Institution: ***Newcastle University***

Unit of assessment: ***1***

a. Overview

The UoA1 return is, at 145 FTE, the largest being made by the Faculty. It emphasises our core activity in translational biomedical research, focussing on, and addressing, the health challenges faced by our ageing population. Our concept is that a step-change in patient care requires excellence in both underpinning basic science and translational activity, an appropriately trained workforce and effective working with stakeholders such as patient groups and industrial partners. Our strategic mix of basic science, translational and clinical academics, coupled with our strong training focus, will ensure we deliver the maximum patient benefit. The UoA1 return includes investigators working in 4 of the 7 Research Institutes in the Faculty: Institute for Ageing and Health (IAH), Institute of Cellular Medicine (ICM), Institute of Genetic Medicine (IGM) and Northern Institute of Cancer Research (NICR). UoA1 research activity is presented in three **domains:** **AGEING & CHRONIC DISEASE** (IAH & ICM), **GENETICS & RARE DISEASE** (IGM & ICM) and **CANCER BIOLOGY & THERAPEUTICS** (NICR). Each **domain** includes basic science, translational and clinical research activity, and operates within research hubs which link laboratory and clinical research delivery facilities; an approach which facilitates the translation of research innovation into practice. In each domain research activity is integrated with training and career development to support the development of future researchers. Our strong commitment to training and development is reflected in the national training roles undertaken by UoA1 investigators with ***Jones***, for example, acting as National Training Lead for the NIHR Infrastructure. In addition to links between the **domains** in UoA1 there are strong links with researchers in other UoAs, particularly where their research is translational in nature. Linked research areas include dementia (UoA4) and oral biology & nutrition (UoA3). We also work closely with applied health researchers in the setting of health implementation (UoA2) and, at the other end of the research spectrum, with researchers in chemistry (UoA8) and structural biology (UoA5) in the setting of cancer drug discovery. A broad and successful network of collaboration is essential for achieving our goal of effective research translation.

b. Research strategy

1) Overview

Our goal is to address the key health challenges facing our ageing population. Our strategy since RAE2008 has been to focus on our areas of research excellence, with a specific emphasis on ageing and chronic disease, developing the inter-disciplinary scientific links, research networks and patient cohorts essential to deliver world-class translational research. Our key strategic partnerships are with the NHS through our major partner trust ***Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH)*** and with industry. A key element of the NuTH partnership is the ***Newcastle NIHR Biomedical Research Centre in Ageing and Age-Related Chronic Disease (BRC)***, the university components of which are largely contained within UoA1. Our three disease-orientated research **domains** are linked by cross-cutting mechanisms and technology-driven **themes** (GENETICS & MOLECULAR BIOLOGY, CELL BIOLOGY, IMMUNOLOGY & FIBROSIS, DRUG DISCOVERY & IMAGING and EXPERIMENTAL MEDICINE & THERAPEUTICS). Novel research opportunities arise at the intersection of disease **domains** and mechanistic **themes**.

2) Developments Since RAE 2008

We have met our stated objectives from RAE 2008, developing in four key, linked, ways. These developments have significantly increased our capacity to deliver high quality research with commensurate impact, and increased our training capacity.

a) Operational Structure: The seven Research Institute structure is now fully embedded in the Faculty, significantly increasing the efficiency of research administration and support. The UoA1 structural model of disease area **domains** and cross-cutting mechanistic **themes** is well established and is generating novel research opportunities. Examples include the linking of cellular and molecular therapeutic approaches across different immune diseases and the application of fibrosis biology advances made in liver disease to renal, cardiac and lung diseases, generating significant industry investment. We have instituted specialist support structures to facilitate bidding for, and subsequently delivering complex translational and/or milestone driven projects.

b) Externally-Funded Research Centres:. We have been highly successful in obtaining funding

for strategically important translational and basic research platforms (total current value £56m). Our BRC was renewed in 2011 with a significant increase in funding **(**from **£7.5** to **£16m).** The ***Centre for Brain Ageing and Vitality (CBAV)*** is one of three prestigious 'lifelong health' research centres established to strengthen multi-disciplinary and collaborative research in ageing. It is part of the Lifelong Health and Wellbeing (LLHW) programme funded by the UK Research Councils. In 2012 the *Wellcome Trust e*stablished its first new centre in 8 years in Newcastle, the ***Wellcome Trust Centre for Mitochondrial Research*** aimed at driving therapeutic innovation and training in the area of mitochondrial disease. The ***MRC Centre for Neuromuscular Disease (Bushby)*** was renewed in 2013. The ***Cancer Research UK (CRUK) Newcastle Cancer Research Centre,*** a key centre for the development of novel cancer therapeutics and their early-phase evaluation was established in 2009 and renewed in 2013.The ***Newcastle Experimental Cancer Medicine Centre*** renewed in 2012, was ranked in the top tier of these Cancer Research UK/NIHR-funded centres. Newcastle was also awarded ***Leukaemia Research Centre of Excellence*** status in 2011. These linked structures are supporting a systematic programme of translational research in cancer which has already resulted in the development (and progression to clinical evaluation) of PARP inhibitors as an important new class of anti-cancer drug. The ***GSK CRAFT Agreement*** is an innovative public/private therapeutic development initiative in fibrosis biology aimed at developing and evaluating novel anti-fibrotic drugs and supported by programme-level funding from GSK (in the form of both project funding and an innovative joint-funded and -managed senior lecturer post (***Kendrick***)) and an MRC MICA Programme Grant (***D Mann, J Mann & Oakley***). Our strength in translational rheumatology is reflected in our ***Arthritis Research UK (ARUK) Experimental Arthritis Treatment Centre*** (with Glasgow & Birmingham), ***ARUK Centres of Excellence in Tissue Engineering*** (with Aberdeen, Keele & York) and ***Rheumatoid Arthritis Pathogenesis*** (with Glasgow & Birmingham)***,*** and our flagship ***MRC/ARUK Centre for Integrated Musculoskeletal Ageing*** (***CIMA)*** (with Liverpool & Sheffield), the award of which reflects our strong focus on age-related research.

c) Capacity Building in Translational Research: We are innovators in the field of translational research training, taking the view that effective research translation in practice requires investigators to have the necessary skills; skills which are typically not taught in conventional research training programmes. Effective translational research training must, if it is to meet the needs of all users, involve those users in its design, development and delivery. This approach is exemplified by our cornerstone ***Masters in Translational Medicine & Therapeutics*** jointly developed and co-delivered with, 5 industrial partners. This programme, which has trained over 100 basic scientists, clinical fellows and intercalating medical students, was developed for our ***Wellcome Trust Translational Medicine and Therapeutics (TMAT) Programme***. It was awarded in 2008 (total value **£5.5m**, one of 4 awarded and the only one to focus specifically on translational skills training to Masters level), and has trained 12 clinical fellows to date. The TMAT training model has been adapted into an Ageing Translational Research Training programme under the auspices of the Newcastle BRC, the NIHR Rare Diseases Translational Research Collaboration (TRC) training programme and 2 EU Marie Curie laboratory technology development and commercialisation training programmes. We are working with NIHR to develop the Newcastle translational training model for use in a national programme for all professional groups for delivery through the NIHR Infrastructure.

d) Research Infrastructure: We have completed a comprehensive building development and refurbishment programme (total value £33.5m) and have invested heavily in cross-cutting scientific facilities to support research in both this and other UoAs. We have developed the innovative ***Campus for Ageing and Vitality (CAV)*** (*see section* **d***. **2)** page 11*) as a comprehensive translational facility for ageing and chronic disease. Re-configuring our laboratory environment has enabled delivery of our research strategy of promoting cross-disciplinary working. The approach is exemplified by the development of the integrated fibrosis facility (total investment £2m) which hosts research activity across multiple disease settings and which has attracted significant industry interest and investment.

3) Research Domains

Our aim is to promote research translation, with real “pull-through” from basic science to therapeutic application in key disease areas, and to promote opportunity by exploring the application of approaches and technologies across diverse disease areas.

