NIHR Imperial Biomedical Research Centre (BRC)

Institute for Translational Medicine and Therapeutics (ITMAT)

CALL FOR EXPERIMENTAL MEDICINE PROPOSALS

DEADLINE: 12pm on 4th May 2015

Up to £1M funding available

Overview and Aims

NIHR Imperial Biomedical Research Centre (BRC) funding has established state-of-the-art phenotyping, genotyping, imaging and biobanking capabilities within the Imperial Academic Health Science Centre (AHSC). It has also developed clinical research informatics infrastructure through the NIHR Health Informatics Collaborative (HIC) programme and works closely with the NIHR/Wellcome Trust Imperial Clinical Research Facility at Hammersmith. We now aim to capitalise on these investments by bringing these capabilities together into the Institute of Translational Medicine and Therapeutics (ITMAT) to accelerate and support your experimental medicine research along the translational pathway into improvements in human health and economic benefit.

With the launch of ITMAT, the NIHR Imperial BRC is pleased to announce an inaugural call for experimental medicine proposals to exploit ITMAT's core platform technologies. Our aim is to promote and encourage the 'pull-through' of discovery science from the Faculties of Medicine, Engineering and Natural Sciences within Imperial College London into potential clinical applications.

Our intention is that successful proposals in this call will demonstrate a feasible route to more comprehensive clinical studies to be funded externally (for example by MRC, NIHR or Innovate UK).

Scope and Criteria

The aim of this call is to provide seed funding support to pilot projects that are based on a workable hypothesis and can demonstrate reasonable promise of success. Our aim is to provide a boost to these promising projects, to provide the additional data and evidence that will support Imperial researchers to apply for larger, follow-on grants from other funders within a period of 12-15 months.

Project proposals should therefore address the following criteria:

- Projects should engage with one or more of the ITMAT core facilities - details of the resources, facilities and platforms available are listed in Annex A;
- Successful projects will have demonstrated the ability to deliver the proposal to a specific timescale, as well as plans/intentions for follow-on funding;
- Principal Investigators should describe consents / approvals already in place and demonstrate operational readiness;
- Proposals which engage with industry or commercial partners are encouraged;
- Proposals which engage with investigators within the Imperial College Faculties of Engineering or Natural Sciences, as well as the Faculty of Medicine, are welcome;
- Funding is initially available only for the 2015/16 financial year (April 2015 to March 2016);
- Funds awarded must be deployed within the NIHR Imperial BRC;

Projects must address the aims and objectives of the NIHR Imperial BRC and be coherent with the BRC Themes - PI's are encouraged to discuss their project with the appropriate BRC Theme Leads before submission, as well as engaging early with the relevant ITMAT core platforms and the NIHR / Wellcome Trust Imperial CRF as required, with respect to planning and feasibility of their proposal.

Eligibility

Any academic member of staff within the Imperial AHSC may apply, although all applicants must hold a contract of employment which extends to at least the end of the proposed project and all must have secured departmental approval prior to submission. Applications are also eligible from Imperial College London substantive employees who are attached to the Chelsea and Westminster NHS Foundation Trust, Royal Brompton & Harefield NHS Foundation Trust, or The Royal Marsden NHS Foundation Trust. **Project work must take place within the NIHR Imperial BRC and therefore a substantive employment association with Imperial is required.**

Project Costs

The NIHR Imperial BRC has allocated up to £1M funding to support this call which we expect will fund between 8 and 12 projects. It is recognised that costs for some proposals may be higher than others; therefore an indicative cost per proposal is not included in this call.

Infrastructure support for projects will be provided through the NIHR / Wellcome Imperial Clinical Research Facility, BRC Biobanking Theme, NIHR Imperial Clinical Phenotyping Centre, NIHR Imperial BRC Genomics Facility, and Clinical Imaging Facility.

Eligible costs may include salary support and consumables, but no items of equipment greater than £5,000 each. Animal costs cannot be supported. Any salary costs requested should not duplicate resources and services already provided for within the cross-cutting Themes. These awards will not support any indirect costs. Projects should be completed by 31 March 2016 and must adhere to BRC terms and conditions.

Project costings should be developed using InfoEd. InfoEds do not need to have been formally approved in advance of review by the ITMAT Management Committee, as successful proposals may be amended, but they will need to have been agreed in outline by the relevant department (an e-mail signifying approval will suffice).

