Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

a. Overview

The School of Medicine consists of five clinical academic research departments within the Faculty of Medicine, Dentistry and Health (FMDH). The School provides administrative support for researchers and, together with the Academic Unit of Medical Education, organises and delivers teaching. In all, the submission consists of a total of 74 members of staff (66 Cat A staff = 63.95 FTE + 8 Cat C) to this UoA. Since 2008, the School has implemented a strategy to focus activity within new Research Centres (**RCs**) in state-of-the-art facilities to deliver research along the translational pathway. The School's Research Centres are:

- **Mellanby Centre for Bone Research**: MCBR (2009)
- **Sheffield Institute for Translational Neuroscience:** SITraN (2010)
- **CRUK/YCR Sheffield Cancer Research Centre:** SCRC (2011)
- **Florey Institute for Host-Pathogen Interactions:** FIHPI (2013)
- **Institute for *in silico* Modelling:** INSIGNEO (2013)

The creation of a new Faculty structure within The University of Sheffield (TUoS) has also promoted interaction with key internal partners such as the School of Health and Related Research (ScHARR) and the School of Clinical Dentistry. The Medical School is a significant partner in initiatives enabling cross-faculty interdisciplinary groupings, within TUoS and further afield, to work together to tackle problems relevant to Medicine and the mechanisms of disease. Examples of such involvement include:

- **MRC Centre for Developmental and Biomedical Genetics** (CDBG joint initiative between FMDH and Faculty of Science)
- **MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing** (CIMA, with Liverpool and Newcastle universities: established 2012)
- **Sheffield Experimental Cancer Medicine Centre** (part of national ECMC Network)

Summary of research groupings in this submission

Our research activities range from basic mechanisms of human biology and disease development, through medical imaging, to drug development and clinical trials. Bone development, ageing, risk factors for fracture and intervention studies are focused within our Mellanby Centre together with our endocrinology group. The Sheffield Cancer Research Centre's activities focus on breast and bone oncology, tumour micro-environment, genetics and genome stability. The School's neuroscientists, based in SITraN, focus on translational research into Motor Neuron Disease, brain ageing and Parkinson's disease. Our inflammation research unites cardiovascular and immunology groups studying mechanisms of thrombosis and haemostasis, respiratory medicine, infectious diseases (Florey Institute) and autoimmune disorders. Cardiovascular research includes fluid dynamics, clinical imaging and medical device research. Our staff includes five Fellows of the Academy of Medical Sciences and three NIHR Senior Investigators.

Some highlights of our achievements since 2008 include:

- £18M Sheffield Institute for Translational Neuroscience opened 2010.
- CRUK Centre status awarded in 2011.
- NIHR Research Professorship awarded to Wild in 2013.
- 15 externally funded Fellowships: from e.g. EU, MRC, industry, Parkinson's UK, BHF.
- Growth in annual funding over the period from £11M in 2008/9 to £15.6M in 2012/13.
- Our researchers have authored over 1200 peer-reviewed research articles since 1/1/2008. These papers have been cited over 27,600 times and include research articles in JAMA, Cell, Science (2), Nature (3), Mol. Cell (3), Lancet Neurology (3), BMJ (6), Lancet Oncology (7), The Lancet (11), J. Clin. Oncol (13); Circulation (13), NEJM (17) and Nat. Genetics (23).

b. Research strategy

SIGNIFICANT CHANGES SINCE 2008: The School has radically redeveloped its internal organisation since 2008. This process has taken the School from a traditional, broad, poly-departmental configuration to a focussed confederation of research groups that collaborate through one or more of our themed Research Centres (RCs). We have physically consolidated our researchers into contiguous accommodation within the School of Medicine/Royal Hallamshire Hospital building. Our neuroscientists are now housed in the purpose built laboratories of SITraN, opened in 2010. These changes maximise opportunities for collaboration and efficient utilisation of facilities and resources. Some staff left to take up senior roles in other organisations including: Hamdy to Nuffield Professor of Surgery, University of Oxford (2008); Dower to Head of Protein Chemistry, CSL Biotherapies, Australia (2009); Rostami-Hodjegan to Chair of Systems Pharmacology, Manchester University; Crossman to Dean of Medicine, UEA (2011); Croucher to Head the Osteoporosis & Bone Programme, Garvan Institute, Sydney (2011); Read to Chair of Infectious Diseases, Southampton (2012); Duff now chairs the MHRA (2013). These movements have been balanced by high calibre recruitments, awards and promotions (see Sect. C).

RESEARCH CENTRES: GROUPINGS, MAIN ACHIEVEMENTS AND STRATEGIES

INSIGNEO/Translational Cardiovascular Research is focused in the areas of Haemostasis and Thrombosis (lead Storey), Inflammation including pulmonary arterial hypertension (lead Lawrie, PAH) and Cardiovascular Biomechanics/Virtual Physiological Human (VPH co-directors Heller; Hose & Lawford UoA12). Hose/Lawford and Heller were instrumental in establishing the Institute for *In Silico* Medicine (INSIGNEO, 2013) bringing together researchers and clinicians from across TUoS and Sheffield Teaching Hospitals NHS Foundation Trust (STH) to collaborate with international partners in industry, academia and healthcare. INSIGNEO addresses the challenges inherent in *in silico* medicine to create integrative models predicting individual future health. There is major strength in cardiovascular and bone (Mellanby Centre) biomechanics involving a large multidisciplinary team linking work on shear stress, mechanosensing and fluid dynamics in cardiovascular disease (Chair Evans, 2011). INSIGNEO supports development of predictive models using MR imaging inputs led by Wild (NIHR Research Professorship) with Kiely (Cat C) enabling assessment and stratification of clinical treatment options for patients with pulmonary hypertension. This new discipline has attracted significant investment (Wellcome Trust/DoH HICF, £800k; BHF/MRC, ~£5M; NIHR, £1M) and partnership in a national MRC/BHF PAH biobank. Through INSIGNEO, MCBR, CDBG and an NIHR CRF, our cardiovascular research group have access to a critical mass of technical expertise including novel methods of MR imaging/analysis, data management, computer modelling and simulation, biobanking, and animal models (zebrafish, CDBG; porcine research facility).

