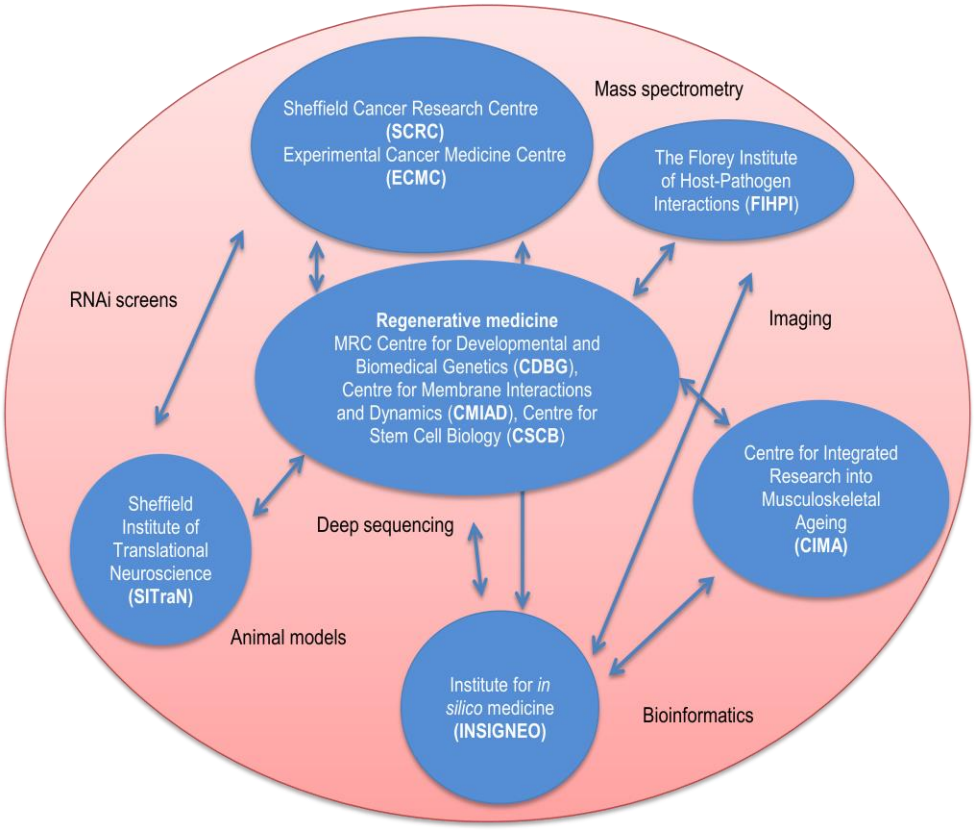
Institution: University of Sheffield

Unit of Assessment: 3C - Allied Health Professions: Biomedical science

a. Overview

Biomedical research that underpins clinical practice at Sheffield spans two faculties: Science and Medicine, Dentistry & Health (Medicine), and is organized into interdisciplinary Research Centres. These centres allow us to focus our staff, training and investment in infrastructure to bring together basic and clinical research scientists across departments and faculties. This ensures progression from (1) basic biomedical science underpinning human health, through (2) translation via drug target validation, compound screening, lead development to drug delivery, screening and devices to (3) clinical science, including policy, practice and public engagement.



Our submission to RAE2008 was small (13 staff) and included only basic biomedical scientists. Our submission to REF2014 includes 66 Cat A staff (64.66 FTEs: 53 non-clinical and 13 clinical) and 4 Cat C staff. This significant increase in size results from our focus on developing links between basic biologists and clinical scientists in disciplines where we can establish an internationally competitive, critical mass. Our principle is to meet regional, national and, ultimately international, clinical need in several broad areas of disease. We have particular expertise in cancer, cardiovascular science, musculoskeletal studies, infection and immunity, neuroscience and clinical practice. The unifying theme is a focus on excellent fundamental biology with a pipeline through translation to delivery, coupled with the development and implementation of cutting edge technology. Since 2008, those returned in this UoA have published >1000 papers in international, peer-reviewed journals including 28 in *Nature, Science* and *Cell* journals. This success has been facilitated by a buoyant research income (£28M) and investment of over £5M in new infrastructure and equipment. The REF period has seen the appointment of 15 new academic staff, creating and reflecting a vibrant and dynamic research endeavour. We are nurturing the next generation of scientists, evidenced by the award of prestigious, internationally competitive fellowships including a CR-UK Senior Fellowship (*Zeidler*), a Wellcome Senior Clinical Fellowship (*Walmsley*), an NIHR Clinical Lectureship in Neurology (*Brockington*) and a British Lung Foundation Fellowship (*Marriott*).

Research investment is targeted to interdisciplinary Research Centres that provide the focus for future expansion. The Figure illustrates the dynamic relationship between these Research Centres and the supporting infrastructure. It also includes a definition of the acronyms used throughout this document. Note that these Research Centres cross departmental and faculty boundaries and, in some cases, extend to other institutions within the UK. CIMA is a collaboration with the Universities of Newcastle and Liverpool, while the Sheffield Experimental Cancer Medicine Centre (ECME) involves a collaboration with 16 other universities.

b. Research strategy

Achievements since RAE2008

Our strategy is to promote a continuum of activity from basic biomedical science through translational applications to improvements in clinical practice. This has been facilitated by targeted investment in Research Centres, which has enabled us to recruit high-calibre staff and students and to establish well-equipped laboratories, to facilitate skills development in basic, translational and clinical research. Our Research Centres ensure good communication, cross-fertilisation of ideas and an environment for efficient exploitation of synergies. They also present a strong external profile, which promotes external engagement and further recruitment. Whilst each Centre has a core of specialist staff, membership is not exclusive and, indeed, many staff are members of several Centres, reflecting the cross-disciplinary and dynamic nature of research undertaken within this UoA. Achievements of the main research groupings are summarised below.

