Institution: Queen's University Belfast

Unit of Assessment: UoA 1

A. OVERVIEW

Biomedical research at Queen's University Belfast has undergone far-reaching changes during this REF period. A new School of Medicine, Dentistry and Biomedical Sciences (MDBMS) has been formed within the Faculty of Medicine, Health and Life Sciences, with advice from an eminent Scientific Advisory Board (SAB) chaired by Prof Teo Forcht Dagi (Harvard Medical School). Our research is conducted within an Institute of Health Sciences (IHS), which integrates strong research teams in four interdisciplinary groupings where we have focused our resources:

- the Centre for Cancer Research and Cell Biology (CCRCB)
- the Centre for Infection & Immunity (CII),
- the Centre for Experimental Medicine (CEM)
- the Centre for Public Health (CPH)*

These Centres provide the critical mass of clinical and scientific investigators needed to deliver ground-breaking, clinically-relevant research. They link seamlessly with our three Education Centres (Medicine, Dentistry and Biomedical Sciences) and collectively create an innovative and dynamic research and learning environment.

**Note: Research conducted within CPH has been returned in UoA2.*

B. RESEARCH STRATEGY

STRATEGIC VISION

At the start of the REF period, Queen's successfully implemented a major re-organisation of biomedical research, creating strategically-focused and international-quality Research Centres that are integrated and aligned to clinical research within the Belfast Health and Social Care Trust (BHSCT). As a result of ongoing success, further expansion and development of the IHS remains the foremost strategic research priority of Queen's into the next decade. The vision for the IHS is to make Northern Ireland a global leader in specific areas of biomedical education and research whilst also serving as an innovation hub for bioscience and technology companies. Supported by national and international partners, the University has committed to a total investment of over £90 Million. This will attract additional academic leaders in our prioritised disease-areas and further enhance our research infrastructure through construction of new facilities and expansion of a range of high-level technological platforms. These will also be aligned closely with government initiatives to drive collaborations between academia and industry. This strategy provides a framework for improving our understanding of disease pathogenesis, developing the next generation of diagnostics, medical products and novel therapies, and informing changes to clinical practice that bridge the innovation gap between scientific discovery and patient application.

The over-arching vision of the Institute of Health Sciences over the next five years is to:

- facilitate the development of high quality, co-ordinated programmes of strategically targeted health-related research, resulting in better patient care;
- attract high quality clinical and basic science researchers to Queen's whilst encouraging the brightest science and clinical graduates to pursue careers in biomedical and medical research and mentor the next generation;
- maximise the future grant-winning potential of our researchers with funding agencies such as the RCUK, EU, Wellcome Trust, health charities, National Institutes of Health (NIHR), Science Foundation Ireland and the biotech/pharma industry;
- enhance undergraduate and postgraduate educational programmes available through the development of innovative modules in biomedical science, molecular medicine, medical training and practice, medical leadership, bioinformatics, bioethics and related disciplines;
- continue to drive the development of the bio-industry in line with the Northern Ireland and UK Technology Foresight Exercise, which provides support for spin-out companies and job creation thereby underpinning the growth of a new enterprise sector in life sciences;
- continue and extend our interactions with the biotechnology and pharmaceutical industries through strategic alliance, contract research and consultancy;
- further contribute to local economic growth through partnerships with successful NI based companies such as Almac, Norbrook, Randox and Andor;

- enrich broader scientific and public debate and raise awareness of ethical and societal issues related to clinical and basic research.

ACHIEVEMENT OF STRATEGIC AIMS DURING REF PERIOD

The changes at Queen's have been highly successful, as emphasised by our recent SAB evaluation, which reported that *"……the changes put in place are transformative. The accomplishments have been profound and challenging goals have been accomplished. There have been notable achievements in providing a deeper understanding of important diseases, generation of new therapeutic approaches and identification of novel biomarkers for diagnosis/prognosis towards treatment stratification"*. Significant achievements over the past five years have been:

- fundamental re-organisation of the strategy, management and delivery of biomedical research, which is now conducted within four focussed Research Centres;
- a dramatic increase in the quality of biomedical research across the entire IHS, as exemplified by the quality of our research outputs, publications and grant awards;
- over £90 million in new grants awarded during the REF period and a 54% increase in research expenditure in this REF period when compared with RAE 2008;
- appointment of 53 new clinical and non-clinical academic staff during REF period;
- establishment of a Cancer Research UK-Cancer Research Centre (CRUK-CRC) leading to enhanced cancer survival rates in Northern Ireland, and the subsequent award of Her Majesty's Diamond Jubilee Anniversary Prize for Higher and Further Education in 2011 for the University Led Comprehensive Cancer Services Programme;
- opening of a new Clinical Research Facility funded by the Wellcome Trust and Wolfson Foundation (£6 Million);
- membership of the NIHR/MRC Respiratory Translational Research Partnership;
- creation of an All-Ireland Hub for Trials Methodology Research (1 of 8 MRC Methodology Hubs across the UK);
- award of a UK Research Partnership Infrastructure Fund grant (£32 Million total funding) for the Centre for Experimental Medicine including the Wellcome Trust – Wolfson Foundation Capital Award (£4.8 Million) for Vision Science;
- commercialisation partnerships with several leading biotech and pharmaceutical companies, including GSK, Novartis, Amgen, Johnson & Johnson;
- development of 5 spin-out companies, currently employing over 200 people generating an annual turnover in 2012-13 of some £7.3 Million.

RESEARCH GROUP ACTIVITY, RATIONALE & ACHIEVEMENTS

The programmes of our Research Centres span "discovery to recovery" and "process to population". These strategies have been developed in association with IHS and University priorities, along with input from Centre-specific Scientific Advisory Boards, which advise on programme development. The Centres have been effective in developing focussed, translationally-oriented research themes, providing critical mass for inter- and intra-group multidisciplinary partnerships, development of self-sustaining research teams and sharing of resources. We have responded successfully to national/international priorities and initiatives. Importantly, researchers across the Centres collaborate effectively, as evidenced by shared grants, joint publications and co-supervision. Details of three of these Centres are presented in UoA1 while the fourth (CPH) is returned under UoA2.