Inflammation and Immunology research has a core focus on innate immune responses in Respiratory Medicine (lead Whyte), host defence against microbial infection (lead Dockrell), nephrology (lead Ong) and chronic disease (lead Wilson). This expertise in innate responses, partnered with excellent microbiology (UoA5), forms the core of the Florey Institute for Host-Pathogen Interactions (FIHPI; co-directors Dockrell, Whyte, Foster [UoA5]). FIHPI, chosen for the ambitious TUoS Futures 2022 funding programme, spans 10 University Departments to form a research hub for Infectious Diseases, delivering novel cross-faculty (Medicine, Science and Engineering) and NHS (STH Infectious Disease Unit) collaborations. The focus is on major therapeutic challenges presented by streptococcal and staphylococcal infections. Pathogens also play increasingly recognised roles in chronic inflammatory diseases such as atherosclerosis and arthritis providing collaborative opportunities with our cardiovascular groups and INSIGNEO. Our rheumatology group has active collaborations with the Mellanby Centre (via MRC CIMA). Whyte is a co-Director of the MRC CDBG, with expertise in non-mammalian disease models, which have been exploited successfully by Renshaw and Johnston to develop models of disease for basic research and translational activity.

The Mellanby Centre for Bone Research (MCBR, director Eastell) is the focus for research in linked areas of Bone Biology and Endocrinology. Our highly translational bone research includes: fundamental bone biology and cell signalling; stem cell differentiation; anabolic influences on bone growth; skeletal ageing (involving **CIMA**); bone oncology (lead Skerry); clinical research in bone

growth and fracture in children (Bishop, Offiah, and Cat C Vora); osteoporosis diagnosis (McCloskey, Eastell) and treatment trials (e.g. NEJM 2010). Joint programme grants link bone biology research and the SCRC (Skerry/Eaton/Holen). In endocrinology, corticosteroid and diabetes research (Newell-Price/Heller) is predominantly clinical with international links to multicentre trials led from Sheffield (e.g. Heller *et al* The Lancet 2010).

Sheffield Cancer Research Centre (SCRC) is unique in that it is the only CRUK Centre with dual sponsorship with a partner charity (Yorkshire Cancer Research, YCR). It hosts research groups in DNA repair (lead Meuth) genetic epidemiology (lead Cox) translational bone oncology (Coleman), and tumour microenvironment (lead Lewis). Clinical translation is facilitated by the Experimental Cancer Medicine Centre (lead Woll), the Cancer Clinical Trials Centre, and future Specialist Treatment Facility. The School's strategy for cancer research was formulated after external review in 2008 (Sir A. Markham and Professor P. Johnson). SCRC strategy focuses resource allocation to existing areas of translational excellence, increasing collaboration between all TUoS Departments conducting cancer research across three Faculties (Medicine, Science, and Engineering) and STH. YCR funding (2009) provided state-of-the-art technology and infrastructure to effect transformational change in the scope and research capacity of SCRC. Further YCR investment is phased through 2011 to 2018 (£6M) supporting translational themes with new infrastructure for proteomics (Orbitrap Mass Spectrometer; Dept. Chemistry) and a human siRNA library for cancer research (siRNA Screening Facility; Dept. Biomedical Science).

SITraN is internationally unique in Motor Neurone Disease (MND) research in bringing together a broad clinical and basic science faculty (10 Cat A UoA1 and 2 Cat C) working within shared facilities to deliver an integrated translational research programme (Director Shaw). Translational research directed towards therapy development integrates disease modelling (primary and immortalised cell lines; iPS cells derived from local patients with sporadic and genetic forms of MND; zebrafish (Bandmann, Ramesh); and transgenic mice) with access to the UK's largest CNS donor bank in MND (Ince, Wharton). Our therapeutics pipeline is based on target identification through transcriptomic and proteomic techniques, high-throughput facilities for drug library screening to identify lead compounds, and downstream pre-clinical efficacy studies. Major research groupings (leads: Azzouz; Ince; Shaw) deliver this research in thematic areas of: patient genotyping (Kirby) and phenotyping; neuronal and glial biology in sporadic and genetic subtypes (deVos; Hautbergue); transcriptomics; drug repurposing; bioinformatics (Lawrence UoA11); gene therapy for CNS delivery (Azzouz); and clinical research directed towards development and evaluation of supportive and assistive technologies to improve patient survival and enhance quality of life (Shaw). The development of a critical mass of bioinformatics expertise to deliver research support and develop innovative approaches to analysis of complex datasets is a hugely successful collaboration between SITraN and the Faculty of Engineering (Lead Lawrence, joint with Computer Science). This group is fully integrated into SITraN. The Institute also houses groups applying the same approach to other major CNS disorders, including Parkinson's disease (Bandmann), dementia and brain ageing (Ince, Wharton), offering added value and synergies.