Regenerative Medicine

Achievements: Basic biomedical science underpinning human health falls predominantly within three overlapping Centres: **The MRC Centre for Developmental & Biomedical Genetics** (CDBG) (MRC Centre grant: £2.3M, Oct 2007-Mar 2014; University of Sheffield investment: £3.1M) co-ordinates research on non-mammalian models of human disease. It brings together developmental geneticists with clinician scientists, creating a focus of expertise in tractable *in vivo* animal models of human disease with the aim of translating novel therapies to clinical practice. Particular progress has been made in understanding cancer (*Van Eeden, Cancer Res, 2012*) and neurodegenerative diseases (*Cunliffe, Hum Molec Gen, 2009*). Through significant (£800k) MRC funding, *Roehl* co-ordinates a consortium that is generating living resources that will enable researchers worldwide to generate stem cells in zebrafish (Zcre.org). *Zeidler* was recruited in 2007 and awarded a CR-UK Senior Fellowship in 2008. With funding from the Wellcome Trust (£1M), he established the Sheffield RNAi Screening Facility, which is a national facility to undertake genome-wide screens for novel genes associated with known disease states, using Drosophila models. Recently, with Yorkshire Cancer Research (YCR) funding, this screening capability has been extended to human systems.

The Centre for Membrane Interactions & Dynamics (CMIAD): Intracellular membrane systems are encoded by a huge range of specific molecules that ensure organelle identity, precise molecular trafficking and signalling, all of which can underlie human disease (e.g. *Winder, Hum Mol Gen, 2012*). CMIAD was established in 2012 to unite cell biologists investigating the basic mechanisms with physical scientists, synthetic chemical biologists, computational biologists and clinicians with the ultimate aim of developing improved therapies. Investment from the University has resulted in an increase in critical mass with the recent recruitment of *Erdmann* (*endocytic regulation of signalling and cancer)* and *King* (*autophagy and cancer*) and initial funding of 4 PhD studentships (£320k) to maximize cross-disciplinary studies in membrane molecular cell biology.

The Centre for Stem Cell Biology (CSCB) is recognized internationally for its research on the biology of human embryonic carcinoma cells, human embryonic stem cells and induced pluripotent stem cells. The research is central to the long-term goal of developing clinical applications for stem cells in regenerative medicine (*e.g. Chen et al., Nature, 2012*). To this end, there is significant expertise in the production of clinical grade cell lines and master cell banks that can meet stringent healthcare regulations. The first clinical trials for human stem cell therapy are now being conducted in the UK using cell-lines derived in the CSCB (see Impact Case study: *Stem Cells*).

Goals in Regenerative Medicine: The potential of regenerative medicine to revolutionise patient healthcare is recognized by both government and funders. The combined expertise of CSCB, CDBG and CMIAD has provided a unique opportunity to develop a platform for regenerative medicine in Sheffield. Within CDBG, developmental biologists are increasingly providing critical insight into adult homeostatic mechanisms, while CMIAD provides the expertise in molecular cell biology essential to dissect these mechanisms, identifying therapeutic opportunities. Understanding the fundamental biology of regeneration will allow the development of appropriate stem cell technologies. A major impetus to this work has been the award, in 2013, of a £7.6M grant from the UK Regenerative Medicine Platform to the Universities of Sheffield, Loughborough and Cambridge to fund the Pluripotent Stem Cell Hub. Led by Sheffield, this initiative aims to scale-up the production of stem cells for therapeutic use. The initial focus will include the treatment of deafness.

Clinical Disciplines

Sheffield Cancer Research Centre (SCRC). The strategy for cancer research was defined following an external review, undertaken by Sir Alex Markham (former Chief Executive of CR-UK) in 2008 and comprised a plan to consolidate the disparate cancer research groups within the School of Medicine into refurbished laboratory facilities as a prerequisite to obtaining a Cancer Research UK (CR-UK) Centre award. This was achieved in 2011, and Sheffield is unique in being the only CR-UK Centre with dual sponsorship with a partner charity (YCR). The strategy of the SCRC has been to increase resource allocation to areas of cancer research for which Sheffield has an international reputation: namely bone oncology (*Ottewell, Mol Can Ther, 2009*), tumour microenvironment (*Tozer, J Clin Invest, 2011*) and genetics/genomic instability (*Bryant, EMBO J, 2009*), and to increase collaboration with bioscientists undertaking cancer research. The award of CR-UK Centre status has been accompanied by significant YCR and CR-UK investment (£1.2M) in training, with 6 clinical and scientific PhD students appointed. Further investment from YCR (£1.3M) in infrastructure (deep sequencing, siRNA screening and mass spectrometry) has created an integrated Functional Screening Programme. Additionally, a Lecturer in Bone Oncology (*Ottewell*) has been appointed. Through the SCRC, staff have access to clinical material (a "biobanking" initiative has been established in collaboration with Sheffield Teaching Hospital) and a vibrant seminar series.

The Experimental Cancer Medicine Centre (ECMC) was funded by a successful CR-UK award (£1.3M; Lead: Woll (UoA1), Co-applicants: *Brown, Sisley* and *Smythe*) and provides a seamless pathway for the translation of novel scientific findings into early phase clinical trials and beyond. SCRC has developed links with other CR-UK Centres, in particular with our neighbouring Leeds Centre. We have held joint workshops in areas of mutual interest, including Cancer Genetics, Tumour Microenvironment, Translational Oncology and Systems Biology. Dual-centre pilot projects have been funded as a result of these interactions, e.g. JAK/STAT-activated miR-155 in cancer cell lines using organotypic cell cultures to *Zeidler* (Sheffield) and Mavria (Leeds).

Goals for Sheffield Cancer Research Centre: Research from this UoA will address the specific aims of SCRC, which are to improve the treatment of cancer patients, particularly as presenting in the Yorkshire & Humber region, although our findings will, of course, be applicable nationally and internationally. CR-UK has encouraged the SCRC to be ambitious in its strategy and to continue to strengthen areas of international excellence, particularly in the areas of the tumour microenvironment, bone oncology and genetics and genome stability. This will be underpinned by our local expertise in model systems (*Drosophila* and zebrafish) within the MRC CDBG (*Roehl, PLoS Genetics, 2008*) and the Sheffield RNAi Screening Facility, our newly acquired Next-Generation Sequencing (NGS) Facility, and the newly expanded and refurbished mass spectrometry suite. Training of the next generation of clinical and laboratory-based researchers will be facilitated by a £1M investment from YCR in grants for Early Career Researchers to undertake independent research.