1. THE CENTRE FOR CANCER RESEARCH AND CELL BIOLOGY (CCRCB)

1a Group development in CCRCB

CCRCB forms the hub of the Belfast Cancer Research UK (CR-UK) Centre, launched in Spring 2009 and the Belfast Experimental Cancer Medicine Centre. CCRCB has recently been awarded one of two Movember/Prostate Cancer UK "Centres of Excellence". Integrated clinical and basic scientific research programmes address clinically-relevant questions and areas of strategic priority, the outputs of which are underpinning improved patient outcomes in high incidence solid tumours of **Gastro-intestinal**, **Prostatic**, **Breast** and **Ovarian** origin. The unifying research theme is to develop translational outputs including biomarkers and/or novel therapeutic strategies that enable CCRCB to be at the forefront of personalized cancer medicine in these prevalent diseases. The

major impact of this research on patient outcomes in Northern Ireland resulted in the University receiving Her Majesty's Diamond Jubilee Anniversary Prize in 2011.

1b Selected research achievements during REF period

Biomarker Discovery exploiting Integrated Molecular Pathology and Bioinformatics Biomarker discovery and validation is led by **Salto-Tellez, James** and **Hamilton**. They have developed a state-of-the-art Clinical Pathology Accredited (CPA)-Molecular Pathology Laboratory (MPL), which incorporates a Regional Cancer Bio-Bank and a Digital Pathology facility. Through partnership with the Clinical Cancer Centre, and the Northern Ireland Cancer Registry, genetic discovery is being linked to patient data, enabling our (BBSRC/EPSRC-funded) bioinformaticians **Emmert-Streib** and **Zhang** to develop new algorithms that mine these datasets and correlate gene expression, next generation sequencing and mutational analysis to clinical outcome. This group is also developing algorithms permitting high throughput analysis of immunohistochemical and cytological data, to facilitate rapid automated quantitative scoring of biomarkers or therapeutic targets in arrayed tumour material. Such capabilities have permitted CCRCB investigator teams to establish and validate *de novo* diagnostic biomarkers and/or predictors of response. For example, **Kennedy**, **Harkin and Johnston** have successfully developed and validated a biomarker signature identifying patients with stage II colorectal cancer, who benefit from the provision of adjuvant chemotherapy post-surgery. **Mills** (EU-funded) has developed biomarkers assisting in sub-classifying myelodysplastic syndromes at differential risk of developing acute myeloid leukaemia, the biology of which is being investigated in advanced disease models by **Thompson**. The MRC funded Leukaemia & Lymphoma Research-Trials Acceleration Programme (LLR-*TAP*) led by **McMullin,** has identified novel mutations in the HIF2α gene and associated signalling proteins, revolutionising the diagnosis of a rare form of erythrocytosis. Finally, **El-Tanani** has discovered the role of Ran-GTPase as a biomarker of elevated risk of metastasis in breast cancer; a finding published in the *Journal of the National Cancer Institute* (JNCI).

Gastro-intestinal Cancer With CRUK Programme grant funding (~£2.5 Million), **Johnston, Lawler, Longley, van Schaeybroeck and Coyle** have established new paradigms of drug resistance, including the importance of ADAM-driven EGFR signalling as a major determinant of treatment-resistance to molecular-targeted therapeutics in RAS-mutant colorectal tumours. Further work by **Longley** has established the significance of c-FLIP as a prognostic marker and a predictive marker of tumour response to conventional chemotherapy and novel molecular-targeted agents. He has successfully used this foundation to leverage funding (£4 Million) from the Wellcome Trust Seeding Drug Discovery Initiative to initiate targeting of this key anti-apoptotic protein in cancer. **Salto-Tellez**, in partnership with the world-leading gastric adenocarcinoma group in Singapore, has also identified key pathogenic features of this disease, findings which have been featured in *Nature*. Clinically, **Wilson** has been a major academic lead of the MRC-funded COIN phase III clinical trial which investigated the impact of key molecular stratifications upon the outcome of chemotherapy and chemotherapy/EGFR therapeutic combinations in colorectal cancer. Ongoing studies by CCRCB investigators are using these tissues to discover and validate novel biomarkers of resistance and sensitivity to these treatments.

Prostate Cancer CCRCB research in prostate cancer is focused on addressing the limited number of clinically-applicable biomarkers and the absence of strategies for personalized cancer medicine. With MRC and CRUK funding, **Waugh** has focused on PTEN-deficient tumours (>40% of prostate tumours) and demonstrated the importance of selective inflammatory IL-8 signalling and up-regulation of c-FLIP as key adaptive survival mechanisms in these tumours, driving the transition to disease which is resistant to castration and current therapies. **Prise** is leading a comprehensive radiotherapy resistance programme, building on his reputation as an international leader in radiation bystander responses. His work has identified the importance of key DNA-damage mediators in modulating direct and indirect cellular responses to radiation and the key biological mediators that orchestrate out-of-field radiation responses. **O'Sullivan** has led early-phase trials of the radionuclide Rhenium in castration-resistant prostate cancer and was lead recruiter and major academic contributor to the successful international phase III study of alpharadin (Radium-223), recently published in the *New England Journal of Medicine*. An expansion of therapeutic targets for urological malignancies is being driven by **McCloskey,** who has uncovered fundamental roles for ion channels in regulating interstitial cells of Cajal in the bladder.