AGEING & CHRONIC DISEASE

A major research focus in UoA1 is the health challenge posed by chronic disease in an ageing population. This **domain** covers research into ageing and the chronic disease processes which impact on our ageing population (including liver disease, fibrosis and chronic rheumatological diseases). The **domain** is fully coterminous with the Newcastle BRC and has its translational hub in the CAV. Areas of research excellence in this **domain** include:

a) Ageing: Our ageing research ranges from basic mechanisms of ageing (DNA damage, telomere erosion, mitochondrial dysfunction and loss of protein homeostasis) to the characterisation of frailty and co-morbidities in the older community-dwelling population. In GENETICS & MOLECULAR BIOLOGY we have made key contributions to understanding the inter-linking impacts of mitochondrial function, telomere dysfunction and DNA damage during cellular senescence (***Passos, Saretzki, von Zglinicki***, *Mol Sys Biol*). ***Passos*** & ***Mann*** demonstrated how cellular senescence induced by genotoxic stress depends on chronic DNA damage resulting from irreparable damage to telomeres (*Nat Comm* with comments published in *Nat Cell Biol* and *Nat Rev Mol Cell Biol).* We have demonstrated that telomerase migrates to mitochondria and impacts significantly on mitochondrial function and maintenance of mtDNA integrity under oxidative stress (***Saretzki, von Zglinicki, Passos,*** *J Cell Sci*,). Work on an "innocent bystander" effect (senescence-induced senescence) has wide implications for cancer survivors and treatment complications (***Saretzki, von Zglinicki, Turnbull, Chinnery***). In CELL BIOLOGY, IMMUNOLOGY & FIBROSIS ***Korolchuk*** (BBSRC New Investigator Award) characterised mechanisms of autophagy regulation, including by calcium (*Autophagy*), reactive oxygen species (*Hum Mol Genet*), reactive nitrogen species (*Mol Cell*) and cellular pH (*Nat Cell Biol*) and demonstrated that compromise in autophagy leads to a reduction of flux through the ubiquitin-proteasome system (*Mol Cell*). These findings are highly relevant to our understanding of age-related neurodegenerative diseases and of the ageing process in general. Through the MRC-funded 85+ study we have published on key aspects of healthy ageing and age-related disease in the oldest old (***Kirkwood (FMedSci)****, Br Med J*). In the area of EXPERIMENTAL MEDICINE & THERAPEUTICS we have key programmes in the regulation of the autonomic system and its role in falls in the elderly (***Parry***, NIHR HTA) and in chronic fatigue syndrome (CFS) (***Newton,*** MRC). Our autonomic clinical service model is widely used and the service was runner-up in the BMJ Innovation Awards in 2012. Newcastle ageing work was recognised by a Queen's Anniversary Prize in 2009 and the BBSRC "Excellence with Impact" runner-up award in 2011.

b) Liver & Fibrosis Biology: We have multi-disciplinary liver research programmes in non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and primary biliary cirrhosis (PBC). Our liver fibrosis work has a strong translational component interfacing with major industrial partners (GSK, Medimmune) and has spawned parallel programmes in chronic renal, respiratory and cardiac disease. Our liver transplant programme (one of 7 in the UK) is hosted within our Institute of Transplantation (the only UK centre offering all-organ coverage and which hosts innovative research programmes around improving donor organ quality (HTA)). In GENETICS & MOLECULAR BIOLOGY the PBC programme (***Jones***, ***Donaldson, Cordell, Kirby;*** MRC & Wellcome Trust) has made key discoveries in the pathogenesis of PBC relating to both genetic and environmental factors underpinning genetic susceptibility (*Nat Genet x2, Hepatology* x2*)*. ***Jones*** leads the UK-PBC research consortium (*section* **e.** ***1)*** *page 13*). Identification of the genetic factors underpinning flucloxacillin-induced liver disease (***Day*** (**FMedSci**)***,*** ***Daly***, *Nat Genet, Gastroenterology)* utilising the DILIGEN cohort (*section* **e.** ***1)*** *page 14*) has contributed significantly to our understanding of important drug toxicities and is informing clinical practice. In CELL BIOLOGY, IMMUNOLOGY AND FIBROSIS ***D Mann, J Mann*** & ***Oakley*** have made key contributions to understanding the epigenetic, transcriptional and hormonal control of fibrosis (*Nat Med*, *Gastroenterology, Hepatology, Am J Path*). The group has programme grant funding from NIH, Wellcome Trust, GSK and MRC (MICA). The fibrosis group is also highly active in the area of DRUG DISCOVERY & IMAGING with a significant interest in anti-fibrotic therapy development and application; the focus of the CRAFT consortium with GSK (currently £1m with 5 year renewal pending). Novel approaches to reversing liver fibrosis under development include $5HT_2B$ antagonists and agents modifying epigenetic regulation of hepatic stellate cells (***D Mann, J Mann, Oakley,*** *Nat Med*). Re-purposing existing drugs represents an additional aspect to our activity, with studies exploring the use of losartan for the treatment of fibrosis in non-alcoholic fatty liver disease (NAFLD, MRC/NIHR EME) and identifying theophylline, acting through modification of histone

acetylation-regulation of cytokine release (***Kendrick, Day,*** *Hepatology*, MRC), as a potential therapy for alcoholic hepatitis (BRC). Our EXPERIMENTAL MEDICINE & THERAPEUTICS liver research is broadly-based. ***Jones*** & ***Newton*** are leaders in the field of symptom mechanisms, assessment and treatment in chronic liver disease, using advanced imaging approaches to identify mechanisms responsible for fatigue in PBC and developing and evaluating novel treatments (*Hepatology, Gastroenterology, BMJ,* MRC, NIHR, MRC/NIHR EME). Our NAFLD programme (***Day, Anstee***), funded by EU FP7 (FLIP) has generated important insights into clinical expression, including development of a robust non-invasive fibrosis prediction score (*Hepatology*).

c) Musculo-Skeletal Disease: Musculo-skeletal research is broadly-based with both basic and translational programmes. In GENETICS & MITOCHONDRIAL BIOLOGY ***Loughlin*** led the arcOGEN consortium (*section e. **1)** page 14*) that identified important susceptibility loci for osteoarthritis (OA) (*Lancet etc)* with follow-on functional studies on GDF5 (ARUK project grants x3 *Hum Mol Gen, PLOS Gen etc)*. ***Young*** demonstrated that mitochondrial dysfunction in OA is associated with a down-regulation of superoxide dismutase 2 (*Arth & Rheum*). ***Isaacs*** is a founding member of the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) which has performed multiple pioneering studies into the pharmacogenetics of TNF blockade, utilising the world's largest cohort of well-characterised patients (*Nature*, *Nat Genet etc).* In CELL BIOLOGY & IMMUNOLOGY ***Mellor*** (NIH, *Immunity x2, PNAS x3 etc*), demonstrated that indoleamine 2,3 dioxygenase (IDO) is essential for immune regulation and is tractable therapeutically. He has been recruited from Georgia Regents University, Atlanta to develop a translational immunology and immuno-therapeutics programme. ***Rowan*** identified the importance of c-fos in driving cartilage degradation and demonstrated key roles for both PI3 kinase and Protein kinase C pathways upstream of this transcription factor (*J Biol Chem x2; Ann Rheum Dis*). ***Young*** in collaboration with ***Kirkwood*** initiated research showing the key role of superoxide dismutase down regulation prior to development of cartilage lesions in animal models of OA (*Ann Rheum Dis*) and demonstrated that both micro RNAs and epigenetic changes control the expression of MMP-13 in OA cartilage (*Arth & Rheum x2, FASEB J*); work that led to the award of ARUK Programme funding with UEA. These studies, alongside the expertise in Ageing Biology, underpinned the award of the MRC/ARUK Centre for Integrated Musculoskeletal Ageing. ***Hilkens*** showed that low strength T-cell activation drives Th17 responses (*Blood*) and that human fibroblasts possess immunoregulatory properties equivalent to mesenchymal stem cells (*J Immunol*). ***Isaacs*** has identified a potential transcriptional biomarker for the earliest stages of RA, linked to IL-6 mediated STAT-3 signalling, with pathogenic significance, and diagnostic and therapeutic implications (*Ann Rheum Dis).* In DRUG DISCOVERY AND IMAGING ***Rowan*** discovered that the serine proteinase matriptase activated PAR2, upregulated MMP-13 and was a key regulator in human OA cartilage breakdown (*Arthritis Rheum*). He has identified lead compounds with MRC DPFS and ARUK Programme funding; these are being further developed with MRC and industry co-funding and are currently undergoing pre-clinical evaluation. This programme of work offers the possibility of oral preventative/therapeutic agents with the potential to reduce the significant burden of OA. In EXPERIMENTAL MEDICINE & THERAPEUTICS we are field leaders in biological and cellular therapies for inflammatory arthritis. ***Hilkens*** & ***Isaacs*** have developed therapeutic tolerogenic dendritic cells (DCs) as a treatment for RA; an approach which is now under phase 1 clinical evaluation in the ARUK-funded AutoDECRA trial. ***Isaacs*** directs the ARUK Experimental Arthritis Treatment Centre and partners the ARUK Centre of Excellence in RA Pathogenesis. In a novel approach funded by an MRC/TSB MICA he is exploring repurposing a small molecule cell cycle inhibitor into RA (in collaboration with Cyclacel). He is a co-investigator in both work packages of the MRC Maximising Therapeutic Utility for RA using genetic and genomic tissue responses to stratify medicines (MATURA) Consortium (£4.5m). ***Van Laar*** has pioneered autologous stem cell transplantation for patients with severe systemic sclerosis, co-ordinating the largest ever RCT in scleroderma across Europe (ASTIS Trial which will report shortly). ***Ng*** established and leads the UK Primary Sjogren's Syndrome (PSS) Cohort and Registry (MRC). ***Foster*** has contributed important work around the delivery of paediatric rheumatology services and established standards of care for children with Juvenile Idiopathic Arthritis (JIA) to improve access to the most appropriate specialist care for children with arthritis through an evidence-based approach. Her assessment tool for JIA has been adopted across the UK and internationally.