MAJOR ACHIEVEMENTS (many set out as goals in our RAE2008 strategies*) include:

- European League Against Rheumatism Centre of Excellence in Rheumatology 2011-2016 and MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing. These recognise strengths in rheumatology and bone biology (Mellanby Centre).
- INSIGNEO and the Florey Institute for Host Pathogen Interactions established in 2013.
- Heller led international clinical trials in Diabetes funded by NIHR, Diabetes UK, HTA, £5.5M) and published results in NEJM (Zoungas et al 2010) and The Lancet (Heller et al 2012).
- Cardiovascular hub Clinical Research Facility established (lead Storey; lead UK investigator for Ticagrelor; *see impact case A1-5*) fulfilling our aim to create a CRF in this area.*
- Chico and Renshaw exploited zebrafish as disease and flow models through the MRC CDBG, leading to publications in Blood and PLoS Pathogens. Award of MRC Senior Clinical and MRC-GSK Industry Fellowships (Renshaw, 2008 and 2012) and an MRC CDA (Johnston, 2012).*
- Pulmonary hypertension and coronary artery disease programmes established: Evans (BHF 2012, £1.1M); Lawrie (MRC CDA 2008 £1.5M; BHF grant, 2011 £500k); partner in £5M MRC

Experimental Medicine Award (local leads Lawrie & Kiely; Cat C). *

- McCloskey developed a new diagnostic algorithm for fracture risk (FRAX WHO risk algorithm) for use internationally (*impact case A1-3* and Osteo. Internat. Paper cited over 660 times) *
- Joint CRUK and YCR Cancer Research Centre* and CRUK Experimental Cancer Medicine Centre (ECMC) status awarded providing a seamless pathway for translation of novel scientific findings into the clinic. *
- Bone Oncology research (Holen and Eaton, CR-UK Programme) benefitted from integration with Mellanby Centre. Substantial increase in academic staff recruitment (69% increase), research grant capture (total value £5.3M per annum over the past 5 years) and lead authorship articles in e.g. J. Exp. Med., J. Clin. Oncol. and New England J. Med. *
- SITraN has significant involvement with DeNDRoN, including leadership of the MND Clinical Study Group (see also section E).*
- SITraN was opened by HM Queen in November 2010. This £18M project included a new building, 4 senior academic posts, provision of state-of-the-art facilities and equipment.*

FUTURE PLANS & STRATEGY

The complex nature of healthcare development drives our integration of basic scientists, technologists & clinicians to deliver effective new devices, drugs, diagnostics and vaccines for human healthcare. The School of Medicine's research strategy is based around our existing core areas of strength and critical mass. We will extend our cross-faculty collaborations with the Faculties of Science and Engineering, and with the School of Health and Related Research (ScHARR), this will allow us to exploit research opportunities as efficiently and effectively as possible. These collaborators are externally recognised as world leading research groupings in their respective areas. Thus, we will generate an environment that will allow unrestrained intellectual interaction and breakdown of academic boundaries. Our vision is to create a nationally and internationally distinct medical sciences hub that delivers impactful research based around large patient cohorts and datasets. We will realise the translational potential of stratified medicine, and become a beacon for innovative new approaches to understanding and treating human diseases based on harnessing technologies and research opportunities emerging in the physical, engineering, chemical and life sciences.

Key to realising these goals is our close partnership with other TUoS centres (e.g. **CDBG**, **INSIGNEO** and **ScHARR**), and the NHS locally (via **STH** Academic Directorates and STH leadership of the Yorkshire CLRN) and regionally (we are developing partnerships in the Yorkshire and Humber AHSN). We will also continue to engage with other NHS, academic and commercial partners wherever there are opportunities to maximise the impact and benefit of our work. We recognise that creative and innovative individuals inspire and lead research, therefore we aspire to retain, develop and recruit the most talented researchers at all levels, from B.Med.Sci/M.Sc. and Ph.D. through ECRs to established leaders (see Section c). Specific examples of our research ambitions linked to the established successes in grant capture and scientific discovery include:

Aim 1) Collaborations within INSIGNEO are leading to developments in cardiovascular, respiratory, and musculoskeletal disease research. We will create one of the largest clusters of clinical leaders in *in silico* cardiovascular medicine in the world. To achieve this we will build on current external funding (~ €20M for VPH Share & VPH Dare), committed TUoS investment of £800k (two 5-year Clinician Scientist posts; recruitment in 2014), and a state of the art 3T human MR scanner (Wellcome Trust ~£1M). Development agreements with GE Healthcare, Phillips and Novartis to develop imaging tools and systems to enhance modelling and simulations will facilitate achievement of this major aspiration. We will continue to focus on theragnostics and endotypes (Lawrie - BHF Fellowship 2013-18) developing anti-osteoprotegerin and anti-TRAIL treatment strategies for PAH linked with clinical studies by Wild (1st NIHR Chair in MR imaging 2013-18) expanding the use of polarised gas imaging as a biomarker in PAH, COPD and CAD. Within the Mellanby Centre, we will model the musculoskeletal system during physiological and pathological challenges (including ageing) at genomic, proteomic, cellular, tissue, organ and structural levels culminating in a clinical trial of a new intervention within 5 years (EPSRC, ARUK/MRC CIMA, ARUK programme, NC3Rs). This funded research will be supported by 6 academic appointments

(2 chair, 2 SL 2 Lecturer posts, see section C), and contribute to the development of virtual physiological human and mouse models.

Aim 2) The newly created Florey Institute for Host-pathogen Interactions houses a multi-faculty (Medicine/Science/Engineering) research cluster focused on developing new antimicrobial interventions. Our existing academic staff, Fellows (MRC CDA, VC Fellow) and studentship networks (Marie-Curie ITN and International Strategic Training Alliance with US/Africa/Europe partners, joint partner funding secured) will be augmented through recruitment of 2 Chairs and 2 Lecturers (from 2014, funding secured) to complement expertise in clinical microbiology and computational modelling. We will exploit the power of zebrafish and Drosophila models through CDBG for mechanistic studies, target validation and drug discovery (MRC, Wellcome Trust fellowships and grants and funded GSK collaboration).