Breast/Ovarian Cancer Research into BRCA1, a major breast cancer susceptibility gene, is a strength permeating our breast and ovarian cancer research. Through CRUK Programme and MRC funding, **Harkin** and **Mullan** have established significant new insights into the function of BRCA1. Their outputs elaborate on the mechanisms by which BRCA1 (i) regulates basal cell marker expression, (ii) underpins selective therapeutic response to chemotherapy agents, and (iii) modulates splicing efficiency to affect a further level of control on gene expression. In addition, they have characterized the role of a novel BRCA1-GATA3 interaction in preventing the outgrowth of cells expressing proliferation and basal-like breast cancer markers and shown that BRCA1 co-operates with p63 to regulate genes involved in breast differentiation, genomic stability and growth control. **Kennedy**'s NIH-funded basic research programme has concentrated on understanding the role of BRCA1 and the Fanconi genes in regulating the response of cells to DNA-damage insults. Together with **Savage**, whose work on DNA-damage mechanisms was featured in *Nature*, he is unearthing new biological insights to underpin improved use of DNA-damage therapy in cancer treatment. A DNA-damage gene signature which identifies tumours susceptible to DNA-damaging agents and PARP inhibitors is in advanced clinical validation and is accepted for publication in the *Journal of the National Cancer Institute*. Finally, our knowledge of oncogene function in these diseases, specifically p53 and p63 is further informed by the MRC-funded studies of **McCance, Patel** and **McDade**, using ChiP/RNA-sequencing analysis to understand the molecular basis of their oncogenic function in solid tumours including breast cancer.

1c Plans for further development of CCRCB

Our future development will consolidate our existing pre-clinical strengths with increasing emphasis on the development and exploitation of advanced models reflecting specific disease stratifications. Using this foundation for discovery, we expect to make significant contributions to personalized cancer medicine in our priority diseases. The recent validation of the ColDX signature in a Cancer and Leukaemia Group B study is an exemplar of the strength of our biomarker discovery platform. A significant number of further biomarkers are in advanced validation and early commercialization, which we will exploit in underpinning further innovative early-phase clinical trials led from Belfast across the UK-wide Experimental Cancer Medicine Centre network. Furthermore, our biological discovery is also underpinning clinical innovation; for example, MErCURIc, a pan-European, phase I/II EU-funded trial (€6.2 Million) is evaluating the novel combination of targeted agents in RAS-mutant colorectal cancer, established by the pre-clinical work of **van Schaeybroeck** and **Johnston. Wilson** leads clinical trials on major international studies, such as the major adaptive phase III trial FOCUS-4 which uses molecular biomarkers to guide patient treatment for metastatic colorectal cancer. He is PI on the Small Bowel Adenocarcinoma trial and Add-Aspirin trials organized by the International Rare Cancers Initiative (IRCI). **O'Sullivan** is also PI for the next trials of the radionuclide Radium-223 in castrate-resistant prostate cancer. Supported by the recruitment of **Jain** and **Coyle**, and further leadership appointments (including in Imaging, Animal Models and Clinical Haematology) we expect this trajectory of conducting biomarker-guided and biologically-informed clinical trials to expand significantly over the next quinquennium. Moreover, £5.5 Million from an Industrial-Academic partnership with Almac Discovery to accelerate drug discovery will increase the capacity of CCRCB to expand the portfolio of targeted cancer agents for exploitation in personalized cancer medicine trials in the future.

2. THE CENTRE FOR INFECTION & IMMUNITY (CII)

2a Group development in CII

CII has evolved from strong respiratory medicine and infectious disease clusters and incorporates a range of researchers from complementary disciplines including immunologists, microbiologists and virologists. Research within the CII is focused on the pathophysiology of a range of human diseases caused by infection and inflammation and the application of innovative new therapies. The Centre has three research themes; **Innate and Adaptive Immunity, Microbial Pathogenesis,** and **Clinical Trials & Biomarkers.** Within these themes there is a strong primary focus on a number of airway diseases especially **Cystic Fibrosis (CF), Acute Lung Injury (ALI)**, **Asthma** and **Cough.** The main focus of CII is to develop translational research, involving basic and applied research devoted to understanding mechanisms of disease and drug discovery/evaluation, through to clinical trials aimed at diagnostic and therapeutic intervention. As with the other Centres, CII has been further strengthened by recent key academic appointments.

2b Selected research achievements during REF period

Innate and Acquired Immunity The Lung Innate Immunity Programme (**Elborn, Taggart, McAuley, Kissenpfennig, Ingram, O'Kane**) was successfully developed following priming funding by the Department for Employment and Learning (DEL) in 2009 (£1.6 Million) to evaluate novel drugs for the treatment of acute lung injury, asthma and cystic fibrosis using relevant animal models of these diseases. This was part of an All-Ireland initiative to stimulate cross-border interaction with colleagues in the Republic of Ireland and resulted in further major funding through an EPSRC Drug Discovery Grant (**Taggart**) to develop nanoparticle-mediated delivery of antibiotics and protease inhibitors to the cystic fibrosis lung. Other significant programmes deriving from the DEL programme grant include a MRC research grant in 2011 (**Kissenpfennig** and **Heaney**) to examine the role of Th2 lymphocytes and Suppressors of Cytokine Signalling (SOCS) in asthma which has resulted in significant discoveries regarding the role of SOCS proteins in the regulation of allergy-induced airway inflammation and macrophage polarisation. The recent appointment of **Moynagh** brings senior leadership to adaptive immunity research. His discoveries on Pellino 3 ubiquitin ligase are focussed on identifying novel targets to regulate mucosal inflammation. Further relevant studies in lung innate immunity include remodelling in the cystic fibrosis airway by **O'Kane** who is an MRC/Dept of Health-funded Clinician Scientist. **Ennis, Dib** and **Schock** have active programmes looking at modulation of inflammation in the CF airways. **Dib** has also been awarded an EU FP7 Marie Curie Fellowship to investigate novel aspects of neutrophil function and integrin binding with the Max Planck Institute in Munich. Appointees to CII are now integrated into the Lung Innate Immunity Programme, including **Krasnodemskaya** (recruited from University of California San Francisco) who is developing a programme to evaluate the use of mesenchymal stem cells in lung tissue regeneration and **Weldon** who is evaluating circulating miRNA in patients with ALI and CF.

