major centre for clinical research.
- **Philips:** our academic collaboration for PET-CT technological development (the International Clinical Science Group) will extend to our cardiac CT work if our capital bid is successful
- We have ongoing international partnerships with Unigene, Celltech, Astra Zeneca, Pfizer Inc, Glaxo Smith Kline, and Novartis around development of novel therapies or clinical trials

#### **North East London strategic partnerships enabling our CV translational research.**

THE BTL NHS Trust is committed to provide strategic leadership and partnership across North East London in pursuit of NIHR/ UK Clinical Research Collaborative (UKCRN) goals. We have invested in creating partnerships that cross the primary/secondary care interface and offer the potential to succeed in the evolving NHS service delivery environment following the Darzi Report.

- **Primary Care Trust Partnerships (PCTs) in NE London** –We work closely with the North East London Centre for Research and Development and its allied Support Unit for Minority Ethnic Health Research which facilitates enactment of clinical research across 7 East London PCTs. Our CV clinical trials programme partners include 120 East London general practices serving 500,000 people, paving the way for patient engagement of our ethnically diverse community in research.
- **The North East London Cardiac Network.** We initiated this CV network of partner hospitals and 7 PCTs, capitalising upon joint clinical appointments. It plays a significant role in commissioning across the sector and offers substantial patient resources for research by bringing together Newham University Hospital, Homerton Hospital, King George Hospital, Queens Hospital, and Whipps Cross Hospital.

#### **UKCRN Engagement and Regional NHS/Academic partnerships as a platform for success.**

- We lead the Comprehensive Local (LRN) Research Network (Lemoine) in partnership with UCL (Caulfield is CV lead for NE London) and conduct adopted studies in the North East London Diabetes LRN (Hitman) and the Thames Stroke LRN.
- Barts and The London (Trust and School) are partners in the Guys/St Thomas's NHS Trust Biomedical Research Centre and have agreed close partnership with University College (NHS Trust and University).

#### **Research translating into patient benefit in the last 10 years.**

Translational studies comprise an increasing proportion of our research Examples include:

- Anglo-Scandinavian Cardiac Outcomes Trial and the Collaborative AtoRvastatin Diabetes Study:** (*Lancet 2003, Lancet 2004 and 2005 x2*) both have changed NICE and European guidelines for lipid and blood pressure treatment. This established our 120 GP partnership (see patient engagement).
- The Rapid Access Chest Pain Clinic** pioneered by Timmis, became the service model for the NSF, with new clinics nation-wide (*Heart 2007*) (*Arch Int Med 2007*).
- Electrophysiology: complex mapping.** Schilling's team are innovators in this field having validated arrhythmia mapping systems (*JACC 2006, Circulation 2007*). They are developing systems using 3-D CT scans to guide ablation which would greatly benefit from the imaging proposed herein (*JCE 2007*).

## 5. RESEARCH PLAN

### **Relevance of this CV NIHR Biomedical Research Unit to public health and patient benefit.**

**The Global importance:** CV disease is now the leading cause of death worldwide, causing 16.7 million (M) deaths across the globe, which is expected to rise to 24.2M by 2030. There are 1 billion people with hypertension worldwide, set to rise to 1.5 billion by 2020. **In the UK** CV death rates fell to 208,000 in 2005 yet CV disease still accounts for 31% of male and 23% of female premature deaths. These statistics do not describe the true national burden of disease with >2M people living with angina, 1.2M having suffered a heart attack and 0.9M with heart failure. In 2003, CVD treatment cost the nation £26 billion <http://www.heartstats.org/>. **The East London CV burden** is among the worst in the country, highlighting the major opportunity for a leading edge CV translational programme here.

### **Translational CV Disease Prevention Programme- aims and objectives for this NIHR CV BRU.**

The BTL partners (NHS Trust and School of Medicine and Dentistry) have a clear strategic commitment to this research plan and have selected very specific translational programmes from our basic science engine that could deliver advances in clinical care over the next 3.75 years if this BRU was funded. Our programme will investigate **novel translational strategies for primary and secondary prevention of CV disease**. Our aims and objectives for this programme include:

1. Investigation of novel approaches to CV stem cell therapy in prevention of progression to heart failure.
2. Studying candidate molecules (e.g. nitrite) that might limit ischaemia reperfusion injury in acute coronary syndromes.
3. Investigating the effect of dietary nitrate on blood pressure and cardiac function in hypertensives.

