Institution: King's College London

Unit of Assessment: 1 - Clinical Medicine

a. Context

Background

The UoA1 return from King's College London (KCL) comprises 144 fte category A and C principal investigators (PIs) from 6 Divisions within the School of Medicine (SoM), namely Asthma, Allergy & Lung Biology (Respiratory); Cancer Studies (Cancer); Cardiovascular; Genetics & Molecular Medicine (Genetics); Immunology, Infection and Inflammatory Disease (DIIID); and Transplantation Immunology & Mucosal Biology (Transplantation). These Divisions manage and deliver research within KCL. Their reach has been purposefully extended to partner NHS trusts (annual turnover £1.8 billion, 1.2M patient episodes) through the creation of Clinical Academic Groups (CAGs) following the award of an Academic Health Sciences Centre to King's Health Partners (KHP). This reorganisation is apposite since the principal beneficiaries of the Divisions' research are patients, the NHS more broadly, and the pharmaceutical/devices industry. Consequently, the 6 Divisions have a clear focus on diseases which align with NHS Clinical Directorates delivering care. Each Division pursues interdisciplinary research for patient benefit and they share excellent infrastructure in cross-cutting enabling technologies, clinical research facilities and staff with expertise in clinical research delivery and governance (see section b). These communal technologies, facilities and staff are also shared and supported by the partner NHS trusts through the NIHR comprehensive Biomedical Research Centre (BRC, awarded 2007, renewed 2012) which is directly aligned to and led by the UoA1 Divisions. This close integration of disease-related research with clinical care and innovation within the NHS is reflected by the impact case studies which provide examples of benefits to patients through improvements in clinical diagnosis and care (1-15), service organisation (1-9), and optimisation of medication and health policy (10-15) (numbers refer to impact case studies in table, section d).

Benefits to Local and National Health Services

The creation of CAGs has ensured that KCL- and NHS- employees are in the same organisational structure thus enabling impact by increasing the relevance of research, enthusiasm to evaluate potential innovations and implement findings within the partner NHS trusts. This benefit to the NHS is illustrated by the provision of part salary funding to 50 clinical academics included in this return. In addition to local impact, the significance of this unit's research disseminates much more widely as illustrated by cases studies 1, 2, 3, 5, 8, 9,10 and 15 where impacts were implemented locally and later adopted nationally and then internationally. Thus, our research impacts on clinical diagnosis, e.g. the early detection of recurrent leukaemia (5), specialist genetic advice in the setting of in vitro fertilisation (1) and muscle weakness (4); where the research has altered national and international practice. We have developed and validated new therapies and treatment strategies, e.g. to prevent MRSA septicaemia (3) and for COPD (8,9), myeloproliferative disorders (11), rheumatoid arthritis (13), renal disease (10,12,15) and breast cancer (14); which have changed national and international clinical guidelines. Research on childhood allergies (7) and HIV transmission during pregnancy (2) has impacted not only on clinical care guidelines but has also had far-reaching impact on public policy and perception.

Benefits to Industry

Many of our impacts have had commercial benefits. Our work on non-invasive ventilation in COPD (9) has had major international impact on the manufacture of non-invasive ventilation devices. Innovative research on PARP inhibitors for the treatment of breast cancer (14) and JAK inhibitors for myeloproliferative disease (11) has led to substantial investment of well over £1.5 billion in large randomised clinical studies initiated by pharmaceutical companies. Similarly, the case studies indicating the benefit of renin-angiotensin blockade in diabetes (10), disease modifying drugs in rheumatoid disease (13) and haematinics in anaemia of chronic disease (12) have been instrumental in benefiting human health and promoting the use of products in these drug classes.

Influencing Policy, Practice and Public Perception

Impact studies 2, 3, 6, 7 and 8 have all influenced policy and practice but there is much greater breadth of influencing activities resulting from research undertaken by our unit. The research Divisions, through KHP, coordinate the South London Academic Health Sciences Network, the

Medicine for Children's Network, and National Health Informatics Collaboration on Transplantation.