Microbial Pathogenesis The thematic focus of this group of researchers (**Valvano**, **Bengoechea, Elborn, Patrick, Lundy, Duprex** and **Power)** is evaluation of human-specific pathogenic bacteria and viruses. CII has been supported by the University with the recent appointment of **Valvano** (from University of Western Ontario, Canada) who is researching the pathogenic role of Gram negative bacteria such as *Burkholderia cepacia.* Another significant appointee is **Bengoechea** from Fundació d'Investigació Sanitària de les Illes Balears in Spain. He has an EU FP7 funded programme investigating bacterial interactions with the lung innate immune system with a particular emphasis on how bacteria such as *Klebsiella pneumoniae* employ strategies to subvert the inflammatory response to infection in the lung. In parallel, there are a number of studies looking at anaerobic bacteria in disease (**Elborn**, **Patrick** and **Lundy**). **Elborn** is PI on an NIH-funded study (£1.7M) investigating the role of anaerobic bacteria in lung disease with a focus on the role of the lung microbiota in pulmonary exacerbations in patients with CF and non-CF bronchiectasis. **Patrick** researches obligate anaerobic bacteria and virulence mechanisms of *P. acnes* and *B. fragilis* whilst **Lundy** focuses on the host defence-peptide response to oral anaerobic pathogens via programmes funded by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3R) and industry. Two new appointments to CII are investigating the innate and adaptive immune response to respiratory infection (**Ingram**) and antibiotic resistance in the Gram-negative bacteria *Klebsiella pneumoniae* (**Schneiders**, recipient of a MRC New Investigator Award). **McMullan** and **Shields**, in collaboration with the biotechnology company Randox, have created diagnostic tests for detection of bacterial infection in patients. With funding from the Technology Strategy Board (£830K), **McMullan** is developing a point-of-care device to guide immediate treatment of patients with sepsis in the intensive care unit. **Shields** has patented a test using the loop mediated isothermal amplification (LAMP) method for the rapid detection of *Neisseria meningitidis*. **Duprex** is active in the area of measles' infection. This includes development of a primate model for measles infection via a successful MRC-funded Models of Disease Programme Award (£1.1 Million) in collaboration with the Erasmus University in Rotterdam. **Power** has established a unique model of RSV infection using primary bronchial epithelial cultures, which is an authentic surrogate for viral infection of airway epithelium *in vivo.*

Clinical Trials & Biomarkers CII is focused on translational research with an ambitious programme in investigator-led (**Elborn, McAuley, Heaney, McGarvey, Blackwood** and **Rooney**) pre-clinical development and integrated collaboration in Phase I, Phase II and Phase III clinical trials which combine investigator-initiated and collaborative studies with the pharmaceutical industry. Phase I

clinical trials in respiratory disease have been funded by Aquinox, Novartis and Pulmatriva (**Elborn**), GSK (**McAuley**), Amgen (**Heaney**) and Chiesi (**McGarvey**). We have an established collaboration with Celerion, a contract research organisation (CRO) with a facility in Belfast that specialises in early-stage clinical trials, for on-going Phase I clinical research. Through three clinical research networks supported by the Northern Ireland Clinical Research Network, i.e., Respiratory Health, Critical Care and Medicines for Children, we undertake a large number of Phase II and III studies. These networks integrate with the UK Clinical Research Network. Nationally we are a Founder Centre in the Translational Research Partnership (Office for Strategic Co-ordination of Health Research/NIHR) and internationally we are part of the European Cystic Fibrosis Clinical Trials Network. CII supports investigator-led research at all levels whilst effectively working with industrial partners. **McAuley** has been funded by MRC's Efficacy and Mechanism Evaluation (EME) programme to test pre-existing therapies for novel evaluation in ALI and, along with **Blackwood,** has established internationally agreed guidelines regarding mechanical ventilation in the critically ill. The role of disease biomarkers is also an area of interest in CII. **Rooney** is funded by the Arthritis Research Campaign to identify circulating biomarkers in rheumatoid patients and **Taggart** is developing a neutrophil-derived lung biomarker as a possible rapid diagnostic test for bacterial lung infection (KTP funded with Randox Ltd). **Elborn, Taggart, Ingram** and **Weldon** have been funded through the EU FP7 programme to evaluate microbiome-directed antibiotic therapy in a CF clinical trial along with partners in Ireland, Germany, France and the USA. This programme is an example of the international collaborations that have been developed during the REF period.

2c Plans for further development of CII

Major investment has been made in recruiting eight new academic research leaders in CII. In particular, the innate immunity research base has been enhanced by the appointment of three professorial leads (**Valvano, Bengoechea** and **Moynagh**) with expertise in respiratory-based molecular microbiology and immunology. Additional senior appointments will be made to further strengthen immunology and clinical investigators in respiratory medicine and immunology will enhance translational research into disease mechanisms in respiratory disorders.

In terms of specific programme development strategies, major research themes will continue in disease mechanism evaluation, currently funded by MRC, NIH and EU FP7, as well as drug discovery and drug evaluation in *in vivo* models, supported by EPSRC, KTP, EU FP7 and pharma. An important aspect to these studies will be to link closely with clinical academics in the clinical trials arena, to bring forward observations from translational studies in pre-clinical models to the important 'first in man' trials, as well as evaluation of repurposed or reconditioned drugs. In this respect, on-going commercial partnerships and support via the MRC's Biomedical Catalyst: Developmental Pathway Funding Scheme will be vital, as will linkage to larger scale collaborations with other UK-based groups via the NIHR Respiratory Translational Research Partnership.

3. THE CENTRE FOR EXPERIMENTAL MEDICINE (CEM)

3a Group development in CEM

The CEM has built on the success and expansion of the former Centre for Vision & Vascular Science (CVVS) and has secured the award of a £32 Million infrastructure grant from the UK Research Partnership Investment Fund (UKRPIF). The new Wellcome-Wolfson CEM building (~5,000m^2) will open in spring 2015. This Centre consists of two inter-linked groups based on **Ophthalmology** and **Diabetic Vasculopathy**, both of which encompass highly integrated clinical and laboratory research. Several PIs' interests span both groups, participating in journal clubs, strategic research discussions and internal grant review. This shared approach across the groups is evidenced by joint grants, co-supervision of PhD students and co-authored publications. During the REF period this synergy has been further enhanced by academic appointments.