GENETICS & RARE DISEASE

This **domain** covers research programmes in genetics and other rare disease areas such as

mitochondrial disease, genetic neuromuscular disease and immunodeficiency. The domain has its translational hub at the ***International Centre for Life (ICfL)***. Infrastructure includes our GMP Facility underpinning the regenerative medicine programme and NHS clinical facilities in the areas of fertility (Newcastle Fertility Centre) and genetic disease (Northern Genetics Service). Areas of research excellence in this **domain** include

a) Mitochondrial Genetics & Disease: The Newcastle Mitochondrial Group has an international reputation in both the clinical and basic aspects of mitochondrial biology, forming a key part of three major Centres (Wellcome Trust Centre for Mitochondrial Research (Director ***Turnbull*** (**FMedSci, NIHR Sen Invest**), the MRC CBAV (***Turnbull***) and the MRC Centre for Neuromuscular Disease (***Bushby***), and represents a key component of the Newcastle BRC (Director ***Chinnery*** (**FMedSci, NIHR Sen Invest**). Newcastle is the lead Centre in the UK for the NHS Highly Specialised Service for Rare Mitochondrial Diseases and provides both expert clinical care and specialised diagnostic tests for patients from all over the UK. ***Chinnery*** also co-leads the NIHR Rare Diseases Translational Research Collaboration. A critical factor in our success in the area of mitochondrial disease has been the establishment of a unique cohort of nearly 1,000 patients (funded by the MRC/NIHR Cohort Call and the MRC Centre). GENETICS & MOLECULAR BIOLOGY are at the heart of our activity. A major part of the Wellcome Trust Centre is devoted to understanding how mitochondria make proteins and how this goes wrong in disease (***Lightowlers, Chrzanowska-Lightowlers, Horvath, Taylor, Chinnery***). Recent highlights include the resolution of the human mitochondrial genetic code (*Science*), and discovery of important new genetic defects (*Am J Human Genet*). A major part of both the Wellcome Trust Centre (***Herbert, Turnbull***) and a Wellcome Trust Senior Fellowship (***Chinnery***) has been to understand the mechanisms involved in the transmission of mitochondrial DNA (*Nat Genet* x3) and, critically, pioneering new clinically relevant methods to prevent the transmission of mtDNA disease (*Nature*). This work, relating to transfer of patient nuclei to de-nucleated ova from donors with normal mitochondria for use in IVF, has triggered significant public debate but opens the way for prevention, for the first time, of mitochondrial genetic disease in the offspring of affected mothers. Our investigators also led a major initiative to identify the true incidence of both mitochondrial DNA mutations and of mitochondrial disease in the population (***McFarland, Chinnery, Turnbull***) (*Am J Hum Genet, Ann Neurol*). Characterisation of the prominent neurological features of the patient cohort (*Brain* x5) is part of the Wellcome Trust Centre, as is investigation of the role of mitochondrial DNA in common diseases such as dementia, stroke and Parkinson's Disease (*Nat Genet, Lancet Neurol*). A further research programme aims to address the nature and extent of mitochondrial involvement in ageing and age-related diseases. This research forms a major part of CBAV and the Newcastle BRC (***Turnbull***, ***Chinnery***). Mitochondria are involved in ageing in both mitotic and post-mitotic tissues due to accumulation of mitochondrial DNA mutations (*Nat Genet* x2). In addition to the preclinical work around nuclear transfer, our activity in the area of EXPERIMENTAL MEDICINE & THERAPEUTICS has been pioneering in the field of mitochondrial disease. This activity includes the first multinational randomised control trial in the field of mitochondrial disease to identify benefit and several studies on lifestyle interventions funded by the MRC Neuromuscular Centre and MRC Cohort call, Newcastle (***Chinnery, Gorman, MacFarland, Turnbull*** (*Brain* x2)).

b) Genetic Neuromuscular Disease (NMD): Our NMD research programme is long established and is fully translational in scope. As with other areas of excellence within UoA1 our success is founded on unique, often international, patient cohorts. Examples include both national (Myotonic Dystrophy, Spinal Muscular Atrophy (SMA), Facioscapulohumeral Muscular Dystrophy (FSHD)) and global (Duchenne Muscular Dystrophy (DMD), SMA, dysferlin etc) disease registry initiatives, all of which we lead. NMD forms a key part of the MRC Centre for Neuromuscular Disease which includes a dedicated biobank and infrastructure support for clinical trials and translational research. In GENETICS & MOLECULAR BIOLOGY we have made substantial breakthroughs in gene discovery, analysis of protein function and modelling of disease in cell culture, zebrafish and mouse model systems (***Bushby, Lochmuller, Straub*** (*Am J Hum Genet, Hum Mol Genet)*). We are funded by MRC amongst others to study cell biology and protein function, NMJ biology, dystrophin restoration and stem cells in neuromuscular disease (***Lochmuller***). Through a large collaborative project (MDEX Consortium) and major grant funding from AFM (France) we have been responsible for cardiac outcome measures in a national consortium which aims to evaluate the pre-clinical efficacy of the next generation of oligonucleotide based therapeutics to induce exon-skipping in NMD, especially with regard to the cardiac manifestations. This effort has been extended to pre-

clinical pharmacokinetic and bio-distribution studies in small animals. In EXPERIMENTAL MEDICINE & THERAPEUTICS ***Bushby*** led the definition of international standards of care for DMD (*Lancet Neurol* x2), defining the standards for the field and setting the benchmark for care internationally. We lead a nationally-commissioned service for diagnosis of rare NMD which underpins our translational diagnostics and therapeutics programmes. The diagnosed patients have provided insights into the characterisation of disease phenotypes (e.g. FKRP (***Straub*** (*Brain*)), ANO5, titin) and provide the basis for our successful recruitment to clinical trials and natural history studies. The undiagnosed patients are now the source of further research aimed at improved diagnostics through the application of next-generation sequencing technologies to genetic diagnosis. We are involved in several international efforts aimed at harnessing the power of this technology to deliver diagnostic data to the patient population (Neuromics, RD-Connect (both EU-FP7)), as well as continuing to contribute to the discovery of new genes (most recently ALG2, CollVII). We are leaders in trans-national clinical trials aimed at defining the critical therapeutic reagents in NMD for the next decade, including steroids in DMD funded by NIH (FOR-NMD), several trials on anti-sense oligo-nucleotide-induced exon skipping in DMD (Wellcome Trust/DH HICF, SKIP-NMD and industry sponsored studies including Sarepta/AVI and Prosensa/GSK), small molecule studies and development of outcome measures. For such efforts to be successful in the rare disease field international collaboration is vital. We have led the establishment and coordination of international collaborative therapeutics initiatives, primarily funded by the EU (*section* **e.** ***1)*** *page 15*).

c) Immunodeficiency: The Newcastle Primary Immunodeficiency (PID) Group is internationally recognised for its work in identifying the molecular pathogenesis of newly identified inherited disorders of cellular immunity; an approach which both sheds light on disease mechanism in affected patients and provides novel insights into basic pathways in human immunology. Major awards include the 2012 Sir Jules Thorn Trust Biomedical Award (5-year programme funding, awarded to a single centre each year; ***Hambleto*****n**, ***Santibanez-Koref***). Our scientific programme is built on, and informs, our flourishing clinical service for children with immune disorders, based at the Great North Children's Hospital and recognised as a Jeffrey Modell Diagnostic Centre. In GENETICS & MOLECULAR BIOLOGY of PID we have focussed on phenotypes characterised by susceptibility to intracellular pathogens (***Hambleton***) which also serve as *in vivo* models to study the origin and differentiation of human dendritic cells (DC) ***Bigley*****,** ***Haniffa*** (Wellcome Trust Intermediate Fellows) & ***Collin****),* susceptibility to fungal infection (**Lilic**), and defects of DNA repair (***Gennery***). Publication highlights include the first examples of human DC immunodeficiency due to mutations in IRF8 and GATA2 (*NEJM, J Exp Med, Blood*), Chronic Mucocutaneous Candidiasis (CMC) associated with gain-of-function STAT1 mutation (*NEJM*), viral susceptibility syndromes caused by deficiencies of FADD and STAT2 (*Am J Hum Gen, PNAS*), and the linkage of Artemis to non-homologous end joining of DNA repair in class switch recombination (*J Exp Med*). The Sir Jules Thorn programme aims to develop and apply whole exome sequencing for early molecular diagnosis of suspected PID. Parallel studies with McLaughlin (PEALS, UoA23) and Ternent (UoA2) will explore its cost-effectiveness and acceptability to patients and families. In CELL BIOLOGY & IMMUNOLOGY ***Collin***, ***Haniffa*** & ***Bigley*** work to define the origin of human DC, their functional specialisations and role in health and disease. **Collin** demonstrated the turnover of DC and macrophages following haematopoietic stem cell transplant (HSCT) and their contribution to graft versus host response (*J Exp Med*). ***Haniffa*** utilised a comparative genomics approach supported by in vitro analysis to identify human tissue CD141hi cross-presenting DC homologous to mouse CD103+ non-lymphoid DC *(Immunity*). This discovery permitted the alignment of human and mouse tissue DC networks and was highlighted in the accompanying editorial. Comparative biology studies also enabled the discovery of IRF4-expressing DC specialised to instruct IL-17 responses in mouse and human mucosal tissues (*Immunity*). In EXPERIMENTAL MEDICINE & THERAPEUTICS we have made significant advances in the application of HSCT for PID (including the use of alternative stem cell sources, improved conditioning regimens and the extension of indications (***Gennery***, ***Cant***)). We have undertaken phenotypic characterisation of PIDs such as DNA repair defects, di George Syndrome and NEMO deficiency, exploiting international collaborations (*J Exp Med*). We have also sought to underpin clinical decision-making with a broader view of the natural history of PID (NIHR). Prevention and therapy of viral disease in the immune-compromised is a longstanding focus and the multi-disciplinary PEPtalk II study (***Hambleton***, NIHR) is comparing alternative methods for prevention of chickenpox after exposure

for unprotected children with cancer. ***Lilic's*** work on CMC has led directly to clinically important diagnostic tests, based on screening for causative mutations in *STAT1* or *AIRE* and testing for cytokine-directed antibodies in Autoimmune Polyendocrinopathy-1 patients (*J Exp Med x2*).

