Institution: The University of Edinburgh

Unit of Assessment: UoA1

a. Overview

Research Policy and Structure; its evolution since RAE2008

The University of Edinburgh (UoE)'s College of Medicine and Veterinary Medicine (CMVM; Head, Prof Sir John Savill *FMedSci, FRS*; Clinical Dean and Regius Chair of Medical Science, Prof John Iredale, *FMedSci*) is an internationally leading force in basic-to-clinical translational research. Our themes are: *genes and populations*, *normal and diseased cells* and *inflammation and tissue repair*.

Since RAE2008, we have expanded and bolstered substantially our capability to make a major impact on medical research internationally. We have continued with our 40-year strategy of integration of basic and clinical sciences. Starting with the formation of the UoE and MRC Centre for Reproductive Biology in 1972, by RAE2008 we had coalesced a host of traditional academic departments, now organised in 8 major Interdisciplinary Research Centres (each with more than 100 staff). Here critical masses of clinical and basic scientists interact closely around their basic-to-translational goals, overcoming boundaries between "wet" and "dry" science and primary and secondary care, adding substantial value and offering the finest research training environments. The excellence of these Centres is evidenced by prestigious external funding awards including: 4 Medical Research Council (MRC) Centres, 2 British Heart Foundation (BHF) Centres, a Cancer Research UK (CRUK) Centre, an Asthma UK (A-UK) Centre for Applied Research, an MRC University Unit (Human Genetics Unit) and a World Health Organisation (WHO) Collaborating Centre on Population Health Research and Training.

In RAE2008, we recognised a higher order of interdisciplinary links, our nascent 'institutes', each consisting of 3–5 interrelated Centres. In the REF2014 period we have built upon this, developing and consolidating 4 major Research Institutes (each with more than 500 staff and postgraduates):

- The Queen's Medical Research Institute (QMRI; Director, Prof Chris Haslett, *FMedSci OBE*) at the new Royal Infirmary of Edinburgh (RIE) campus (returned here UoA1);
- The Institute of Genetics and Molecular Medicine (IGMM; Director, Prof Nick Hastie, *FRS FMedSci CBE*) at the Western General Hospital (WGH) campus (returned here UoA1);
- Edinburgh Neuroscience (Director, Prof Charles ffrench-Constant; returned UoA4);
- The Roslin Institute (incorporating the Royal [Dick] School of Veterinary Sciences and Edinburgh Infectious Diseases; Director, Prof David Hume, *FMedSci*; returned UoA6).

There is a free flow of ideas and technologies between all CMVM Institutes and their encompassed Centres. Crucially, the co-location of QMRI and IGMM adjacent to the two Edinburgh research and teaching hospitals ensures that CMVM research reaches into the provision of NHS services for the benefit of patients, and our science prospers in environments rich in clinical material and data. Several CMVM academic clinicians co-lead NHS services, for example, in cardiology, imaging and cancer. In keeping with our inter-disciplinary drive, we have now embedded academic research staff from UoE's Schools of Chemistry, Engineering, Biological Sciences and Informatics within our Institutes. Since RAE2001, we have invested over £160M in new infrastructure to house QMRI and IGMM.

Our long-term strategy anticipated the current drive to co-locate clinical and basic science groups with state-of-the-art infrastructure and facilities that enable 'close to the patient' data-rich research. Clinical academic medicine has flourished in Edinburgh, built on the scientific catalysis created by our Centres and culture of encouraging clinical and basic scientists to develop their careers together in a supportive environment. We have established field-leading career development programmes for both clinically qualified (Edinburgh Clinical Academic Track; ECAT) and non-clinical (Edinburgh Scientific Academic Track; ESAT) researchers. To drive translation and interactions with industry partners, we, together with NHS Lothian (NHS-L), Alexandria Real Estate and Scotland's national development agency (Scottish Enterprise), have formed and developed Edinburgh BioQuarter (EBQ), engendering a step change in the translation and commercialisation of research (described in detail in REF3a; £36M of new funds to Edinburgh). In creating this vibrant new infrastructure, we have expanded the ambitious plans laid out in RAE2008 in which we were rated 40% 4*, 40% 3*, 20% 2* in Hospital-Based Clinical Subjects (RAE2008, UoA4).

Selected Headlines for Institutes and constituent Centres are:

The Institute of Genetics and Molecular Medicine (IGMM):

- **MRC Human Genetics Unit (HGU):** £49.9M quinquennial renewal in 2012 and merger with UoE; £9.8M MRC "glue" funding (including a 4-year PhD programme); STED and STORM next-generation imaging (joint with Heriot Watt University - £2.0M MRC);
- **Centre for Genomics and Experimental Medicine (CGEM)**: Wellcome/Wolfson, MRC and UoE award (£11.8M total) to construct state-of-the-art Systems Medicine Building;
- **CRUK Edinburgh Cancer Research Centre (ECRC)**: core Centre award 2009-2013 £4.3M (renewed until 2017); key investments in imaging infrastructure; unique bespoke multiphoton/SRS microscope for *in vivo* label-free imaging (£0.4M CRUK, UoE, MRC); High-content and Phenotypic Imaging platform (0.5M European Research Council (ERC) and UoE);
- **Centre for Population Health Sciences (CPHS):** encompassing the A-UK Centre for Applied Asthma Research (£2M), the WHO Collaborating Centre on Population Health Research and Training, and hosting the Scottish node of the MRC-led Farr Medical Informatics Institute - a collaboration involving UoE School of Informatics and the University of Dundee (£5M MRC, £2M Chief Scientist Office (CSO)).

The Queen's Medical Research Institute (QMRI):

- **MRC Centre for Inflammation Research (CIR)**: second renewal of core funding (£1.6M MRC); EPSRC Imaging Inter-disciplinary Research Centre with UoE School of Chemistry and Herriot-Watt University (£11.6M EPSRC);
- **MRC Centre for Reproductive Health (CRH)**: core Centre award (£1.2M MRC); Director recruitment (Prof J Pollard; Wellcome Trust (WT) Senior Investigator Award (SIA) £4.4M; next-generation imaging award £1.7M MRC);
- **BHF Centre for Cardiovascular Sciences (CCVS)**: original BHF Centre of Excellence award in 2008 (£7.6M); renewal in 2013 (£3M); the second BHF Centre funding for Vascular Regeneration awarded in 2012 (£2.5M);
- **MRC Centre for Regenerative Medicine** (**CRM**): renewal of core funding (£1.8M 2008; renewal £2.2M 2013, MRC); Anne Rowling Regenerative Neurology Clinic (£12.8M); MRC Hub for "Engineering and Exploiting Stem Cell Niche (£5.6M); state-of-the-art new CRM building completed 2011 (£54M, UoE, MRC and other donors); UK-RMP (Regenerative Medicine Platform) Centre for Chemical and Computational Biology of the Niche (£5.1M MRC and UoE);
- QMRI also hosts the adjacent state-of-the-art imaging facility, the Clinical Research Imaging Centre (CRIC); with UoE investment of £20M, CRIC is equipped with 3T-MRI, ultra-high-resolution CT, CT/PET camera and cyclotron - uniquely (in the UK) integrated into one facility.

Capacity Building and Career Development:

- Establishment of **Edinburgh Clinical Academic Track** (ECAT) 'run-through' scheme for clinician scientists (£5.5M 2007; renewal £6.2M 2013, WT);
- Establishment of 37 tenure track positions, and the development of the **Edinburgh Scientific Academic Track** (ESAT) career structure for non-clinical scientists (£8M UoE investment; on-going programme of recruitment); investment in ESAT also from BHF through BHF Centre award (£3.0M) and from MRC through Centre award to CRM (£1.0M);
- Establishment of **Scottish Translational Medicine and Therapeutics Initiative** (STMTI) led from Edinburgh (£2.6M WT, Wyeth (now part of Pfizer));
- Establishment of 5 new 4-year **PhD programmes** (with a total of 150 students).

Translation and Commercialisation:

- Establishment of **Edinburgh BioQuarter** (EBQ; £18M);
- MRC **Development Pathway Funding Scheme** (DPFS) and **Confidence in Concept** (CIC) awards (£2.7M MRC);
- **GSK DPAc** award (one of only 10 awards in first global tranche; £3M), and strategic **pharmaceutical alliances** (£4M from Eli-Lilly, GSK, AstraZeneca, Pfizer, GE Healthcare).

b. Research Strategy

Our submission to UoA1 has 8 Centres of Excellence as listed above, organised in two Institutes, each adjacent to one of Edinburgh's two major research and teaching hospitals.

The first is **IGMM** (adjacent to the Western General Hospital (WGH)), in which there are 4 Centres that broadly focus on *genes and populations* and *normal and diseased cells* to study development and disease mechanisms. The Centres are grouped strategically to exploit common strengths in genetic and genomic analysis, and protein, cell and tissue regulation in disease, with emerging emphasis on innovative *basic and translational science*, from molecules to man and populations to process. The second is **QMRI** (conjoined with the Royal Infirmary of Edinburgh (RIE)), in which there is a strategic grouping of 4 Centres, equipped to address major disease challenges. Research is broadly focussed on *normal and diseased cells* and *inflammation and tissue repair***.** In QMRI the research emphasis is towards *clinical-translational science,* with two-way iteration from bench-to-bedside. Centres within Institutes 'hub' inter-disciplinary research and training, and investigators collaborate widely, fostering the beneficial sharing of knowledge, ideas, skills, scientific cultures and infrastructure.

We now describe examples of key research findings, selected submitted papers for individuals and notable funding successes. This is done Centre by Centre, as these are the operational units of our research structure. For major funding, we record the amount awarded here, and we denote 'early career' ECAT (clinical) or ESAT (non-clinical) research fellows. We define programme grants, or their equivalents, e.g., fellowships etc., as awards of four or more years duration. Our Category C colleagues are marked with an *.

THE IGMM: STRATEGY, FUNDING AND RESEARCH SUCCESS

b.1 MRC-Human Genetics Unit (MRC-HGU; Director Hastie FRS)

UoE/MRC-HGU, the largest MRC Unit in the UK, aims to *understand genetic mechanisms underlying human disease and associated biology, and ultimately to translate this knowledge for patient benefit*. In 2012, the HGU became an MRC-University Unit, when it joined UoE, enhancing translational potential through formation of the IGMM. Following the most recent review in November 2011, the MRC-HGU received an award of £49.9M to fund its core programmes over the next 5 years. The Director was also awarded £9.8M to support IGMM-wide activities, including a 4-year PhD programme, recruitment of early career scientists in key strategic areas and vital new infrastructure. The MRC-HGU has 25 Category A staff who, in addition to 16 MRC core programmes, have brought in 6 competitively won programme grants, or their equivalent, including 2 ERC grants, 1 WT-SIA, 2 MRC Senior Fellowships and 1 WT Career Development Award (WT-CDA).