3b Selected research achievements during REF period

Ophthalmology research group Research into pathogenesis and treatment of age-related macular degeneration (AMD) is a major theme in this group. They have developed unique *in vitro* and pre-clinical models combined with patient samples to demonstrate that ageing promotes innate immune responses and associated pathology in the neural retina and retinal pigment epithelium (RPE). With sustained funding from sources such as MRC, the Welcome Trust, Fight for Sight and

BBSRC, **Chen, Lois, Simpson, Stitt** and **Xu,** have identified a range of innate inflammatory mechanisms that are linked to age-related neural and vascular pathology and AMD risk. The recent addition of **Fitzgerald** as a T-cell biologist has further enhanced this research by demonstrating the role of neuronal inflammatory responses driven by Th1 and Th17 cells.

Basic science accomplishments are driven by interactions with clinical science and the group consisting of **Chakravarthy, Lois, Azuara-Blanco, Silvestri** and **Hogg** have large, well-characterised cohorts of patients with AMD, Stargardt's disease and glaucoma. These clinical researchers have achieved considerable grant success from MRC, Wellcome Trust, NIH and NIHR, which have supported several pivotal genetic studies, disease phenotyping and clinical trials. Indeed, leadership in clinical trials has developed considerably over the REF period, linked to unique AMD, glaucoma and diabetic retinopathy cohorts. Phenotyping protocols have been defined by the Central Angiogram Reading Facility (CARF; http://www.gub.ac.uk/carf/), which co-ordinates the systematic analysis of ophthalmic imaging outputs and provides management service to angiographic reading centres throughout the UK. Of particular note is the ongoing "IVAN" trial (Inhibit VEGF in Age-related choroidal Neovascularisation) which is a 22 centre study with **Chakravarthy** as the principal investigator and funded by NIHR-HTA (£3 Million). IVAN has evaluated clinical benefit and cost effectiveness of intravitreal VEGF neutralising antibodies (bevacizumab versus ranibizumab) in the treatment of neovascular AMD. Funded by MRC and several NIHR-HTA grants (~£4 Million total), **Azuara-Blanco** has a global Programme on glaucoma with active partnerships in the UK, Europe, US, Australia and Singapore. This research has informed the National Screening Committee and policymakers on best practice for glaucoma treatment.

Research on ischaemic retinopathies and retinal vascular disease has been a sustained strength of ophthalmic research in Belfast. There have been several new academic appointments and awards of significant national and international project and programme grants from sources including EU FP-7, MRC, BBSRC, BHF, Fight for Sight, The Jules Thorn Trust and The Juvenile Diabetes Research Foundation (JDRF). Selected achievements of the group (**Chen, Curtis, Gardiner, Lois, McDonald, McGeown, Medina, Margariti, Simpson, Stitt and Xu**) include identification of key pathogenic mechanisms leading to vascular cell dysfunction and death during diabetes. They have also developed the concept of cell therapy for the ischaemic retina by using highly defined vascular progenitors and stem cells. They have shown that human cells can result in significant microvascular regeneration and reperfusion. Indeed, during this period the group have identified important vasoactive proteins and micro RNAs that control angiogenesis and vascular repair and collectively their publications have made a highly significant contribution to the growing recognition that drug and cell-based strategies may be used to re-vascularise the ischaemic retina.

Diabetic vasculopathy research group The vascular complications associated with diabetes mellitus form a core element of our research programme. The breadth and depth of this area has been further enhanced by the recent (July 2013) appointment of **Lyons**, former Director of the highly-respected Diabetic Institute at the University of Oklahoma. Having re-located to Belfast, his work focuses on the role of enhanced post-translational modifications of proteins and lipids that occur in diabetes and how these modulate vasculopathies such as pre-eclampsia and retinopathy. The **Lyons, Jenkins** and **Yu** team has built on the strong reputation of diabetic vasculopathy research established by **Brazil, Curtis, Gardiner, McGeown, Stitt** and **Xu**, who have integrated programmes funded by Diabetes UK, BBSRC, MRC, Fight for Sight and JDRF. This research has provided significant insight into the pathogenesis of diabetic retinopathy and nephropathy. For example, critical discoveries have been made on microvascular pathophysiology, and mechanisms identified that modify blood flow during progression of retinal disease. Such ion channel, oxidative enzymes and disease biomarkers research also links to the broad cardiovascular expertise of **Collins, Grieve, Harbinson** and **Zholos,** who have demonstrated key mechanisms in vascular and cardiac pathology. Remodelling and regulation of vascular repair has also evolved as a theme in this group which further integrates with the ophthalmology programme in the CEM. For example, miRNA regulation of gene expression in the vasculature has been developed by **Collins, Margariti** and **Simpson**. Furthermore, **Margariti** (formerly King's College London) has demonstrated key mechanisms, including micro RNAs that control reprogramming of induced pluripotent stem (iPS) cells towards vascular cell differentiation. This newly developed research area crosses both groups in CEM and offers a further exemplar of the synergy and shared perspective that has been achieved during this REF period.

3c Plans for further development of CEM

Infrastructure development: Post-REF, the CEM will move into the new Wellcome-Wolfson research building. This will immediately impact on the further development of the IHS, since it will be linked to the CCRCB building and will be adjacent to CII, the Wellcome Trust-funded Clinical Research Facility (CRF) and the Schools of Pharmacy, Nursing and Biological Sciences. Proximity to, and integration with, these other research entities on a single campus will facilitate sharing of intellectual and physical resources. Collectively this will augment the biomedical research infrastructure that has been developed since 2007, and which, in terms of comparably sized institutions, ranks amongst the best in the UK.

Development of strategy and programme development: CEM has been highly successful in recruiting new academic leaders, including 4 clinical professorial appointments. These staff arrived in 2013, and their study programmes and scientific leadership form a major component of the research strategy. Maintenance of research focus has been a building block of our success, and targeted recruitment of staff has further enhanced these key areas. Therefore, it is anticipated that the reputation of Queen's in retinal disease and diabetic vascular complications will continue to grow. From this position of strength we will be targeting large-scale and long-term funding initiatives, including major international consortia, that will enable us to achieve our goal of further strengthening basic science discovery and connecting it to improvements for patients.