CANCER BIOLOGY & THERAPEUTICS

We have high quality research programmes in the areas of childhood cancer (including leukaemia/lymphoma and solid tumours) and drug discovery, development and early phase evaluation. The domain translational hub is the ***Sir Bobby Robson Cancer Trials Research Centre*** (*section* **d.** ***2)*** & ***3)*** *pages 12 & 13*). Drug discovery, experimental medicine (early phase clinical trials) and paediatric oncology and haematology are major strengths in this **domain**. Newcastle is a CRUK Centre and Leukaemia and Lymphoma Research Centre of Excellence, with the attraction of significant programmatic funding from the MRC, ***Endicott, Noble***), DH/CRUK (ECMC, ***Plummer***), CRUK, (***Clifford***, ***Newell*** ***(*****FMedSci*****), Plummer, Vormoor***), EU (***Harrison*** ***(*****FMedSci*****), Reeves, Newell***), LLR (***Harrison, Moorman, Allan***) and industry (including an alliance with Astex Pharmaceuticals worth £5m over 5 years). Newcastle researchers won the inaugural CRUK Translational Research Team Prize in 2010 for their work on the development of PARP inhibitors, taking them through from target identification to first-in-human trials. Subsequent work has confirmed single agent activity in BRCA mutated tumours (*JNCI*). In GENETICS & MITOCHONDRIAL BIOLOGY the Leukaemia Research Cytogenetics Group (***Harrison, Moorman*****)** hosts an internationally acclaimed leukaemia cytogenetics database and has published extensively on the prognostic value of chromosomal and molecular evaluation in childhood and adult leukaemia which has led to proven improvements in outcome (*Lancet Oncol*, *Blood*). The childhood medulloblastoma group (***Clifford, Williamson*** CRUK Programme Grant) has strongly influenced the design of clinical trials based on molecular stratification. In CELL BIOLOGY, IMMUNOLOGY & FIBROSIS our DNA repair group has made significant contributions to the understanding of synthetic lethality and its potential as a therapeutic target in cancer (***Curtin, Newell***, ***Austin*****,** *Nat Med, Cancer Res, Clin Cancer Res*). ***Tweddle*** has published key papers on the role of p53 as a MYCN transcriptional target in neuroblastoma (*Cancer Res, Oncogene*). Observations made by ***Vormoor*** and ***Heidenreich*** have challenged the orthodox views regarding stem cell hierarchy in childhood leukaemia using xenograft mouse models (*Cancer Cell, EMBO Mol Med*). In the DRUG DISCOVERY & IMAGING domain our Drug Discovery and Imaging group led by ***Newell*** is one of only 2 established academic cancer drug discovery groups in the UK. It was amongst the first academic teams to apply structured-based drug design (SBDD) to the discovery of new anti-cancer medicines, an approach that resulted in the discovery of the first-in-class and first-in-patient PARP inhibitor rucaparib, the clinical development of which was led locally. The partnership between the biology group, medicinal chemistry (UoA8) and Astex Pharmaceuticals also used SBDD to develop the FGFr inhibitor JNJ-42756493 which entered clinical trials in 2012. Anti-cancer drug discovery has been recently strengthened by the recruitment of ***Endicott*** and ***Noble*** (*Nat Nanotech, PNAS, Chem Biol*), who hold an MRC Programme Grant investigating CDK-containing macromolecular assemblies, and of ***Wedge*** who has extensive experience of working in the commercial sector with AstraZeneca. In EXPERIMENTAL MEDICINE & THERAPEUTICS we have an active phase I trial programme located in the Sir Bobby Robson Centre (*section* **d.** ***2)*** & ***3)*** *pages 12 & 13)* and we are an active centre in the Experimental Cancer Medicine Centre Network. Adult early phase trial work is complemented by a paediatric early phase trials team at the Great North Children's Hospital (***Vormoor***) which is part of the national paediatric ECMC network. We have had successful MHRA, CRUK and external sponsor audits for quality of research to drug registration regulatory standards. ***O'Brien*** has led large multicentre phase 3 trials comparing tyrosine kinase inhibitors in chronic myeloid leukaemia, including a collaboration with ARIAD Pharmaceuticals Inc. worth £12m. ***Burn*** demonstrated that a highly cost-effective approach to treatment, through use of aspirin is associated with significant reduction in colorectal and other cancers in high risk individuals (*Lancet*). There are on-going collaborative projects with ***Isaacs*** (arthritis and drug development synergies (MRC DCS)) and ***Newton*** (fatigue in cancer and its treatment).

4) Future Strategy

Our goal is to undertake world-class science and translate it into clinical practice, industrial products or public policy. The following steps will be critical for building on our current success.

a) Ensuring Investigator Critical Mass: We have a 'twin-track' approach of recruiting world-class investigators in key areas whilst developing our own talented junior researchers. Over the next five

years we will develop both, with targeted recruitment (with a goal of sustainable development in areas of strategic importance, including through proleptic appointments to ensure continuity) and significant expansion of, and investment in, our nationally-recognised career development programme, including through the establishment of Dean-level leadership. Critical mass is key at local level and we will bring together investigators with shared interests in physical settings which support cross-cutting and collaborative work, maximising the value of our **domain** and **theme** model.

b) Developing our Informatics Capacity: Our strong links with NHS partners, in particular with NuTH, who operate a full electronic patient record, regional referral pattern and internationally recognised patient cohorts, put us in a strong position to link detailed patient information with research data sets and biobanked material. This presents an important opportunity for translational research in collaboration with industrial partners. At present, however, these potentially powerful datasets are not systematically linked. We are currently developing the collaborative links, including with the MRC Farr Institute, which will enable us to undertake a major informatics programme, piloted in areas of strategic importance, to transform our translational capacity through effective linking of informatics data-sets.

c) Increasing Translational Opportunity & Delivery: A newly created Translational Deanery will further increase translational opportunity by working with both clinical and basic science researchers to identify areas of novel translational opportunity and develop a fully integrated "user-friendly" translational research infrastructure (which will maximise the value of our highly effective, but currently independently operated facilities). The new Translational Deanery will host a comprehensive translational delivery structure which will substantially increase our capacity to deliver projects effectively and to milestones.

d) Harnessing the Opportunity Offered by Partnership with Industry and the NHS: The principal users of translational advance in the area of biomedical research are the NHS and industry, and effective partnership is essential both for the identification of critical questions and areas of unmet need and the delivery of effective solutions. Through the vehicle of the Deanery of Translational Research we will build on the real successes of the last 5 years to develop effective and responsive collaborative structures.

c. People:

We have a strong ethos of supporting personal development which benefits all professional groups. This is reflected in academic staff recruitment, retention and development successes, and the success of our post-graduate programme. Our strong commitment to training and professional development is reflected in the national training roles undertaken by UoA1 investigators.