The HGU has three key research themes: *medical and developmental genetics, chromosome biology and gene expression* and *biomedical systems analysis*. HGU researchers work closely with colleagues in CPHS on complex genetic traits in populations (see b.4.1).

b.1.1 Medical and Developmental Genetics (**Head: FitzPatrick and I Jackson**; Bicknell, Dorin, Hastie, Hayward, Hill, Hurd, A Jackson, Mort, Patton, Vitart, Wright)

Major themes include disorders of the eye, growth, cancer and cilia. A Jackson (ERC Starter grant (€1.5M) identified a number of genes mutated in microcephaly and primordial dwarfism and showed that these likely affect centrosome function, checkpoint pathways and the basic DNA replication apparatus, establishing a key role for RNAse H2 in Aicardi-Goutières syndrome (**Nat Genet, 2008; Cell, 2012; Mol Cell, 2013**). In collaboration with colleagues in Vienna, A Jackson has demonstrated that organoids produced by induced pluripotent stem (iPS) cells from microcephaly patients are smaller, with evidence of premature differentiation **(Nature, 2013).** FitzPatrick and Hill have shown how mutation of very-long-distance enhancers can lead to human dysmorphologies and limb disorders (**Nat Genet, 2009; Science, 2009; Dev Cell, 2012**). I Jackson is a leader in the effort to sequence multiple mouse strains (**Nature, 2011**), and, together with Patton, has used genetic models to identify mechanisms underlying melanocyte development and melanoma (**Dev Cell, 2013)**. On the developmental theme, Hurd (early career ESAT Fellow) has identified genes associated with ciliary disorders (**Nat Genet, 2012; Cell, 2012**), while Hastie has dissected the mechanisms underlying developmental disorders arising through mutations in the Wilms' tumour gene, *WT1* (**Nat Genet, 2010; Dev Cell, 2011**). Collaborative HGU/CPHS studies

have identified numerous new genetic loci, e.g., identification of networks regulating urate transport (**Nat Genet, 2008 and 2012**) and a master regulator of glycosylation (**PLoS Genet, 2010**).

b.1.2 Chromosome Biology and Gene Expression (**Head: Bickmore**; Adams, Caceres, Gilbert, Kagansky, Kudla, Meehan, Wood)

This team leads international work on chromosomes, epigenetics and RNA biology. Bickmore (ERC Advanced Grant, €1.7M) provided novel insights into chromosome positioning and folding in relation to gene function (**Cell, 2013**), while Gilbert (MRC Senior Research Fellow, £3.4M) has elucidated chromosome architecture in relation to gene expression (**Mol Cell, 2010; Nat Struct Mol Biol, 2013**). Adams has elucidated the pathways by which germ cells are protected from genetic insults (**PLoS Genet, 2008**), while Kagansky (early career ESAT Fellow), established the relationship between RNAi heterochromatin and centromere function (**Science, 2009; Cell, 2010**), linking to the work of Caceres (WT-SIA, £1.5M) on micro-RNA processing (**Mol Cell, 2008; Nat Struct Mol Biol, 2012**). Kudla (early career ESAT fellow; WT-CDA, £0.95M) has pioneered genome-wide analysis of microRNA interactions (**Cell, 2013a**), and taken new approaches to determine the function of synonymous codon changes (**Science, 2009; Cell, 2013b**). Wood (early career ESAT, WT Henry Dale Fellow, £1M) described the first organism-level use of gene-editing nucleases (TALENs), including first modification of cis-acting sequence motifs (**Science, 2011**).

b.1.3 Biomedical Systems Analysis (**Head: Baldock**; Haley, Navarro, Overton, Semple, Sims, Taylor)

The analysis and integration of exponentially increasing data sets, particularly those arising from next-generation sequencing (NGS), represents an emerging challenge. Baldock pioneered the Mouse 3D Atlas programme (**Nat Methods, 2010; PLoS Biol, 2011; Bioinformatics, 2011**), while Semple and Taylor use computational approaches to interrogate NGS data in an evolutionary context to develop hypotheses about promoter function, genome organisation and transcriptional networks (**Nat Genet, 2009; Nat Comms, 2012**). Navarro has analysed complex human genome-wide association data (**PLoS Genet, 2012; Nat Genet, 2012**).

b.2 UoE-Centre for Genomics and Experimental Medicine (CGEM; Director D Porteous)

CGEM comprises 14 Category A staff with 7 programme grants, or their equivalent, and 1 ERC grant. Awarded £11.8M to develop Systems Medicine in 2010 (£3.5M WT; £3.2M MRC; £5.1M UoE), the CGEM mission is *to use genetics and genomics to understand the mechanisms of disease and inform novel intervention strategies.* CGEM has four main clinical themes: *cystic fibrosis, psychiatric disorders, bone and joint, and gastrointestinal disease*.

b.2.1 Medical Genetics (**Head: D Porteous**; Abbott, Boyd, Evans, Harris, Millar, M Porteous*, Ramsahoye, Thomson)

D Porteous leads Generation Scotland (GS; http://www.generationscotland.org), a collaboration between the Scottish Medical Schools and the NHS (£10M from CSO). GS comprises 30,000 population- and family-based participants, with full demographic, lifestyle, clinical and genetic information, designed to study genetic determinants of ill health (**Nat Genet, 2010**). D Porteous is also the genetics lead for the MRC-Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE (UoA4)), demonstrating genetic contributions to cognition and change in intelligence over the life course (**Nature, 2012)**. D Porteous, Thomson and Evans have defined the genetic contributions to risk of schizophrenia and other major mental illness (**Mol Psych, 2008; 2009; 2011; 2012; 2013)**. Boyd and D Porteous are members of the UK Cystic Fibrosis (CF) Gene Therapy Consortium, and lead a pioneering CF gene therapy translational and clinical research programme (**Nat Biotech, 2008**), funded by a CF Trust Programme Grant of £2.6M and by the National Institutes of Health Research/MRC Efficiency and Mechanism Evaluation Programme (NIHR EME; Edinburgh share, £1.3M). The strong links between the Medical Genetics research team and NHS-L South East Scotland Regional Genetics Service/Molecular Diagnostics Lab (Director, M Porteous*), accelerate technology transfer into the NHS of novel routine analyses, such as mismatch repair and *BRCA1* and *BRCA2* gene testing.

b.2.2 Rheumatology (**Head: Ralston**; Albagha, Borjesson, Irdis, Simpson)

A key focus is on the genetics and biology of bone disease. Albagha (ERC, €1.5M) and Ralston (2 Arthritis Research-UK Programme Grants, £1.4M and EU-FP7 grant; Edinburgh share, £0.3M)

have identified susceptibility loci for Paget's disease through genome-wide association (**Nat Genet, 2010; 2011**), and have played key roles in identifying *loci* that predispose to osteoporosis and bone fractures (**Nat Genet, 2009**; **2012**). Idris and Ralston showed that the type 1 and type 2 cannabinoid receptors regulate peak bone mass and age-related bone loss in mice (**Cell Metab, 2009; Endocrinology, 20011**), while Ralston also identified a novel syndrome of osteoporosis caused by neutralising antibodies to osteoprotegerin (**New Eng J Med, 2009**). Borjesson (early career ESAT Fellow; Swedish Travelling fellowship, £0.3M) found a key role for estrogen receptor-α in bone cell function (**PNAS, 2012**).

b.2.3 Gastrointestinal Disease (**Head: Satsangi**; Nimmo, D Wilson)

The genetics of inflammatory bowel disorders (IBDs) has been a long-term focus for Satsangi (EU-FP7 £9.2M (Edinburgh share, £1.7M); CSO, £1.2M; MRC, £3.2M; and WT, £0.7M). Satsangi's work has led to definition of the molecular architecture of IBD (**Nature, 2013**; **Nat Genet, 2008; 2010**), including functional studies investigating nucleotide-binding oligomerisation domain-containing protein 2, hedgehog signalling and autophagy (**PLoS Med, 2008**). Satsangi and Nimmo determined the efficacy and safety of novel therapies, including biologics and stem cell transplants in Crohn's Disease. With D Wilson (MRC £1M strategic award), Satsangi identified genes and biomarkers implicated in paediatric IBD (**Gastroenterology, 2008; Nat Genet, 2009; Nature 2012**).

b.3 (Edinburgh) Cancer Research UK Centre (**ECRC; co-Directors Frame** and **D Cameron**)

The Edinburgh Cancer Research Centre (ECRC) transcends laboratory and clinical science: themes are *basic and translational cancer cell biology, colon cancer genetics (risk and prevention)* and *therapeutics and cancer medicine*. ECRC comprises 22 Category A staff, with 13 competitively won programme grants, or equivalent, (including 1 ERC grant and 5 personal fellowships to early career researchers). The ECRC is one of a network of CRUK Centres, and a partnership between UoE, CRUK and NHS-L. Cancer research funding in Edinburgh from multiple sources has totalled £113M during 2008–2012 (http://www.ncri.org.uk/; figures for 2013 not available). The research in ECRC is underpinned by a core CRUK Centre Award (2009-2013), £4.3M (renewed for 2014-2017), and also benefits from UoE infrastructure and collaborative science (e.g., within IGMM (MRC-HGU, CPHS) and at the QMRI (MRC-CIR, MRC-CRM and MRC-CRH).

b.3.1 Basic and Translational Cancer Biology (**Head: Frame**; Acosta, Ball, Brunton, Carragher, Ditzel, Finch, Gammoh, Hupp, Melton, P Pollard, Serrels, Unciti-Broceta, Wilkinson)

In cancer biology studies, Frame and Brunton (CRUK Programme Grant, renewed May 2013, £2.0M; and ERC Advanced Grant, €2.5M) have shown that adhesion-linked oncoproteins (FAK or kindlin-1) control cancer cell polarity, a novel cancer cell autophagy survival mechanism, spindle assembly and cell division (**Curr Biol, 2010; Dev Cell, 2010; Nat Cell Biol, 2012; Curr Biol, 2013; Cancer Cell, 2011; Nat Comms, 2013**). Wilkinson (early career ESAT Fellow; CRUK Career Development Fellow (CDF), £1.9M) discovered the mechanism of hypoxia-selective autophagy in cell survival (**Genes Dev, 2009**), and Gammoh (early career ESAT Fellow) has elucidated key core autophagy mechanisms and links to apoptosis (**Cell, 2011; PNAS, 2012; Nat Struct Mol Biol, 2013**). Ditzel (early career ESAT Fellow; BBSRC Career Establishment Award, £0.6M) has discovered how key effector caspases are controlled by ubiquitination and regulate apoptosis (**Mol Cell, 2008**; **Mol Cell, 2010**). P Pollard (early career ESAT Fellow, ERC Starter Grant €1.5M) has elucidated crucial interplay between genetic mutation and cellular metabolism in renal cancer (**Nature, 2011; Cell Metab, 2012**; **Cell Reports, 2013**), while Finch (ESAT Fellow) performed seminal work on modelling c-Myc inhibition in tumorigenesis (**Nature, 2008**), and unravelled the mechanism of Shwachman Diamond Syndrome (**Genes Dev, 2011**). Acosta (early career ESAT Fellow; CRUK CDF, £1.4M) has established the role of the chemokine receptor CXCR2 in senescence, and how this contributes to cancer (**Cell, 2008**; **Genes Dev, 2009; Nat Cell Biol, 2013**). Unciti-Broceta has brought chemical biology expertise to cancer biology, devising novel chemistry approaches to biological problems (**Nature Chem, 2011; Nature Protoc, 2012**). To enhance translation, Carragher was recruited from AstraZeneca as an RCUK Fellow to head the Edinburgh Cancer Discovery Unit (ECDU). With funding from CRUK Drug Development Office, EBQ and industrial partners (total £1.2M), he has developed innovative biology-led approaches to drug discovery and testing (**Mol Canc Ther, 2010**; **EMBO Mol Med, 2013**). Close links to the

