VISION

- The UCLH/UCL BRC will be recognised as a globally leading centre in Experimental Medicine accelerating the development of novel therapeutics, diagnostics and devices for patient benefit
- We will support NIHR's national mission and impact by engaging in strategic partnerships with our AHSC & BRCs/BRU, plus other BRCs and key international partners
- We will deliver patient benefit and population gain from Experimental Medicine through active engagement with industry, patients, and in collaboration with UCL Partners
- We will seek out the brightest and best minds in Experimental Medicine and teach, train and support them to research independence in the NHS

We will realise our vision and a step function in the BRC's impact through a relentless focus on world-class activity of greatest therapeutic/diagnostic potential. That focus will be achieved by:

Scientific Focus

- Condensing activities from our themes into four synergistic Programmes (Cancer, Neuroscience, Cardiometabolic Science and Infection/Immunity/Inflammation), under strengthened leadership.
- Aligning basic science 'pull through' from the Francis Crick Institute and the established UCL Domains of the same name (cancer, cardiometabolic, III, and neuroscience) and our wider partnership strategy.
- Maximising the opportunities of our unique group of partner specialist hospitals including the Eastman Dental Hospital, Royal National Throat, Nose & Ear Hospital, Elizabeth Garrett Anderson Hospital, Hospital for Tropical Diseases, National Hospital for Neurology & Neurosurgery and the Heart Hospital.
- Fulfilling the translational potential of our world-class activities in nanotechnology, gene therapy, cell therapy/regenerative medicine, bioengineering and computer science.
- Optimising Experimental Medicine facilities, platform technologies and technical expertise for each Programme.

Resource model

- Introducing a resource allocation model that incentivises world-class activity and rewards the leveraging of other funds
- Creating dedicated joint UCLH/UCL philanthropic support for the four Programmes

Governance and Engagement

- Revising our governance structure to reflect the Programme focus, common goals between UCLH and UCL and the needs of an ambitious Experimental Medicine agenda
- Embedding industrial liaison officers in each Programme working to the Director of Industrial Partnerships

Education

- Supporting the development of a new generation of Experimental Medicine researchers through the Academic Careers Office
- Interaction with the Francis Crick Institute through Clinical Research Fellows
- Embedding Experimental Medicine experience within all postgraduate training programmes

EXPERIMENTAL MEDICINE

We will focus on

- 1. New therapies, including novel devices and first-in-man studies
- 2. Improvements in diagnosis, treatment selection and evaluation of response
- 3. Repurposing of therapies

We will maximise the use of the NIHR Bioresource to evaluate predictors of disease and response, and invest in the infrastructure to fuel development of new interventions. Our extensive national and international collaborations across Themes are outlined within our original bid documents (section 5).

1. Cancer Programme

We will bring together the current cancer theme with the cancer-related activities within the following BRC themes: Cell and Gene Therapy, Respiratory, Anaesthetics and Critical Care (RACE), Oral Health, Imaging, Women's Health, and Neurodiagnostics.

Prediction and Stratification: Genomic and epigenetic approaches will track tumour heterogeneity to assess their importance in: informing stratified care; determining mechanisms of resistance; and predicting outcome. We will:

- Define the phenotype and genotype of 'relapse initiating cells' and the role of stem cells and genetic heterogeneity in the initiation of drug resistance for our key tumour types
- Develop whole ultra-deep cancer genome sequencing approaches to rapidly characterize tumour heterogeneity and cancer clonal evolution during therapy
- Implement at least three or more adaptive trials within five years that will stratify patients based on molecular knowledge

Interventions:

<u>Drug Development and Optimisation of Targeted Therapy</u>: An integrated programme will include comprehensive sequencing, proteomics analysis and RNAi screens undertaken on xenografted primary tumours, cell lines and circulating tumour cells to define putative drug targets and mechanisms of drug resistance for key tumour types (AML, glioblastoma, HNSCC, NHL, NSCLC, osteosarcoma, ovarian, renal cancer). We will accelerate development of in-house cancer therapies (immuno-, Ab-based and small molecule). We will:

- Identify new putative drug targets for key tumour types
- Initiate at least three early phase clinical trials based on in-house conceptualised therapies

<u>Targeted Investigative Cancer Therapy:</u> We will use informatics approaches to correlate genetic heterogeneity with functional imaging. We will exploit novel functional imaging for targeted treatment (surgery, radiotherapy, laser and photodynamic). We will:

- Implement a clinical programme of image-guided treatment for prostate and brain cancer, exploiting the radiological phenotype to deliver new first-into-man treatments
- Delineate the role of MRI-PET and new molecular imaging technologies in targeted cancer therapy and personalised care

Partnerships and Alignment: We have a Cancer Research UK Centre, Experimental Cancer Medicine Centre (ECMC), CR-UK UCL Clinical Trials Centre (CTC), Leukaemia and Lymphoma Centre of Excellence, as well as a dedicated Cancer Clinical Research Facility (CRF). UCL's imminent merger with the London School of Pharmacy will enhance existing programmes in cancer therapeutics and formulation. Early trials are supported by the Sarah Cannon Research Institute (USA). UCLP's recently commissioned integrated cancer care leadership for North East and North Central London offers greater patient access and impact. During the past 5 years, UCLH and UCL have invested over £170 million in cancer-specific clinical care and research infrastructure, and the planned Proton Beam Treatment Centre will add further significant research capability.

2. Neuroscience Programme

We will bring together activities within the themes of neurodiagnostics, neuroimaging, neurotherapeutics neurodegeneration and neonatal neuroprotection work within the Womens' Health theme.

Prediction and Stratification: Utilising our international strengths in imaging and genetics, we will:

- · Explore disease mechanisms of depression and schizophrenia
- Translate discoveries into diagnostics
- Deliver novel pre-symptomatic neuroimaging diagnostics in MS, epilepsy, Alzheimer's Disease and other neurodegenerative disorders (e.g. functional MRI in pre-manifest Huntington's disease)
- Stratify patients both in terms of prognosis and therapeutic response e.g. through our high-dimensional outcome prediction in stroke project in our Hyper-Acute Stroke Unit (HASU)

Interventions: We will accelerate development and delivery of new therapies through delivering first-in-man studies in the following areas:

- Humanised monoclonal antibody in prion and Alzheimer's diseases
- Depletion of serum amyloid P in Alzheimer's disease
- Heat shock protein upregulation in inclusion body myositis
- Targeting mitochondrial function in juvenile Huntington's disease
- Novel neuroprotection strategies in MS
- Antisense therapy in Duchenne and myotonic muscular dystrophy
- Potassium channel upregulation [lentiviralKV1.1] in intractable focal cortical epilepsy
- Microelectronic devices for wireless vital life function monitoring
- 3D multimodal brain imaging to direct neurosurgery, leading to robotic intervention
- Neuroprotective strategies in the neonatal brain

Partnerships and Alignment: We align with the new UCL Faculty of Brain Sciences including major strengths in sensory systems (Institute of Ophthalmology, Ear Institute, Institute of Cognitive Neuroscience and Institute of Neurology) and mental health (Psychology, Psychiatry and ICN), as well as the MRC Prion Unit, Wellcome Trust Centre for Neuroimaging and MRC Neuromuscular Centre. We will benefit from close interaction with the new Sainsbury Wellcome Centre for Neural Circuits and Behaviour. Stronger alignment now exists with SLaM / KCL in Mental Health and QMUL Mental Health. A strategic partnership with the Max Planck Society has resulted in the establishment of a joint Unit at Queen Square.

3. Cardiometabolic Programme

We will bring together activities within the BRC themes of Cell & Gene Therapy, Body Imaging, Oral Health, RACE, and Neurotherapeutics with our core cardiovascular theme.

Prediction and Stratification: We will:

- Implement and evaluate novel preclinical prevention strategies targeting recognized cardiovascular risk factors in the young
- Develop novel technologies with industry to measure CV performance. This will enable an interactive national programme (within 3 years) for blood pressure monitoring and vascular disease prevention
- Utilise UCL led innovations in linkage of electronic records to couple point-of-care phenotype data to endpoint/mortality registries (including NICOR) and new bio-repositories/ tissue banks for subsequent sequencing and –omics analysis
- Through genotyping and extensive phenotyping pre and post-operation, we will define the genetic and pathophysiological determinants of a beneficial response to surgery
- Enable cost effective clinical gene testing for inherited cardiac disease
- Implement genetic approaches into diagnostic and prognostic evaluations in premature "sudden death syndromes"

Interventions:

- CRP is a therapeutic target in acute MI and stroke. A small molecule inhibitor is effective in experimental models. We will develop an optimised compound with industry and test it clinically (early study 2012)
- A world-leading Programme at the National Amyloidosis Centre has invented the first therapeutic approach
 to eliminate visceral amyloid and novel small molecules targeting transthyretin. We will now assess clinical
 efficacy together with the development of a novel CMR based method to quantitate myocardial amyloid
- Recent recruitment and the establishment of the Yale UCL Device Development Centre will provide a
 unique trans-Atlantic infrastructure to perform preclinical studies, develop novel biological compounds and
 implantable therapeutic and monitoring devices and perform early clinical studies enabling a world-leading
 program in this arena where percutaneous techniques have the potential to replace conventional surgery

Partnerships and Alignment: We align with the new UCL Institute for Cardiovascular Science, plus the UCL-hosted National Institute for Cardiovascular Outcome Research (NICOR), and benefit from close interaction with the GOSH BRC and the BLT BRU in Cardiovascular Disease, plus the joint Yale-UCL Institute of Cardiovascular Science. Major strengths also include the new Prevention and Outcomes Unit and Genetic Epidemiology group.

4. Infection, Immunology and Inflammation Programme (III)

We will bring together activities from the BRC themes I&I, Cell and Gene Therapy, Cardiovascular, RACE, GI/Hepatology, Body Imaging and Oral Health.

Prediction and stratification: Through access to some of the largest patient cohorts in the UK, we will undertake first-in-man studies in the next five years including:

- Whole genome sequencing and quantitation of viruses (HIV, HCV), to produce pathogen predictors of outcome and therapy response
- · Whole blood transcriptomic analysis of febrile patients to identify infection specific signatures
- Metabolomics in SLE to predict renal disease
- Radiological characterisation of therapy responses in lung fibrosis to guide early clinical trials
- Immunophenotyping in HIV, transplantation and cancer to predict outcome and guide novel immunotherapies

Interventions:

- We will use gene therapeutic approaches (viral vectors) to modify T cells for immunotherapy of inflammatory arthritis, as well as HBV and EBV, and to deliver genes to treat HIV and haemophilia A
- Novel preventative and therapeutic vaccine strategies against CMV, HIV, HBV and HCV will reach clinical evaluation within 5 years
- We will develop new therapeutic modalities for HIV within the flagship cross-BRC Programme on strategies to eradicate HIV (CHERUB)
- We will use disruption of cell signalling pathways and/or immunotherapy for lung fibrosis, Crohn's disease, as well as ageing related disorders, and a unique drug-antibody approach to amyloidosis (Pentraxin-GSK) will be launched
- We will accelerate advanced development of antibiotics through structural biology modelling, plus photo activation

Partnerships and Alignment: We align with unique international strengths including the largest stem cell transplant centre in Europe at UCLH (Cancer Centre) and the RFH; leadership of an international Collaborative HIV and Anti-HIV Drug Resistance Network (Paris, Barcelona, Rome, Rotterdam); a joint UCLH/GOSH Arthritis Research UK-funded Adolescent Rheumatology Trial Centre; the new Bloomsbury Institute for Pathogen Research (incorporating UCL and the London School of Hygiene and Tropical Medicine); the UCLH Hospital for Tropical Diseases, and antimicrobial therapeutics at the London School of Pharmacy (now merged within UCL). We will work with the NIHR Translational Research Partnerships in Respiratory and Arthritic Inflammatory Diseases at UCL, the National Amyloid Centre/GSK Partnership (RFH/UCLP) and our leadership in the WT Sanger Institute Virology Programme.

BRC RESOURCE ALLOCATION

To fuel a step function in world-class Experimental Medicine activity we will take the following steps:

- 1. BRC resource will be allocated according to the following criteria:
 - · World-class science
 - · Conforming to our Experimental Medicine definition
 - · Alignment with Programme strategy
 - Leveraging external funding that align with goals of each Programme
- 2. In 2012 we will appoint major clinical academic leaders to each Programme.
- 3. In 2012-13 we will review consultant PA and non-consultant support at Programme level.
- 4. From 2013 onwards, we will increase the focus of funding from current salary support (consultants/non consultants) towards activities (including UCL staff support as well as NHS employees) compatible with the overall goals of the BRC (above).
- 5. From 2013, service support costs will be increasingly focused on the goals of the BRC, through more explicit accounting processes.
- 6. We will provide dedicated BRC support for the scientific leaders, including coordinated management, finance and industry liaison functions for each Programme.