1) Staffing Strategy and Staff Development

Our staffing development strategy combines targeted recruitment of inspirational research leaders with a proactive career development structure supporting early career researchers in all professional groups. The success of this approach is reflected in this return, with many of our highest performing researchers being products of our career development pathways.

a) External Recruitment: We have been highly effective at strategic recruitment of both established field leaders and researchers with the potential to attain leadership. ***Mellor*** (NIH) was recruited from his position as Professor of Medicine at Georgia Regents University Cancer Center, Atlanta, USA to a newly created Chair of Translational Immunology to complement our existing strengths in translational immunology and therapeutics. ***Simpson*** (DH/Wellcome Trust HICF and MRC DCS) was recruited from Edinburgh to a Chair of Respiratory Medicine with the goal of developing the translational research programme in this field. ***Endicott*** and ***Noble*** were recruited from Oxford to expand our structural biology capacity in the context of cancer drug discovery (MRC Programme Grant). ***Briggs*** (Wellcome Trust Senior Research Fellow, EU FP-7) was recruited from Manchester into the Chair of Skeletal Genetics and works on genetic control of bone growth plate function. ***Loughlin*** (ARUK Special Purpose Grant) was recruited from Oxford University and works on the genetic basis of OA. ***Miranda-Saavedra*** was recruited from Osaka, Japan, to develop our bioinformatics programme.

b) Clinical Academic Career Development: Newcastle pioneered integrated management of clinical academic careers, linking all aspects of the career pathway from undergraduate research opportunity to SL level under a single management group led at Dean level. Our integrated and mentorship-led approach ensures coherence in the links between individual elements of the pathway and continuity in training, enhancing retention on the academic career track. We are

influential nationally in terms of policy and practice in clinical academic training with ***Jones*** appointed as National Training lead for NIHR Infrastructure and sitting on the NIHR National Dean for Trainees Advisory panel.

At undergraduate level we host an Academy of Medical Sciences/Wellcome Trust INSPIRE medical student academic programme and work closely with a thriving student academic medical society to increase medical student participation in research. Medical student academic activity is also supported by an endowment from the Barbour Trust (£1m) and the charitable "1834" fund celebrating 175 years of medical education in Newcastle. The programme has pioneered "near-peer" mentorship of medical students by early career academic trainees; an approach which has contributed to a significant increase in the number of students choosing to intercalate over the last 3 years. Newcastle launched the first Academic Foundation Programme in the UK and is still unique in offering a 2 year, academically-focussed programme with 4 month academic slots in both FY1 and FY2. Our ACF programme is amongst the largest in the UK with a progression rate to externally-funded PhD fellowship of >90%. Fellows all receive formal clinical research training in the form of a Certificate in Clinical Research. Options for clinical academic PhD level support include personal fellowships (with a bespoke application support approach), PhDs funded by the Newcastle BRC and BRU (which have funded over 50 PhD students to date in all professional groups) and the TMAT programme. Our NIHR ACL programme is tailored to the needs of our high-flying PhD fellows (as well as welcoming incomers from other units) allowing, subject to performance, seamless progression from PhD to post-doc activity. ACLs are individually mentored by senior clinical academics with an intermediate or higher fellowship track record, as well as being sign-posted to the AMS mentoring scheme.

Within UoA1, 34 returned investigators are products of Newcastle career development structures. These include ***Day*** (Faculty PVC and former MRC Clinician Scientist Fellow), ***Jones*** (Dean of Translational Research and former MRC Clinician Scientist Fellow), ***Chinnery*** (BRC Director and current Wellcome Trust Clinical Senior Fellow), ***Fisher*** (Director for Clinical Fellowships and former Glaxo-Wellcome Senior Clinical Fellow), ***Rajan*** (current Wellcome Trust Intermediate Clinical Fellow), ***Kavanagh*** (current Wellcome Trust Intermediate Clinical Fellow), ***Yu Wai Man*** (current MRC Clinician Scientist Fellow), and ***Heer*** (current CRUK Senior Fellow). A striking example of the value of our approach is the Immunodeficiency Group highlighted above where all the PIs are graduates of the career pathway (***Collin*** (former LRF RD Bennett Fellow), ***Hambleton*** (former MRC Clinician Scientist Fellow), ***Haniffa*** (current Wellcome Trust Intermediate Clinical Fellow) and ***Bigley*** (current Wellcome Trust Intermediate Clinical Fellow).

We are now integrating non-medical clinical academic career development into the broader faculty clinical programme to build on recent successes with academic allied health professionals at professorial level (***Trenell*** NIHR Senior Fellow (Exercise Physiologist), Adamson NIHR Research Professor (Dietician, UoA2) and Rochester (Physiotherapist, UoA4)).

c) Basic Science Academic Career Development: We have been working since 2006 to improve the support we offer to non-clinical early career researchers (ECR). Our flagship Career Pathways Scheme, which supports the career development of all our ECR (stable at 400-450) has aims that map closely with those of the Concordat to support the Career Development of Researchers: active career management, continuity of employment and knowledge exchange. Intervention points are mapped on to the scheme at 3 months (induction), 9 months (career awareness workshop) and 2 years (career planning workshop) and complement annual Performance and Development Review. Pathway activity is supplemented by workshops, mentorship schemes and individual support aimed at supporting all ECR within the faculty. A key element of our strategy is the identification, recruitment and support of those ECR with the greatest potential to become research leaders of the future. Such support is focused around our **Faculty Fellowship Scheme (FFS)** which: helps with placement in the very best academic environments, offers mentorship, helps with fellowship application crafting, and provides financial support for the highest quality ECR (including newly-appointed Lecturers). In the REF period we have supported 18 such ECR, the majority of whom have progressed to make successful external fellowship applications (including BBSRC David Phillips, Wellcome/Royal Society Sir Henry Dale and British Heart Foundation Intermediate) or to obtain a tenured academic appointment. Our career development highlights over the REF period indicate the emerging success of this approach. ***Passos*** was awarded a BBSRC David Phillips Fellowship in 2010 and promoted to lecturer level, establishing his own research team working on molecular mechanisms of ageing and recently published a landmark senior author paper in *Nature*

Communications. ***Borthwick*** was awarded a Marie Curie International Outgoing Fellowship to develop his interests in macrophage biology and fibrosis at NIH Bethesda before returning to a lecturer post. Further successes include award of an ARUK Intermediate Fellowship to ***Milner,*** a Parkinson's UK Fellowship to ***Hudson***, a Diabetes UK RD Lawrence Fellowship to ***Arden***, and a British Heart Foundation Intermediate Fellowship to ***Phillips***. ***Rand*** *and* ***Russell*** have been awarded external fellowships from the LLR (Bennett Fellowship) and Kay Kendall Fund for their studies on genetic prognostic markers in paediatric lymphoma and leukaemia respectively.

d) Athena SWAN Strategy: We have a strong commitment to equal opportunity. This is reflected in the equal gender balance of the ECR featured in this document. The University has an institutional Athena SWAN bronze award, whilst ICM, which manages >50% of the returned academics has silver status. Our Athena SWAN status reflects our commitment to individual career development, the value of our career development pathways, and the fostering of a work culture and environment where everyone can reach their full potential. Our particular focus on fellowship development combined with the commitment to equal opportunities is reflected in the success of our female intermediate and senior fellows over the REF period. Examples of success include ***Cordell*** (Wellcome Trust Senior Fellow, *Nat Genet),* ***Hambleton*** *(*MRC Clinician Scientist Fellow, *New Engl J Med),* ***Horvath*** *(*ERC*, Nat Genet)* and ***Haniffa*** (Wellcome Trust Intermediate Fellow *Immunity, J Exp Med*).

2) Research students

a) Recruitment: Since 2008, the entrance requirement for PhD students has increased to include both a first degree at 2:1 level or above and a relevant masters degree (or equivalent). Our proportion of clinically qualified PhD students is steady at 20%. 22% of the 2012 intake is registered for our 4-year integrated MRes-PhD programme, with modular MRes teaching largely delivered by UoA1 staff; progression to PhD is contingent on gaining the MRes with merit. We had 364 PhD completions during the REF period.

b) Training, satisfaction and completion: All PhD candidates receive the equivalent of 10 days' formal training in transferable and generic skills each year by selection from 155 optional courses designed specifically for these students. These courses are fully compliant with the QAA Code of Practice and UK Research Councils Joint Statement on Skills Training, and receive excellent student feedback. Audit shows that careful performance monitoring, mentoring and attendance of appropriate taught courses by both PhD students and their supervisors has resulted in very high rates of 4-year PhD thesis submission (>89%) and successful degree completion (>95%). PhD students present regularly during our well attended weekly seminar series and also attend specialist journal clubs and locally organised external meetings, such as the British Society for Immunology-sponsored *Immunology NorthEast*. Students in this UoA organise an annual NorthEast Postgraduate Students' Conference; in 2012 this conference attracted 380 PhD student delegates drawn from all the universities in the northern region (www.nepg12.co.uk). Results of the 2013 PRes survey show that PhD students in this UoA expressed a remarkably high level of overall satisfaction with the experience of their degree programmes (question 17a: 94% positive responses). Non-clinical PhD students also enjoy excellent employment prospects, with 100% of responding graduates leaving for full-time employment or further study (HESA DLHE data).