Sheffield Institute for Translational Neuroscience (SITraN)

Achievements: Opened in November 2010 by HM The Queen, SITraN is an £18M facility with state-of-the-art laboratories housed in a new building, which is dedicated to the fight against motor neuron disease and other common neurodegenerative disorders (*Ning, Science Trans Med, 2010*). Since SITraN opened, research grant capture in this area has exceeded £6.4M per year. SITraN has a translational therapy pipeline with one orphan drug already identified from a drug screening programme and two other clinical trials underway. *Establishing SITraN was the Department of Neuroscience's primary objective stated in RAE2008 UoA5. Similarly, the Allied Health submission in RAE2008 recognised that neuroscience excellence lacked co-ordination, communication, and cross-fertilisation because of a diversity of locations. The establishment of SITraN has resolved these issues and significantly strengthened collaboration with CDBG (e.g. non-mammalian models of neurodegenerative diseases, including zebrafish models of Parkinson's Disease (Grierson) and epilepsy (Cunliffe)).*

Goals for SITraN: The key vision of SITraN is to develop an international centre of excellence in basic science linked to applied research in neurodegenerative disease. Specifically, research programmes based on induced Pluripotent Stem Cell technology will be established by building on genotypically and phenotypically well-characterised patient cohorts to model treatment targets based on fully realistic patterns of gene expression. *Ning* with Shaw (UoA1) has been awarded an

MRC-China Initiative Grant, 'Characterisation of the motor neurons obtained from induced pluripotent stem cells in Amyotrophic lateral sclerosis', in collaboration with Tongji University. This award will be followed by a Phase 2 application. Funding has been earmarked for Chairs in Translational Stem Cell Biology, Drug Metabolism and Bioinformatics in 2014.

SITraN will continue to accelerate drug repurposing for neurodegenerative diseases and has already 2 published patents in this area (WO2010046710, WO2009081141), together with a European Medicines Regulatory Agency 'Orphan Drug' Designation granted for the compound S[+]apomorphine for the treatment of Motor Neuron Disease (ongoing), as well as an MRC-AstraZeneca Compound Collaborative Grant to evaluate AZD1080 (GSK-3inhibitor) (1 of only 15 awarded) in a preclinical mouse model of motor neuron disease (*Mead* with Shaw, UoA1).

Centre for Integrated Research into Musculoskeletal Aging (CIMA)

Achievements: The University of Sheffield has an excellent track record for basic, translational and clinical musculoskeletal research, and is ranked 4th in the world for university-based osteoporosis research (ScienceWatch). In recognition of this, staff from this UoA contributed to the establishment of CIMA via the successful award of £2.5M from the MRC and Arthritis Research UK (2012). CIMA is a collaboration among centres of excellence at the Universities of Liverpool, Newcastle 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. Synergies with INSIGNEO (see below) have led to awards of Arthritis Research UK programme and MRC-China Initiative Grant pump-priming support (*Bellantuono*, PI total *ca* £1M), and NC3Rs support for new *in vivo* micro CT equipment (only the third such machine in the UK, *Bellantuono*, PI).

CIMA Goals: CIMA provides an unrivalled opportunity for this grouping to integrate their studies within a wider community of expertise, to facilitate increased understanding of the adverse effects of ageing in tissues of the musculoskeletal system and of how these processes may be modelled, ameliorated or prevented. A unique feature of CIMA research is its focus on the whole musculoskeletal system, integrating individual tissue components to provide translational advances, leading to the development and testing of novel approaches to reduce age-related deterioration of the musculoskeletal system through combined nutrition, exercise and pharmacological interventions.

The Institute for *In Silico* Medicine (INSIGNEO, established 2013) brings together researchers and clinicians from across the University and Sheffield Teaching Hospitals NHS Foundation Trust to address the challenges inherent in *in silico* medicine, e.g. in creating integrative models to predict individual future health. INSIGNEO has particular expertise in cardiovascular and musculoskeletal biomechanics, inflammatory mechanisms, and thrombosis and haemostasis.

Achievements: Clinical validation of hypotheses generated from *in silico* studies and reverse translation is facilitated through close collaborations with Academic Directorates in Sheffield Teaching Hospitals NHS Foundation Trust. Data relating to meticulously phenotyped clinical cohorts of patients with coronary artery disease and pulmonary arterial hypertension are being gathered, and biological sample collections are being maintained for future study. Funding includes awards from NIHR, Wellcome/DoH HICF and MRC/BHF as part of a national Grand Challenge Award to Cambridge (£4.7M).

Goals: INSIGNEO aims to develop personalised approaches for the treatment of coronary arterial disease, pulmonary arterial hypertension and osteoporosis using fundamental biomedical science discoveries, and virtual physiological animal-based technologies. For example, modelling of the biomechanics of the cardiovascular system has emerged as an interdisciplinary research initiative that has identified shear stress and fluid dynamics as important components in the development of cardiovascular disease. Through INSIGNEO, our cardiovascular research groupings have access to a critical mass of technical expertise including novel methods of MR imaging/analysis, data management, computer modelling and simulation, biobanks, and animal models (including a porcine research facility).

The Florey Institute of Host-Pathogen Interactions (established 2013)

Achievements: This UoA has significant expertise in the fundamental molecular microbiology of pathogenic bacteria, especially those leading to hospital-acquired infections, and aims to elucidate host-pathogen interactions and identify targets for antimicrobials (*Fagan, PLoS Pathogens, 2011*).

A second focus is on innate responses to infectious disease through collaboration between microbiologists within Science and clinicians specialising in infection and immunity, together with the NHS via Sheffield Teaching Hospital Foundation Trust and its dedicated Infectious Disease Unit (*Marriott, Amer J Resp Crit Care. 2008*).

Goals of FIHPI: Research within FIHPI focuses on the major therapeutic challenges presented by streptococcal and staphylococcal infections, and the increasingly recognised roles that pathogens play in chronic inflammatory diseases such as atherosclerosis and arthritis. These overlapping interests will be exploited through collaboration with cardiovascular groups and INSIGNEO. The rheumatology group already actively collaborates with CIMA and CDBG (*Walmsley, J Clin Invest, 2011; Elks, et al., Blood, 2011)*. In particular, the zebrafish facility will be exploited to develop models of infectious disease such as *Cryptococcus*, for basic and translational research.