We propose to create an environment for intensive characterisation of patients by developing and optimising novel CV imaging strategies for each of these translational studies.

### **Adding value to translational concepts within this proposed NIHR BRU.**

This BRU proposal will enable us to extensively characterise patients in early phase programmes in new CRF space placed in the midst of our translational researchers within our new Heart Research Centre. Furthermore, through this initiative we will be able to create academic advanced imaging expertise and infrastructure, not merely to apply this technology to these programmes, but to use this BRU as a platform for imaging innovation. This intensive characterisation by advanced imaging may offer broader clinical utility in judging early phase efficacy of future translational concepts in these areas.

**Imaging structure and function:** Although structural and functional cardiac characterisation has advanced with our 1.5T research MRI, the merits of cardiovascular MRI compared to 256 slice CT and combined PET/CT (64 slice time-of-flight PET/CT available here) are still to be determined. It is likely that a combination of modalities would be required for optimal assessment of biological parameters such as cardiac perfusion, viability, angiogenesis and inflammation as well as stem cell tracking. Our established expertise in molecular imaging will greatly enhance the cardiovascular imaging research. The quantitative information derived from PET will be used in comparative imaging studies to validate and further advance cardiovascular MRI and high resolution CT. We can assess this in our translational stem cell programme below to gauge the most optimal future strategy for structural and functional cardiac imaging with particular emphasis on combined imaging modalities (PET/CT, SPECT/CT, PET/MRI) either by image co-registration or advanced (non-rigid) software fusion. In our PET radiopharmacy (currently being developed) we will establish a variety of molecular imaging markers for functional characterisation of tissue. In addition, our imaging research will explore the most appropriate surrogate markers for each intervention within our translational research programme.

- **Imaging ischaemia reperfusion:** Using the advanced imaging team from this BRU, alongside existing molecular imaging faculty (Avril), we will be able to evaluate, within patient, the diagnostic information of MR perfusion, by comparison with contrast enhanced high resolution CT (included in this bid) and 64 slice PET/CT (available) using Rubidium-82, within our ischaemia reperfusion programme. This offers the opportunity to compare and combine perfusion imaging modalities using hard- and software fusion for MRI, CT and PET. Our imaging research will focus on combining data acquired by CT angiography and myocardial viability from MRI and PET to establish a spatial relationship between the diseased coronary artery distribution and the myocardium at risk/or salvaged. These programmes may lead to patient benefit from pre-revascularization planning and reduced invasiveness of the diagnostic process.
- **Novel cellular imaging approaches:** We will investigate novel cell tagging strategies in experimental models using microPET/CT and nanoSPECT/CT to evaluate engraftment and longevity of stem cells in the heart. We will seek to develop these tagging approaches through this BRU for evaluating the fate of grafted cells in humans. In particular we will explore concurrent imaging techniques for non-invasive assessment of the survival, distribution, and differentiation of stem cells including imaging with magnetic particles (MRI), radiotracers (PET, SPECT) and reporter genes (MRI, PET, SPECT). We are currently establishing dynamic tracking during intracoronary injection of F18-FDG-labeled progenitor cell therapy

for myocardial infarction with PET/CT and also have expertise in imaging reporter gene expression.

This advanced imaging programme thereby becomes much more than simply applied imaging and adds value by improving our understanding of how best to characterise patients in translational programmes for cardiac stem cells, ischaemia reperfusion injury and blood pressure lowering. This BRU will be underpinned by excellent bioinformatics infrastructure and will thereby create a superb environment bringing our clinicians and scientists together to create translational step change.

### **1. Cardiovascular stem cell therapy.**

**Suzuki with Mathur, Thiemermann and Rothman (see section 2 of Basic Science on page 3).**

**Aims and objectives:** Our goal is to establish a translational programme within this BRU investigating the therapeutic potential of stem cell therapy in patients with myocardial infarction and with heart failure. We propose a portfolio of studies investigating crucial issues of graft survival, therapeutic efficacy and safety combined with mechanistic studies and could offer new treatment modalities for patient benefit.

#### **1.1. Early phase translational studies in acute myocardial infarction and ischaemic heart failure.**

**Translational programme.** Based upon encouraging pilot functional data in experimental models we lead two novel clinical trials of bone marrow-derived autologous progenitor cells. With £1.2M from the UK Stem Cell Foundation we are recruiting 100 patients with acute anterior myocardial infarction into the REGENERATE-AMI trial, which capitalises upon Barts and The London Heart Attack Centre. In a second trial in the programme, known as REGENERATE-IHD, 400 patients with heart failure will receive stem cell therapy. Although functional improvements have occurred in experimental models there are data indicating that only 1-2% of bone marrow mononuclear cells, exist in the heart at day 3 after intra-myocardial or intra-coronary injection so identifying the fate of these cells is mechanistically important to future study design.