QMRI Centres MRC-CRM and MRC-CIR (on cancer stem cell biology and inflammation, respectively) is cemented by the recent ECRC joint appointments of Kranc (**Cell Stem Cell, 2009**) and S Pollard (**Cell Stem Cell, 2009; Genes Dev, 2013**), and by collaborations from QMRI researchers Iredale, Forbes and ESAT Fellows Feng (**PLoS Biology, 2010**) and Qian (**Nature, 2011**).

b.3.2 Colon Cancer Genetics (**Head: Dunlop**; Arends, Din, Farrington, Stark)

Strengths in colon cancer surgery, and research into risk and biology, has led Dunlop (CRUK Programme Grant, £2.5M) and Farrington to elucidate colon cancer susceptibility loci, risk factors and the genetic aetiology of Lynch syndrome (**Nat Genet, 2008a; 2008b; 2008c; 2008d; 2010; 2012**). Din (CRUK Clinician Scientist Fellowship, £0.75M) has elucidated chemopreventative signalling effects of aspirin via mTOR (**Gut, 2010; Gastroenterology, 2012**)**.** Arends has used genetically engineered models of colon cancer to identify roles for structure-specific nucleases, the genotoxic effects of alcohol-induced aldehydes and genes that counteract these, and a key role for nucleophosmin (**Nat Genet, 2011a; 2011b; Nature, 2011; Nature, 2012**). Arends will establish a new Centre for Molecular Pathology in 2014, led from the ECRC and IGMM.

b.3.3 Therapeutics and Cancer Medicine (**Head: Cameron**; Brennan, Dixon*, Gourley, Kunkler*, Langdon, Wall*)

Cameron has led studies showing that CNS relapses are common in HER2-positive breast cancer (**Lancet Oncol, 2013a**), that stroma-related gene signatures predict resistance to neo-adjuvant chemotherapy (**Nat Med, 2009**), and that there may be a sub-group of triple negative breast cancer patients who benefit from bevacizumab (**Lancet Oncol, 2013b**). Cameron (**New Eng J Med, 2011**) co-authored the recent report on the benefits and potential risks of breast cancer screening (published in the **Lancet, 2012**). Gourley (CSO Post-PhD Clinician Scientist Fellowship, then a Scottish Senior Clinical Fellowship, £0.37M) made the seminal observation of extension of the ovarian BRCA-ness phenotype (**J Clin Oncol, 2010**), and was key in the resulting clinical studies that deduced the value of olaparib (PARP inhibitor) maintenance therapy in platinum-sensitive, relapsed ovarian cancer (**New Eng J Med, 2011**). Our NHS Category C colleagues bridge scientific research to clinical trials and practice. Key examples are Dixon* (co-PI on Breakthrough Unit grant, £4.7M), who has evaluated early and late endocrine resistance in breast cancer (**J Clin Onc**, **2009**), Kunkler* (MRC, £2.1M), who has reported the value of radiotherapy in early breast cancer (**J Pathol, 2012**; **Int J Radiat Oncol Biol Phys, 2012**) and Wall*, who has shown beneficial effects of systematic management of depression in cancer patients (**Lancet, 2008**).

b.4 UoE-Centre for Population Health Science (**CPHS; co-Directors: Campbell, Sheikh**)

CPHS works collaboratively to understand the causes of disease, evaluate new approaches to disease control and translate findings into action at a population level. CPHS comprises 32 Category A staff, including 3 early career researchers and 5 programme grants, or their equivalent, as well as 10 EU grants (CPHS staff leading 2 of these). CPHS research grant awards totalled £37M (£27M to those returned here in UoA1) during 2008–2013. CPHS encompasses an A-UK Centre, an MRC Hub for Trials Methodology Research and a WHO Collaborating Centre on Population Health Research and Training. The research is aligned with our UoA1 theme of *genes and populations,* and can be subdivided into *molecular epidemiology, asthma/allergy and e-health research and global health epidemiology*.

b.4.1 Molecular Epidemiology (**Head: J Wilson**; Anderson, McQuillan, McKeigue, Polasek, Price, Theodoratou, Weller)

This CPHS group works with MRC-HGU staff to establish new cohort studies, with data on up to 800 quantitative traits and associated high-quality biobanks, including those from the Orkney, Shetland and Croatian islands. This work attracted substantial international funding (£10.1M). These studies have made prominent contributions to the identification of genetic variants underlying complex disease, with contributions from CPHS to 45 collaborative publications in **Nature, Science** and **Nat Genet** since 2008. This group led the first genome-wide association studies of lipidomic and glycomic traits (**PLoS Genet, 2009; 2013**), exploring translational potential through the development of a plasma N-glycan biomarker for Maturity Onset Diabetes of the Young (MODY3) (**Diabetes, 2013**; pre-patent filed). This leading role in glycomics was recognised by awards of 3 EU-FP7 glycomics grants in 2012 (total £20M; Edinburgh share, £2.3M) to develop

novel technological and statistical methods and to establish glycan biomarkers in IBD (co-coordinated with Satsangi (CGEM; b.2.3 above). McKeigue and McQuillan developed innovative statistical analytic methods in Mendelian randomisation, pleiotropy identification and homozygosity analysis (**Am J Hum Genet, 2008; Int J Epidemiol, 2010; PLoS Genet, 2012**), forming the platform for J Wilson's leadership of the international ROHgen homozygosity consortium (**Nat Genet, 2010a; 2010b; 2010c; 2010d**). In cancer epidemiology, Campbell and Theodoratou worked closely with Dunlop (ECRC; b.3.2 above) to identify novel genetic variants and evaluate the potential of genetic risk scores (**J Nat Can Inst, 2012; PLoS Genet, 2011**), and Price has quantified the impact of aspirin on cancer incidence and mortality (**Lancet, 2011**; **Lancet, 2012a**) and metastasis (**Lancet, 2012b**).

b.4.2 Asthma, Allergy and E-health Research (**Head: Sheikh**; Bhopal, Levy, McKinstry, Morrison, Nurmatov, Pinnock, Simpson, Schwarze)

The A-UK Centre for Applied Asthma Research (£2M core support, with additional £4M in co-funding to Sheikh), is building strong relationships between the MRC-CIR, the Edinburgh MRC Hub for Trials Methodology Research (£2.8M; G Murray, see below) and the Scottish eHealth Informatics Research Centre (£5.9M from MRC and funding partners to the founder consortium, led in Edinburgh by Sheikh). Medical Informatics and eHealth have been bolstered with an additional £5M to host, in Edinburgh, the Scottish node of the UK-wide, MRC-led Farr Institute for Health Informatics Research. This co-locates leading Edinburgh informaticians, the Scottish Digital Healthcare Innovation Centre (£10M, returned in UoA11), key NHS Information and Statistics Division staff and CPHS e-health expertise to drive 'discovery from data'. Sheikh, working with Simpson, Pinnock and Levy, leads the A-UK and the European Respiratory Society Respire2 Centres, and has made significant progress in understanding the epidemiology, clinical management and societal implications of respiratory and allergic disorders (**Lancet, 2012; Lancet Inf Dis, 2012**). Underpinned by a series of programme grants (Department of Health, £1.8M; NIHR, £2M; CSO, £1.1M), innovations in eHealth-based research represent a major strategic focus of the A-UK Centre (**Br Med J (BMJ), 2008; 2009a; 2009b; 2010; 2011a; 2011b; 2011c; 2012; PLoS Med, 2009**).

b.4.3 Global Health Epidemiology Group (**Heads: Campbell and Rudan**; Chalmers*, Chan, Fischbacher*, Morling, Nair, S Murray, Polasek, Wild)

This group has produced evidence for public health policy and action, with funding from the Gates Foundation, WHO and UNICEF (total £3M). Rudan, Chan, Wild and Morling have led work on the estimation of current and future burden of dementia (**Lancet, 2013a**; with Deary (CCACE in UoA4)), peripheral arterial disease (**Lancet, 2013b**) and diabetes (**Nat Genet, 2011**; **PLoS Med, 2012**). S Murray established new models for end-of-life treatment (**BMJ, 2008; 2009; 2010**) in malignant and non-malignant disease and in the developing world (funded by the Tropical Health and Education Trust, £1.5M).

Campbell, Rudan and Nair are experts in pneumonia (the leading cause of child death globally) on the WHO Child Health Epidemiology Reference Group (CHERG; Campbell is deputy Chairman 2011–3). This group has driven global child health policy (CHERG published 45 Lancet papers from 2008–13). Campbell and Rudan defined the disease burden and trends, risk factors and effective interventions against pneumonia in a series of high-profile papers that included the most highly cited Lancet paper (underlined) in the past 3 years (**Lancet, 2010; 2012; 2013c; 2013d; PLoS Med, 2013**). This resulted in a new Global Action Plan against Pneumonia and Diarrhoea in 2013. Nair led a series of studies detailing viral causes of pneumonia (**Lancet, 2010; 2011; 2013**), contributed to the new WHO BRaVe initiative (Battle against Respiratory Viruses), developed a WHO field manual on influenza and advised WHO on influenza policy. CPHS research was recognised by recent designation as a WHO Collaborating Centre on Population Health Research and Training (2013–2018). Rudan, Chan and Theodoratou developed novel methodology that is now widely used (e.g., by WHO, UNICEF, Gates Foundation) for evidence-based research priority setting (**Lancet, 2009; PLoS Med, 2011**). Chalmers drew attention to inequalities in mortality rates in Scotland (**BMJ, 2009a; 2009b**) and Fischbacher* demonstrated the impact of legislation restricting smoking on asthma and acute coronary syndrome (ACS; **New Eng J Med, 2010**).

b.4.4 The MRC Hub for Trials Methodology Research (**Head: G Murray**; Butcher, Lewis, McHugh, Weir)

This group has developed new ordinal regression techniques and methods for meta-analysis of ordinal and continuous outcomes (MRC Programme Grant, £2.8M). These new methods resulted in substantial power gains, e.g., IST-3 trial reporting on 3000 patients compared with the initial calculated requirement of 6000 (**Lancet, 2012**). Murray was vice-chair of the European Brain Injury Consortium and led the analysis of several important clinical trials (**Lancet, 2011; 2013a; 2013b; Lancet Neurology, 2013**). The group innovated in trial statistics in analyses of CPHS-led studies (e.g., **J Am Med Ass, 2008; 2010; Lancet, 2008; BMJ, 2008a; 2008b**), and made key contributions to the analysis of international collaborative trials (e.g., **Lancet, 2008; 2009; PLoS Med, 2008; 2009; Thorax, 2008; 2012**).