Aim 3) The Sheffield CRUK/YCR Cancer Research Centre will translate novel basic science discoveries into clinical benefit in early and late phase clinical trials which are key aims of the Sheffield CRUK Experimental Cancer Medicines Centre (2012-17), in partnership with STH and the Cancer Research Clinical Network. Current foci are: Holen's innovative expertise in bone oncology and pain management in advanced in vivo model systems combined with a clinical trial of a repurposed compound (MRC/Astra Zeneca award, 2013-16) and Chantry's use of in vivo model systems of myeloma bone disease, testing combination therapies and novel agents, and making use of advanced bone imaging in the MBC (LLR Programme), and links with bone biology and modelling. Catto's group will perform clinical trials of a new chemotherapeutic drug combination in advanced bladder cancer (YCR Programme 2010-15).

Aim 4) We will grow our existing programmes of commercial development of research findings and stimulate new activity in the following areas: Antibody and small molecule approaches to cancer and osteoporosis will be progressed by investments into our spin-out SME based on US and European patents (Medella Ltd; Director Skerry - MBC, FusionIP and VC funding), exploiting RDA and BBSRC CASE support and by seeking DPFS and Wellcome SDDI support; Cushing's disease therapies based on orphan drug status (EU/3/10/978) and patent applications (Newell-Price) will target funding from UKTSB, MRC DPFS and NIHR in collaboration with STH; In partnership with Diurnal Ltd (Director Ross), a new treatment for adrenal insufficiency in infants will be trialled in a €5.6 million EU funded, Sheffield led programme.

Aim 5) Through SITraN, we will extend our translational activities in neurodegeneration. To do this we will: Exploit our induced pluripotent stem (iPS) cell models of realistic gene expression to identify treatment targets for neurodegeneration through collaboration with Tongji University (MRC-China initiative funding) and Ohio State University (EU Marie Curie Fellowship, 2012-2015); Recruit a Chair of Translational Stem Cell Biology to support exploitation of iPS technology and a Chair in Drug Targeting to build our drug repurposing and target identification for ALS/MND and PD, and our translation of gene therapy (programmes based on 'Orphan Drug' Designations - EU/3/12/954; EU/3/11/876 and granted patents - WO2010046710; WO2009081141). Conduct a phase I trial of gene therapy in SMA in 2016 enabled by current MRC DPFS and an ERC Senior Investigator award (2012-2017); Develop our Supportive care and assistive technologies for ALS/MND (NIHR Senior Investigator Award; 2013-8) in collaboration with ScHARR and NHS partners and extend research leadership in NICE Guideline development (CG105; Non-Invasive Ventilation); extend clinical trialling of diaphragm pacing (NIHR HTA/MNDA) and gastrostomy methodology (20-centre study); develop our neck collar design (NIHR I4I) and home support (Telehealth; NIHR Fellowship). Senior Fellowship (Parkinson's UK), and new lecturer (MNDA/philanthropic donor) positions funded in 2013-2018 will further add to our critical mass.

Responsiveness to national and international priorities: Our RCs are established to respond to key areas of national and international need. School staff are also members of complementary centres based in the Faculties of Science & Engineering; e.g. Krebs Institute (Mechanistic Biology) and the Centre for Stem Cell Biology (CSCB). Each of these groups bring clinicians and basic scientists together to forge collaborative programmes. Working with other leading research institutions, funders and policy makers (e.g. CIMA links TUoS with Liverpool University and the University of Newcastle as the national MRC/ARUK centre) our RCs are well placed to both influence and deliver national and international healthcare priorities. As examples, MRC Strategic Aim 2 (Research to People) relates to translational work at the heart of all our RCs: CIMA is well placed to engage with the MRC Lifelong Health and Wellbeing programme; SITraN & SCRC are

responding the CRUK 'unmet needs' brain tumour call; and SCRC and SITraN contribute to national biobanking (Breast Cancer Campaign Biobank, MRC Brain Bank Network).

Interactions with the NHS: **STH** 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. A recent report commissioned by STH will inform future strategy to maximise the impact of medical research carried out in Sheffield. Integration of NHS clinical staff is highlighted by the presence of 8 Cat C staff in the UoA1 return. The **Joint Clinical Research Office** (between TUoS and STH) provides comprehensive assistance to researchers conducting clinical research. By working closely with our colleagues in the NIHR Research Design Service for Yorkshire and the Humber, the University of Sheffield Clinical Trials Research Unit and the NIHR Sheffield **Clinical Research Facility** (CRF), a streamlined service supports stimulation, development, set-up, costing, and management of clinical research in Sheffield. In 2012 NIHR funding (lead Newman; £3.1M over 4.5yrs to establish the CRF) supported the growth of experimental medicine research within Sheffield. Studies using the CRF rose from 110 in 2008/09 to 331 in 2012/13. Since 2008 Sheffield has attracted grants in excess of £15.6M to support 36 studies. The CRF currently supports 51.4% of all research within STH. During the period 1/1/2008 -31/12/2012 they handled 26,384 visits.

Research Dissemination, Research Promotion, Culture and KE Activity: During the assessment period, School staff have authored 42 clinical/diagnostic guidance articles each averaging 46 citations (total > 1945), over 1200 research articles (27,603 citations), 216 reviews (cited over 5144 times), 700 meeting abstracts, and 160 letters and editorial contributions in the scientific literature. A Faculty Research and Innovation Committee promotes new collaborations, distributes pump-priming funding and co-ordinates strategic bids. Annual Medical School Research Days provide an opportunity for the entire School's staff to share current research and are attended by industry representatives (e.g. from GSK, Pfizer, AstraZeneca). Our RCs host regular Medical-Engineering-Science conferences, and focused meetings with other groupings from across TUoS, to promote cross-disciplinarity.