VISION AND FUTURE STRATEGY (2014-2019)

External funding is increasingly being focused on Centres of Excellence. In recognition of this, our overall aim is to foster and to extend our current strengths in our Centres. We aim to do this by:

Development of a Bioinformatics Hub

Developing Bioinformatics was a strategic aim in RAE2008. To this end, *Milo* was appointed in 2012, bringing expertise from a clinical setting having been bioinformatics research fellow in the Sheffield NIHR-funded Cardiovascular Biomedical Research Unit (*Chico et al., J. Path. 2010*). Additionally, the University has made three new appointments (Chaudhuri, Elhaik and Sudbery) who will be in post in 2014 to establish a Bioinformatics Hub to underpin biomedical research within Science and Medicine. Members of the hub will act in synergy with existing computational groups to develop high-throughput data pipelines and algorithms for modelling complex experimental, phenotypic and sequencing data generated from patient cohorts and animal models. Release of funding from the YCR endowment (£250k) will create a Fellowship in Cancer Bioinformatics to co-locate within the new Bioinformatics Hub and will support the NGS, RNA and Proteomics facilities. Combined funding from YCR and the University (£150k) will support initial development of high performance computing for the Hub.

Exploiting synergies between existing Research Centres.

We recognize the effectiveness of Research Centres for enabling translation of basic research into the clinic. We will continue to invest in and support existing Centres via staff recruitment, internally-funded studentships and University contributions towards external grant applications. While each Research Centre has individual goals, as articulated above, there is overlap in membership that facilitates synergies between them. Examples of how we will develop these synergies include:

• Strengthening the links from basic biomedical science within the platform for regenerative medicine to the SCRC, SITraN, FIHPI, CIMA and INSIGNEO. Specifically, we are building a pipeline of clinician scientists, initially through support for intercalated BMedSci projects and then through support of Academic Training Fellowships. CDBG has already successfully sponsored and nurtured MRC Clinical Training Fellows (Watson, Novodvorsky, appointed in 2009 and 2010, respectively) and *Zeidler* currently hosts Thomas, a CR-UK funded Clinical Training Fellow. There is a pressing and national need for basic and clinician scientists to work together to advance the understanding of diverse disease mechanisms, and CDBG is recognised as an exemplar for interfacing between basic scientists and clinicians, and currently hosts the research laboratories of two clinicians scientists, Renshaw and Chico (UoA1).

• Development of neuro-oncology: CR-UK has announced its intention to make a call for new strategic developments, within CR-UK Centres, in 2014. In anticipation of this call, the SCRC is developing an enhanced strategy with additional focus on neuro-oncology (identified by CR-UK as an area of unmet need). This will synergise with Sheffield's world-class neuro-imaging and neuropathology research, and the strong basic neuroscience and neuro-oncology research within Science and SITraN. The first joint SCRC and SITraN neuro-oncology workshop was held in 2013. A joint SCRC-INSIGNEO workshop (2013) has led to a project to investigate modelling of cancer growth (PhD studentship call).

• Enhancement of links between SITraN with INSIGNEO through development of a major programme on vascular factors in dementia integrating stroke, neurology, laboratory science and neuropathology. To facilitate this, the University has recruited a Professor of Cerebrovascular Neurology (*Majid*, 2013) and the first workshop between SITraN, Academic Directorate of

Neuroscience (Sheffield Teaching Hospitals) and INSIGNEO was held in September 2013.

• New approaches to staphylococcal and streptococcal infections: Sheffield is committing significant support to enable FIHPI to become an internationally leading centre in its field. The commitment goes beyond the traditional mechanisms for grant-specific bids over a ten-year plus period. In 2013, *Fagan* and *Mesnage* have been recruited and the University has funded a Doctoral Training Cohort of 7 home and international PhD students, with a second cohort planned with an international mobility focus. Future investment will create further academic posts, including a senior academic to act as Director. Zebrafish models of infection and inflammation, within the MRC CDBG, will be further developed to exploit their potential for drug discovery and for understanding the impact and molecular controls of ageing of the immune system.

PROMOTING AND SUSTAINING AN ACTIVE RESEARCH CULTURE

Research organisation: We have achieved an active and vibrant research culture by organising research policy discussion at regular weekly and monthly meetings within individual Centres. This allows a "bottom-up" identification of emerging research areas. The involvement of large numbers of staff in national and international funding and policy bodies (listed in (*e*)) ensures that we are at the forefront of both formulating and responding to new initiatives. This researcher-led approach is complemented by a structure in which the Pro-Vice Chancellors for Science and Medicine carry joint responsibility for the strategy and infrastructure for Allied Health, including governance of the Research Centres. Faculty Directors of Research & Innovation chair research committees that include the Directors of Research Centres. Pro-Vice Chancellors have their own Faculty units for Finance and Human Resources, which means that opportunities for recruitment and investment are communicated efficiently and can be implemented without delay.

Recruitment: We have implemented schemes to attract and retain the very best research students, postdocs and academic staff (see staffing strategy). Schemes include targeted scholarships, research fellowships and academic appointments allocated to specific Research Centres.

Independent Research Fellows (IRFs) play a vital role in maintaining our vibrant research culture. In recognition of this, the University instituted a Vice-Chancellor's (VC) Fellowship scheme in 2012 to recruit high calibre young scientists to establish their research groups in Sheffield. *King* was recruited under this scheme. *Zeidler* was awarded a CR-UK Senior Research Fellowship and *Walmsley* currently holds a Wellcome Trust Senior Clinical Research Fellowship. *Brockington* held an NIHR (Walport) Clinical Lectureship in Neurology, *Marriott* a British Lung Foundation Fellowship, while *Bryant* and *Streets* held RCUK Fellowships. Building on these successes, a key component of our future strategy is to increase the number of IRFs through applications to external agencies such as CR-UK (we have 4 applicants submitting full applications in the current round), the MRC, the Wellcome Trust and the British Heart Foundation.

Postgraduate students: We have been successful in attracting excellent students and have in place plans that should conserve this funding stream (see section (c)). We ensure that students and their projects benefit from the broader context of the Research Centre to which they are affiliated. Our strategy is to support interdisciplinary interactions with a particular emphasis on the interaction between basic biomedical and clinical scientists, since these provide both an excellent training and can encourage collaborations leading to novel therapeutics.

Seminar programmes: The achievement of excellence requires a collegiate environment in which new research areas and synergies can be identified and acted upon. There is a wide range of seminar programmes (>10), providing a fantastic variety of opportunities for researchers to learn about the latest research being performed both within the UoA and by internationally renowned scientists from the UK and abroad. These are complemented by one-day symposia (both research group-specific and interdisciplinary). In addition, each Centre runs its own internal seminar series to which all research students are expected to present at least annually.