THE QMRI: STRATEGY, FUNDING AND RESEARCH SUCCESS

b.5 MRC-Centre for Inflammation Research (CIR; Director: Iredale)

MRC-CIR comprises 35 Category A staff with 16 competitively won programme grants, or equivalent, including 9 early career researchers or intermediate-level clinician scientists. There are 4 major research themes that transcend laboratory-based and clinical questions, including *immune modulation and inflammation, and tissue remodelling and regeneration***.** These dovetail with our work on *pathway medicine***,** which takes a systems approach to studying host–pathogen interactions in human disease**.**

b.5.1 Immune Modulation and Regulation of Inflammation (**Head: Anderton**; Conway-Morris, Davidson, Dransfield, Feng, M Gray, Gregory, Haslett, Ho, Howie, MacNee, Paidassi, Rossi, Savill, Schwarze, Yao, Walsh, Wigmore)

Anderton and colleagues (MRC Programme Grant, £1.9M) have identified a critical role for T-regulatory cells in mediating the outcome of inflammation in autoimmune encephalomyelitis (**JI 2008; J Exp Med, 2012a; 2012b**), while Yao (ESAT Fellow) found new links between T-cell function and prostanoid signalling (**Nat Med, 2009a; 2009b; Proc Nat Acad Sci (PNAS), 2010; 2011**). M Gray and Savill (MRC Awards, £0.6M) have identified a critical immunoregulatory role for B-cells in arthritis after engulfment of apoptotic cells (**J Immunol, 2009; PNAS, 2012**). Mole (Academy of Medical Sciences (AMS) Clinician Scientist Fellow; GSK DPAc Award £3M) has identified that kynurenine metabolites mediate the lung and kidney injury of acute pancreatitis. MacNee has established a rational definition of risk associated with different nanoparticles based on size, structure and composition (**Nat Nanotech, 2008; New Eng J Med, 2010**). Howie and Ho (MRC Clinician Scientist Fellowship, £1.1M) have identified complementary roles of *hedgehog* signalling and enhanced mitochondrial-mediated oxidative stress in mucosal injury (**Gut, 2008**), while Davidson (MRC Senior Clinical Fellowship, £2.4M) found an important role for bactericidal peptides in the innate immune response (**Am J Resp Cell Mol Biol, 2010**). Schwarze (MRC Awards, £1M) found that dendritic cell subsets are important in the development of persistent pulmonary inflammation (**Nat Med, 2008; JI, 2012).** Walsh **(Nature, 2012)** co-led work with Conway-Morris (early career; **AM J Resp Crit Care Med, 2009)** on Intensive Care Unit-related infection and immunity, working with Hume and Baillie (UoA6) to establish models for influenza susceptibility. Feng (ESAT Fellow; **PLoS Genet, 2009; PLoS Biol, 2010; Curr Biol, 2012;** WT Henry Dale Fellow, £1.2M), has developed a tractable zebrafish model to visualise inflammatory cells during tumour initiation, while Gregory (LLR Programme Grant, £1M) has established a critical role for macrophage debris engulfment during lymphoma progression (**Blood, 2008**; **JCI, 2009**). Rossi (MRC Programme Grant, £2.5M) established that CDK inhibitors promote neutrophil apoptosis, accelerating 'resolution' of both acute and chronic inflammation and scarring (**FASEB, 2009; Cell Death Differ, 2012**)**.**

Imaging, Inflammation and Fibrosis (**Head: Haslett**; Dhaliwal, R Gray, A Hill*, van Beek)

Excitement around the potential of new chemical imaging-based methodologies for detecting inflammation and scarring, including highly specific micro-dose Smartprobes (led jointly by Haslett, Bradley (UoE School of Chemistry) and Dhaliwal (Senior Clinical Lecturer; **Am J Resp Crit Care Med, 2011**), has attracted significant funding (MRC and WT Programme Grant, £6.4M to include 'first in man' studies, EPSRC/MRC Inter-disciplinary Research Centre, £11.6M (joint with Heriot-

Watt University)). These activities link with the CRIC (van Beek; **PNAS, 2010; New Eng J Med, 2011; 2012**), and other studies of biomarkers (R Gray, WT Intermediate Fellow, £0.8M) and chronic disease models (Hill*; **BMJ, 2013**).

b.5.2 Tissue Remodelling and Regeneration (**Head: Iredale**; Dear*, Garden, Hayes, Henderson, Hughes, Jenkins, Kendall, Kluth, Michaelidou, Parks, Plevris*, Simpson, Vermeren)

Iredale and Forbes (MRC-CRM; MRC Programme Grant, £1.9M) have defined the specific phenotype of the macrophage subset responsible for the resolution of fibrosis across several organs (**PNAS, 2012**; **Hepatol, 2011**; **2012).** Macrophage phenotype studies identified roles for intrinsic and recruited macrophages in health and disease, exemplified by the work of Jenkins (early career ESAT Fellow; MRC New Investigator Research Grant (NIRG), £0.5M, **Science, 2011)**. Kendall (WT Intermediate Fellowship, £0.9M; **Hepatol, 2009**), works with Hastie (MRC-HGU) to study WT1 function in hepatic development, inflammation and fibrotic disease. Hughes and Henderson (WT Intermediate Fellow, £0.8M) have defined galectin-3 as a putative fibrogenic target and are developing links with companies to model therapeutic approaches (**Am J Pathol, 2008a; 2008b**). Henderson also recently defined key roles for alphaV integrins in mediating fibrogenesis (**Nat Med, 2013; PNAS, 2013**), while Vermeren established the relationship between angiogenic and inflammatory signalling (**Science Signalling, 2010; Blood, 2011**). Iredale's 15-year investment in the potential role of relaxin as an antifibrotic and portal hypotensive agent (**Hepatol, 2013**; AMS/Healing Foundation, £0.7M) has resulted in phase II clinical trials, with outcome expected in 2015. This work is complemented by Simpson and Dear's* work on inflammation in fulminant hepatic failure (**J Immunol, 2011; Hepatol, 2011; 2013**). Garden (**BMJ, 2012**) and Parks (**Lancet, 2008**) have established key new surgical aspects of pancreatic and hepatic inflammatory and malignant disease, while Plevris* (EU-FP7 grant, €6M; Edinburgh share, €1M) continues to refine physiologically relevant hepatocyte cultures for bioartificial liver therapy in acute liver failure (**Liver Int, 2012**).

b.5.3 Pathway Medicine (**Head: Ghazal**; Bachmann, Dickinson, Leen*, Stenson*)

In studies on infection, Ghazal and Dickinson have linked systems pathway approaches to infection biology, finding new inflammatory transcriptional determinants of viral infection (**Nat Neuroscience, 2008; PLoS Biol, 2011; PloS Pathog, 2012**). They have elucidated regulatory pathways of interferon antiviral responses (**PNAS, 2010),** and discovered a new metabolic-immune axis in host protection that couples interferon to the sterol metabolic network in innate immunity (**Immunity, 2013)**. Bachmann and Dickinson are working with Stenson* and Leen* to link pathway modelling research programmes with clinical diagnostic services, e.g., in paediatric infectious diseases (**New Eng J Med, 2011; 2013; PNAS, 2013**) and in estimating life expectancy of people with HIV (**BMJ, 2011**).

b.6 MRC-Centre for Reproductive Health (CRH; Director: J Pollard)

CRH was awarded a 5-year core MRC Centre award (£1.3M) in 2011, and the high-profile recruitment of J Pollard (from Albert Einstein in New York) brought vibrant leadership to the new MRC-CRH. J Pollard has obtained a WT-SIA (£4.4M) and a Wolfson/Royal Society Merit Award (£0.15M). MRC-CRH comprises 17 Category A staff, with 17 competitively won programme grants, or equivalent, including 5 early career research or intermediate clinical fellowships. MRC-CRH has three inter-connected major research themes: *resilience biology in reproduction, the niche in germ cell function and tissue regeneration* and *developmental programming by steroids and reproductive resilience*.

b.6.1 Reproductive Cancers and Resilience Biology (**Heads: J Pollard and Critchley**; Glasier*, Hillier, Saunders, Horne, Kitamura, Maybin, Qian, Wallace*)

J Pollard pioneered the study of the role for tumour-associated macrophages in promoting metastasis in women's cancers, and established a role for oestrogen in epithelial cell proliferation (**Nature, 2011; PNAS, 2012**). He has also established roles for macrophages in developmental angiogenesis (**Nat Cell Biol, 2011**), and defined the lineages for major macrophage populations (**Science, 2012; Immunity, 2012**). Early career researchers Qian (ESAT Fellow; **Nature, 2011**) and Kitamura (ESAT Fellow; **Cancer Cell, 2011**) have elucidated key roles for chemokines such as CCL2 and the receptors CCR2 and CCR1, which promote macrophage-dependent cancer phenotypes.

Critchley and Hillier discovered the importance of cortisol metabolism in endometrial angiogenesis, leading to an entirely novel therapy for menorrhagia (MRC proof-of-concept clinical trial**,** £1.4M; **J Clin Endo Metab, 2008; 2011**)**.** Saunders has provided the first evidence for local oestrogen production in the human decidua **(J Clin Endo Metab, 2013)** and for androgen action in the repair of the endometrium **(J Clin Endo Metab, 2011).** In MRC-CRH, our Category C clinical colleagues provide vital links to NHS-L, linking MRC-CRH science with clinical research and practice. Glasier* provided the evidence that led many countries to make emergency contraception available 'over-the-counter' (**Lancet, 2010**), and Wallace's* work has shown that assisted conception does not increase the risk of childhood cancer (**New Eng J Med, 2013**).

b.6.2 The Niche in Germ Cell Function and Tissue Regeneration (**Head: R Anderson**; Duncan, George, Mitchell, Smith, N Gray)

R Anderson (MRC Programme Grant, £2.5M) has shed light on the molecules that regulate the establishment of primordial follicles, including members of the TGF-β superfamily (**Stem Cells, 2010**). Smith, with Saunders and Sharpe (with MRC Programme Grants of £2.4M, £3.9M and £2.8M, respectively) have vastly improved the understanding of mechanisms regulating Leydig cell testosterone, identifying a foetal 'male programming window' that determines testis size and sperm production (**JCI, 2008**). Smith also provided the first definitive evidence that androgen action, via peritubular myoid cells, is essential for male fertility (**FASEB J, 2009**) and that katenin p80 has a key role in sperm formation (**PLoS Genet**, **2012a**). He also co-identified the microtubule-severing protein KATNAL1 as a novel regulator of male fertility (**PLoS Genet, 2012b**). N Gray has provided definitive evidence for the fundamental role played by multifunctional proteins from the DAZL and PABP families in spermatogenesis and reproduction (**PNAS, 2011**).

b.6.3 Developmental Programming by Steroids and Reproductive Resilience (**Head: Norman**; Stock, Sharpe); incorporating Tommy's Centre for Foetal and Maternal Health (£1.5M)

Preterm birth is the single biggest cause of neonatal mortality and morbidity; a perinatal database study by Norman highlighted the increase in preterm births in Scotland during the last 25 years (**PLoS Med, 2009**). Stock and Norman revealed that elective induction of labour results in reduced perinatal mortality in twin pregnancies (**BMJ, 2012**), and that progesterone does not prevent preterm labour. Both findings resulted in a change in international guidelines (**Lancet, 2009**). Sharpe has shown context-dependent effects of endocrine disrupters, such as phthalates, eliciting debate about these environmental agents (**J Clin Invest, 2008; Hum Reprod, 2010**).