TUoS has committed £650k during the assessment period to fund the Sheffield Healthcare Gateway (**SHG**). SHG offers support to increase interaction with business and industry. It provides an access point for business into our facilities and expertise. Business development managers provide assistance with approaches to industry and to attract translational funding (e.g. GSK, MRCT, Pfizer presentation days). SHG staff are active in organising major conferences (e.g. ENCALS, Sheffield 2013) and SET weeks. Whyte has been an Academy of Medical Sciences Clinical Research Champion and mentors the student-led Sheffield Academic Medicine Society. This partnership recently obtained an award through the INSPIRE Programme. We participate enthusiastically in the Science in Schools Programme and stage regular café scientifique events. A flagship exhibit at the Royal Society Summer Science Exhibition 2011 focussed on CDBG. A Wellcome Trust Arts Award funded "Primitive Streak" a ground-breaking science meets fashion public exhibition (Sheffield Winter Gardens 2011). Our involvement in the MRC Cognitive Function and Ageing Study contributed to the Wellcome Trust funded Mind over Matter exhibition (Shoreditch Town Hall 2011). Our RCs hold regular public open days for patients, carers and research funders in collaboration with national disease charities e.g. British Heart Foundation, MNDA, YCR and others.

c. People:

i. Staffing strategy and staff development

The School employs a strategy of recruiting the highest calibre staff possible and is committed to their support and development and the provision of an excellent, fair and equal environment in which to flourish. To balance the effect of departures and retirements we have a vigorous strategy of new appointments, internal promotions, and fellowship opportunities. Recent appointments include at professorial level, Evans (from Imperial), Brown (from Leeds), 6 new Lecturer/Clinical Senior Lecturers and 21 of our existing staff were promoted to professor/reader, and 2 to SL in the period. Incoming Fellowship holders include: Johnston (MRC CDA 2012), Collis (CRUK Senior Fellow 2009) and Ferraiuolo (EU Marie Curie). TUoS has invested in Early Career Research (ECR) Fellowships providing salary and project funding for Evans (2013), Fragiadaki (2013), James (2012), Elks (2012), Akhtar (2013) and Wilkinson (2012).

The creation of SITraN has been a development of national significance. This £18M project includes funding for 5-7 new academic appointments, including 4 chairs. Through philanthropic donation these new appointments will not impact on our core budget for 10 years and will deliver significant improvements for patients with MND. Joint appointments in SITraN stimulate genuine interdisciplinary working. For example 2 chairs in Bioinformatics with Computer Science will develop new approaches to machine learning applications in systems biology in addition to providing expertise and capacity in biostatistical analysis of large datasets. In addition, the School also has funding to enhance research capacity through appointments to the following posts:

- Chair in Musculoskeletal Ageing and Senior Lecturer (SL) in bone biology.
- Clinical SL in osteoporosis (recruitment in 2015) and a Lecturer in Bone Mechanobiology (recruitment in 2014).
- Two Chair posts in Child Health (by early 2015) including Clinical Chair funded by Sheffield Children's Hospital Trust.
- Two new Clinical Chair posts in infectious diseases will bolster the Florey Institute and Rheumatology (CIMA/MCBR link; early 2014).
- Two clinical Chair posts in cardiovascular research and biomechanics linked with INSIGNEO.
- SCRC Strategy funding includes up to five new clinical and non-clinical posts at all levels.
- Chair of Translational Stem Cell Biology (SITraN, 2014; funding agreed).
- Chair of Drug Targeting (SITraN, 2014; funded agreed).

These incoming researchers to recent and planned appointments demonstrate sustainable management of our staffing structure. 12 of our 66 Cat A staff are ECRs.

Staff Development for ECRs: In 2012 TUoS secured the European Commission's HR Excellence in Research Award in recognition of a developing high-quality research environment for non-tenured research staff and postgraduate researchers. The Early Career Group champions ECR professional career development. It steers the School's 'Think Ahead' programme of training events as one component of the Think Ahead framework of support for ECRs. The framework extends to tailored induction and a suite of career support and mentoring opportunities that inculcate independence amongst ECRs. The School's Think Ahead framework of support is a major vehicle whereby the School promotes the TUoS Concordat for ECR, and the School's model has been adopted by the University as a whole to the benefit of all TUoS ECRs. Content is balanced between provision for ECRs aspiring to be independent researchers and ECRs aspiring to other careers. Highlights include *Crucible* and *Spring Board for Women.* Many events facilitate networking across disciplines (e.g. *Broadening Horizons; GradSchool, Mentoring*). The Early Career Group aims to ensure that ECRs can access support appropriate to their career trajectories. The group's work was shortlisted in the Times Higher Education 'Outstanding Support for ECRs' in 2011.

The Industrial Knowledge Forge (InKForge), launched in 2012, develops closer links with industry and embeds development of industrial knowledge for ECRs through networking and partnering for research projects, across the Faculty of Medicine, Dentistry & Health. The School has been particularly active within the programme. Since its launch, 41 industrial visitors (from companies including GSK, Lonza, AstraZeneca, UCB, Lilly, IDS, Unilever, Novartis, and at least 6 others) have taken part in 22 events, including seminars and workshops. Seven industrial guests from 3 different companies attended the School's annual research meeting in 2013. Approximately 130 ECRs have attended InKForge events (average attendance 15-20 ECRs). Peer support is also encouraged through our Early Career group and the Medicine, Dentistry and Health Research Staff Association. Senior academics mentor ECRs to increase grant capture (grant writing workshops, internal review process, and Faculty seed-corn funding), improve publication quality, and PGR capture success. Mentoring and translational research awareness is delivered via the SHG and has become an integral part of this process.