Application, Selection and Award Process

Applications should be made on the attached application form and submitted by 12pm on 4th May 2015 to brcofficer@imperial.ac.uk

The application will be a single-stage process, with further iteration and work-up post-award as necessary.

Proposals will be assessed by the ITMAT Management Committee, a subcommittee of the AHSC Research Committee, consisting of representatives from the NIHR Imperial BRC cross-cutting Themes and core facilities. Proposals will be evaluated on the basis of scientific excellence and unmet clinical need, the potential for further funding, effective and appropriate use of the BRC/ITMAT core facilities and resources and suitable arrangements for statistical/bioinformatics analysis. Proposals should also describe clearly the hypothesis underpinning the proposed work, together with any supporting data. We do not encourage proposals which simply aim to characterise patient cohorts without a credible underlying hypothesis.

Following short-listing of proposals by the ITMAT Management Committee on the 18th May 2015, successful applicants will be formally notified of the outcome in the same week. At this point, formal InfoEd submission will be requested (if not already complete). Award letters will be issued before 15 June 2015 and projects may start from 15 June 2015 at the earliest:

Key Dates:

27th March 2015	Call launch
4th May 2015 (12pm)	Deadline for submission of completed proposals
18th May 2015	Subcommittee review of proposal shortlist
9th June 2015	Ratification of proposals to be funded by AHSC Research Committee
11th June 2015	Notification of successful proposals
15 June 2015	Earliest project start date
31 March 2016	Completion of projects and submission of final report

Award Uptake and Reporting Requirements

Projects must be activated within 3 months of the date of the award letter, otherwise funding will be withdrawn and may be re-allocated. Successful project-holders will be required to complete a final report, on a template provided by the BRC Office. These reports will be reviewed by the ITMAT Management Committee and the AHSC Research Committee. Progress of projects will be monitored against key milestones. If progress is deemed unsatisfactory, continuation of funding may be terminated and the funds re-allocated. Due to the short nature of these awards, extensions will not be supported.

Expected Project Outcomes

We expect projects funded through this call to have clear expectations in terms of follow-on funding or support. Successful projects will deliver on time and then apply for continuation funding through schemes such as the MRC Experimental Medicine Challenge Grants or Biomedical Catalyst: Developmental Pathway Funding Scheme (DPFS), the NIHR Efficacy and Mechanism Evaluation (EME) programme or Innovate UK (formerly the Technology Strategy Board).

We encourage publication outputs before June 2016 for potential inclusion in the NIHR BRC re-application process.

Enquiries

General enquiries relating to the scope and objectives of this call should be directed to Dr Kelly Sheehan-Rooney in the BRC Office: brcofficer@imperial.ac.uk.

Specific enquiries concerning the resources and technical support available within the core platforms and technologies should be discussed with the relevant contacts listed in Annex 1.

Annex 1: Resources, Facilities and Platforms Available

Please discuss your specific requirements with the individuals listed below for each facility.

Imperial Clinical Phenotyping Centre

Contact: Prof Jeremy Nicholson, BRC Theme Lead (hod.surgery.cancer@imperial.ac.uk)

The Imperial Clinical Phenotyping Centre & Surgical Metabolomics Laboratory links closely with the MRC-NIHR Phenome Centre and with the Division of Computational & Systems Medicine. It provides state-of-the-art metabolic phenotyping capabilities and the integration and correlation of the data with other data sets on the same samples. The facilities include cutting edge NMR and UPLC-MS/MS infrastructure, as well as core analytical and project management staff.

The aim of the Centre is to improve clinical decision making by developing new paradigms for patient journey Phenotyping, i.e. identifying significant changes in phenotype (biomarkers) that correlate with developments, changes or subtypes of diseases or their treatment. This will be achieved by integrating clinical diagnostic information, chemical pathology with advanced –omics data. Current approaches include developing real-time diagnostic biomarkers and identifying prognostic and patient stratification biomarkers. With these aims, the Centre has a preference for studies of longitudinally collected samples derived from interventional studies, but all high quality projects will be considered.