c) Research outputs: PhD students in this UoA are fully integrated in its research culture. The recruitment and support of high quality postgraduate students contributes directly to overall research productivity, with 37% of REF returned papers co-authored by these students. High profile journals publishing papers first authored by students in the UoA include: *Nat Med, Cancer Cell, Cell Stem Cell, PLoS Biol, J Cell Biol, PLoS Genet, EMBO J* and *J Exp Med*. All PhD students are expected to present data to at least one major international conference during their period of study. To enable this, travel grants of up to £800 per student are made available by the faculty. The success of our students is frequently recognized by awards, which include: *MRC Centenary Awards, the Pexieder Award (European Society of Cardiology), Max Perutz Science Writing Award (MRC), Young Scientist of the Year (2009; International Union of Biochemistry and Molecular Biology), NIHR Knowledge Mobilisation Fellowship* and a *Merit Prize of the American Society for Clinical Oncology.*

d. Income, infrastructure and facilities

1) Income

The UoA has an extensive and diverse income stream. Total income over the REF period was £265m and total expenditure £154m. We have substantial income from externally funded centres (*see section* b. ***2)*** *page 2*) and from personal fellowship awards and fellowship programmes (from MRC, Wellcome Trust, NIHR and key AMRC charities), reflecting our commitment to individual career development. At PhD level our flagship programmes are the Wellcome Trust (TMAT) programme and the NIHR BRC Clinical Fellowship Programme. Our structured approach to career development, with trainees supported along well-developed training pathways, will ensure a robust future funding stream from fellowships. We have an extensive translational funding portfolio including 4 NIHR/MRC EME and 2 MRC DPFS awards as well as NIHR HTA, MRC DCS, TSB Biomedical Catalyst and DH/Wellcome Trust HICF awards. We lead an MRC Stratified Medicine Programme (and are co-investigators in two others) and host substantial translational awards from the EPSRC and EU FP7 (>£15m total value) in the areas of medical device development and application. Conventional RCUK and AMRC project grants award income is robust. Particular highlights include our track record in MRC New Investigator Research Grants (4 held during the REF period) again reflecting our career development ethos, and our success in targeted award competitions, exemplified by successes in the recent MRC CFS/ME call with 2/5 awards and >50% of the awarded funds, and the ARUK Experimental Medicine call with 2/6 awards going to investigators returned here. Effective translation in biomedicine requires us to engage successfully with industry and many of our funding streams reflect such successful partnerships. Our flagship industrial collaborations are in the form of the TMAT programme (AstraZeneca, Roche, GSK, Genentech, PTC Therapeutics), the GSK CRAFT Consortium (linked to an MRC MICA Programme Grant (PI ***Mann***), a £5m joint drug development programme with Astex, the £6m PBC MRC Stratified Medicine Programme (GSK, J & J, Novartis, Intercept, Falk Pharma, Medigene, Novimmune, Abbott, Innova & Lumena and the MRC/ABPI RA-MAP consortium (£4.5m, Janssen, UCB, GSK, Roche, Abbvie, Amgen, Astra Zeneca, Pfizer, Medimmune, Eisai, BMS, Grunenthal). We also lead the NOCRI Translational Research Partnership in Joint and Related Inflammatory Diseases. As industrial partnerships often evolve from successful smaller scale projects we prioritise funding opportunities which will foster development of links with potential industrial partners. During the REF period we have hosted 6 KTP projects, 73 CASE studentships and 3 TSB grants with diverse companies including AstraZeneca, Stiefel, GSK, Procter & Gamble and Unilever. In 2013 the NIHR appointed Newcastle as one of 4 Diagnostic Evidence Cooperatives (DECs), with the aim of improving evaluation and clinical implementation of in vitro diagnostics.

2) Infrastructure & Facilities

Our research infrastructure has undergone significant expansion and refurbishment since RAE 2008. Investigators working in the **AGEING & CHRONIC DISEASE domain** are located on the extensively refurbished main medical school campus (directly linked to the Royal Victoria Infirmary (RVI), one of the 2 teaching hospitals within NuTH (we benefit from the fact that Newcastle has a single acute hospital trust managing all facilities)) and on the innovative translational ***Campus for Ageing & Vitality (CAV)***, developed with a total of £26m investment since 2003**.** CAV hosts a vibrant research environment and consists of an academic building complex committed to delivering world-class translational research in ageing. Core to these facilities is the ***Clinical Ageing Research Unit (CARU)***, a clinical research facility (CRF) funded by the Wellcome Trust and Wolfson Foundation and purpose-built with the elderly/chronic disease participant in mind. Adjacent to CARU is the research-dedicated ***Newcastle Magnetic Resonance Centre (NMRC)*** developed to enable the clinical and translational research application of magnetic resonance spectroscopy & imaging and PET/CT. Over the REF period the number of active studies supported by the centre has increased by 47% and the number of research-funded scans by 100%, with a substantial increase in translational activity including the development and application of novel imaging modalities as trial outcome measures. Central to the strategic development of the CAV is the £11m ***Biomedical Research Building (BRB)***, substantially funded though a NIHR Capital Award and European Research Development Fund Funding. This features a novel clinical concept ***(CRESTAs: Clinics for Research and Service in Themed Assessment)***, led and managed by the NHS and aimed at providing high quality service through a “one-stop” multi-disciplinary visit, but also geared for recruitment of patients for participation in early phase trials. The CRESTA concept

will play a key role in future implementation of research-driven innovation into normal clinical practice, an example being a fatigue CRESTA which is pioneering a systematic approach to the management of fatigue in chronic inflammatory disease. Investigators mapping to the **GENETICS & RARE DISEASE** domain are principally based within recently refurbished space at the International Centre for Life (£5m invested in 2010) and on the main campus (Mitochondrial Group, £4m in 2009). Areas of infrastructure investment include £2m on genetic and epigenetic platforms (Roche FLX, Illumina GAII, Illumina MiSeqx2), and associated bioinformatic clusters, £6m on 14 dedicated stem cell laboratories, including a human GMP-grade suite, £3m on confocal, fluorescence and laser dissection microscopy and £2m for on-site zebrafish facilities. This site also hosts the European and MRC Muscle and Cell Biobank, and the joint Wellcome-MRC Human Developmental Biology Resource, which have both recently received external funding renewals for 5 years. Investigators mapping to the **CANCER BIOLOGY & THERAPEUTICS** domain have access to purpose-built biomedical and medicinal chemistry research laboratories adjacent to the medical school on the main campus. Patients are assessed in the newly constructed ***Great North Children's Hospital*** pending our planned development of a dedicated Children's CRF or the ***Sir Bobby Robson Cancer Trials Research Centre*** at the Freeman Hospital (the second NuTH site). Cancer Research Facilities include pre-clinical and clinical research dedicated MR and PET/CT, research radiochemistry with an ABT Molecular Imaging cyclotron and a PET Radiopharmacy Facility, dedicated protein purification facilities to support structural biology and FACS sorting and circulating tumour cell analysis using an Imagestream system. Cancer investigators also have access to state of the art GLP facilities for the preparation and storage of complex translational samples (blood and tissue derived) which are essential for achieving translational goals.

The faculty has invested significantly in cross-cutting scientific facilities and has funded 5 Senior Experimental Scientific Officer posts to supervise and lead in each area. The cellular ***Flow Cytometry*** and ***Cellular Bioimaging*** facilities have benefitted from £2M investment, with new/upgraded/enhanced platforms across all sites and investment in novel technologies such as the UK's first N-SIM/N-STORM super resolution imaging system allowing spatial resolution down to 20nm. The Newcastle University ***Protein and Proteome Analysis*** facility provides mass spectrometry, electrophoresis and chromatography based-support to research groups throughout the University (providing support on sample preparation, LCMS/MS analysis, data processing and analysis and data submission to public research repositories). It is equipped with 4 LCMS systems (Dionex U3000 coupled to Thermo Orbitral LTQ XL, Dionex U3000 coupled to Bruker maXis 4G, Dionex U3000 coupled to ABSciex QTrap4000 and a Dionex U3000 coupled to Bruker HCT) Protein Discovery System) and a MALDI-TOF/TOF together with proprietary and open source software tools for proteomics data analysis. The ***Electron Microscopy*** facility offers a fully supported service (to both internal and external, industry users) and has a Philips CM100 Transmission EM with Compustage and digital image capture and a Cambridge Stereoscan 240 Scanning EM with digital image collection. Our ***Bioinformatics Support Unit*** works with both our ***High Throughput Screening Unit*** and with data derived by external suppliers to provide a bespoke data analysis and interpretation support service. We collaborate extensively with other HEIs in the N8 grouping to access other key technologies not available on site (including NMR with Manchester).

3) Interface with the NHS

The relationship with our key partner trust NuTH is managed via the joint oversight body **Newcastle Biomedicine** (www.ncl.ac.uk/biomedicine) whose board reports to both the NuTH and Faculty Board. Newcastle Biomedicine has, for some time, led internationally competitive patient-focussed research within North East England, acting as a hub for regional, supra-regional specialist, and national clinical services, many of which are regarded as the international benchmark (we host 13 Nationally Commissioned Services, all of which are led by, or have significant input from, clinical academics within this UoA, and which are shaped by their research). Unlike many of our comparators our "hub-and-spoke" model has always had clearly defined geographical boundaries, leading to a natural and close relationship with the regional healthcare community in the North East and Cumbria. The intimate relationship between one University Medical Faculty, one major NHS Foundation Trust, and the regional AHSN and HENE ensures that patients, providers, researchers and educators are committed to a single, region-wide, common goal. Research and business development opportunities at the interface between the Newcastle Biomedicine partners are managed by Joint Research and Business Executives respectively. Key

to our effective joint working are our clinical academic investigators (40% of the investigators returned in this UoA1 are clinical academics working between the 2 organisations) and the clinical research infrastructure managed jointly between the organisations and in which we have made significant investment.