New lecturers are supported by a mentoring scheme, resources and reduced teaching loads. The Staff Review & Development Scheme (SRDS) provides annual reflection on progress over the previous 12 months, sets realistic targets, identifies barriers to progress, and resolves problems in a constructive manner. Staff at all levels from HoD to those in their first leadership or management role are supported through the extensive TUoS's Leadership and Management Development program. Specific training courses in a wide range of generic transferable skills, and more specific

technical training are readily available.

Career Development Successes: Our policies of preparing candidates for fellowships, underwriting of permanent posts (subject to probation) for those winning major fellowship awards, and funding of Medical School 3 year Fellowships (Graves, Berry-Simpson) have attracted high flyers who can compete for career development awards from major funders. Examples include: Dockrell, appointed clinical lecturer, awarded Wellcome Senior Clinical Fellowship 2005, promoted to professor in 2011; Sabroe, MRC Clinician Scientist Fellowship (2000), MRC Senior Clinical Fellowship until 2009, promoted to chair 2010; Renshaw, MRC Senior Clinical Fellowship (2008), now Reader and MRC-GSK Industry Fellow; Collini, appointed clinical lecturer (2006) now MRC clinical training fellow; Lawrie, MRC Career Development Award 2008, now BHF Senior Fellow; Mortiboys, post-doctoral scientist 2006, now a Parkinsons UK Fellow (2013). Iwan Evans subsequently awarded a Royal Society/Wellcome Trust Sir Henry Dale Fellowship (Nov. 2013).

Clinical Academic Staff are embedded throughout the School and make up 50% of the UOA1 (Cat A). Specific mentoring programmes and Follett joint academic/clinical appraisal are geared specifically for this group. Some NHS clinicians deliver research and all participate in clinical teaching and hold honorary contracts with TUoS. Eight are returned as Cat C staff in this submission. The Clinical Academic Working Group advises the School on its Undergraduate and Postgraduate Clinical Academic Training Strategy and is composed of representatives from Academic Staff, the local NHS Trusts and the Postgraduate Deanery. The School hosts 8 clinical Fellows (NIHR, NIHR/BHF, NIHR/HRUK, MRC) working on aspects of cardiovascular medicine. Since 2008, SITraN has hosted 4 MRC or MRC MNDA-Lady Edith Wolfson Clinical Fellows, and NIHR Clinical Lecturers. The School has hosted 126 Academic Foundation Trainees (42 current), 60 Academic Clinical Fellows (28 current) and 39 Clinical Lecturers (19 current) since 2008.

Evidence of how the submitting unit supports equality and diversity (E&D)

The School received an **Athena SWAN silver** award in 2013 and is 1 of only 4 Medical Schools in the UK with this status. The School embraces a strong commitment to equal opportunities. Flexible working practices enable those with external commitments to be accommodated. Diversity and unconscious bias training is compulsory for those chairing appointment committees and is offered to all staff. Our E&D committee continually monitors progress against the Athena SWAN action plan and objectives. The University has a flagship Women Academic Returners Programme (WARP) offering female researchers, returning after a career break, funding to concentrate on research for their first semester, and funding to backfill leave of absence breaks to minimise the impact on active project work. Thirty five of our researchers have benefitted from this programme since 2008. Two of five current HoDs in the School are female and three of the constituent departments have had a female HoD since 2008. With 26% of female professorial staff in the School we are ahead of the institutional average. Female Cat A staff comprise 30% of the return.

Fostering Good Research Practices (GRP)

Amongst the Russell Group the University is a leader in fostering GRP, recognising that excellence requires intellect and integrity and that research environments must be underpinned by a culture of integrity. The University's *Good R&I Practices Policy* (published in 2011 and reflecting world-wide best practice) sets the tone and clarifies that GRP is as much about how people are respected as about the rigour of doing research. One important dimension of integrity is how to ethically undertake research with human participants. In 2010 the University Research Ethics Committee (UREC) 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* and specialist guidance including on *research with adults who lack capacity to consent* (the School contributed to the drafting of the Policy). In 2012 Newman became Chair of the UREC and one of the two PGR representatives on the UREC is from the School. Sheffield is the only Russell Group university to deliver compulsory GRP training for all its research students (PGRs) and this training is delivered along 5 cognate discipline lines by academics and ECRs in the disciplines (delivered by Guesdon and Vivekananda-Schmidt). 92% of 128 PGRs who completed training agree that their understanding of research integrity has developed (sector average = 83%). Health care research is particularly regulated. TUoS *Research Governance Framework* applies to all healthcare research and the University interprets health care research broadly. Our online University Research Management

software requires staff to disclose details of governance requirements from the point of project proposal. Researchers are required to comply with all relevant legislation.

ii. Research students

The University's Research Student Proposition, published in 2012, and against which the disciplines benchmark themselves, outlines what research students can expect from TUoS and what TUoS expects in return. The QAA's institutional review of 2012 praised TUoS. Aspects of our provision for research students were highlighted as good practice and no criticisms were made. This marked significant progress on the previous audit in 2008. QA now consists of an annual review in which research students themselves contribute their perspectives on the quality of provision, a thematic review and a biennial survey. New students avail themselves of a Faculty peer-mentoring scheme, and attend a 7-day Postgraduate Induction Course, designed to assist with the transition to PGR and provide an introduction to the skills they are expected to gain during their PhD. Elements of induction are covered at University, Faculty and department level and the QAA regarded this as thorough. Topics include: networking; plagiarism and unfair means; literature searching and IT; how to be an effective researcher; scientific thinking; health and safety; essential laboratory skills and data handling; research ethics and integrity.