Samples must be fit for purpose –applicants should confirm with us that their samples are suitable for analysis before applying (see further comments below), and that the sample size is feasible / affordable. The Centre can provide the following tests / profiling methods (which vary from routine to bespoke per study, and in terms of cost);

NMR spectroscopy

- Proton NMR of urine and/or blood plasma and other biofluids
- Solid state NMR of tissue biopsies

Currently offered Mass Spectrometry-based assays

- Untargeted Liquid Chromatography-Mass Spectrometry for urine and blood products
- Positive/Negative ion HILIC (Highly polar metabolites)
- Positive/Negative ion Reversed Phase (most classes of major intermediary metabolites)
- Positive/Negative ion Lipidomics (all lipid classes)

Targeted Liquid-Chromatography-Mass Spectrometry

- Acylcarnitines
- Amino acids/ Organic amines
- Bile acids/ Oxysterols
- Carbohydrates
- Eicosanoids/ Oxylipins
- Fatty acids
- Lipids
- Organic acids
- Peptides
- Phenols
- Steroids

Data Fusion Technologies (a wide range)

Additional Comments and Guidance for Applicants:

Metabolic phenotyping serves as a powerful tool for biomarker discovery and for providing deep mechanistic insights into pathological disease states. However, as with all '-omics' approaches a sound experimental design is essential if it is to deliver a robust and meaningful analysis. Preference will be given to applications that address the following aspects of their experimental design:

1. Standardisation: metabolic systems analysis requires a robust sampling approach that ensures sample stability and in turn that sampling bias is minimised;
2. Biofluid studies should seek to capture multiple biofluid types during the course of the protocol where possible. This allows the phenome to be interrogated across biological compartments and it thus provides a greater insight into whole organism metabolic signalling and system function. Moreover, differing biofluids provide unique metabolic signatures due to their organ specific biological functions and outputs;
3. Tissue samples: this not only provides an opportunity to study metabolism in the target pathology, but from an analytical perspective molecular imaging technologies can also be deployed for studying spatially resolved metabolic processes in histologically validated specimens;
4. Study design: metabonomics by definition provides multi-parametric, time dependent insights into pathological processes. Therefore, studies should aim to capture multiple sampling time points as part of a longitudinal design where possible. Individuals can then serve as their own controls and it permits predictive modelling to be performed to validate candidate biomarkers. Randomised control trials or observational studies require standardisation of sampling protocols across groups with balanced sample acquisitions. Obvious confounding variables that are known to influence metabolic data sets (e.g. diet or pharmacological interventions) should also be minimised or recorded and accounted for;
5. Power: as with all studies, this is essential but it is particularly pertinent in systems metabolism where hundreds or thousands of metabolic endpoints may be studied simultaneously. Therefore for longitudinal or randomised clinical studies, there should be a clear evidence of a power calculation, and around 50 patients is the minimum required to generate a meaningful analysis. For single time point studies or those with limited biofluids or samples, then much larger sample numbers are likely to be required to generate meaningful insights;
6. Clinical metadata: It is essential that all proposed studies are able to produce this at the time of the analysis and that there are no barriers to accessing this critical component;
7. Scientific metadata: stratified systems medicine increasingly relies on the integration of omics data sets to provide mechanistic insights into disease pathology. Therefore, studies that are able to generate genomic, transcriptomic or other large scale systems level data will be at an advantage;
8. Study endpoints: the study should have well defined clinical endpoints with objective measures that are known at the time of the analysis.

Genetics & Genomics

Contacts: Prof Jorge Ferrer, BRC Theme Lead (j.ferrer@imperial.ac.uk)
Dr Michael Mueller, Facility Manager / Head of Genome Informatics (michael.mueller@imperial.ac.uk)
Dr Anna Zekavati, Head of Genome Laboratory (a.zekavati@imperial.ac.uk)

The Imperial BRC Genomics Facility provides integrated support for the application of next-generation sequencing in clinical and translational research within the AHSC. The facility provides a wide range of services covering every step of the next-generation sequencing work flow from experimental design, to library preparation and QC, to sequencing and downstream data analysis.

The facility runs an Illumina HiSeq 2500 sequencer for large-scale and an Illumina MiSeq for small-scale sequencing projects.

Multiple HiSeq 2500 configurations allow tuneable output from ~10 Gb or ~300 million single-end reads in seven hours to 600 Gb or six billion paired-end reads in 11 days depending on application needs or project deadlines. The MiSeq system can generate up to 15Gb or 25 million paired-end reads per run with very fast run times, ranging from 3.5 hours to 55 hours.

The facility has access to dedicated high-performance computing resources at the Imperial High Performance Computing Service and Data Centre and maintains analysis pipelines for large-scale genomic datasets from a wide range of sequencing applications including variant detection, expression quantification, metagenomic profiling and methylation analysis utilising cutting edge bioinformatics algorithms and tools.