Examples of our policy impact at the highest National and International levels include Moxham (Chair, Action on Smoking and Health; underpinned by research outputs on smoking-related lung disease, see REF2); Lechler (Chairman of Expert Advisory Group on novel biological agents for the Committee for Safety of Medicines; underpinned by research outputs on biological agents to alter inflammation, see REF2); Watt (House of Lords Science and Technology Committee inquiry into Regenerative Medicine; underpinned by research outputs on stem cells and tissue repair, see REF2); Young (UK Advisory Group on Non-Ionizing Radiation within Public Health England, and United Nations Environment Programme; underpinned by research outputs on the effects of ultraviolet light on the skin, see REF2).

International leadership of societies that influence policy include the European Society for Dermatological Research (Barker, McGrath), European Society for Microcirculation (Mann), European Society of Cardiology Heart Failure Association (Shah), Federation of Clinical Immunology Societies (Nestle), International Psoriasis Council (Barker), International Society for Heart Research (Avkiran), International Society for Stem Cell Research (Watt), Society for Free Radical Research International (Mann), International Society of Twin Studies (Spector).

PIs participate in a wide range of outreach activities to influence the public's awareness of medical research, e.g. at the British Science Festival, the Cheltenham Science Festival (http://goo.gl/3nWdxL), the Big Bang Fair (http://goo.gl/4qT6P6) and MRC Centenary events. We also work with local schools (e.g. www.kcl.ac.uk/innovation/REF/UoA1/Walthamstow-Academy.pdf), national press (e.g. http://www.theguardian.com/science/video/2011/nov/11/affairs-heart-heartbeat-video) and museums (e.g. http://www.youtube.com/watch?v=CDt_ebModRo) to foster public understanding. A formal outreach programme to pupils at non-selective schools in South London promotes medicine and research as a career (see http://www.kcl.ac.uk/medicine/study/outreach/index.aspx).

b. Approach to impact

Our strategy is to optimise the institutional framework to generate impact by engaging with individual researchers and research groups to identify and foster novel projects with intellectual assets and outstanding reach and significance. This exercise is distinct from usual academic activity. Impact and academic indices are recorded in the matrix used to formally appraise staff performance and used as metrics for promotion. These clear and transparent personal incentives to maximise impact are further underpinned by aligned investments to remove bottlenecks to impact (see below). Our submitted impacts were built on a platform of excellent research, informed by early engagement and dialogue with key stake holders. Our current scientific partnerships with local NHS Trusts, big pharma, biotech and technology companies together with clear institution-wide strategy, infrastructure, and performance management framework underpin our future impacts. Activities to influence policies, practice and public perception are also encouraged.

Identifying, fostering and protecting research

We support staff to generate impact in numerous ways. At institutional level, the King's Commercialisation Institute provides expertise on Intellectual Property, patenting, technology transfer, industrial partnerships and commercialism. Within this UoA, considerable technical and infrastructure support is provided by way of core facilities that underpin our ability to work with our NHS Trusts and industrial partners. This has been further fostered through the appointment of Commercial Development Directors within key CAGs to identify and exploit emerging research. These individuals report to the King's Commercialisation Institute board that holds strategic funds to overcome bottlenecks obstructing valued research assets and acts as a focus for interaction and exchange of ideas (e.g. http://goo.gl/kjkvoy). Recent examples illustrating the success of this framework include biological therapy for rheumatoid disease (http://goo.gl/l5Z9gL), a new device to measure central blood pressure (www.centrondiagnostics.com/), and a novel peptide therapy for type I diabetes (http://www.wellcome.ac.uk/News/2012/News/WTVM055001.htm).