b.7 BHF-Centre for Cardiovascular Science (CCVS; Director: Walker)

CCVS (BHF Centre of Research Excellence funding, £7.6M; renewed, £3M, in 2013) comprises 38 Category A staff with 23 competitively won programme grants, or equivalent, including 12 early career researchers or intermediate fellows. Cardiovascular stem cell research is also a core theme of the MRC-CRM (b.8 below), reinforced by £1M BHF capital investment in the new MRC-CRM building, a £2.5M BHF award to Newby to develop a new BHF Centre for Vascular Regeneration and by re-location of BHF-funded Professor Peault and Intermediate Fellow Mills into the new MRC-CRM building, cementing vital links between cardiovascular science and stem cell research. CCVS research is organised into 3 thematic areas: *vascular injury and repair*, *metabolic risk factors* and *renal and hypertensive risk factors***.**

b.7.1 Vascular Injury and Repair (**Head: Newby**; Caporali, Cruden*, Denvir, Diaz, Dweck, Fox, A Gray*, G Gray, Hadoke, Heck, Jansen, Langrish, Mills, Pennings, Semple)

Fox has elucidated the effects and clinical value of novel anti-platelet strategies and prediction of response (**New Eng J Med, 2009; 2010; 2011; 2012**), whilst Newby and Mills isolated nanoparticles in diesel exhaust as causative agents in ACS (**Eur Heart J, 2008**). Smoke-free legislation was shown to prevent ACS (Newby; **New Eng J Med, 2008**), and Mills established that highly sensitive troponin assays improve the diagnosis of myocardial infarction (**J Am Med Ass, 2011**). CCVS scientists have developed new tools to allow: i) revolutionary use of MRI USPIOs (Ultra Small Particles of Iron Oxide) for cell tracking and new understanding of the natural history of aortic aneurysm (Newby, Semple and Dweck (early career Clinical Lecturer; **Circ Cardiovasc Imaging, 2012**; **Lancet, 2013**; **J Am Med Ass, 2013**), with parallel preclinical work by Hadoke and Smith (**MRC-CRH**), identifying *COL3A1* to be a novel causative locus; ii) PET for inflammation in

aortic valve disease and; iii) predictive testing in aortic stenosis (**J Am Coll Cardiol, 2011**); and iv) sodium fluoride PET for coronary atheroma stability (**J Am Coll Cardiol, 2012; Lancet, 2013**). With proven application for regeneration in myocardium (**J Am Coll Cardiol, 2008**) and blood (**Blood, 2008**), cell-based therapies have now entered clinical trials. The recruitment of Caporali (BHF Intermediate Fellow; **Circulation, 2011**) provided a complementary focus on miRNA therapy in vascular lesions. Substantial impact has also been achieved through clinical studies; e.g., A Gray*'s work on non-invasive ventilation in acute cardiogenic pulmonary oedema (**New Eng J Med, 2008**).

b.7.2 Metabolic Risk Factors (**Head: Walker**; Andrew, Benezech, Chapman, Drake, Forbes, Hughes, Morton, Reynolds, Seckl, Stimson, Strachan*, Webster)

Walker (BHF Programme Grant, £1.5M) led studies into 11β-HSD1 as a tissue-specific amplifier of glucocorticoid action (**Diabetes, 2012a; 2012b; J Clin Endo Metab, 2009**). He has collaborated with Hadoke and Chapman on athero-protection (**FASEB J, 2013**), with Seckl (joint Walker/Seckl WT Programme Grant, £1.5M) on cognition (**J Neurosci, 2010; Biol Psychiatry, 2012**), and with Morton (WT-NIA, £1.5M) on pancreatic islets and in intra-adipose inflammation (**Diabetes, 2012; J Biol Chem, 2012**), the latter reinforced by the recruitment of Benezech (early career ESAT Fellow; **Immunity, 2012**). In parallel, Webster, Walker and Seckl (WT Seeding Drug Discovery Award, £7.2M) have developed a small molecule 11β-HSD1 inhibitor through to phase 1 clinical trials. Investigation of other pre-receptor steroid-converting enzymes in mice and humans by Andrew has revealed effects of 5α-reductase 1 in liver failure (**J Hepatol, 2010**) and with Walker in critical illness (**New Eng J Med, 2013**). Reynolds and Drake (Scottish Senior Fellow, £0.9M) have shown that epigenetic mechanisms control early human and rodent programming of cardiovascular risk (**J Clin Endo Metab, 2010**), probably mediating the adverse effects of maternal obesity (**BMJ, 2013**), which is being targeted clinically in an MRC EME EMPOWAR trial with Norman in MRC-CRH (£1.2M). Strachan* and Reynolds, together with Price (CPHS), have delivered the Edinburgh Type 2 Diabetes Study (MRC, £0.4M; **Diabetologia, 2010**; **Diabetes Care, 2011; 2013**), allowing mechanistic/genetic studies of neuroendocrine, cognitive and microvascular abnormalities in diabetes.

b.7.3 Renal and Hypertensive Risk Factors (**Head: Mullins**; Bailey, Conway, Cudmore, Dhaun, Eddleston, Kotelevtsev, Webb)

Webb and Dhaun (early career BHF Intermediate Fellow, £0.8M) have established novel urinary biomarkers, and further demonstrated that endothelin-A antagonists reduce proteinuria (**Hypertension, 2009; 2010; 2011; J Am Soc Nephr, 2013**). Bailey and Mullins have dissected the roles of 11β-HSD2 and 11β-hydroxylase in control of sodium balance using novel mouse models (**Hypertension, 2009; 2011; 2012**), while Conway (Scottish Senior Clinical Fellow, £0.9M) has established new genetic rat models of diabetic nephropathy (**J Am Soc Nephr, 2012)**. Cudmore (ESAT Fellow, an inaugural MRC Centenary postdoctoral fellow now with an MRC NIRG award of £0.8M) has defined novel signalling mechanisms by VEGF-R dimers (**Nat Comms, 2012**). Toxicology is a major strength, with Eddleston delivering treatments for pesticide poisoning in the developing world (**Lancet, 2008; PLoS Med, 2008; 2009; 2010**), and Webb (with colleagues in MRC-CIR) delivering trials of paracetamol poisoning (**Lancet, 2013**).

b.8 MRC-Centre for Regenerative Medicine (CRM; Director ffrench-Constant)

Our core vision since RAE2008 has included the development of CRM, initially under the directorship of Wilmut (recently retired), succeeded by ffrench-Constant (returned in UoA4 as Head of Edinburgh Neuroscience). The purpose was to nucleate our expanding interest in Regenerative Medicine by bringing together stem cell biologists from the School of Biological Sciences, with basic and clinician scientists from CMVM to work on repair in specific tissues, including the roles of macrophages in tissue regeneration. By integrating these groups into a single research centre, and developing close interactions with researchers in both MRC-CIR (b.5 above) and the Centre for Neuro-Regeneration (returned in UoA4), we have created a powerful research environment that unites internationally leading expertise in the biology of stem cells, inflammation, development and tissue formation, while striving to discover novel therapies. The CRM has major focus on *tissue regeneration and repair* in 4 areas: *neural, hepatic, haematopoietic* and *cardiovascular disease*. The award of MRC Centre status (£1.8M in 2008, renewed in 2013, £2.2M) is testament to the

excellent CRM environment. The synergy created by the co-location of all groups into a single purpose-designed facility (UoE cost of £52M) has led to £55M of new grant support from multiple funders, a £1M investment by BHF, and a £12.8M philanthropic donation to create the linked Anne Rowling Regenerative Neurology Clinic. The new MRC-CRM comprises 17 Category A staff with 12 competitively won programme grants, or equivalent, including 6 early career researchers or intermediate fellows.

b.8.1 Basic Stem Cell Biology and Discovery Science (**Head: Chambers**; Blackburn, Dzierzak, Hay, Kaji, Kranc, Medvinsky, Morrison, S Pollard, Rambukkana, Tomlinson, Wilson)

Kaji (ERC Starter grant, €1.5M) has built on his ground-breaking work on reprogramming iPS cells (**Nature, 2009**), identifying key pathways and surface markers involved in specific differentiation and maintenance of the pluripotent "ground state" (**Nature, 2013**). Rambukkana has demonstrated a remarkable example of this process occurring naturally, namely mycobacterial reprogramming of Schwann cells to promote their migration and differentiation of the resultant stem/precursor cells (**Cell, 2012**). This work has been complemented by identification of the role of the key transcription factors Nanog and Oct4 in the control of pluripotency by Chambers (**Science, 2008; Cell, 2009; Nature, 2010;** MRC and BBRSC total funding of £1.6M), Tomlinson (**Cell Stem Cell, 2009; 2012**) and Wilson (**Dev Cell, 2009; Cell Reports, 2012;** MRC Programme Grant, £0.6M), while Smith developed novel targeting strategies enabling translation to the use of human cells (**Cell Metab, 2009; Genes Dev, 2011; Cell Reports, 2012**).

The formation and differentiation of tissue stem cells, a critical question for regenerative biologists, has been addressed by Medvinsky **(Cell Stem Cell, 2008; J Exp Med, 2011a; 2011b;** MRC and LLR Programme Grants of £1.5M and £1.3M, respectively**)** and Blackburn **(PNAS, 2008; Nature, 2010; PLoS Genet, 2010; 2011)**, describing the critical transcription factors that instruct haematopoietic cells to form bone marrow and the developing thymus (with the latter underpinning Blackburn's leadership of the EU-FP7 €2.2M grant awarded in 2013). Kranc (CRUK Senior Fellowship, £2M) has identified Cited2 as a regulator of adult haematopoietic stem cells (**Cell Stem Cell, 2009; Blood, 2013),** while Dzierzak (ERC Advanced Investigator Grant, €2.5M) was the first to show that human placenta is a potent niche for haematopoietic stem and progenitor cells throughout development (**Cell Stem Cell, 2009; Cell, 2009; Nature, 2010**), and that Runx1 is crucial for the endothelial-to-haematopoietic cell transition (**Nature, 2009**). Extrinsic signals that cooperate with intrinsic transcription factors have been identified by Brickman **(Cell Stem Cell, 2008; PLoS Biol, 2010),** and Morrison (early career ESAT Fellow; **Cell Reports, 2012**), elucidating a pivotal role for FGF signalling and Oct4 in determining stem cell fate.