**Deliverables from this BRU Programme.** The advanced imaging team will compare structural and functional MRI with PET/CT after stabilisation at day 3 and 6 months as part of understanding the efficacy of cellular therapy. This will inform future strategies for structural and/or functional imaging of translational concepts. With the new advanced molecular imaging centre Chair and existing expertise in molecular and functional imaging as well as in radiopharmacy, a PET/CT and SPECT/CT programme will be developed for cellular imaging correlated with functional imaging (see below) to allow us to determine whether the grafted cells take up residence within the human myocardium, their longevity and function. This will help unravel whether there is any influence of stem cells on cardiac function and if this a direct effect of engraftment or a paracrine effect on native myocardial cells. All of the imaging requirements for these studies in terms of functional MRI and PET/CT is funded by a DOH Technology Platform award (£800K). This programme will benefit from the advanced imaging team and the capability to follow patients in these trials within our Heart Centre CRF, and archive the raw data from these images, alongside key clinical data using our proposed BRU funded integrated bioinformatics initiative. This will create a data repository for future interrogation and image reconstruction using new analytical approaches.

#### **1.2. Investigating bioengineered cellular sheets to improve stem cell therapeutic efficiency.**

**Translational programme.** Our programme will validate a novel bioengineering technology using cellular sheets for surgical grafting onto damaged myocardial tissue within experimental models (developed with Tokyo Womens and Osaka Universities). The cell-sheets allow cells to spontaneously detach from dishes as mono-layers in response to temperature change without damage. The most efficient and safest cell source (e.g. mesenchymal stem cells) will be determined in experimental models before translation into patients with heart failure. Efficacy will be assessed in terms of improved survival, and physical activity measured by telemetry, and cardiac function assessed by echocardiography and catheterization, while complications (unwanted differentiation, carcinogenicity, arrhythmogenicity) are monitored.

**Adding value with Advanced Imaging;** We will capitalise upon existing high resolution small animal microPET/CT and nanoSPECT/CT imaging facility within our biological services unit for both functional and cellular tracking studies. To track stem cell engraftment we can transfect a proportion of stem cells with the sodium iodide symporter gene encoding a protein that facilitates the uptake of iodine/technetium into the cells which can be traced via various radionuclides for microPET/CT and NanoSPECT/CT. This will allow us to image the fate of engrafted cell sheets and potentially the subsequent progeny of these cells thereby offering potential for acute and chronic studies. We will seek to translate our experience from stem cell imaging with magnetic particles (MRI), radiotracers (PET and SPECT) and reporter genes (MRI, PET and SPECT) as described above for imaging cell-sheets if translated into human studies.

**Relationship to NIHR CV BRU strategy and Patient Benefit.** Depending upon the safety and efficacy of this therapy in models we plan to initiate early phase trials of autologous cell-sheet therapy in patients with post-ischaemic heart failure. Patients will be very closely monitored for adverse effects and efficacy. In the event that this progresses to translation a vital part of these studies will be functional MRI to determine changes in cardiac function and the effects on regional wall defects in the heart. We propose to use the high resolution 256-slice CT scanner requested herein to conduct longitudinal studies for cell sheet

calcification signals as part of early safety monitoring. An additional important benefit from this BRU initiative will be to develop molecular imaging using PET/CT approaches described above so that the fate of these engrafted cellular sheets can be determined. The development and implementation of these imaging strategies will draw upon the multidisciplinary imaging team, the Heart Centre CRF for patient follow up and bioinformatics for raw image data capture as proposed in this BRU application. In the event that the clinical trial programme looks promising we will progress this into larger scale multi-centre trials. The early pilot work for the cell sheet concept is underway and we are currently seeking separate funding for more detailed experimental model experiments.