Early engagement with industry

There are extensive collaborations with the pharmaceutical industry including GSK, Pfizer, Genentech, GE Healthcare, Novartis, Beckton Dickson (BD) Biosciences, Edwards Life Sciences and many others (£42.8M research contracts). Specific strategic partnerships for early discovery

include BD Biosciences to develop immunology platforms for clinical diagnostics and research application, Sanofi in type I diabetes (with JDRF), Pfizer in metabolomics in the UK Twin cohort, ImmuNext in renal transplantation, Serco in pathology, Edwards Life Sciences in our Transcatheter Aortic Valve Implantation programme, and a $150M licensing agreement with Johnson & Johnson Pharmaceuticals in oncology. Many of our impact case studies (10-14) emerged from similar early engagement and dialogue. Our spin-off share sales at £7.95M are 1st in the UK (2011/12).

Core facilities to aid translation and assess impact significance

Since 2008 a number of very substantial investments have been made by our Unit to enhance the likely impact of our research assets through detailed study of their clinical effect.

Clinical Research Facilities (CRFs; £35M investment) are used to gauge clinical impact by detailed measurements of effect size on surrogate disease endpoints. They were established through joint investments by our UoA and its partner NHS trusts. CRFs have been built in the Experimental Medicine Hub at Guy's campus (see below) as well as the King's College Hospital and St Thomas' Hospital campuses. Each CRF provides excellent purpose-built general facilities to access local patients while also housing dedicated campus-specific specialised facilities, e.g. measurement of cardiovascular and metabolic risk, a research PET/MRI facility with cyclotron and synthetic chemistry to measure tumour oxygenation and vascularity, an intensive care facility to measure systemic inflammation and haemodynamics in acutely ill patients, and a paediatric facility for controlled exposure to allergens. Discoveries during 2013 that would not be possible without these facilities include the basis of arterial stiffness (PMID 23339166) and the allergic potential of peanut protein in the environment (see PMID 23608730). These facilities are and have been used to examine the potential benefit of our Unit's research to decide which assets should be progressed (see impact case studies 9, 10, 15) so that our efforts can concentrate on those likely to deliver greatest impact. Our approach and the infrastructure created to asses impact, has also attracted Quintiles- the largest Clinical Research Organisation in the world- which has built a 30-bed state-of-the-art Phase 1 clinical trials facility within our unit**.**

GMP-grade Cell Therapy Suites (ca. £20M investment) are located in the Guy's Experimental Medicine Hub (see below) and the King's College Hospital CRF, focusing on immune cell therapy and haematopoietic/solid organ transplantation respectively. The TSB Cell Therapy Catapult provides clinical, technical, regulatory and business expertise and infrastructure designed to accelerate the transfer of new cell therapy products into the clinic, synergising perfectly with our research expertise in this area (see impact case studies 1, 5 and 11).

The BRC Experimental Medicine Hub (£18M investment) located on the Guy's campus of KCL contains outstanding infrastructure to capitalize on our research and ensure its impact. The facility delivers clinical research studies ranging from proof-of-concept experimental medicine and early translational work through to clinical trials. It includes (a) a GMP Pharmacy Manufacturing Unit for formulation of small molecules for first-in-man use (for example an inhibitor of neuronal nitric oxide synthase, see PMID 23436331 and 23479261); (b) a Phase 1 Clinical Trials Unit (partnership between Quintiles and KCL); (c) a Joint Clinical Trials Office which provides advice on study design, ethical/R&D approval, MHRA approval, and consultancy services in clinical trials management and biostatistics; (d) an Immune Monitoring Core with cell sorting facilities enabling new lines of research (for example ThRIL: a 'first-in-human' study evaluating the safety, tolerability and efficacy of Tregs in liver transplant recipients, an MRC DFS award of £2.1M to start Oct 2013); (e) a Genomics Core with state-of-the-art services for next generation genomic DNA/RNA sequencing, high throughput SNP genotyping and genome-wide gene expression analysis on microarrays; (f) a Bioinformatics Core comprising a team of data managers, bioinformaticians and statisticians who provide bioinformatic analysis of sequence and array data, interrogation of publicly available datasets, integration into network and pathway analysis, development of databases for integrated analysis of clinical, genomic and other biological data, and provision of computing capacity for analysis of data and secure storage. This interdigitating set of facilities, purposefully designed in one location to facilitate clinical translation and prioritisation of our research property, is probably unique in Europe.