An important goal of MRC-CRM has been the application of this work to disease modelling and drug discovery. Hay (UKSCF Programme, £2.3M) defined mechanisms controlling specific endodermal differentiation of stem cells, using these to develop drug-screening platforms for hepatocytes from embryonic stem or iPS cells (**PNAS, 2008**; **Hepatol, 2010**). S Pollard (early career ESAT Fellow) has characterised the tumour-specific phenotypes of adherent glioma stem cells and their use in glioma discovery science (**Cell Stem Cell, 2009; Genes Dev, 2013**).

b.8.2 Tissue Regeneration and Repair (**Head: Forbes**; Bird, Boulter, Davies, de Sousa, (ffrench-Constant UoA4), Forrester, Miron, Peault, Williams)

Our increased understanding of pluripotency and tissue stem cells, lineage specification and the signals required for growth and differentiation in tissue culture and embryonic development has permitted the identification of extrinsic signals that maintain and/or activate stem cells within their natural microenvironment - the niche. Forrester has established that the transcription factor HoxB4 contributes to tissue (haematopoietic) stem cell development by promoting niche-like properties in differentiating embryonic stem cells (**Cell Stem Cell, 2008**; **Stem Cell Res, 2013**), while Forbes (**Gut, 2011)** and Bird (early career ECAT Fellow; **Gut 2010; PNAS, 2013)** showed that laminin and integrin interactions within the niche are vital during development and repair. Their expertise has led to recent funding to develop: i) an MRC hub for 'Engineering and Exploiting the Stem Cell Niche' in MRC-CRM (£5.6M; led by Forbes), and ii) a UK-RMP Centre for Chemical and Computational Biology of the Niche (£5.1M MRC and UoE; led by Forbes). In these, biology will be integrated with chemistry-based studies such as those performed by de Sousa **(Nat Comms, 2013)** and Bradley (returned in UoA8), optimising chemically engineered substrates for stem cell growth and computational biology. In models of hepatic inflammation and cirrhosis, Forbes (Jules Thorn Trust, £1.2M) and Boulter (early career ESAT Fellow; Leverhulme Trust Fellowship,

£0.07M), together with Iredale (MRC-CIR), have identified a critical role for macrophages in proliferation and lineage specification of hepatic progenitor cells, regulated by TWEAK/FN14 and Wnt signalling, respectively **(Nat Med, 2012**). This has now also been applied to other systems, such as kidney regeneration by Davies (**Development, 2008**). Developing knowledge of tissue repair towards therapies, Forbes has commenced the world's first randomised clinical trial of stem cell therapy for liver cirrhosis (the REALISTIC study): a multi-centre, phase II, open-label randomised trial of repeated infusions of autologous CD133+ve bone marrow stem cells mobilised by G-CSF in patients with cirrhosis. He is also developing clinical tools to stimulate liver regeneration and reduce scarring, specifically using a macrophage cell therapy based on pre-clinical work (funded by MRC, £0.9M, and Scottish Enterprise, £0.5M). Further cell-based therapeutic approaches are being developed by Peault (funded by the Californian Institute of Regenerative Medicine, £3.4M) based on his discovery of the mesenchymal stem cell-like properties of the pericyte (**Cell Stem Cell, 2008; Blood, 2012**). Together with colleagues in Glasgow and the Scottish National Blood Transfusion Service, Forrester is pursuing the generation and expansion of red blood cells from adult human embryonic stem cells (WT, £3M, and Scottish Funding Council, £3M), aiming for first-in-human studies in 2016.

c. People, including:

i. Staffing Strategy and Staff Development

Our strategy is to recruit outstanding established scientists and the most promising junior investigators into an excellent environment that will promote the highest level of science and its translation. We have an on-going programme of recruitment at senior and early career levels, coupled with excellent mentoring and support to create optimal opportunities. We have established structured career tracks for both clinical and non-clinical academics, ensuring that Edinburgh nurtures and inspires its early career bio-medical researchers, producing future leaders and promoting gender equality. We have also appointed 23 new Professors since 2008, these are: **Al-Shahi Salman, Arends**, **Brunton, Caceres**, **Dzierzak**, **Eddleston**, **Forrester**, **Gilbert**, **Gourley**, **Gray**, **Hoskins**, **Hughes**, **A Jackson, Kranc**, **Lawton**, **Mayer**, **Peault**, P **Pollard**, **Reynolds**, **Smith**, **van Beek** and **Wild**. In addition, Honorary Chairs include: **Alison***, **Dixon*, Harrison*, Irvine***, **McCallum***, **McKnight***, **Plevris*, Stenson*** and **Strachan***. Strategic senior appointments have been made, including **Arends** to the Chair of Pathology (linking cancer research to molecular and systems pathology, promoting training in 'modern' pathology), **J Pollard** to a Chair linking reproductive health and cancer, **Dzierzak** to the Chair of Regenerative Medicine, linking stem cell biology to inflammation, tissue repair and regenerative medicine, and **Peault** to the Chair of Cardiovascular Regeneration, linking cardiovascular science with regenerative medicine. Key appointments were also made to support infrastructure; e.g., **van Beek**, recruited to the SINAPSE (Scottish Imaging Network: A Platform for Scientific Excellence) Chair of Radiology in CRIC.

Investment in early career researcher excellence: We have established two complementary career development tracks. The first is a new sector-leading, carefully structured **Edinburgh Scientific Academic Track (ESAT)**, comprising RCUK-like, tenure track positions for early career scientific researchers, targeted to areas of strategic priority or "discipline-hopping" that promote innovation. Selection is on the basis of potential and likely success, hence there is the expectation of appointment to permanent University staff after a review at four years. This has represented a massive investment of £30M across the University. Since 2008, we have appointed 37 such early career scientific researchers to IGMM and QMRI (returned here in UoA1), with an average commitment of £430K per appointee, including support and start-up costs. Those appointed have already demonstrated research leadership qualities and include: **Morton** (WT-NIA, £1.4M), **Hay** (UKSCF, £2.3M; PNAS, 2008), **Moran** (Scientific Lead EBQ Team, see REF3a), **Carragher** (CRUK Drug Development Office, £1M; EMBO Mol Med, 2013), **Bagnaninchi** (PNAS, 2011), **Anderton** (MRC Programme Grant, £1.9M; JI, 2008), **Feng** (WT/Royal Society Henry Dale Fellowship, £1.2M; PLoS Biol, 2012), **Boulter** (Leverhulme Trust Fellowship, £0.1M; Nat Med, 2012), **Caporali** (BHF Intermediate Fellow, £0.5M; Circulation, 2011), **Acosta** (CRUK CDF, £1.4M; Nat Cell Biol, 2013), **Wilkinson** (CRUK CDF, £1.9M; Genes Dev, 2008), **Jenkins** (MRC NIRG, £0.5M; Science, 2011), **Yao** (Nat Med, 2009), **Vermeren** (Science Signaling, 2010), **Finch** (Genes Dev, 2012), **Kitamura** (PNAS, 2010), **S Pollard** (Genes Dev, 2013), **Chan** (Lancet, 2013), **Marioni**

(Diabetes, 2010), **Qian** (Nature, 2011), **Hurd** (Cell, 2012), **Kagansky** (Cell, 2010), **Benezech** (Immunity, 2012). A further tranche of up to 17 early career tenure track ESAT Fellows will be made in 2014/2015, starting with the recent appointments of **Morrison** (Cell Stem Cell, 2008) and **Borjesson** (Swedish Research Council Fellowship, £0.3M; PNAS, 2012). All of these prestigious ESAT fellowships are expected to lead to permanent academic UoE posts, and are occupied by 'high-potential' researchers, mentored and equipped with the necessary inter-disciplinary skillsets and collaborative opportunities to become leaders in their fields. It is a key part of our strategy, outside REF, to be the UK's leading institution supporting the development of early career academic staff. We are supported in this by UoE's Institute for Academic Development (http://www.ed.ac.uk/schools-departments/institute-academic-development), with its >30 full-time staff.

The second career track, for medically qualified academics, is the **Edinburgh Clinical Academic Track (ECAT)** programme, with mentoring to promote future clinician scientist fellowship readiness. Underpinned by £5.5M WT investment (2007–2013, renewed in 2013, £6.2M), this allows the brightest clinical researchers to study for a PhD, while embedded within UoE/NHS Education Scotland-funded Clinical Lectureships (representing a £5M investment). This is facilitated in Edinburgh by the unique flexibility to allocate Clinical Lectureships to trainees in any clinical discipline. We currently have 29 'high-potential' clinical academics in post, at various stages of their career development, and funding is in place for a further 5 per year for the next 5 years (£6.3M investment from UoE/National Education for Scotland (NES) matching the £6.2M PhD portfolio renewed by WT). This "cradle to consultant" research training (http://www.ecat.ed.ac.uk) has facilitated the placement of clinicians with excellent supervisors, including those outside a standard clinical pool, and has attracted excellent applicants from a wide range of so-called "orphan" academic disciplines. The first cohort of ECAT lecturers has exited PhD studies and entered NES Lectureships/postdoctoral clinical and research training in the last 12 months and includes Brennan, Neurosurgeon (**Nature, 2011**). The ECAT scheme has now become a paradigm for clinical academic training in the devolved administrations, exemplified by the £10M investment from the Welsh Assembly and Welsh Universities to establish a similar scheme (WCAT). Furthermore, pan-Scotland, Edinburgh-led PhD programmes are modelled on ECAT, i.e., the Scottish Translational Medicine Training Initiative (STMTI), underpinned by a £2.6M investment from WT and Wyeth (now part of Pfizer) and further clinical PhD studentships aligned to ECAT have been leveraged from MRC (× 3) and CRUK (× 4). Further investment in clinical academic training has been achieved through strategic use of CMVM endowment funds and Roberts Funding, linking PhD programmes and *ad hoc* fellowship appointments. Through these programmes, we provide career advice and mentorship from early days at medical school through academic foundation years, and core and specialist training (the ECAT website receives >1500 hits/month). Support is provided by a team of senior clinical academics, and coordinated by a dedicated UoE-funded administrator. Importantly, our structured approach to clinician scientist training has engendered high success with external Intermediate/Clinician Scientist Fellowships, with 5 awarded in 2012 and 6 to census date in 2013. The award of *ad hoc* externally funded clinical PhD fellowships has been enhanced rather than diminished by our programmatic funding award for ECAT. By October 2013, there were also 91 non-ECAT clinicians in doctoral studies, including18 with Clinician Scientist/Intermediate Fellowships and 9 with Senior Clinical Fellowships.

Support for staff development: Clinical academics are appointed to a 50:50 NHS:UoE contract, but with extra academic activity funded by UoE, facilitating research momentum in the face of busy NHS practice. All clinical and non-clinical academic staff have an annual appraisal and personal development meeting. All members of staff (PhD, postdoctoral, clinical and non-clinical) have access to the award-winning Transkills programmes available at UoE, and to all activities supported by the Institute for Academic Development. **Iredale** (Clinical Dean), **Farqharson** (Medical Director, NHS-L) and **Reid** (Postgraduate Dean) meet regularly to ensure optimal career development for all clinical academics.

ii. Research Students

We attract the highest calibre scientific and clinical post-graduate (PG) students, with training programmes from the WT, CRUK and BHF, as well as the UK's fourth largest MRC Doctoral Training award. To deliver excellence in doctoral training, we have capitalised on our experience of

delivering 4 year (1 + 3) PhD training (including via the first WT-funded cohort). Our PG research strategy (directed by Prof Philippa Saunders, *F Med Sci*), has aligned doctoral training with our theme- and Centre-based organisation, also reflecting the strategic objectives of our major PG research funders, e.g., MRC, WT, BHF and CRUK. As a result, **PG research student numbers have increased by 30% since RAE2008**. Four-year PhD programmes established in this REF2014 cycle include: BHF-funded programme in Cardiovascular Biology (24 students enrolled since 2008), BHF Centre of Research Excellence Award programme (15 students enrolled since 2009), IGMM 4-year PhD programme (MRC-, CRUK-funded; 66 students enrolled since 2008), MRC PhD Programme in Inflammation (8 students enrolled since 2010), MRC PhD programme in Reproductive Health (5 students enrolled since 2011) and MRC-CRM 4-year PhD Programme (7 students enrolled since 2008). A new 4-year PhD programme in Tissue Repair and Regeneration will begin next year (2014), with £1.0M investment from UoE/MRC over the next 5 years. Our PhD programmes aim to equip future bio-medical research leaders with diverse skill sets, and expose them also to business and entrepreneurial possibilities. All PhD students receive induction, pastoral support and close monitoring by local Centre-based thesis committees (which include two supervisors), fostering a culture of two-way dialogue and feedback.