Promoting translation: The nature of the Research Centres with their mix of basic scientists and clinicians is such that translational opportunities are easily identified and maximised. In addition Sheffield Teaching Hospital has developed Academic Directorates as NHS/University partnerships focussing on core research strengths and increasing translational activity. These include Neuroscience, Specialised Medicine, Cardiology and Cardiothoracic Surgery, Specialised Cancer, Respiratory Medicine, Diabetes and Endocrinology, and Communicable Diseases. Opportunities

for external engagement are exploited by a £1.6M university investment in the newly established Sheffield Science and Healthcare Gateways, which each provide dedicated staff to assist with, and promote translational research (described more fully in our Impact Template).

(c) People: Staff Strategy and Development

Sustainability: Recruiting, mentoring, supporting and developing all staff is central to achieving our future strategy and goals. This is underpinned by our commitment to provide a thriving, mutually supportive research environment that grows and retains talent. Since 2008, we have recruited 15 new staff to this UoA, 8 of whom are Early Career Researchers (ECRs), to promote strategic development of areas identified in (b) and to maintain a balance between senior and junior staff. Our current recruitment strategy for academic positions is focused on the ongoing investment into the Research Centres, described above.

Since the research focus of this UoA is geared towards translating fundamental biological findings into effective therapeutics, there is active engagement between the two contributing faculties through reciprocal attendance at annual research retreats and more formally by representatives of Science attending Medicine board meetings and by reciprocal membership of interview panels for academic positions. The success of this approach is evidenced by the success of the cross-faculty Research Centres, described above.

Staff support: Early career lecturers and IRFs are supported by a mentoring scheme, targeted resources and reduced teaching loads to help them establish their research programmes. Our mentoring scheme for early career staff places emphasis on skills of writing grant proposals and papers, and on research supervision. Evidence of this success, e.g. is the award of an MRC New Investigator Research Grant to ECR *Parker*. New staff are supported *via* access to state-of-the-art labs and a culture of equipment sharing, and are given start-up funding, including PhD studentships. Additional University funds are provided for international mobility. Intellectual and pastoral support is provided by allocation of an experienced academic mentor, and via the Staff Review and Development Scheme. Clear promotion procedures allow for career progression of all staff: several of the UoA gained promotion during the period (e.g. *Baker*, *Borycki, Craven, Grierson* to Senior Lecturer, *Goldman* to Professor), demonstrating our readiness to reward achievement.

Early Career Researchers (ECRs): The HR Excellence in Research Award from the European Commission achieved by The University of Sheffield in 2012 recognises the internationally high-quality environment we provide for ECRs and acknowledges our commitment to the 7 principles of the UK concordat for the development of researchers. Our strategy is to train and mentor postdoctoral research assistants and ECRs to enable them to undertake research of the highest academic quality and importance, to communicate their findings in high-visibility journals and through international conference presentations, and to engage in knowledge exchange with leading academics and end-users. Our Centres help them to identify key research priorities, to build collaborations and to gain increasing recognition of their skills and achievements, and in turn to obtain successful independent funding for a future career in research. We are proactive in encouraging participation in *Professional Development* activities that facilitate networking across disciplines and that provide training, mentoring and support for career planning (including for non-academic positions).

The 'Think Ahead' programme, which originated in Medicine, has been extended across the University. 'Think Ahead' is a comprehensive blend of training workshops, career mentoring, and carefully selected work-based opportunities. It aims to ensure that every researcher has a career trajectory and access to tailored development activities, including the flagship SURE (Sheffield Undergraduate Research Experience) scheme for primary supervision by ECRs of summer student projects. A successful bid to The Wellcome Trust has established the Institutional Strategic Support Fund (£500k per annum, plus University matched funding), which has supported the creation of two distinct awards to support early career staff in the biomedical field. The Wellcome Trust Discipline Hopping Fellowship enables staff to move to a distinctly different discipline to develop new skills or to explore innovative ways of applying existing knowledge to an issue of biomedical importance, e.g. Gill (a synthetic chemist) was funded to investigate the utility of ruthenium polypyridyl complex-induced cell death in cancer cells with *Tozer*. The Wellcome Trust Bridging Grant supports post-doctoral researcher salaries for up to six months between research grant support (*Walmsley* was thus supported prior to her Senior Fellowship award). Two professional development staff are dedicated to ensuring opportunities for ECR professional and

career development. One exemplar initiative is 'The Sheffield Crucible', a flagship programme to offer participants three intensive residential workshops focussing on: (1) Looking Outwards: the Role of Researchers and Research in Society; (2) Your Research Community: Your Networks, Collaborative Research Opportunities; and (3) Yourself: Skills required to be a more Innovative, Enterprising and Creative Researcher.

The University's Research Leaders' Programme provides further generic training in grant application, research management, commercial awareness and communication skills. The success of these support mechanisms has contributed to our RAs and PhDs securing positions as IRFs (Wilkinson: Graves Fellow, Sheffield (UoA1); Knight, BBSRC David Phillips Fellow, Kings College London); *Walmsley:* Wellcome Senior Clinical Fellow; *Marriott:* British Lung Foundation Fellow, then Lecturer; *Streets:* RCUK Fellow; as academics in major Bioscience Departments in the UK (Watson, clinical lecturer University of Sheffield; Shepherd, Lecturer, University of Kent; Keating Senior Lecturer, University of Hertfordshire) and abroad (Hassuna, Lecturer, Minia University, Egypt. Jiraviriyakul, Lecturer, Naresuan University, Thailand); as senior scientists in pharmaceutical companies (e.g. AstraZeneca); as managers in companies in the healthcare sector (e.g. Qiagen); and as analysts in healthcare economics (e.g. GfK Bridgehead).

Technical staff: To ensure future sustainability and skills-transfer from our experienced senior technical staff (who maintain central facilities and conduct various analyses), in 2010 the University instigated a technician apprenticeship scheme to which we recruited new staff with excellent potential. Apprentices are trained over 2 years, during which they rotate between the main research laboratories and facilities, gaining in-depth knowledge of all the main types of research work conducted, familiarity with staff and their expertise, and training to maintain critical research activities as senior staff retire. By these means, we have trained an exceptionally versatile and skilled cadre of new technical staff who can be deployed in any area as needs arise.