We have a comprehensive portfolio of clinical and translational research facilities which are integrated into a single management structure. **CARU, NMRC** and **CRESTA** are fully integrated with the **RVI CRF** and the **Sir Bobby Robson Cancer Trials Research Centre**. In 2012-13 the combined CARU/CRF supported 158 studies recruiting 3441 patients that resulted in 8948 patient visits (increases of 60%, 383% and 128% respectively over the REF period). Since opening in 2009 the Sir Bobby Robson Centre has initiated 51 new early phase studies (28 phase 1, 23 phase 2) and 8 late phase studies, and over the REF period there has been a year-on-year increase in the numbers of patients being treated in this unit, with 1510 patient treatment visits over the last 12 months. CRF/CARU leveraged grant awards in excess of £13.5M during 2012-13 with 46% of active studies being industry funded, underlining our commitment to the UK growth agenda. In 2012, the integrated CRF/CARU was one of only 19 trials facilities in the country to be awarded NIHR Infrastructure funding for experimental medicine (£4m over 5 years). Our state of the art clinical facilities are supported by the **Newcastle Biomedicine Biobank**, which provides integrated biobank governance support, sample banking and tissue handling facilities (developed on the main medical school campus with £1.5m investment in 2010) and a fully accredited **GMP facility** for therapeutic grade cell isolation and propagation. These support both our active and highly successful adult and paediatric bone marrow stem cell therapeutics programme and our translational cell therapeutics research programme in diabetes (islet cell allo-transplantation), pancreatitis (islet auto-transplantation), eye injury (limbal cell transplantation), osteoarthritis (cartilage tissue engineering) and rheumatoid arthritis (tolerogenic dendritic cell therapy). In addition to these laboratory-orientated support structures we benefit from an accredited **Clinical Trials Unit** and NIHR supported **Research Design Service**.

4) Interface with Industry

Interaction with industry is essential for successful translation of research and is strongly supported by the institution. Creation of a Translational Research Deanery with a remit to foster and develop joint working with industry reflects the faculty priority. We have also invested significantly in support for commercial activity. Our business development managers are part of a Faculty **Research & Enterprise Service** team which advises staff on all aspects of opportunities (intellectual property, research contracts for services, consultancy, professional education, CASE studentships, Knowledge Transfer Partnerships and the route to market for translational research projects). Our facilities are available to industry and we provide incubation space for start-up companies. All staff are encouraged to develop skills in commercialisation through seminars by successful practitioners and through participation in our programme on entrepreneurship and enterprise (joint with the Business School). Examples of highly successful interfacing with industry include the Wellcome Trust TMAT programme, GSK CRAFT partnership and MRC Stratified Medicine Programme detailed elsewhere in this document. We take active steps to both encourage investigators to work with industry and to attract new industrial partners to Newcastle. A floor of the Biomedical Research Building is given over to providing facilities for Commercial Engagement, supported by ERDF funding and facilitates links with Regional Small-Medium Enterprises (SMEs). Our commitment to effective working with industry is reflected in the increase in industry-linked income from £11.1m in 2011/2012 to £25.6m in 2012/13 (an increase of 228%).

e. Collaboration and contribution to the discipline or research base

1) Collaboration

We collaborate widely, leading numerous significant national and international consortia

AGEING & CHRONIC DISEASE: In ***Liver and Fibrosis Biology***, the **UK-PBC Research Consortium** (**PI *Jones***), consisting of 4 academic, 11 industrial and 2 patient group partners was established to provide a unique research platform to study the autoimmune liver disease PBC (www.UK-PBC.com). Originally developed to study the genetic basis of PBC (Wellcome Trust WTCCC3, *Nat Med x2*) it has now evolved to undertake landmark studies of the clinical impact of the disease (*Gastroenterology, Hepatology*) and its treatment with MRC Stratified Medicine funding (£5m). The UK-PBC patient cohort (currently 5000 patients, representing 30% of all UK patients) is the largest and best characterised such cohort in the world and supports a unique portfolio of

international clinical trials utilising novel approaches to disease stratification identified and validated by our scientific programme. The UK-wide **DILIGEN** consortium (***Day***, ***Daly***) has established a unique clinical and genetic resource for patients experiencing drug induced liver disease which has generated landmark studies identifying the mechanisms of key toxic drug reactions for agents such as flucloxacillin which are already influencing clinical practice (*Nat Genet*). The Europe-wide **D-LIVER Consortium** (***McNeil***) is funded by the EU FP7 programme (£9M) and includes investigators from the UK, Germany and Italy as well as 10 European companies. The goal of the Consortium is to use advanced monitoring and ICT to develop a unique home monitoring and therapy support system for patients with advanced liver disease. It offers the prospect of improved care through enhanced monitoring and the opportunity for early intervention and reduced healthcare cost by avoiding the need for hospitalisation. In ***Musculo-Skeletal Disease*** UoA1 investigators lead a significant proportion of the national translational structures. The **MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing** (***Cawston***, www.CIMAUK.org) is a collaboration between Newcastle, Liverpool and Sheffield that brings together complementary expertise in skeletal muscle, bone, cartilage and tendon biology, ageing research, nutrition and exercise interventions and clinical excellence in musculoskeletal disorders. CIMA will develop an integrated approach to understanding the processes and effects of ageing in tissues of the musculoskeletal system, including how ageing contributes to diseases of the musculoskeletal system and how these processes may be ameliorated or prevented. The **MRC/ABPI Immunology & Inflammation Initiative** (***Isaacs***) is a national initiative (£4.5m) involving 9 academic and 12 industrial partners with the goal of developing immune biomarkers of disease state in patients with RA, with relevance to diagnosis, prognosis and therapeutic stratification. The ultimate aim is to develop laboratory assays that quantify immune function. It gave rise to the MRC MATURA consortium which is led from QMUL and involves 10 UK centres. The **ARUK Centre of Excellence in RA Pathogenesis** (***Isaacs***) links basic and translational scientists working in Newcastle, Glasgow and Birmingham, to discover the initiating and persistence factors involved in RA pathogenesis. The **NOCRI Translational Research Partnership for Joint and Related Inflammatory Diseases** (***Isaacs***) is a consortium of 9 academic partners working with colleagues from industry to develop and perform first-in-man studies of novel anti-inflammatory and immune-modulatory small molecule and biologic drugs. The **arcOGEN** consortium is an ARUK-funded national GWAS consortium (***Loughlin)***, which has led to the identification and functional characterization of OA susceptibility loci and the use of this information for the identification of new prognostic and therapeutic targets, including biomarker development (*Lancet*). The **UK Primary Sjogren's Syndrome Registry** is a resource, established by ***Ng*** with funding from the MRC (and which has leveraged more than £2m of additional funding), has been utilised by researchers worldwide, including the US NIH. **ASTIS** is a consortium of 28 centres (27 in Europe and one Canadian) led by ***Van Laar*** which has enrolled 156 patients into an RCT of autologous stem cell transplantation in scleroderma. This is the largest RCT ever to be conducted in systemic sclerosis and the first to provide evidence-based therapeutic guidance. In ***Respiratory Medicine*** the **DEVELOP-UK** consortium (***Fisher***) involves all 5 UK adult lung transplant centres and 3 academic centres (Imperial College, Newcastle University and University of Manchester) and was established to evaluate donor ex-vivo lung perfusion (EVLP) as a means to increase UK lung transplant activity and reduce waiting list mortality. The consortium is currently undertaking a £1.4M HTA-funded trial. The consortium and the DEVELOP-UK HTA trial are cited by the British Transplant Society and NHS Blood and Transplant as an example of how future trials across the UK transplant network should be performed. The **VAPRapid** group is a 14 centre, UK-wide consortium, led by ***Simpson***, established to study sepsis in the ICU setting with a particular focus on ventilator-associated pneumonia. The group is currently undertaking a multi-centre Wellcome Trust/DH HICF-funded trial of early diagnosis. In ***Diabetes***, the **UK Islet Transplant Consortium** led by ***Shaw*** (involving Newcastle, Bristol, Edinburgh, King's College London, Manchester, Oxford, and the Royal Free London) is the first programme in the world fully reimbursed as a clinically proven intervention for type 1 diabetes complicated by life-threatening severe hypoglycaemia. This has underpinned a national experimental medicine, biomedical and psychosocial outcomes study in all UK islet recipients and has facilitated international industrial (e.g. Pfizer, Athersys, Dompe) and academic collaborations (e.g. Collaborative Islet Transplant registry; Universities of Alberta, Arizona and Minnesota; Deakin University, Australia). In ***Haematology*** the **CELLEUROPE** MarieCurie Initial Training Network (ITN) (***Dickinson***), is one of

two led from this UoA, aimed at developing novel diagnostics and cellular therapies to improve haematopoietic stem cell transplant outcome. This £2.5M FP7 project consists of 10 partners including 3 from industry and is recruiting 9 early stage researchers (PhDs) and 3 experienced researchers across the consortium. One of the partners is a Newcastle spin-out company, Alcyomics, testing the safety and efficacy of novel monoclonal antibodies and cellular therapies eg mesenchymal stem cells.