## **2. Ischaemia reperfusion injury in acute coronary syndromes.**

**Webb, Ahluwalia, Nourshargh, Perretti, Thiemermann with Timmis, Mathur and Rothman.**

**Aims and objectives;** Acute myocardial infarction (AMI) still results in significant mortality and morbidity despite advances in treatment, such as, primary percutaneous coronary intervention (PPCI), which have resulted in ~50% reduction in mortality at 30 days. Novel therapies that reduce the infarct size beyond PPCI could have further significant impact upon progression to heart failure and death. We have developed several molecules that limit ischaemia reperfusion in experimental models and are ready for phase 1 translation into humans, or will be very shortly. As part of this BRU programme we will be able to offer the advanced imaging infrastructure and follow up within the CRF to facilitate evaluation of the potential of nitrite to limit ischaemia/reperfusion injury post-myocardial infarction. This could serve as a template for translation of other molecules in advanced development (see below) and could lead to important new therapies for myocardial salvage reducing morbidity and mortality.

### **2.1 Nitrite for ischaemia reperfusion injury in acute coronary syndromes.**

**Webb and Ahluwalia, with Mathur, Timmis, Rothman.**

**Translational programme:** We have shown in pre-clinical testing, that nitrite via its bioconversion to NO reduces infarct size (Webb PNAS 2004), and that pharmacological doses of dietary inorganic nitrate, that are well tolerated and safe, increase plasma nitrite and thereby prevent ischaemia-reperfusion (I/R) induced endothelial dysfunction in phase 1 translational studies in the human forearm (Webb et al Hypertension 2008). We propose to test the effect of nitrite on ischaemia reperfusion injury in acute ST elevation myocardial infarction by enrolling 72 patients undergoing PPCI at Barts and The London Heart Attack Centre. The participants will receive a low dose infusion of nitrite versus blinded concurrent saline control delivered over 10 minutes via intracoronary injection initiated within 30-60 seconds after re-establishment of antegrade epicardial flow by PPCI. We will profile and store samples for other CV biomarkers over the first 72 hours (area under the curve analysis). In parallel mechanistic studies, based upon our preclinical experiments, we will explore the protective effect of nitrite in endothelial dysfunction using flow-mediated dilatation of the brachial artery at 3 days post-infarct. Samples will also be taken for determination of plasma and red blood cell xanthine oxidase activity, an enzyme upregulated in ischaemia-reperfusion that we have shown facilitates conversion of nitrite to NO. **Adding value with Advanced Imaging;** The primary endpoints of infarct size and left ventricular function will be captured by cardiac MRI at 6 and 12 months (144 MRI scans funded by this programme). Secondary endpoints include incidence and severity of heart failure, cardiovascular events and mortality. The advanced imaging team will compare the degree of microvascular obstruction determined by the degree of late enhancement on cardiac MRI (72 MRIs) compared with high resolution 256 slice CT perfusion at 3 days (72 CT scans requested from this BRU). This new CT scanner offers rapid acquisition times for whole heart imaging with less motion artefacts and better stent assessment. In addition, we will assess myocardial viability at 3 and 6 months by comparing contrast enhanced MRI with FDG-PET/CT tissue metabolism imaging. **Relationship to NIHR CV BRU strategy and Patient Benefit.** The advanced imaging multidisciplinary team blinded to the treatment allocation will define the spatial extent, transmural, and total scar score of the infarct and the 256 slice CT scanner proposed herein will be used for complimentary CT perfusion studies. Patient follow up will be via the Heart Centre CRF. As Barts and The London performs 755 primary angioplasties per year we would expect to achieve 72 patients over 12 months with a timeline of 2 years to know whether this is of patient benefit. If successful we would also trial this protocol in non-stemi infarcts and large-scale mortality and morbidity studies will be undertaken. **We are requesting funds for the imaging elements (216 MRI scans, 144 PET/CT scans and 72 CT scans) from this BRU.**

### **2.2 New concepts in ischaemic reperfusion injury (see section 4.1-4.3 in basic science).**

Our cross-cutting strengths in leukocyte trafficking, inflammation and ischaemia reperfusion (I/R) led by **Nourshargh, Perretti and Thiemermann** linked into cardiology offer potential for therapeutic innovation in I/R injury in acute coronary syndromes. Based upon the experience in the first patients entering the nitrite studies above we will refine our study design and seek to translate our other candidate molecules as soon as they complete appropriate pre-clinical safety and toxicology. **Annexin biology:** We have shown that the anti-inflammatory peptide, annexin 1, can limit myocardial damage in experimental models and are

partnering Unigene Inc to generate and test novel peptides with favourable pharmacokinetics (**JBC 2007**). **EPO analogues:** In a distinct programme the proposal that tissue-protective effects of EPO are due to activation of a novel receptor are under investigation. With Warren Pharmaceuticals we have developed peptide analogues of EPO selectively targeting the tissue protective EPO-receptor, avoiding increases in haematocrit, which enter early trials this month. Subject to safety and tolerability we propose to evaluate these EPO-analogues in ischaemia-reperfusion injury. **Relationship to NIHR CV BRU strategy and Patient Benefit.** Each of these new candidates if successfully translated will be able to capitalise upon the Heart Research Centre CRF, the multidisciplinary imaging team and the integrated bioinformatics infrastructure of this BRU investigated for potential patient benefit.