Support for equality and diversity: In 2008, UoE implemented the Concordat through its own Code of Practice for the Management of Research Staff. This was recognised by the European Commission with the award of the Human Resource Excellence in Research Award in 2010, retained following review in 2013. As part of a strong on-going commitment to promoting gender equality, our clinical Schools are applying for a bronze Athena Swan award in November 2013. Working with staff at all grades, we have piloted a new mentoring scheme, conducted staff feedback surveys and developed an action plan for their imminent application. In UoA1, 30% of returned staff members are female, compared with 25% submitted in 2008 to Hospital-based Clinical Subjects, an upward trend we are working hard to improve further.

d. Income, Infrastructure and Facilities

Research Vitality and Sustainability: Our estates and facilities strategy is focussed on providing world-leading researchers with world-leading laboratories and cutting-edge core infrastructure, facilities, services and staff scientists. As a result, research vitality is evidenced by consistent increase in combined IGMM / QMRI (UoA1) research spend since 2008, (£47.8M in 2008–2009, £53.1M in 2009–2010, £52.6M in 2010–2011, £55.5M in 2011–2012, £56.5M in 2012–2013), making a total research spend of £265.5M during the REF period. Testament to this success, our grant application success is 42%. Moreover, we have invested £66M in capital and infrastructure including, a £52M state of art building for the MRC-CRM and a £12.8M translational facility, the Anne Rowling Regenerative Neurology Clinic.

This has been complemented by other CMVM strategic builds to which medical researchers submitted to UoA1 have access, e.g., £104M invested in the development of the Royal [Dick] School of Veterinary Studies and Roslin Institute at UoE's Easter Bush Campus (UoA6). We recently commenced the Wellcome-Wolfson/MRC/UoE-funded Systems Medicine building at the IGMM (budget £11.8M) to physically link the three component Centres of the IGMM. During the next 12 months, we will also begin relocation of UoE's non-clinical neuroscience and physiology activities (split between UoA1 and UoA4) from the WGH site and central campus to the RIE, adjacent to QMRI. This move includes relocating the NHS-L Department of Clinical Neurosciences to the RIE, consolidating all neuroscience research and clinical practice, and physiology (UoA4) to the QMRI/RIE campus. Furthermore, these relocations will be facilitated by UoE investment of £1.3M for restructuring, as well as the purchase of a new 3T MR research scanner (£3M) from the UoE capital projects budget. The new research scanner will be placed in UoE space immediately adjacent to the Accident and Emergency, juxtaposing NHS-L scanning facilities. This exciting development will permit "hot scanning" of acute and post-resuscitation, and neurological, pathologies presenting at the "front door". As with imaging equipment in CRIC (described below), this scanner will be available for use by NHS-L staff when not being used for academic research, demonstrating true operational synergy between UoE and NHS-L in imaging. Further robust 'win:win' intertwining between NHS-L clinical services and CMVM research is evidenced by the accommodation of NHS-L Clinical Genetics within the new IGMM Systems Medicine building,

ensuring proximity to the WT Clinical Research Facility. Finally, in partnership with NHS-L, UoE will contribute to the new Children's Hospital (build cost, £184M) at the RIE campus, adjacent to the QMRI. A £3M joint investment by UoE, NHS-L and the Scottish Government will provide clinical research facilities and permit UoE research within this new state-of-the-art paediatric hospital.

Major Grants and Awards to our Institutes: All relevant grant funding is documented in REF4, substantive strategic infrastructure awards to our Centres are bulleted in Selected Key Headlines (5a above), and major programme or personal awards are described and attributed to researchers (5b above) in our Centres. Here we describe how major awards have been deployed, or used to leverage further funding.

i) IGMM. During the inaugural quinquennial review late in 2011, the MRC awarded the IGMM £59.7M for five years (led by **Hastie**; this includes the MRC-HGU core grant of £49.9M). The additional IGMM funding is for the IGMM PG PhD studentship programme, and to pump-prime early career investigator fellowships in genetics, experimental medicine and cancer. Sixteen HGU core programmes were funded in full at the MRC-HGU quinquennial review (the majority of which scored 9/10 or 10/10). There are also 25 programme (or programme-level) grants across the IGMM, including from WT (× 2), CRUK (× 7), Research Councils (× 7), European Commission (× 6) Arthritis Research UK (× 1), CF Research (× 1) and CSO (× 2). There are also 3 ERC Starter grants, and 2 ERC Advanced Investigator grants, demonstrating IGMM competitiveness internationally. IGMM scientists include 1 WT-SIA, 1 MRC Senior Non-clinical Fellow, 4 CDF or Career Establishment Awards (2 CRUK, 1 MRC, 1 BBSRC), and 3 Clinician Scientist awards (1 CRUK, 1 MRC and 1 CSO). We anticipate (by projecting from the past three years) that the IGMM-wide research-spend during this REF period (Jan 2008–Nov 2013) will be £145M. In 2010, the ECRC became a CRUK Centre (co-led by **Frame** and **Cameron**; Centre award of £4.3M from 2009–2012.

The new IGMM Systems Medicine Building, with competitive awards from Wellcome-Wolfson (£3.5M) and MRC (£3.5M), will provide first-class dry lab space to build mathematical and computational science capacity (a key area of strategic focus) to interrogate genomic and biological data from clinical datasets. Importantly, the new Systems Medicine building provides both physical and intellectual connectivity across the IGMM with "omics" and imaging platforms that provide state-of-the-art technologies. This will optimise scientific output and innovation, maintaining our world-class status in the data-rich era, and in linking genotypes to phenotypes. Examples of services provided by IGMM infrastructure include: a) DNA sequencing (collaboration between ARK Genomics (BBSRC), GenePool (NERC, MRC and IGMM (HGU and WTCRF)) to form *Edinburgh Genomics* (http://genomics.ed.ac.uk), the second-largest-capacity sequencing facility in the UK after the Sanger Institute; b) advanced microscopy (standard operating microscopes, including confocals and multi-photon, plus super-resolution (STED, PALM; funded by MRC Next Gen Imaging Award, £0.68M (IGMM share of £2M award) to **Bickmore** and **Frame**), and a world-leading bespoke Raman-based multi-modal imaging system (CRUK/MRC/UoE award to **Frame**, total £0.5M), both of these in collaboration with colleagues in Engineering and Image Informatics at UoE and at Heriot-Watt University; c) a state-of-the-art mass spectrometry facility including a new Qstar 323 and associated staff (funded by MRC core IGMM award and UoE staff, total £0.5M); d) animal (and fish) services, including iPS and embryonic stem cell technologies, knock-out/knock-in facilities (including TALEN gene-editing technology) and whole-body and intra-vital imaging of tissue and bone in small animals.

ii) QMRI. The 4 Centres comprising QMRI all received core-funding awards during 2008–2013. In 2010 the MRC-CIR (Director: **Iredale**) achieved its second successive renewal, and the underpinning £1.6M award leveraged UoE support for three existing core infrastructure posts, additional investment in a new 4-year PhD programme in inflammation, and an important capacity-building post in molecular imaging. The BHF renewed its Centre of Research Excellence status (Director: **Walker**; with BHF Core funding of £7.6M, renewed in 2013, £3M) within CCVS, and received funding for a further BHF Chair (**Newby**, £1.2M). The MRC-CRH (Director: **J Pollard**) was established in 2011, underpinned by a £1.2M centre grant and 5 further MRC-supported programmes (total MRC funding, £13M), as well as core funding for the flagship Edinburgh Tommy's Centre for Foetal and Maternal Health (Director: **Norman**, £1.5M). The MRC-CRM was renewed in 2013 (£1.8M). The recent award of A-UK Research Centre status to a group within CPHS, with core funding of £2M (Director: **Sheikh**), has created an exciting new multidisciplinary

link between the MRC-CIR and CPHS, bridging research between QMRI and IGMM. Together, the component Centres of QMRI hold programme grants from MRC (× 7), BHF (× 2), ERC (× 2), WT and Scottish Enterprise, Jules Thorn Trust and the Leukaemia and Lymphoma Research (LLR) Fund. Personal awards include a WT-SIA, a WT-NIA, MRC Senior non-clinical Fellowships (× 2), Scottish Senior Clinical fellowships (× 4), a Lister Prize Fellowship, AMS/Healing Foundation Clinician Scientist fellowships (× 3), WT Intermediate Fellowships (× 2), a BHF Intermediate Fellowship, an MRC Clinician Scientist Fellowship, a WT/Royal Society Henry Dale Fellowship, a Sir Henry Wellcome Fellowship, MRC-New Investigator grants (× 3) and a WT CDF.

A key cross-college theme has been capacity-building in intra-vital imaging. Led from the QMRI, the cutting-edge £20M CRIC (Clinical Research Imaging Centre) was commissioned in 2011. Comprising 3T-MRI, ultra-high-resolution CT, a CT/PET camera and cyclotron (uniquely (in UK) integrated in the same facility), this is now having major translational benefits, particularly in cardiovascular disease. With 7 research-dedicated 'hot-cells' and a team of talented radio-chemists, the cyclotron is now generating bespoke reagents stemming from QMRI research, and is used for PET imaging of patients from the adjacent RIE. A newly awarded MRC 'Next-Generation Light Microscopy' grant (**J Pollard,** £1.7M) provides a unique, integrated 2-photon/spinning disk confocal microscope, which will be crucial in translating research from cells, through animal models, to humans. In collaboration with UoE School of Chemistry, whose researchers (led by Bradley (returned in UoA8)) occupy dedicated space in **QMRI**, where respiratory clinician scientists have developed a groundbreaking technology to image disease mechanism-specific, exquisitely sensitive chemical 'Smartprobes' deep in the human lung *in vivo*. The strong partnership between UoE and NHS-L that resulted in the establishment of CRIC means that the 35% of the CT scanner research "down time" is used by NHS-L for routine scanning, providing true benefit from an exemplary academic and public sector partnership. Complementary pre-clinical imaging facilities have been funded through the BHF-CCVS awards (2005–2010, £2M) and WT equipment grants to support ultrasound and mass spectrometry (£0.6M and £0.7M, respectively). 'Next-generation' bio-medical imaging in Edinburgh has been supported by £6.4M from MRC and WT, and recently by a £11.6M investment from EPSRC via an Interdisciplinary Research Centre, bridging the gap between pre-clinical studies and human applications, with enormous future translational potential. Further contributions to **QMRI** infrastructure include the BHF-funded zebrafish facility, supported by a WT infrastructure grant of £0.7M.