GENETICS & RARE DISEASES: In ***Mitochondrial Genetics and Disease***, we are the lead and coordinating centre for the **National Commissioning for Rare Mitochondrial Disorders of Adults and Children** (***McFarland)*** which now embraces all patients with mitochondrial disease in England and Scotland. Additionally, the **MRC Neuromuscular Centre Mitochondrial Disease Cohort** is led from Newcastle, an MRC/NIHR funded cohort, which covers >1000 patients with mitochondrial disease from all over the UK. In ***Genetic Neuromuscular Disease (NMD)***, the **MRC Centre for Neuromuscular Disease (CNMD)** led by ***Bushby*** has been instrumental in the establishment and coordination of international collaborative initiatives, primarily funded by the EU. This includes coordination of major initiatives in NMD with the FP6 network of excellence **TREAT-NMD** (***Bushby***) continuing past its funding period as the TREAT-NMD Alliance and generating >72,000 web hits annually from 164 different countries with a comprehensive approach to support for trial readiness in NMD. The TREAT-NMD resources have contributed to several other translational EU funded initiatives including **BIO-NMD**, **Eurobiobank, NMD Chip** and **CARE NMD (CNMD)**. The increased international profile of the group in rare diseases in general is reflected in the recent successful grant awards led from Newcastle: RD-Connect (FP7), and the EUCERD Joint Action on Rare Diseases (EAHC). These have consolidated the position of the CNMD as a key leader in both research and policy development in the rare disease field. The CNMD is directly involved in trans-national clinical trials, typically developed and delivered in conjunction with industry, aimed at defining the critical therapeutic reagents in NMD for the next decade. The Centre works closely with RD-Connect, an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research, funded by the EU-FP7 programme which is directed by Lochmuller. The **BIOIMAGE-NMD** EU-FP7 consortium, led by ***Blamire*** and consisting of 3 SMEs and 6 academic centres in 5 European countries, delivers combined structural and molecular imaging biomarkers for the detection of therapeutic effects in patients with rare neuromuscular diseases (NMD). Objectives include the development of a new generation of muscle diffusion MRI, to augment existing methodology for quantitative muscle imaging for use in Duchenne Muscular Dystrophy and novel simultaneous Positron Emission Tomography (PET)/MRI technology to advance innovative drug development programmes for personalised medicines based on Antisense Oligonucleotide technology. In ***Immunodeficiency***, **PEPtalk** is a national cross-specialty group (***Hambleton***) established to carry out, a UK-wide survey of varicella zoster post-exposure prophylaxis (PEP) in children with cancer. This emphasised the need to develop a secure evidence base for informed physician and patient choice of PEP, resulting in a pilot RCT now in progress. ***Hambleton*** and colleagues are key members of the national NIHR BRIDGE-PID study and associated Translational Research Consortium in Rare Diseases.

CANCER BIOLOGY & THERAPEUTICS: The **Leukaemia & Lymphoma Research Cytogenetics Database,** a national resource, run by ***Moorman*** and ***Harrison,*** is the largest of its kind in the world and contains samples from more than 25,000 adults and children with acute leukaemias. Data derived from this collection has been used to establish robust prognostic markers and identify novel potential therapeutic targets. The **National Children's Cancer and Leukaemia Group Biobank**, containing samples collected as part of a national initiative to centralise the banking of samples from children with cancer, is held in Newcastle in a project funded by CRUK (***Hall***). Access to the collection is open to research groups throughout the UK and abroad following an assessment by an independent panel and forms an important resource to further understanding of the pathogenesis of these rare tumours.

2) Contribution to the Research Base

Our investigators make a substantial contribution to the national and international research base. We have returned **7 Fellows of the Academy of Medical Sciences** and **4 NIHR Senior Investigators**. The returned UoA1 investigators hold **8 International Journal Editorships** as well as 10 further Deputy and Associate editorships and 33 editorial board memberships. UoA1 investigators also held **6 Research Council, Wellcome Trust or NIHR Panel Chairs** during the REF period, as well as **24 Panel Memberships**, and **67 Chairs or Memberships of AMRC**

Funding Panels. Returned investigators organised **29 National or International Scientific Meetings** during the REF period. In a reflection of our commitment to impact, which requires the implementation of research into practice, our investigators report **126 Chairs or Memberships of Influential National and International Policy Committees.**

In terms of specific contributions, our leading contributors include ***Prof Christopher Day*** (**FMedSci, NIHR Senior Investigator**), the Pro-Vice-Chancellor for the Faculty of Medical Sciences in Newcastle, who is a member of the MRC Council and a former Secretary of the British Association for the Study of the Liver. ***Prof Sir John Burn*** (**FMedSci**) chairs the British Society for Genetic Medicine, the Genetics Specialty Group of the NIHR and is a member of the NHS Genomics Strategy Board. He was Knighted for services to Medicine and Healthcare in 2010. ***Prof Patrick Chinnery*** (**FMedSci**, **NIHR Senior Investigator**), the Director of the Newcastle NIHR BRC, is Joint Lead for the NIHR Translational Research Collaboration in Rare Diseases and a Member of the MRC Neurosciences and Mental Health Board. He was awarded the Foulkes Foundation Medal by the Academy of Medical Sciences in 2011. ***Prof David Jones***, Dean of Translational Research in the Faculty of Medical Sciences, is National Training Lead for the NIHR Infrastructure playing a national role in developing training in translational research methodology and is a member of the NIHR DRF panel. ***Prof Tom Kirkwood CBE*** (**FMedSci**) is President of the Scientific Board, AXA Research Fund and has been an external Scientific Advisor, for EU FP6 MiMAge (mitochondrial mechanisms of ageing) and EU FP7 IDEAL (integrating development and ageing across the lifecourse) programmes. He gave the Ipsen Foundation Medal Lecture, the Graham Medal Lecture for the Royal Philosophical Society, Glasgow and the Menzies Campbell Lecture, Royal College of Surgeons. ***Prof Herbie Newell*** (**FMedSci**) chairs the MRC Biomedical Catalyst: DPFS Panel and was Director of Translational Research for Cancer Research UK (CRUK). ***Prof Doug Turnbull*** (**FMedSci**) chaired the Wellcome Trust Clinical Interest Group (2006-2007) and chaired the Molecular and Cellular Neuroscience Panel (2007-2011). He has been a member of the NIHR Fellowship programme since 2005 and chaired the programme between 2007 and 2010. He is Director of the Newcastle Centre for Brain Ageing and Vitality (supported by BBSRC, EPSRC, ESRC and MRC), Director of the Wellcome Trust Centre for Mitochondrial Research and Head of the National Highly Specialised Services for Rare Neuromuscular Disorders of Adults and Children.

Amongst other contributions ***Prof Kate Bushby*** (**NIHR Senior Investigator**) is one of the founding coordinators of the TREAT-NMD network for accelerating therapy development in neuromuscular diseases and is Vice President of the EU Committee of Experts on Rare Diseases. ***Prof Zosia Chrzanowska-Lightowlers*** is a member of the Euromit International Scientific Advisory Committee and Organising Committee. ***Prof Paul Corris*** is recent past president of the European Society for Heart and Lung Transplantation, the International Society for Heart and Lung Transplantation and the British Thoracic Society. He is research champion for the UK National Pulmonary Hypertension Service. ***Prof Mary Herbert*** was winner of a Business for Life Innovation award in 2009 and prize winner in the Blueprint Business Planning Competition, in 2008. ***Prof John Isaacs*** gave the Sir Michael Perrin Lecture to the Royal College of Physicians of London in 2013. He a member of the MRC Translational Research Group, Stratified Medicine and DPFS/DCS funding panels, MHRA Expert Advisory Groups on Clinical Trials and on Gastroenterology, Rheumatology, Immunology and Dermatology (Committee on Safety of Medicines, CSM). ***Prof John Loughlin*** is President of the Osteoarthritis Research Society International, while ***Prof Robert McFarland*** is a member of the International Co-ordinating Committee for Standards of Care in Mitochondrial Medicine and Paediatric Neurology lead for the Nationally Commissioned NHS Service for Rare Mitochondrial Diseases of Adults and Children. ***Prof Robert Pickard*** is Chair of the Academic Section of the British Association of Urological Surgeons. ***Prof Nick Reynolds*** chairs the Research subcommittee of the British Association of Dermatologists and the British Association of Dermatologists Biologic Interventions Register (BADBIR) and is President-elect of the European Society for Dermatological Research. ***Prof Robert Taylor*** is National Organiser of the UK National External Quality Assessment Scheme. ***Prof Thomas von Zglinicki*** is an International Advisory Board Member for the Institut fuer Umweltmedizinische Forschung, Duesseldorf and the Robert & Arlene Kogod Center on Ageing at Mayo Clinic.