In terms of specific programme development post REF, we will continue to promote the translational ethos and joint working between basic and clinical scientists. Recently funded programmes will continue into the next 3-5 year period such as a Jules Thorn Biomedical Science Award, Career Development Awards, FP-7 and commercial partnerships. For instance, we are currently undertaking primate studies using vascular stem cells as a foundation for planned clinical trials for central retinal and branch vein occlusion. These outcomes will be used as a test bed to treat more common ischaemic disorders. Furthermore, there is an ongoing Europe-wide collaborative effort to harness a population of stromal stem cells (SSCs) that can replace degenerative pericytes in the diabetic retina with a first-in-man trial planned with STENO in Copenhagen.

Clinically, we will continue to develop disease prediction biomarkers and lead new innovative clinical trials in the ophthalmology and diabetic complications arena. Our traditional strengths have been in AMD and these will continue to grow. For example, £3 Million was recently awarded by NIHR (August 2013) to evaluate methods for identifying neovascular AMD progression in non-treated eyes. It is anticipated that large cohort epidemiology studies and trials will be conducted in diabetic pregnancy, diabetic retinopathy and glaucoma.

C. PEOPLE

i. Staffing strategy and staff development

Academic Staff profile: Since 2008, we have undergone significant academic recruitment to further strengthen research leadership and quality in strategic areas. Over the REF period we have attracted a total of 53 new clinical and scientific academic staff. The staffing profile in the IHS now provides for long-term stability and succession planning. Importantly, our strategic recruitment has reinforced collaboration with cognate specialties in clinical disciplines within the NHS and further strengthens the translational ethos of our research endeavours.

Strategy for New Academic Staff: New academic appointments are monitored by our Tenure Review Board (TRB) with a typical probationary period lasting between 3-5 years. These staff have reduced teaching loads and are assisted with career development. In particular, they are assigned mentors to guide towards confirmation in post. To this end, progress is formally assessed on an annual basis by a separate probation review committee which highlights strengths and areas for improvement. New academics are provided with start-up funding (commensurate with grade), including allocation of PhD studentships, research support staff, running costs and also resources to enable development of meaningful collaborative partnerships with international leaders.

Strategy for Academic Staff Development: Academic leadership is provided by the Centre Directors and Deputy Directors with guidance from Centre-specific international SAB panels. All academic staff are involved in important administrative roles through membership of one of the committees responsible for postgraduate training, infrastructure, health and safety, or the senior management board. Centre issues are discussed at general academic board meetings and regular away-days to

clarify strategy and delivery of research excellence.

Academic appraisal and mentorship emphasises the need for ongoing personal development. Continued academic excellence is achieved through careful performance management to ensure quality research outputs, external income, postgraduate training, contribution to undergraduate teaching and realisation of research impact. Progress is reviewed against previously agreed annual key performance indicators (KPI) and defined profiles for promotion. This process is carried out by Centre leadership and reviewed by the Dean. Over 30 internal academic promotions across all academic grades have been made within the School during the REF period.

Strategy for Postdoctoral Support and Early Career Development: These staff groups are challenged to reflect on their personal development needs through appraisal. They are then provided with training resources to meet these needs. For early career scientists, generic support is also in place at IHS level including careers advice, personal career coaching, and relevant staff training courses. This programme is shaped around the seven principles of the 2008 'Concordat to Support the Career Development of Researchers' (http://www.gub.ac.uk/research-centres/crs/Concordat/). The IHS has added significant resource to support this programme, such as providing postdoctoral fellows (and postgraduate students) who are presenting authors a travelling scholarship to attend at least one international conference annually.

A Postdoctoral Society, formed in 2009, organises regular training days and career symposia and forums for the exchange of research data with national and international leaders invited as keynote participants. In conjunction with the Postdoctoral Society, Research Centres organize mentorship committees to assist postdoctoral careers. We have had success with nationally/internationally competitive Fellowships from funders such as Cancer Research UK, Breast Cancer Campaign, JDRF, Fight for Sight, MRC, Wellcome Trust and NIHR. Whilst training the next generation of academic leaders, the IHS is equally pro-active in organizing events aimed at advising researchers who wish to pursue non-academic careers. This exploits associations with our local and national biotechnology and pharmaceutical industry partners to educate our contract staff on options for employment within these sectors.

Strategic Development of the Training Environment for Clinical Researchers: Recognizing the national short-fall in academic medicine we seek to provide the highest quality training environment for clinicians who are committed to an academic career. For medical students, this begins with a Summer Studentship Scheme, which offers an 8-week training opportunity to undertake a research project within one of the Research Centres. The IHS provides up to 45 placements per year whilst others are funded via external awards from the Wellcome Trust, The Physiological Society and the Biochemical Society. These studentships offer an opportunity to gain valuable insight into research and are highly competitive. Many of these medical students subsequently choose to conduct intercalated degrees in Biomedical Science and Human Biology, which include a double-module research project within one of the Research Centres. Intercalating medical students have increased from 15 (in 2007/08) to 46 (2013/14). Having successfully obtained funding through the Academy of Medical Science's £1 Million INSPIRE initiative, our medical students have formed a Queen's University Academic Medicine Society (QUAMS) which seeks to enhance opportunities for students to engage with researchers.

We have effectively implemented the Walport Scheme and the IHS now has over 20 Academic Clinical Fellows (ACFs) and Academic Clinical Lecturers (ACLs) with a further 40 junior medics engaging in research as part of the F2 programme. These young clinical researchers are encouraged to engage with mentors from outside Northern Ireland, as facilitated by the Academy of Medical Sciences and a number have successfully competed for RCUK or other personal fellowships. This Clinical Academic Training Programme (CATP) is resourced by the IHS, with representation from the Belfast Health and Social Care Trust and, importantly, the Northern Ireland Medical and Dental Training Agency which is responsible for postgraduate clinical training within the Northern Ireland Deanery. This promotes an integrated approach to the research and clinical training of aspiring clinical academics. Although some trainees entering this programme may not take on academic appointments, we believe that research will become an increasing component of clinical leadership and this experience will have a positive, career-long impact.

ii. Research students

We have developed a successful doctoral training programme. Provision of funding for PhD and

MD students typically comes from a variety of sources including local government (DEL awards), NHS R&D Office, RCUK and various research charities. We also have a number of CASE awards in partnership with BBSRC. The IHS's commitment to postgraduate education and training is underwritten by studentships funded from endowments totalling ~£400K annually. These are particularly targeted at international students which is a priority area for growth. The IHS also offers MSc-level degrees in Public Health, and Translational Medicine. Postgraduate training and research are specifically promoted through visits by academic staff representing the IHS's research programmes to target institutions in South East Asia, Brazil and China. The internationalization agenda is further promoted by student exchange programmes, including British Council funded students from India and the Ukrainian government. Strategy and progress in all areas is routinely reviewed by the IHS Internationalisation Working Group.