Goals for staffing strategy: We will continue to:

• Recruit the best basic and clinical scientists at all levels. A particular focus will be the recruitment of IRFs via outside funding agencies. We will continue to treat our IRFs as permanent faculty with equal provision of PhD studentships, office/laboratory space and services.

• Build on our pioneering work in training clinicians in basic science by increasing the number of clinician scientists who can facilitate the translation of basic biomedical science into clinical applications. To further this aim we are establishing and nurturing a pipeline of medical students who spend time in labs gaining experience in basic biomedical science, with a view to ultimately becoming Academic Clinical Fellows funded by awards from MRC and charities including Wellcome Trust, CR-UK and the British Heart Foundation.

• Maintain our mentoring of postdoctoral researchers to ensure they have the maximum opportunity to gain funding for an independent research career or, alternatively, that they have the time and access to skills training for a non-academic career trajectory.

Equality and diversity: We support equality and diversity in all aspects of staffing policy. Women have taken leading roles in the UoA (e.g., HoD, Research Directors), so providing role models for more junior staff in our highly successful Impact Mentoring and Researcher Development Programme. We support flexible working practices, enabling those with, e.g., caring commitments, to adjust their work time accordingly. Members of this UoA (*Ottewell, Bryant, Brockington, Walmsley, Parker*) have benefitted from the Sheffield Women Academic Returners' Programme, which provides funding (£15k) to enable those returning to research after a maternity leave or career break to concentrate on research for at least one semester. The University has achieved Athena Swan bronze status and Medicine was one of only four Medical Schools to achieve silver status in October 2013.

Ethics: Amongst the Russell Group, Sheffield is a leader in fostering Good Research Practice (GRP), recognising that research environments must be underpinned by a culture of excellence with integrity. One critically important dimension of integrity concerns the ethical approach to experimentation involving human participants or biological material provided by them. In 2010 the University Research Ethics Committee published the University's *Ethics Policy for Research Involving Human Participants, Personal Data and Human Tissue* which contains specialist policy notes, including on *ethics review of health research* and *research involving human tissue*. The University is one of the few to require all research students to undertake training in GRP. The

University of Sheffield *Research Governance Framework* applies to all healthcare-related research. Our online University Research Management software requires staff to disclose details of governance requirements from the point of project proposal. Ethics modules are compulsory for graduate students, and ensure that ethical research principles are embedded in our junior scientists from the start of their scientific careers.

ii. Postgraduate Research students

PhD training: PhD students make a major contribution to our research and a hallmark of our training is the opportunity to work in an interdisciplinary environment. More than 200 PhD students have been under supervision in REF2014. Training is organised via departmental postgraduate committees. Working with supervisors, they implement the University's Doctoral Development Programme, manage mentoring and progress reports, and ensure an excellent level of pastoral care. All students are assigned a primary supervisor and an independent advisor as an impartial mentor. In year one, all students participate in formal courses in generic professional and research skills. In addition to attending research seminars, preparing research reports, and giving regular presentations, training is also provided in teaching skills. A Training Needs Analysis and Personal Development Plan ensure that training is tailored to the needs of each student. For example, many students participate in the National Biotechnology Young Entrepreneurs Scheme and a team from the *Goldman* and *Poole* labs was a Yorkshire and Humber level Winner and National level Finalist in 2009.

A measure of the effectiveness of this training is that the QAA praised Sheffield with no criticisms (marking progress on the previous 2008 audit). A further measure of the success of our training is the large contribution our students make to academic research. Thus, many of the outputs submitted for REF by this UoA have Sheffield-based PhD students as authors (e.g. *Gill et al, Nature Chem; Welford et al., J Clin Invest.*) Attendance at national and international research meetings is actively encouraged, and 16 students from this UoA have won prizes for posters and presentations at meetings (e.g. Lipscomb, Muscular Dystrophy Campaign Annual Meetings, 2011 and 2013; Tahir, International Workshop for Pulmonary Functional Imaging, Madison, USA, 2013). Results from the Postgraduate Research Experience Survey indicate that the proportion of PGRs who believe the research ambience stimulates their work is significantly higher than the rest of the sector. A sense of community is fostered through events such as the 2-day residential PhD student conference funded by the UoA: 100 students will attend this year.

Funding and capacity building. We have robust plans in place to maintain the numbers of studentships over the next 5 years. Members of the UoA are eligible to apply for studentships from the BBSRC-funded Mechanistic Biology Doctoral Training Partnership, and the MRC CDBG Joint studentship programme; the latter which, in particular, promotes a convergence between the basic and clinical sciences mindsets and approaches, enabling students to be effectively 'bilingual' in clinical and basic science. The translation of our findings results in collaborations with industrial partners, which we will exploit via CASE studentships. It is our aspiration to expand significantly our capability in this area in the next 5 years (in the current REF period, we had 4 with GSK, AstraZeneca, UCB and Pfizer), facilitated by pump-priming funds from the University. *Erdmann* leads an EU-funded Initial Training Network (Total value: €3.8M), which he has transferred to Sheffield and plans to apply for renewal in 2014. The University has allocated £1.3M for studentships per year to Centres within this UoA, which are available through open competition. We are developing a number of doctoral training centres (DTC) from RCUK and University/alumnus funding sources, which will ensure a large and sustainable funding stream for PhD students closely aligned with our overarching research strategy. The aim of the DTCs is to equip students to become excellent scientists, with the potential to excel in clinical, academic and non-academic careers, and to engage fully with end-users (from industry to policy).

Masters programmes: The establishment of a number of successful Masters courses across the UoA (e.g. Stem Cell and Regenerative Medicine, Molecular and Cellular Basis of Disease, Translational Neuroscience and Clinical Neurology) ensures a good pipeline (>60) for home and international students, many of whom progress to our PhD programmes.

d. Income, infrastructure and facilities

Income: Increasing diversity and level of funding has been our goal over the REF period. Since 2008, the UoA successfully obtained >£28M funding. Research activities are underpinned by

funding from Research Councils (>£8M) and major biomedical charities (>£11.5M), including, for example, the Wellcome Trust (£4M) and CR-UK (£3.5M), as well as a spectrum of other sources including industrial partners. Longer-term funding from CR-UK and YCR supports the SCRC; from MRC supports CDBG; from MRC and Arthritis Research UK supports CIMA. Wellcome funding supports the Sheffield RNAi Screening Facility and the Light Microscopy Facility.