In vivo imaging (>£50M): The SoM has established comprehensive infrastructure and facilities for pre-clinical and clinical in vivo imaging which are world-leading. These include dedicated research MRI (1.5, 3, 7 and 9.4 Tesla; hybrid XMR), multinuclear and hyperpolarized spectroscopy, PET/CT,

SPECT/CT, PET/MRI, embedded chemistry for design/synthesis of new probes, and physics/maths/computer science for novel image acquisition, processing and co-registration. This cross-cutting investment dovetails with the clinical research facilities, immune monitoring core and GMP manufacturing unit in the experimental medicine hub (see above) through the design and manufacture of probes to image complement activation (for example PMID 21494666), regulatory T-lymphocytes (see 23574314 and 22043296) and specific sequences for cardiovascular imaging (for examples during 2013 see PMID 23833284, 23582358, 23498674, 23403334, 23383687, 23375929, 23246014).

Biological services (£20M). Each of the 6 Divisions has access to new or recently refurbished animal research units close to their research laboratories. These provide comprehensive facilities for breeding, genomic manipulation and specialist phenotyping, including advanced imaging by MRI, CT, SPECT and infrared fluorescence imaging. These facilities aid in enabling models that recapitulate human disease with endpoints that match those used later in the clinic.

Core Facilities to optimise discovery and drug design

The Centre for Biomolecular Spectroscopy (£3M) established in 2010 with Wellcome Trust support houses outstanding expertise and equipment to determine protein and small molecule structure, protein-drug, and drug-drug interaction, with analyses by NMR spectroscopy, surface plasmon resonance, isothermal titration calorimetry, optical spectroscopy and related techniques. These have been used to gain biological insights at the atomic level that are likely to lead to new therapies (examples during 2013 include activation of a kinase that aggravates myocardial infarction PMID 24037507) and the mechanism of allergen recognition by IgE (PMID 23933509).

The Nikon Imaging Centre (£4.5M) for advanced microscopy was established in 2012 in partnership with Nikon. It is one of only 8 such Centres worldwide and provides the very latest advanced cell/tissue imaging approaches, e.g. FRET, FLAP, GFP-complementation; spinning disk/laser/multiphoton/STED/ STORM super-resolution microscopy; and intravital microscopy. These examine biological processes and the actions of drugs at the cellular and subcellular level.

The Randall Division of Molecular Biophysics provides core expertise in biophysics and has facilities for single-molecule force-spectroscopy; protein purification and crystallization; robotic screening; site-directed protein labelling; fluorescence polarisation microscopy; muscle fibre reconstitution; and muscle X-ray diffraction analysis. Three of the Divisions in this Unit have particularly close interactions with the Randall through joint staff appointed on peer-reviewed Centre awards, namely the BHF Centre of Excellence, the MRC Transplantation Centre and the MRC/Asthma Research Centre.

Other core institutional facilities that enhance the impact of research include comprehensive mass spectrometry facilities for proteomics, metabolomics and specialist assays; transmission and scanning electron microscopy and a human ES cell production unit associated with the Assisted Conception Unit.

c. Strategy and plans

Our strategy to ensure future impact has major focus on maximising the potential of our workforce to capitalise on the support structures and infrastructure described above through structured development, the nurturing of early career researchers and the recruitment of established research groups. The vitality and attractiveness of our unit will be maintained through further reorganisation, investments in infrastructure and a closer alignment with our partner Trusts.