Alignment of charitable support

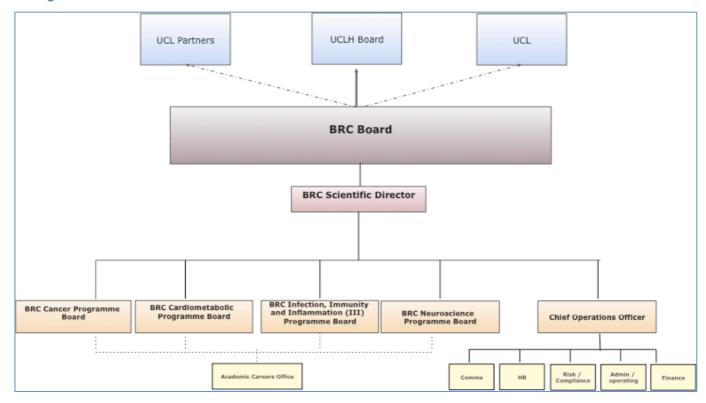
UCL and UCLH both have fundraising operations, and we will now align these to support the activities of the four Programmes. The outcome of this alignment would be to support the development of the programmes and associated infrastructure e.g. UCL Cancer Institute and UCLH Macmillan Cancer Centre (Cancer), Queen Square Experimental Medicine facility (Neuroscience), UCL Institute for Cardiovascular Science (Cardiometabolic) and the Bloomsbury Institute of Pathogen Research (III). In addition, UCL Development Office will discuss with RFH the opportunities for the development of the planned Institute for Immunology, Infection and Transplantation.

BRC GOVERNANCE

The engine room of our BRC will be four Programme Boards, to drive exciting and innovative Experimental Medicine. To ensure implementation and achievement of these scientific objectives, our new governance structure encompasses the following changes:

- 1. Four Programme Boards: To lead the scientific activities of the BRC and closer alignment between UCL and UCLH, ensure that excellence within existing Themes are developed and fully supported with improved engagement with industry, and maximise leverage of external resources. Each chaired by a BRC Programme Director and to include UCLH Medical Directors and Research / Industry Liaison Coordinators.
- 2. BRC Scientific Director: to lead development and delivery of agreed strategy; coordinate delivery across programmes; provide external interface to NIHR, industry, BRCs etc; report progress to the Board, lead the executive and programme boards and oversee the transformation of the BRC into a scientific business.
- 3. BRC Board: will meet quarterly to: agree strategy and plan, oversee governance, review allocation of resources and review progress against agreed plans. Members will be UCL Vice Provost, UCLH CEO, BRC Scientific Director, UCL Partners Managing Director, Programme Directors and 2 external non-executive representatives from industry. The 2 non-executive directors will provide the highest-level external scientific scrutiny along with an industrial perspective.
- 4. Dedicated BRC Operational Management, including Chief Operations Officer, who will lead the operation of the BRC to support day to day delivery of agreed strategy; oversee finance, HR risk and administration; collate reporting to the Board, NIHR and other external parties; oversee documentation of external grants and funding; collate and report risk / compliance to the Board and support strategic planning and bid preparation.

Management Structure



IMPLEMENTATION PLAN

- The management structures and relevant meetings will be established immediately
- Financial audits will commence in April 2012; translational funding decisions will conform to new criteria
- Industrial liaison officers for each Programme will be appointed and relate to the new Director of Industrial Partnerships
- · Joint charitable funding vehicles will be established
- Detailed KPIs will be developed to aid monitoring and performance management of the Programmes in line with the ambition

Key Goals and Metrics

* Indicates within first 12 months

Experimental Medicine: Major clinical academic appointments for each programme*; increase early phase study patient recruitment by 3-fold; increase external financial leverage to 3:1; increase by 50% the number of BRC faculty engaging with industry.

Education: Establish single Academic Careers Office*, appoint first round of clinical fellows to NIMR and LRI pending opening of FCI*; establish MSc programmes in Musculoskeletal Medicine, and Medical Statistics; 20 BRC clinical trainees emerging as independent PI's.

Partnerships: Establish NIHR Bioresource*; establish partnership agreements with at least 2 major biomedical industries; establish cross-UCL Partners clinical data management system; pan London BRC and BRU projects for each Programme*.

Management: Establish new management support structure*; enhance audit and control of staff and service support expenditure in order to support explicit scientific goals of programmes*.