Furthermore, the Facility can assist investigators with data interpretation and provides tools and support for the prioritisation and reporting of genomic information for research and diagnostics.

Further information on the Imperial BRC Genomics Facility can be found at www.imperial.ac.uk/genomicsfacility . Please send an email to igf@imperial.ac.uk to request details of service costs.

Imaging

Contacts: Professor Eric Aboagye, BRC Theme Lead (e.aboagye@imperial.ac.uk)
Dr Albert Busza, CIF Manager (a.busza@imperial.ac.uk)

The Siemens Biograph 6 PET/CT scanner features 6 slice CT, a multi-detector ring system and 3D reconstruction. Suitable for assessment of e.g. inflammation/cell tracking, substrate utilisation. There is an adjacent tissue/blood processing lab with gamma counter and HPLC for tracer metabolite analysis.

A broad range of PET research can be carried out in the CIF, including:

- Tissues pharmacokinetic studies
- Radio-ligand binding studies (displacement/competition studies)
- Pharmacodynamic studies
- Basic research in disease physiology
- Characterisation of disease progression (prediction of outcome)

The Siemens 3T Verio MRI scanner comprises a 70cm diameter open-bore, short-axis magnet. It has been equipped with a comprehensive range of transmit/receive coils suitable for many body regions and studies, including a 32-channel head coil.

A range of advanced software packages including applications for neuro-imaging, fMRI, diffusion tensor imaging, tractography, real time imaging, cardiovascular imaging, blood flow measurement, MR angiography and spectroscopy has been installed. A stimulus-response system for functional MRI is available.

Radiographer support will be provided by the Imperial College Clinical Imaging Facility (CIF) and funded by the NIHR Imperial BRC.

Biobanking

Contacts: Professor Paul Elliott, BRC Theme Lead (p.elliott@imperial.ac.uk)
Mr Andrew Heard, School of Public Health (a.heard@imperial.ac.uk)
Paul Downey, Senior Scientific Development Manager (p.downey@imperial.ac.uk)

Located at the Hammersmith campus, the Biorepository provides for long term archiving of biological samples in vapour phase liquid nitrogen. It has a potential storage capacity of 1.92 million × 2 ml aliquots using 24 x Taylor-Wharton LABS80K dewars. Approximately 550,000 aliquots remain at Hammersmith, using 10 of the 11 installed dewars. In addition, we have approximately 200,000 aliquots in working storage. In total, these samples were donated by c. 43,000 participants.

The facility is fully "lights-out" in respect of filling and temperature monitoring, and supports remote operational control when necessary. Samples are identified within the Biorepository using fully anonymised barcode identifiers, the key to which is stored at a separate secure location. Using this key, database systems support rapid linkage to identifiable individuals according to detailed properties of their phenotype.

Genotyping has been carried out on c. 17000 participants. Imputation of 2000 of these genotypes has been completed, and the remaining 15,000 should be complete by summer 2015. Genotyping of a further 23,421 participants is in planning.

Tissue Bank

Contact: Professor Gerry Thomas, Imperial Tissue Bank (geraldine.thomas@imperial.ac.uk)

The Imperial College Healthcare Tissue Bank underpins translational research at Imperial College London and ICHT. It provides deemed ethics for non-interventional studies, and ensures that human tissue is collected and stored in accordance with the Human Tissue Act. Additional biological samples for research can be obtained from patients that are providing similar samples for diagnostic use under the Ethics provided by project approval by the Tissue Bank. Full details are given on the Tissue Bank webpages (www.imperial.ac.uk/tissuebank).

ICHTB facilitates collection of and access to:

- human tissue from surgical operations carried out within ICH Trust, and is surplus to diagnostic requirements;
- extra samples of biopsy or fluids taken specifically for research purposes at the same time as similar samples are taken for diagnostic purposes;
- fluid (e.g. blood/urine/sputum) samples taken from healthy volunteers;
- material used for xenografting;
- material that has been already used for diagnostic purposes;
- ICHTB also provides a mechanism by which human material, supplied by others (e.g. from clinical trials or cohort studies), can be brought into Imperial College and held under the College's HTA licence for use in research. Such studies usually have generic consent for future use of samples, and are initially covered by separate Ethics approval. When this ends, these collections are brought under the wing of the tissue bank, providing there is agreement with the suppliers of material that this may be done and there is an agreed protocol for access for further research studies. They remain as separate sub-collections within the tissue bank;
- All collections of human samples, whether subject to regulation by the HTA or not, are registered in the web-accessible on-line database, OLD (https://cisbic.bioinformatics.ic.ac.uk/tissue_bank/), which serves as a tracking database for collection and release of samples;

- Access to the database is username and password protected: all users must be approved initially by the Tissue Bank Manager;
- All data stored on OLD is anonymised –an alphanumeric code that provides coded information on the PI, the PI's department and a unique identifier for each sample from an individual donor.