Staff Development

Our appraisal scheme has recently been simplified to focus on an agreed Structured Personal Development Plan which is actively supported and closely monitored. The KCL Researcher Development Unit (RDU) provides >300 workshops/year covering topic such as leadership, management, entrepreneurial skills, mentorship, and becoming a PI (http://www.kcl.ac.uk/study/pg/school/training/RDPTrainingBrochure.aspx). The RDU is leading on implementing the Concordat for the Career Development of Research Staff and obtaining HR Excellence in Research badging from the European Commission. It provides a lead for College policy and strategy on personal, professional and career development and hosts the Vitae London Hub (http://www.vitae.ac.uk), shaping national policy on researcher development.

Nurturing Young Investigators

At the unit-level, we nurture Early Career Researchers (ECR) though a dedicated mentoring scheme to hone their research fellowships, ensure the clinical relevance of their work and support their early independence. We also introduce them to a culture of innovation and commercialisation though workshops and competitions such as a local Lion's Den (http://goo.gl/j4CGH) and encouraging involvement in National Competitions (http://goo.gl/DUfcfz). The Divisions support ECR Fora to facilitate interaction and networking independent of senior researchers. Investment in 18-24 month Career Development Fellowships has proven particularly effective in the independent development of the brightest postdocs (recruited from outside KCL or internally) and this scheme will be extended through the Wellcome Trust Institutional Strategic Support Fund (£1M pa), a partnership with Nomura, and the major Centres hosted by our Divisions (e.g. the BHF and MRC Centres). We are also investing in Crick Lecturer positions (see below), and at least 4 of these positions will be based within this UoA.

Recruiting Established Research Groups

During the past five years there have been strategic appointments at a Senior level to consolidate and advance existing areas of translational research. Importantly, research impact is central to our recruitment strategy with several appointments to enhance our activities in cell therapy (e.g. Fiona Watt FRS, to lead the King's Centre for Stem Cells and Regenerative Medicine), cardiovascular ageing (e.g. Kinya Otsu a new BHF Chair) and immune tolerance in transplantation (e.g. Randy Noelle, Wellcome Trust Principal Fellow).

Aligning University and Trust Resources

The establishment of KHP is a major boost to the alignment and integration of academic and clinical strategy across this UoA. The 6 Divisions each form the core academic component of a KHP CAG (see section a) and are each linked to nationally and internationally-leading clinical services. Each CAG was formed with a unified, well-developed and extensively-reviewed vision and strategy for the delivery of excellence in clinical care, research and education. This integration of KCL-based and NHS-based research and service work has had significant impact on clinical and translational research, capacity-building and research training, as well as the clinical service, and we expect these positive effects to further accelerate over the next few years. A powerful driver that has supported and synergised with KHP CAGs is the co-development of our NIHR comprehensive BRC. This has not only enhanced the translational research of our CAGs, each of which contribute to specific themes within the BRC, but also facilitated effective integration across CAGs. In the future this integration will be enhanced by the consolidation and synergy offered through our 4 new BRC Clusters (i.e. Experimental Medicine & Therapeutics; Biomarker, Devices, Co-diagnostics & Imaging; Population Science; School of Translational Research) and the outstanding and rapidly evolving core clinical research infrastructure that supports our work (described in section b). In addition we are extending the role of the CAG-based Commercial Development Directors (see section b, Identifying, fostering and protecting research) to enable a better understanding of and alignment with commercial concerns, thereby improving liaison with industry and impact of our research. Such liaison enables us to harness our clinical throughput to improve care and examples include innovations in therapy for valvular heart disease (e.g. on-going trials on which we lead include NCT01238835, NCT01238497, NCT01742598, NCT01493284, NCT01598844), the use of biomarkers to refine the diagnosis of heart disease (see PMID 23345538, 23283721, 23255316, 22813605, 22261194), and a collaboration with Somalogics focused on new proteomics-based technology for biomarker discovery.