Research income is widely distributed amongst staff, with an average of £0.44M per FTE. This broad income distribution reflects the strength and breadth across the whole of our research activities, ensuring that our research buoyancy is not dependent upon a few individuals or research activities. Moreover, given that a significant number of PIs being returned to this UoA are ECRs (8, of whom 7 have been appointed within the last two years) we expect to increase significantly the income per FTE in the next REF period. Industrial collaborations have yielded a number of funding successes including Axordia, Asterion (Impact Case studies: *Stem Cells* and *Asterion Spin-Out*), BioServ and Zilico. Through the recently established Sheffield Science and Healthcare Gateways, we can respond with agility to future commercial opportunities.

Our high level of external funding enables us to compete effectively across all our areas of research and allows University funds to be used to strengthen research activities, particularly with regard to provision of dedicated facilities and technical support (see below).

Infrastructure: Our high-quality research is facilitated by a comprehensive array of world-class facilities, which are run on transparent business models, to provide sustainability through income from users whilst retaining the flexibility to underwrite pilot projects and to prime research ideas. Our principle is to provide skilled technical support for all core equipment to enable facilities to be managed and serviced effectively, to provide training to all users, to facilitate marketing and to maintain open, equitable access through online booking.

Our facilities for **non-mammalian model systems**, including zebrafish aquaria with capacity for 100,000 fish and environmentally controlled *Drosophila* laboratories, are unparalleled within the UK, providing key support for the outstanding outputs based on animal models of human disease. Approximately 1000m^2 of high quality space supports **mammalian research** (mice, rats, pigs). Training courses are provided for Home Office Licence applicants.

The ***Sheffield RNAi Screening Facility*** provides a local and national service for genome-wide RNAi screening experiments in *Drosophila* and human cells. This can be used to discover genes involved in biological processes and disease, to identify potential drug targets and to screen for small-molecule drugs (*e.g. Fisher et al., BMC Genomics, 2012*). With funding from YCR, the service has been expanded to include screening in human cells, in line with our strategy of establishing excellent fundamental science that can be translated to human disease. The MRC CDBG ***Zebrafish Drug Screening Unit*** facilitates screening in a vertebrate model organism. Zebrafish are small in size and easy to breed, providing a cost-effective means to screen compounds for potential toxic effects and therapeutic activity in whole animals prior to rodent studies (*e.g. Cunliffe et al., Dis Mod Mech, 2012*). We have significantly strengthened our **biological mass spectrometry** capability with the purchase of both a YCR-funded £1M Thermo Orbitrap Elite Mass Spectrometer and a £0.75M Waters Sinap for metabolomics and proteomics. These state-of-the art machines have been integrated into our new (2013) Mass Spectrometry facility, with 300m^2 refurbished lab space providing access to 14 mass spectrometers (value >£5M). *Collins* has been appointed as a lecturer in biological mass spectrometry. A major aim of this facility is the identification of disease biomarkers, prognostic indicators, and the identification of cellular targets of bioactive molecules.

Research in cell biology is underpinned by the **Light Microscopy Facility,** established with Wellcome Trust/University funding in 2007, which includes deconvolution and laser-scanning confocal microscopes. In recognition of the constant advances in light microscopy, further additions to the Facility over the REF2014 period have included a Nikon A2 TIRF/confocal microscope, (Wellcome Trust equipment grant), and two super-resolution microscopes, a Nikon STORM and OMX, funded by the MRC/BBSRC/EPSRC Next Generation Optical Microscopy Initiative with additional support from the University.

SITraN hosts a ***microarray facility*** and specializes in running Affymetrix Gene Chip microarrays on a large scale, as well as a variety of smaller-scale assays from other platforms, with available chips and protocols. Available assays include expression analysis, single nucleotide polymorphism analyses and resequencing, including a human mitochondrial genome chip, exon arrays for the

analysis of alternative splicing and arrays for chromatin immunoprecipitation on chip experiments for the investigation of gene promoters. This facility been successfully used for biocomputational analysis of auditory stem cells (e.g. *Chen et al., Nature, 2012*).

Major External Shared Facilities

• In 2009, a consortium of the Universities of Liverpool, Manchester, **Sheffield** and Lancaster was awarded £1.8M from MRC for advanced DNA sequencing housed in the Advanced Genome Centre Next Generation Sequencing Facility at the University of Liverpool.

• A Next Generation Sequencing Facility in the Sheffield Children's NHS Trust (2013) provides facilities to deliver diagnostic standard data for NHS and UoA researchers. The facility consists of an automated pipeline for sample preparation with Illumina MiSeq and Life Technologies PGM sequencing machines. Initial funding came from The Children's Hospital Charity.

• Structural analysis of pathogen proteins is carried out at Diamond Synchrotron (e.g. *Cruz-Migoni et al., Science 2011, Haydon et al., Science 2008*).

Ongoing plans for enhancing our infrastructure:

• The University is investing with the NHS in a jointly funded high-throughput next-generation sequencing facility (£500k), for diagnostic and research projects. Appointments to the Bioinformatics Hub provide the essential expertise required to fully analyse and model the data generated from these screening approaches.

• The University is funding improvements to our electron microscopy facility (equipment and an academic position), which will complement the existing light microscopy facilities.

• The Sheffield Cancer Biobank will be established with funding from YCR (£850k), Sheffield Teaching Hospitals (£250k), CR-UK (£360k) and the University (£210k).

e. Collaboration or contribution to the discipline or research base

Collaborations: 28% of publications from this UoA over the REF period were co-authored by researchers in Europe, Asia, North and South America and Australia and New Zealand, indicating the international reach of our collaborations and impact. Members of the UoA have written over 100 reviews (>1700 non-self-citations). We have been successful in securing major collaborative international projects, e.g. *Borycki* was a member of the Executive Committee and Coordinator of the EU FP6 Network of Excellence MYORES (2005-10), which was the first European Network dedicated to study normal and aberrant muscle development and involved 37 research groups spread over 7 European countries and Australia. *Furley* is a partner in FP7-HEALTH-2013-INNOVATION-1 Supporting Action, ANIMPACT: an initiative to investigate decision making in animal research (2013-). MRC-China Initiative awards include *Ning* with Shaw (UoA1) with Tongi University, and *Bellantuono* with Sun at Nanjing University. Such collaborative work is facilitated through research sabbaticals and the provision of University travel funds for conferences.