Data on individual samples are further annotated by linkage with the National Cancer Registry Service for cancer outcomes, and, in a limited number of cases by data returned from NGS provided by CRUK's SMP2 project, or from NHS molecular pathology tests that have been run for clinical diagnostic need.

Currently, there are more than 200 individual sub-collections of human samples. More than 83,000 samples of surgical material that is surplus to diagnostic need from more than 20,000 patients is currently archived. In excess of 26,000 samples have already been issued for research.

NIHR/Wellcome Trust Imperial Clinical Research Facility

Contacts: Prof Martin Wilkins, Director (m.wilkins@imperial.ac.uk)
Dr Karen Mosley, CRF General Manager (k.mosley@imperial.ac.uk)
Mr Ben Lodge, Lead Nurse (Benjamin.lodge@imperial.nhs.uk)
Prof David Lewis, CRF Head of Clinical Studies (d.lewis@imperial.ac.uk)

Inpatient: The CRF has 13 in-patient beds, configured as male and female wards and 3 side rooms providing 24h stay and continuous monitoring. The CRF can also provide telemetry for inpatient monitoring and Holtor monitors for outpatient monitoring. Two side rooms are specialised for handling airborne toxins with negative pressure and one is equipped with a small lab containing a class II microbiological cabinet for adenovirus preparation. These side rooms are suitable for patients involved in protocols demanding isolation, e.g. gene therapy, virus challenges, sleep studies and radioisotope studies. All beds have IntellivueMP50 monitors linked to a central nursing station. Two rooms have been modified to support sleep studies, with continuous EEG and vital signs monitoring, infrared video surveillance and audio links to a remote laptop to allow overnight monitoring. A lounge area with television, PCs and games consoles provide entertainment for long-stay volunteers. IPads and laptops are also available for participant use within the clinical areas.

Day case studies: Two large rooms, each currently able to accommodate four recliners or beds are available for day case studies, although one has currently been reconfigured to allow 24h stay. The rooms have flexible partitioning allowing them to be split. A diet kitchen and three calorimeters provide for metabolic studies. Cardiopulmonary exercise testing is available for cardiovascular studies. Four consulting rooms, one interview room and a clinical measurement room cater for consenting and medical examinations for studies.

Laboratory space: A clinical laboratory enables on site centrifugation and preparation of biological samples for storage. Minus 80 and 20 laboratory freezers provide space for the short-term storage of specimens.

Staff: In addition to the facilities, the CRF are able to provide medical, clinical and operational staffing support

Applications to use the CRF are considered by the Protocol Review Board (PRB). This comprises members with expertise in human pharmacology, toxicology and statistics. It gives consideration to suitability and resource implications for CRF support. It meets twice monthly and works with the PI to ensure best outcome. Early engagement to discuss prospective studies is advised. Further details may be found on the CRF website: http://imperial.crf.nihr.ac.uk/

Annex 2 Additional Tests

For the following tests please contact Professor Zoltan Takats (z.takats@imperial.ac.uk);

Direct Mass Spectrometry

- Positive/Negative Chip-based nanospray
    - Untargeted (full scan)
    - Targeted (MRM on QQQ)
- REIMS of tissues with histopathology
- Direct ESI-REIMS of biofluids incl. faeces
- REIMS of bacteria/fungi
- REIMS/DESI of cell cultures
- Paperspray of biofluids
    - Enzyme assays

Gas-Chromatography-Mass Spectrometry

- Fatty acids
- Untargeted GC-MS

Imaging Mass Spectrometry

- Untargeted DESI imaging
- Targeted DESI imaging
- Imaging of bacterial presence

Additional Mass Spectrometry and sequencing assays

- Histological validation
- 16S rDNA sequencing by Sanger method
- Full bacterial genome/Metagenome sequencing by next generation sequencing