Reorganisation of Health Research within KCL

We constantly appraise our Institution's structure and adapt it to ensure best-fit for purpose. Our most recent review has highlighted that high quality fundamental basic science researchers are not necessarily within sight of the relevant clinical research groups and that neuroscience research occurs across different Health Schools. This fragmentation; founded in the historical division of preclinical, clinical and postgraduate medical teaching; is hindering research synergy, reducing efficiency and impeding translation. To maximise the impact of our research findings we plan to reorganise the Schools of Biomedical Sciences, Medicine and the Institute of Psychiatry to create a Faculty of Life Sciences and Medicine (FLSM) and an Institute of Psychiatry, Psychology and

Neuroscience (IoPPN). Following the recent completion of an extensive review, consultation and iterative reshaping of strategy, we expect the new structure to be implemented in Sept 2014.

Further Focussed Investments in Infrastructure

The Francis Crick Institute (FCI). KCL is investing £40M in partnership with the MRC, CRUK, Wellcome Trust, Imperial and UCL in this new Institute which will be operational during 2015. Our unit will embed key staff in the FCI and FCI scientists will be seconded to our unit. This exchange will focus on exploitation and clinical translation of the fundamental and outstanding science within the FCI. About 100 FCI PhD students will have King's co-supervisors. King's has recently appointed 11 new lecturer/senior lecturer positions linked to FCI (e.g. Arnold, Barrall, Schulz, Ciccarelli within this submission).

A new Cancer Centre. This £80M new build, between our Unit and a partner trust, will have dedicated space for clinical research trials, biobanking and bioinformatics to enable the evaluation of therapies personalized to tumour characteristics. An additional £15M has now been awarded from the UK Research Partnership Investment Fund (UKRPIF) towards a ***Research and Innovation Hub*** within the new Centre.

Britannia House. This £14M refurbishment will house a dedicated pharmaceutical industry standard research facility for computational and synthetic chemistry to generate lead compounds based on discovery screens undertaken in Divisional facilities.

A Science Gallery. To further Public Engagement, we have raised £7M for a Science Gallery to open in 2016 on the Guy's Campus as a founding member of an international network of Science Galleries including Dublin and New York.

d. Relationship to case studies

A table summarising our impact case studies appears below. The identification numbers of each study is used throughout sections a and b to illustrate their relationship to our beneficiaries and how they have shaped our strategy to maximise impact. The key sections in which these case studies are highlighted are "a" (benefits to local and NHS services, benefits to industry and influencing policy and practice) and "b" (early engagement with industry and core facilities to aid translation).

ID & Division	*Abbreviated Title*	*Summary of Impact*
Service Organisation/Diagnostics		
1. Genetics	PGD diagnosis	Blastocyst selection for best outcome in IVF
2. DIIID	HIV in pregnancy	Reduced mother to child transmission of HIV
3. DIIID	MRSA eradication	Fewer in-hospital systemic MRSA episodes
4. Cardio	Genetics of muscle disease	Improved diagnosis and counselling
5. Cancer	Detecting leukaemia	Early detection of new/recurrent APL
6. Cancer	CV risk of hormone therapy	Reduced CV events in patients with prostate cancer
7. Resp	Peanut allergy	Less allergy through purposeful exposure
8. Resp	Rehabilitation for COPD	Reduced readmission and improved quality of life
9. Resp	Non-invasive ventilation	Reduced mortality during exacerbations of COPD
Pharmaceuticals		
10. Cardio	Kidney failure in diabetes	Use of RAAS inhibitors to slow renal failure
11. Cancer	Myeloproliferative neoplasia	Use of JAK inhibitors to improve prognosis
12. Transplant	Anaemia in kidney disease	Less transfusion and improved quality of life
13. DIIID	Drugs for Rheumatoid	Less active disease and improved quality of life
14. Cancer	PARP inhibitors for breast and ovarian cancer	Reduced growth of BRCA associated tumours
Surgery		
15. Transplant	Botulinum toxin for OAB	Improved urinary continence