Within the UK we collaborate closely with Leeds and York via the White Rose Consortium (which provides funding for regional collaboration and PhD networks, and co-ordinates our £6M BBSRC Doctoral Training Program). There is a close collaboration with Liverpool and Newcastle via CIMA. Most recently *Bellantuono* has been elected to the steering committee of Shared Ageing Research Models (ShARM) – a partnership between CIMA and MRC Harwell, funded by the Wellcome Trust, as a non-profit organisation that aims to accelerate research into ageing through sharing of resources. **The Pluripotent Stem Cell Hub** links the Universities of Sheffield, Cambridge and Loughborough to develop large-scale production of therapeutic stem cells.

NHS: The **Joint Clinical Research Office** between the University and Sheffield Teaching Hospitals provides comprehensive assistance to researchers conducting clinical research by supporting development, set-up, costing, and management of clinical research in Sheffield.

Industry: Our researchers have active engagement with industrial partners. During the REF period, two spin-out companies were formed (Zilico and BioServ) and 16 PIs had industrial collaborations. *Moore* was contracted by Pfizer to develop clinical grade stem cells (Case study: *Stem cells*). SITraN holds 1 of 15 MRC-AstraZeneca Compound Collaborative Grants (2013). *Wyld* is Chair of the Education and training Committee of ESSO (2012-17).

Grant review committees: Members of the UoA (19 PIs) have been members of 25 international grant review bodies, as well as 43 UK research council grant committees (34 PIs). These include major UK councils (BBSRC, EPSRC, MRC) and charities (Wellcome Trust, CR-UK and British Heart Foundation). This indicates the esteem with which members of this UoA are held and their contribution to UK and international science. Specific examples of international activity include:

Borycki: Scientific Board of Association Francaise contre les Myopathies (2007-); *Roehl:* Multiple Hereditary Exostoses Scientific Advisory Board USA (2008-); *Furley:* Advisor on genetics and biotechnology to EU-wide consortium (PRIVILEGED) determining the ethical and legal interests in privacy and data protection for research involving the use of genetic databases and bio-banks (2007-2009). *Kiss-Toth:* EU FP7 Health Panel member. Nationally: *Moore* was a member of the MRC liaison committee on embryonic stem cells (2002-2010); RCOG/Wellbeing committee for research activities (2007-2011) and the MRC working group on commercialisation of stem cells (2008-2011). *Holley* was Chair of the Action on Hearing Loss (formerly RNID) postgraduate grant panel (2010-2012); panel member for Translational Research in Hearing (TRIH) for Action on Hearing Loss (2011-2013); panel member for NC3Rs (April, 2013-).

Regulatory and clinical guidelines: Members of the UoA have made a significant contribution to the development of regulatory and clinical guidelines. For example: in 2013 *Cork* and *Pacey* contributed to the NICE clinical guidelines on the use of detergents in emollients and on fertility, respectively. *Tozer* was expert member and section lead for the Co-ordinating committee for setting guidelines for the use and welfare of animals in experimental cancer research (NCRI, 2008-2010) while *Powers* is a Member of the Scientific Advisory Committees on Nutrition and Vitamin D for the Department of Health. *Moore* participated in a Foreign Office sponsored visit to California in 2009 to explore Regenerative Medicine and Technology Transfer. *Roehl* was an Advisor to RSPCA on Housing and care of aquatic species Zebrafish (2010); *Pacey* was a member of the Human Fertilization and Embryology Authority Donation Review Committee (2010-2011).

Contributions to Charities and Learned Societies: Further evidence of contribution to the discipline comes from the involvement of 24 PIs from the UoA in learned societies and biomedical charities. For example: *Pacey* was elected Chairman of the British Fertility Society; *Brown* is President Elect of the British Microcirculation Society; *Holley* was Trustee of Action on Hearing Loss (formerly RNID) (2007-2013); *Sayers* is Trustee and Director of the Biochemical Society and Portland Press. *Fazeli* was Chairman of the British Andrology Society (2009-2011).

Journal editing: >40% (31) PIs within the UoA acted as editors or associate editors for over 51 journals during the REF period. These included: *Tozer:* Intravital (2008), Radiology and Oncology (2011-); *Sayers:* Biochemical Journal (2008-); *Holley:* Tissue and Cell (1985-); *Fazeli:* Reproduction (2005-); *Gartland:* Haemophilia (2009-); *Hellewell:* British Journal of Pharmacology (2001-12); *Ottewell:* Open Journal of Oncology (2013-); *Pacey:* Journal of Human Fertility (2008-), Reproduction Journal (2009-), Fertility and Sterility Journal (2011-); *Poole:* J Biol Chem (2008-), Advances in Microbial Physiology (1995-); and *Kelly:* Microbiology (2010-).

Contribution to PhD student training: In addition to training over 200 PhD students, members of the UoA have acted as external examiner for 36 PhD students internationally and a total of over 130 PhDs in the UK from a range of major universities. The number and quality of our own students, and our role in examining students at a national and international level, represent a significant contribution to the research base.

Courses and conferences: During the REF period, members of the UoA organised 26 international conferences. These included a biannual EMBO workshop on modelling human disease (*Cunliffe*) and an annual Pluripotent Stem Cell Conference (*Moore*). In addition, colleagues organised 30 sessions at international meetings and gave 264 invited talks and over 100 plenary talks at a total of over 350 international conferences.

Summary Overview: Since 2008, research activity in this UoA encompassing Allied Health Professions, Dentistry, Nursing and Pharmacy at the University of Sheffield has undergone unprecedented transformation in scale and organization. The establishment and growth of our Interdisciplinary Research Centres has provided an outstanding platform and focal point for integrating basic biomedical research, with translational and clinical outputs of national and international importance. We have developed a thriving research environment that has been strongly underpinned by major new investment in people, infrastructure, equipment and facilities from The University of Sheffield, biomedical research charities, and research councils. The strength and success of our strategy and vision is reflected in the nearly six-fold increase in staff returned to this UoA compared to RAE2008, accompanied by a trajectory of growth, income generation, and increasing international standing and esteem of our staff. We are in an exceptionally strong and buoyant position to continue our leading role in developing integration and synergies between basic science and clinical disciplines over the next REF period.