The postgraduate research programme is managed by the IHS Postgraduate Research Board, chaired by the Deputy Head, and consists of the Centre Directors and Chairs of each Centre's Postgraduate Research Committee. Student representatives are encouraged to bring forward student concerns relating to training and course management. An integrated programme of postgraduate training, designed and organized by the Postgraduate Committee Chairs under the overall control of the Board, runs alongside each student's research project. General training also includes scheduled classes on research ethics and communication skills, whilst each Research Centre provides a specialist lecture course introducing the range of research techniques focussing on the students' immediate research environment. On-going training includes career development and writing skills for papers/grants. Each student project has a minimum of two supervisors, to help ensure appropriate management. Progress is monitored annually by a Progress Review Panel which through interview assesses written submissions and project development.

iii Equality and diversity

Gender equality and diversity now permeates all aspects of our culture. We have appointed a senior academic (0.2 FTE time commitment) as MDBS Director of Gender Equality, with dedicated clerical support, to monitor relevant statistics at all levels, from under-/postgraduate balance to professorial advancement. Specific practical measures have been implemented, such as research-only periods for academics returning from maternity leave. MDBS was recently awarded a Silver SWAN Award from Athena, reflecting its commitment to identifying and implementing good practice to support the careers of female academics and all contract research staff.

D. INCOME, INFRASTRUCTURE & FACILITIES

During the REF period the IHS has attracted over £90 Million of new research grants, including £16.8 Million in Research Council income; even though Northern Ireland researchers were ineligible for NIHR funding until late 2012. Investigators across the IHS have also developed significant income streams through research partnerships with Pharma and Biotech including Amgen, GSK, Pfizer, Novartis, Johnson & Johnson and AstraZeneca.

In parallel with increased project/programme grant support, we have attracted significant funding to develop research infrastructure. Through competitive national schemes and international partners, the University has led several large-scale developments and already invested £90 Million in the Health Sciences Campus. In addition to the IHS research facilities, the Campus includes the McClay Research Centre for Pharmaceutical Sciences, Education Centres for Medicine, Dentistry and Biomedical Science and a large teaching hospital (Belfast City Hospital; 850 beds). Fundraising initiatives have led to several notable successes, such as establishment of a state-of-the-art cancer research building (opened 2007). This encompasses 5000m^2 of dedicated research space, organized around open-plan cellular and molecular biology research laboratories on the four main floors of the building. Specialist laboratories for Medicinal Chemistry and Molecular Pathology have also been included, ensuring that we have the full spectrum of research capabilities and enabling technologies to undertake critical inter-disciplinary research. CII occupies a new purpose-built facility (the Health Sciences Building, opened July 2010) and newly refurbished laboratories in the Medical Biology Centre (MBC), with a combined research space of 5250 m^2. CII also obtained a Wolfson Laboratory Refurbishment Grant (2010) which facilitated the acquisition of major microscopy equipment. The ophthalmology and vascular groups (formerly the Centre for Vision & Vascular Science) currently occupy buildings on the Royal Group of Hospitals campus of the Medical School. The total cost of these infrastructural improvements exceeded £48 Million.

The building to house the CEM is our next major infrastructure project and construction is

well underway. This facility will bring ophthalmology and diabetic vasculopathy research together on the Health Sciences Campus and has been funded through UKRPIF (£32 Million total cost). This funding package included funding from a Wellcome Trust–Wolfson Foundation Capital Award (£4.8 Million), Atlantic Philanthropies (£15 Million), Insight: The Trust for the Visually Impaired (£1.5 Million) and The Queen's University Foundation (£1.9 Million).

Core facilities for the IHS: The Wellcome Clinical Research Facility (CRF) (opened 2013) was financed through the Wellcome Trust's Clinical Research Infrastructure Award scheme with support from the Wolfson Foundation and the Research & Development Office, Northern Ireland (the local funding arm of the Department of Health). The CRF currently accommodates patient-based research in the IHS. Various Core Technology Units (CTUs) are also sited on the Health Sciences Campus, including Bioimaging, Pharmacology, Genomics and Biochemical Phenotyping, and Medicinal Chemistry. A College of American Pathologists/Clinical Pathology Accreditation-accredited Molecular Pathology Laboratory (MPL) has been formed which incorporates the regional cancer Bio-Bank and a Bioimaging/Bioinformatics Unit. Notably, the current CTU portfolio includes a state-of-the-art Biological Resource Unit for in vivo studies, constructed at a cost of £7 Million (opened 2009). This provides both specific pathogen-free and conventional barrier facilities for a wide range of pre-clinical model systems and incorporates *in vivo* animal imaging equipment and full technical backup.

Further development of institutional research support structures: The University has invested almost £4 Million in the development of a new Research and Enterprise Directorate. This provides strategic support for research, including identification of new research funding opportunities (national, EU and international), expert guidance on the development of research funding applications, multi-disciplinary research activity, co-ordination of large-scale or strategic institutional bids, training activities and engagement with key external stakeholders. The Directorate also manages research integrity and governance through implementing regulations, policies and procedures for research involving human participants and/or animals. There is also a dedicated research governance team to support and advise academics.

E. COLLABORATION & CONTRIBUTION TO DISCIPLINE OR RESEARCH BASE

Collaborations: Collaboration, interdisciplinarity, commercialization and translation to and from the clinic are central to our research strategy. We have nurtured close links with NHS partners, as exemplified by the success of the CRUK-CRC, creation of the Welcome CRF and the new Northern Ireland Biobank. There are also strong research links with other Schools e.g. Pharmacy, Mathematics and Physics, Chemistry, and Chemical Engineering.