### **3. Dietary nitrate in hypertension and vasoprotection.**

#### **Ahluwalia with Webb and Mathur.**

**Aims and objectives;** Diets rich in fruits and vegetables reduce BP and adverse cardiovascular events. These protective effects have previously been attributed to the high antioxidant vitamin content, yet large-scale clinical trials have failed to provide evidence to support this thesis. The greatest protection against coronary heart disease afforded by a change in diet is that associated with the consumption of green leafy vegetables (e.g. spinach and lettuce), which have a high inorganic nitrate ( $\text{NO}_3^-$ ) content. We plan to evaluate the potential of inorganic nitrate, as a source of endogenously generated nitrite to lower blood pressure and restore endothelial function in the prevention of cardiovascular disease. **Translational Programme:** Recently, we conducted preliminary experiments testing the hypothesis that dietary nitrate, via bioconversion to nitrite, represents an intravascular source of NO. Inorganic nitrate once consumed enters the entero-salivary circulation where it is reduced by bacterial nitrate reductases on the tongue, to form nitrite, some of which is reduced to NO on entry to the stomach, but some of which is then reabsorbed to enter the circulation. In addition to green leafy vegetables, many root vegetables, also contain high nitrate levels including beetroot. We have shown that ingestion of beetroot juice leads to a significant rise in plasma nitrate, followed by a secondary increase in nitrite that is accompanied by a 10/8 mm Hg fall in blood pressure, which persisted for systolic pressure over 12-24 hours in healthy volunteers. In addition, the rise in nitrite led to enhanced endothelial function (flow mediated dilatation) and reduced platelet aggregation. We have just been awarded a BHF Special Project Grant (£490K) to extend this translational programme. To do this we will construct an acute dose response curve for beetroot juice and equivalent doses of orally ingested inorganic nitrate tablets and examine the effects of chronic administration in terms of nitrate/nitrite levels attained and the effects on blood pressure in healthy volunteers, flow mediated dilatation and platelet aggregation in studies using our CRF. This therapy is safe and well-tolerated to date (levels are way below those that cause methaemoglobinaemia). Furthermore our use of inorganic nitrate offers the advantage of little, or no tachyphylaxis over organic nitrates e.g. GTN and the side effects to date are largely due to beetroot causing red secretions. We intend to take this concept in to phase 2 studies of pre-hypertensives (<140/90), grade 1 hypertensives and then into severe hypertensives (64 patients in each group) exploring both the effects of beetroot juice and potassium nitrate tablets on blood pressure, endothelial function in patients derived from our European Hypertension Centre of Excellence at Barts and The London and our Primary Care Partnership. These studies, conducted within this BRU, will allow us to confirm the kinetics of nitrate and nitrite are the same in hypertensive subjects. **Adding value with Advanced Imaging;** In severe hypertension diastolic dysfunction is found by echocardiography in 40% of patients. We propose to evaluate the chronic effects of nitrate-derived nitrite on cardiac function at baseline and 6 months by comparing structural and functional MRI with PET/CT and echocardiography. This will help determine whether nitrite is having beneficial effects on cardiac function either through blood pressure lowering or improved vascular function and will use this study to determine the optimal functional imaging modality for diastolic dysfunction by drawing upon our multidisciplinary advanced imaging team. **This is not funded by the BHF award and we seek funds for 128 MRI and 128 PET/CT scans from this BRU.**

#### **Advanced Imaging Research Programme.**

We recognise that the new Chair in Advanced Imaging and their team will bring or generate independent leading edge programmes within this BRU. In this submission we have sought to depict opportunities to create innovative imaging strategies using translational concepts around CV disease prevention as the platform. We are currently limited by the lack of academic imaging expertise in MRI and high resolution CT. A multidisciplinary imaging team provided with high resolution CT and MRI added to existing strength in PET/CT and SPECT/CT is vital for a modern translational programme will create the opportunity to establish an international leading BRU for therapeutic innovation and imaging which will become a major UK cardiovascular centre of excellence for training and research.