iii) Inter-disciplinary Translational Science. Capitalising on our cohort of established and early career investigators across different disciplines (**Carragher**, **Patton**, **Unciti-Broceta**, **Webster** (together with **Bradley**), we have purposely developed capacity across **IGMM** and **QMRI** for innovative chemical biology, medicinal chemistry and biological evidence-led translational science. This is efficiently generating exciting interrogation tools and molecularly targeted new chemical entities, and high-content phenotypic screening platforms to co-develop unique discovery science approaches based on disease phenotypes and biological mechanisms. We have also invested in an industry-leading chip-based proteomic platform (Reverse Phase Protein Arrays) for pathway modelling and disease network analysis, complementing genetic studies with pathway and phenotypic analysis. This new and integrated approach, embedding applied chemistry, biological screening and deep phenotyping technologies within our Institutes, has already led to funding success, e.g., in securing several major drug development awards (WT Seeding Drug Discovery, £5M, to **Walker**, **Webster** and **Seckl**; £3M, GSK-DPAc award to **Webster** and **Mole** (one of only 10 awarded worldwide)), and several new-style pharmaceutical/academic alliances, e.g., from GSK (£0.5M), Galapagos (£1M), Eli-Lilly (£0.5M), all brokered by EBQ. Enhancing research-led academic drug discovery and commercialisation opportunities in Edinburgh are increasingly important future goals of our cross-Institute activities. Further details on interactions with industry are provided in REF 3a.

e. Collaboration or Contribution to the Discipline or Research Base

i) Collaboration within and between our Centres and Institutes:

Our research structure is inherently collaborative with our two inter-disciplinary Institutes each comprising four strongly collaborative Centres, working closely together with common themes. The organisation and free-flowing exchange of technologies and ideas within, and between, our

Centres and Institutes is geared to maximise the inter-disciplinary potential of UoE medical science, and optimise translation. The flexible structure catalyses research collaborations, evidenced by the large number of publications co-authored by investigators from different Centres.

IGMM: By merging three UoE Centres with the MRC-HGU into the IGMM, with unified governance and infrastructure, we have brought together distinct expertise that is maximising scientific discovery and clinical/translation of IGMM science. Through the Edinburgh-wide Systems Medicine consortium, we have fostered interactions with colleagues in other disciplines, providing added value to our research. Integration of the MRC-HGU into UoE has enhanced close links with CMVM's other Institutes and Centres, including QMRI, Roslin Institute, the Royal [Dick] School of Veterinary Sciences, the MRC-CCACE (Director: Deary, Co-Director **Seckl**; Genetics Lead, **Porteous**), the Centre for Chemical and Translational Biology and UoE Schools of Chemistry, Engineering and Informatics. A major IGMM theme is 'genomic science in medicine'. For this, we have amassed key groups with different skillsets, specifically genetics/genomics and computational biology/informatics. IGMM makes use of *Edinburgh Genomics*, which provides state-of-the-art high-throughput and bespoke sequencing capacity to basic scientists and clinical researchers. The united IGMM vision is game-changing for IGMM scientists, revolutionising capability to interrogate clinically important samples, databases and defined genetic cohorts, in keeping with the goals of stratified medicine. The IGMM is contributing to world-class genomic science, particularly across the life-course and in multiple contexts, e.g., paediatric, metabolic, bone and joint, neurodevelopmental, mental illness, cognitive brain ageing, inflammatory disorders and cancer. Collaboration with the pharmaceutical industry (Pfizer, AstraZeneca, Galapagos, Eli-Lilly, GSK and others) has been enhanced through new-style 'academia–pharma' alliances brokered by EBQ.

QMRI: Key strategic developments in the **QMRI** include the establishment of the new MRC-CRH, capitalising on existing scientific strengths in QMRI to link reproductive biology with each of: BHF-CCVS (Developmental/Foetal Programming co-applicant **Seckl**), MRC-CIR (Scarless Healing/resilience biology, co-applicant **Iredale**) and MRC-CRM (Gonadal Stem Cell Niche, co-applicant **Forbes**). Also, the establishment of the MRC-CRM has, for the first time, brought together scientists from the Institute for Stem Cell Research and clinician scientists previously based in the MRC-CIR, BHF-CCVS or MRC-CRH. These complementary teams are now co-located in the new £52M CRM building. Cardiovascular research has also been established as an emerging theme in the MRC-CRM, reinforced by £1M BHF capital investment in the CRM building and by co-location there of BHF-funded Chair (**Peault**) and Intermediate Fellow (**Mills**). The Centres in QMRI are linked by shared infrastructure, MSc programmes, and by use of pooled MRC Centenary awards that provide pump-priming fellowships for non-clinical scientists. Centres have formal international links with joint funding, e.g., MRC-CIR with associated QMRI staff Lacey-Hulbert in Harvard, BHF-CCVS, with trainee exchanges with the Universities of Durham (for imaging research) and Brigham and Women's Hospital, Boston, USA (for zebrafish research).

ii) Collaboration with NHS-L:

The partnership between UoE, NHS-L and National NHS bodies is strong and effective. Indeed, we have returned 16 of our NHS colleagues as Category C staff, and over 200 NHS-L staff hold honorary UoE contracts. Integration is facilitated by joint appointments at the highest level from both organisations, including **Savill** who was non-Executive Director of Lothian Health Board (LHB) until 2010, **Iredale** (Dean and non-Executive Director of LHB and Chair of LHB Service Redesign Committee, co-Chair of LHB Strategic Delivery Group), **Newby** (Professor of Cardiology and Director of NHS R&D), **Cameron** (Director of ECRC and Head of NHS-L Oncology Services) and **M Turner** (Professor of Transfusion Medicine and Director of Scottish National Blood Transfusion Service). We have a proactive approach to joint academic/health service delivery, facilitating access to patient material for research and the reciprocal efficient deployment of new research-led therapeutic or service developments. Importantly, we have linked LHB with translational and commercialisation opportunities beyond that of "traditional" NHS R&D, by appointment of LBH Chief Executive Davison and LHB Medical Director Farquharson to the EBQ Board (EBQ described above and in more detail in REF3a).

Described in detail in REF3a, CMVM and LHB NHS R&D management is fully integrated. Moreover, the Edinburgh Clinical Research Facility (CRF) provides fully equipped adult patient care facilities in the WT Millennial CRF at the WGH, and at its RIE sister facility; this is widely used by NHS-L and UoE researchers alike. Paediatric facilities are established in the Children's CRF at

the Royal Hospital for Sick Children. In 2012, the Edinburgh CRF had over 350 active clinical studies led by more than 200 investigators, and over 8000 subject visits were recorded. Importantly, nearly 200 papers have been published from work conducted with the Edinburgh CRF. Also, the CRIC (described in detail in **5d** above) represents a unique joint UoE/NHS-L facility, which provides state-of-the-art cross-sectional and radio-ligand imaging for both research (65%) and service (35%) purposes, including the generation of NHS PET reagents (by the UoE cyclotron).

iii) Recognition and Contribution to Wider UK and International Bio-medical Science:

Senior staff have been recognised through the civil honours system with the awards of knighthoods (**Savill**, **Wilmut** (recently retired)), CBE (**Hastie**, **van Heyningen** (recently retired)) and OBE (**Haslett**, **D Porteous** and **Dixon***). During the REF2014 period, four of our staff were Fellows of the Royal Society (**Hastie**, **Savill**, **van Heyningen** (recently retired), **Wilmut** (recently retired), 21 were Fellows of the Royal Society of Edinburgh (current committee contributions: **Iredale**, **Satsangi**, **Seckl**, **Walker**, **Critchley** and **Frame**), 19 were Fellows of the Academy of Medical Sciences (council and committee or working party contributions: **Seckl**, **Iredale**, **Critchley**, **Frame**), and 7 Members of EMBO (**Bickmore**, **Caceres**, **Frame**, **Hastie**, **Jackson**, **D Porteous** and **van Heyningen**). Our academics have delivered many named prestigious lectures: e.g., **Hastie** (Genetic Society Medal), **Bickmore** (Jenkinson memorial Lecture (Oxford University), **Dunlop** (Langer Lecture Canadian Association of Surgeons), **Jackson** (GSK Biochemical Society prize), **Wright** (ARVO Fellow Silver medal for services to the eye and vision community), **Seckl** (Geoffrey Harris prize from the European Society for Endocrinology and Archibald Byron Macallum Lecture, Toronto), **Newby** (Parmley Prize from the American College of Cardiology and the Strickland-Goodall Lecture at the British Cardiovascular Society), **Fox** (Lord Raynor Lecture at RCPL). **Haslett** recently won the Royal Society of Edinburgh James Black Medal (2013) for his contributions to medical research.

Early Career Researchers have received awards from international and national societies including: **Eddleston** (Best Emerging UK Medical Researcher and Lister Research Prize), **Reynolds** (Nick Hales award from International Society for Developmental Origins of Health and Disease), **Stimpson** (Endocrine Society), **Conway** (Renal Association) and **Dweck** (American College of Cardiology).

Major Personal European Awards have been obtained by **Bickmore, Frame** and **Dzierzak** (ERC Advanced Investigator Grants), **Albagha, A Jackson, P Pollard** and **Kaji** (ERC Starter Grants, respectively). Other prestigious Fellowships have been described in Centres (**5b**) and People (**5c**).

Editorial Positions with major journals were held by over 40 members of staff, contributing to the Editorial Boards of, amongst others: Cell, Developmental Cell, EMBO J, Mol Biol Cell, Nuc Acid Res, Biochem J, Genes and Dev, Hum Mol Genet Mol Can Res, Hepatol, PLoS One, PLoS Genet, PLoS Biology and many others.

Funding Panels and Scientific Advisory Boards also benefitted from our staff, with more than 70 substantive contributions to National and International grant funding committees (for a period of 3–5 years) or prestigious external advisory boards. **Savill** was Chief Scientist for Scotland (2008–2010) and is presently Chief Executive Officer of the MRC. Other important work has been undertaken for organisations ranging from the ERC, WT, CRUK and MRC, and for smaller charities such as the Lister Prize Fellowship, Breakthrough Breast Cancer, and the Children's Liver Disease Foundation. QMRI and IGMM academics have played major roles as chairs and deputy chairs of grant funding and review bodies, e.g., **Abbott** (Deputy Chair CRUK studentship panel), **Walker** (Chair WT Clinical Interview Committee), **Bickmore** (Deputy Chair WT: Molecular Basis of Cell Function Expert Review group), **Frame** (Chair CRUK New Investigator Panel), **Hastie** (Chair of Scientific advisory boards for: CIMR Cambridge, WT Sanger Institute Scientific (2004–10), Beatson Scientific Advisory Board, NIHR BRC for Mental Health IoP, King's College London and the WT Centre for Human Genetics, Oxford), **Iredale** (Chair of both WT and AMS Starter Grants for Lecturers and Children's Liver Disease Foundation grant award panel), **Wright** (Chair Senior Surgical Fellowship panel AMS/Healing Foundation) and many others. **Cameron** was a member of the Marmot Review on Breast Cancer Screening in the UK.