Collaborations have been established with leading Universities nationally (such as University College London, King's College London, Oxford, Edinburgh, Cambridge, Manchester, Liverpool and Ulster) and internationally (such as Harvard, University of California San Francisco, Johns Hopkins, Mayo Clinic, University of North Carolina, Chapel Hill, Albert Einstein College of Medicine, Duke, NIH (National Cancer Institute, National Eye Institute), University of Sydney, University of Buenos Aires, University of Pavia, Norwegian College of Veterinary Medicine, Ludwig-Maximilians-Universität München, University of Maastricht, University of Zurich, Pasteur Institute). Each Research Centre has an internationalisation budget that serves to nurture new collaborations. There have also been several visiting professorships for staff in the IHS. This strategy has led to successes in collaborative programme and project funding and significant multi-institutional outputs.

New Strategic Linkages: Research development has been enhanced by several important strategic linkages. For example, the recent award of the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) (Phase 1 £3.7 Million) has commenced recruitment of 8,500 subjects aged over 50 to be followed over at least 15 years. This study illustrates the advantages of our juxtaposition and close managerial relationships with the major academic hospitals in Belfast and the Public Health Agency (PHA). The broad remit of NICOLA is to investigate the dynamic social and economic relationships that shape health as we age. It is anticipated that this will be a unique resource with which to study initiation and progression of ophthalmic, diabetic complications, cancer, cardiovascular and respiratory diseases in an ageing population.

Evidence of Contributions to the Discipline Within Assessment Period: Our academic staff hold

many key positions within national and international bodies. For example, **Azuara-Blanco** is Chair of the UK and Eire Glaucoma Society and is a member of the Committee on Global Research and Screening of the World Glaucoma Association. **Chakravarthy** serves on the Advisory Board of Excellence in UK Ophthalmology and is Chair of the UK Clinical Research Network (Ophthalmology) and member of the Association for Research in Vision and Ophthalmology International Committee. **Elborn** is currently President of the European Cystic Fibrosis Society (ECFS) and is a Trustee of CF Trust UK and Chair of its Research Advisory Committee. **Johnston** is the current Chair of the MRC Translation Research Group and a member of the MRC Strategy Board, CRUK Scientific Advisory Board, Japan Cancer Advisory Board and American Society of Clinical Oncology/Chinese Society of Clinical Oncology and was Chair of the Organising Committee of the NCRI Annual Cancer Meeting 2011/12 and member of the NCRI All Ireland Cancer Consortium. He was a RAE 2008 panelist, is a REF 2014 UoA1 panel member and was also part of the REF Pilot on Impact Case Studies. **Lyons** is Chair of the Selection Jury for the Harold Hamm International Prize for Biomedical Research in Diabetes and also Chaired the Grant Review Study Section, American Diabetes Association (2009) and the National Institutes of Health/Heart, Lung and Blood Institute Study Section (2007-10). **Salto-Tellez** is a member of the Executive Group of the Confederation of Cancer Biobanks, National Cancer Research Institute. **Waugh** serves as Hon Secretary of the Irish Association for Cancer Research (2008-2012) and sits on the European Association for Cancer Research President's Advisory Council.

Many of our academics serve as research grant panel or scientific advisory board members for a range of national and international bodies such as MRC, CRUK, Science Foundation Ireland, Fighting Blindness Ireland and JDRF. Our staff are actively involved on editorial boards for many specialist and general journals and they deliver numerous keynote lectures at international meetings. We have also organised a range of UK or pan-European symposia and conferences, such as the European CF Society.

Awards, Prize Lectures & Fellowships: A range of prizes have been won across all academic grades within the IHS. Notable ones have been election to The Academy of Medical Science (**Johnston**, 2011); The Pinedo Prize 2013 (Society for Translational Oncology) (**Johnston**); Award of the CBE (**Elborn**); Royal Society Wolfson Merit Award (**Stitt**, 2010); The Jules Thorn Biomedical Science Fellowship for 2011 (**Stitt**); The Romain Pauwels ERS award (**Taggart**, 2008); Henkind Prize, Macular Society (**Chakravarthy**, 2012); GL Brown Prize, Physiology Society (**McGeown**, 2010); The Tom Crone Founder Prize Lecture (2012) from the Irish & American Paediatric Association (**Shields**); The American Academy of Ophthalmology (AAO) Achievement Award (2008) and the NHS Scotland award for clinical excellence (2010) (**Azuara-Blanco**); Zeller Senior Scientist Award (2012); Tier I Canada Research Chair in Infectious Diseases and Microbial Pathogenesis (2009); CSM (Roche) Award (2008) (**Valvano**). As a group, CCRCB won Her Majesty's Diamond Jubilee Award 2012.

Commercialisation and Interactions with Industry: Opportunities to commercialise our research have been transformed by the complete reorganisation of the University's Research and Enterprise Directorate and QUBIS (the University's commercialisation arm). InvestNI has funded several "proof-of-concept" schemes to promote commercialisation activity from academia. Our success is borne out by Queen's University being presented with the Times Higher Entrepreneurial University of the Year award in 2009. Investigators across the IHS have developed significant commercialisation partnerships with Pharma and Biotech including Randox, Amgen, GSK, Pfizer, Novartis and Johnson & Johnson. For example, Orbsen Therapeutics is an embedded commercial partner in the FP-7 programme, REDDSTAR. Furthermore, we have a commercial agreement with GSK (~£1.5 Million investment to date) in the area of pathogenesis and target development for diabetic macular oedema. This successful collaboration has already provided the necessary preclinical evidence to enable progression of the LP-PLA2 enzyme inhibitor (darapladib) to a GSK international clinical trial for diabetic macular oedema (http://tinyurl.com/p7p76lt). We have developed a number of companies including Almac Diagnostics, Fusion Antibodies, PathXL Diagnostics, TruCorp, and Lewis Fertility. These spin-out companies, which had a combined annual turnover of some £7.3 Million in 2012/13, employ over 200 people and several have won a number of national and international innovation awards.