Candidates registering for PGR programmes within the School rose from 53 in 2008 to 69 in 2012/13). Two thirds were UK/EU students. They are supported by scholarships from RCUK (MRC, BBSRC, EPSRC), BBSRC DTG (with Department of Materials Science and Engineering), BHF, CRUK, NIHR, EU (Marie Curie Early stage researcher programme), Kidney Research UK, Age UK, UCB Ltd, TUoS and other sources. Clinical staff are encouraged to engage in research by waiving their study fees. A PhD by publication route was introduced for staff candidates to encourage timely completion using their existing research. A robust QA process assures our programme quality and was recently endorsed by a wholly positive QAA outcome.

Management and Monitoring of Students is overseen by the School Graduate Research Committee (SGRC), which reports to the Faculty Graduate School Committee (FGSC). In addition to informal meetings with their supervisors, students have documented supervisory meetings (9 p.a.) to discuss progress against project milestones (the QAA noted that mechanisms to monitor formal meetings with supervisors were effective). Students also meet with their personal tutors (2 p.a.) to discuss progress and any difficulties they may have. Progression to year 2 is subject to satisfactory performance in a 'confirmation review', based on progress in the DDP (see below), completion of a written report, and *viva voce* with two independent examiners. Progress is also assessed at days where students give oral (years 1/3) or poster (year 2) presentations describing their findings. After 2 years, students submit a document outlining plans for thesis completion.

The University's framework of support for Research Supervisors is increasingly holistic and in 2012 Sheffield published the *Sheffield Supervisor Statement* which outlines our expectations regarding the professional qualities and responsibilities of supervisors. New supervisors complete a Certificate in Learning and Teaching and are paired with experienced supervisors, receive regular updates on PGR provision and access development sessions including Faculty-wide 'bite-sized' sessions. Students participate in the **Doctoral Development Programme** (DDP – noted positively by the QAA), which maps to the Vitae Researcher Development Framework. One of a PGR's supervisors has lead responsibility for supporting the PGR student's professional development. Support is tailored to meet a PGR student's needs and aspirations. Plans are based on an initial Training Needs Analysis, and repeated annually. Each year, students register for "shell modules" for each of four skills sets (generic skills; subject-specific advanced training; subject-specific craft skills; broad scholarship). The shell modules comprise menus of Masters and DDP accredited modules, training units/seminars, opportunities for experiential learning and workshops available through the Think Ahead framework of support. In 2011 the PhD Intensive Clinical Experience module was offered to students across the Faculty: non-clinical PGRs engaged in research on specific aspects of human health and disease gain a deeper insight of their subject by meeting patients affected by the diseases/illnesses that they are investigating; the programme is being repeated. 95%/128 PGRs who completed PRES 2013 agree that the programme developed their skills in applying research methods, tools and techniques (sector average = 88%).

Students belong to and manage their own **Medical Postgraduate Society (MPGS).** It aims to enhance student experiences by improving communication and social interactions. It meets

regularly with 3 SGRC members as the Staff Student Liaison Committee to discuss student issues. Those which cannot be resolved are taken forward for discussion by the SGRC or the FGSC. Students have further opportunities to be heard and suggest improvements to PGR provision, and the SGRC seeks their opinions on potential new initiatives at regular forums. A Faculty-wide PGR Day, organised by and for PGR students, exemplifies recent innovation involving the MPGS.

CASE Studentships: An increased focus on recruitment of PGRs to CASE awards is planned as part of the strategy for growing PGR numbers in future years using pump priming funds from the Faculty's research committee and active brokering with external partners mediated by the Sheffield Healthcare Gateway. Recognising that well-trained and motivated graduate students contribute to our research output and represent the future of scientific research and development, we aim to further increase PGR student recruitment by complementary strategies: encouraging interdisciplinary research that is likely to attract funding; supporting a vacation scholarship scheme that attracts high ranking undergraduate students into research (SURE – which also allows ECRs to experience research supervision); introducing add-ons to the DDP that attract students interested in translational research (e.g. clinical experience for non-clinical candidates); strategic use of fee waivers to attract high-ranking overseas students from PGT into PGR programmes; improving the student experience through high quality supervision and response to feedback.

Our improving performance in PGR recruitment can be ascribed to increased involvement of our RCs e.g. the FIHPI 6 and SCRC 7 new studentships in 2013.

d. Income, infrastructure and facilities

Since 01/01/2008 the value of new awards to the School's UoA1 staff has exhibited:

- Growth in annual funding from £11M in 2008/9 to £15.6 M in 2012/13: Total £89M.
- Sustained increase in grant income from CRUK and Yorkshire Cancer Research (25% increase FY 2008/09 - FY 2012/13, £12.1M in total).
- Sustained increase in BHF funding from £156k in 2008/9 to £1.48M in 2012/3: Total £2.8M.
- Doubling of RCUK grant values in 2012/13 compared with 2008/9: Total £14.8M.
- Other funding highlights include: £7.1 million from NIHR; £6.5M from Department of Health; EU Framework funding totalling £7.4M; Philanthropic donation of £1.9 M to SITraN.
- Recent individual grants of note: ERC £2M, LLR £1.14M, BHF £800k, EPSRC £900k.
- Industry funded awards amounted to over £8.7 million to UoA1 staff.

INFRASTRUCTURE & FACILITIES WITHIN THE SCHOOL: All our laboratories are designed to Containment Level 2 specifications. We also have a Containment Level 3 suite for e.g. HIV and TB work. Our **Core Facilities** offer pay-for-service (sustainable business models implemented) and/or training and access for individual researchers as appropriate for technologies including: **Core Genetics** (DNA sequencing & genotyping); **FACS** (incl. service-run FACSAria, FACsCalibur, FACArray and LSRII machines); full **Histology services**; Microarray suite offering Agilent 2100 Bioanalyser and Affymetrix Gene Chip systems plus associated scanners; **Microscopy**; 2 multiphoton/confocal microscopes, 4 widefield microscopes, 2 configured for live cell/time-lapse fluorescence and the others for fluorescence and colour imaging of fixed specimens; **Bone Analysis Lab**. comprised of ex vivo microCT machines, new in vivo microCT scanner, full hard tissue histology suite; SITraN has invested in drug screening facilities including: Seahorse XF24 bioanalyser; Automated liquid handling facilities include an Echo 550 tipless liquid dispenser; and the Incell2000 high content screening platform; and HiScanSQ next generation sequencing and array facilities with whole-genome and SNP discovery capabilities.

INFRASTRUCTURE WITHIN TUOS: We benefit from other TUoS infrastructure including: a high speed switched network (speeds of up to 1Gbps) and access to the Polaris High Performance Computing cluster (as a member of N8); The Chemical Engineering at the Life Science Interface institute (Biol. &Chem. Eng £4.3M) provides mass spec. and proteomics capabilities; **Magnetic Resonance Imaging**, including a new £1.5M state of the art pre-clinical 7 Tesla facility for functional MRI, cardiac MRI and pre-clinical spectroscopy; **Sheffield RNAi Screening Facility (SRSF,** housed within BMS, £1M The Wellcome Trust 2010), provides a national service for genome-wide RNAi screening experiments; The **Light Microscopy Facility & Electron Microscopy** facilities (BMS) include deconvolution and laser-scanning confocal microscopes, wide-field system for FRAP and FRET, Optigrid system for optical sectioning, Nikon A2

TIRF/confocal microscope and two super-resolution microscopes (MRC/BBSRC/EPSRC Next Generation Optical Microscopy Initiative); **Mass Spectrometry Facility** (established 2012) including Thermo Orbitrap Elite Mass Spectrometer with state of the art post-translational modification analyses (funding from Yorkshire Cancer Research); **Zebrafish Facilities** supported by a staff of 9 fish-welfare technicians for drug discovery as well as mechanistic studies; **Fly Facilities** comparable to the best in the world and also supported by full time technical staff; **Biological Services Unit** laboratories with ample facilities for small animal research.

Major External Shared Facilities

- The Universities of Liverpool, Manchester, Sheffield and Lancaster consortium awarded £1.8M (MRC) for advanced DNA sequencing, housed in Liverpool's Advanced Genome Centre in 2009.
- Next Generation Sequencing Facility in **Sheffield Children's NHS Trust opened in 2013** provides facilities to deliver diagnostic standard data for NHS and School researchers. The facility consists of an automated pipeline for sample preparation with Illumina MiSeq and Life Technologies PGM sequencing machines. Initial funding from The Children's Hospital Charity.
- Access to structural biology facilities at Diamond Synchrotron *via* collaborations with MB&B (TUOS), as well as external collaborators e.g. Sanders (SCRC) with Antson (York).

Policy and practice in relation to research governance: The University of Sheffield Good Research Practice Standards; Department of Health Research Governance Framework for Health and Social Care Research; The Data Protection Act; The European Commission Clinical Trials Directive; Professional guidelines and any funding-body specific guideline. The DoH requirements for the management of research appears in their Research Governance Framework and the University applies this through its own 'Good Research Practice Standards', which apply to all staff and students undertaking 'healthcare research'. Consideration of ethics issues is integrated from the point of project conception through to implementation e.g. our online University Research Management software requires details of ethical requirements from the point of project proposal. All researchers comply with relevant legislation governing the use of genetically modified organisms and with TUoS's Ethical Policy on the Use of Animals.

Plans for enhancing our infrastructure: We have a ring-fenced budget of £500k to support developing cancer genetics projects through the Sheffield Children's Hospital Next Generation Sequencing Facility. *siRNA Tecnologies:* Endowment support for this facility and use of the human library (£250k) to facilitate drug screens/target validation. *Biobanking:* SCRC will invest £850k towards infrastructure/staffing of a new collaboration with Sheffield Teaching Hospitals (£250k), CRUK (£360k) and TUoS (£210k) – the Sheffield Cancer Biobank (2014-2017). We have allocated £550k (2014-2018) to enhance our *Core pre-clinical imaging facility* by acquiring Cell-IQ continuous live cell imaging system and ancillaries to complement existing MRI, Multi-photon and Micro-CT systems (in the Mellanby Centre).

Financial Support Available: The School has access to approximately £2.5M of Faculty Strategic Reserves for strategic investment. With the University's Strategic Development Fund, the Faculty also has access to another £5.4M for strategic investment as matched funding from TUoS.

e. Collaboration and contribution to the discipline

Examples of our numerous collaborations and contributions to the discipline include:

With the NHS - Productive collaborations between STH NHS Trust and the School are exemplified by: the establishment of Joint Research Office and CRF; Sheffield MND Care & Research Centre (lead Shaw); EULAR Centre of Excellence (Wilson) and new initiatives such as INSIGNEO.

Wider UK - Examples of effective collaboration include our: MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing (TUoS, Liverpool and Newcastle); The MRC COPD MAP Consortium (Whyte/Dockrell, with Imperial, Manchester, Leicester, AZ, Pfizer, GSK and others); Experimental Cancer Medicine Centre Network (Lead Woll); MRC Cognitive Function and Ageing Studies Brain Bank consortium (Sheffield PI Ince) and; MRC-CIMA Centre.

Industry - Our researchers have acted as scientific advisors/consultants to companies such as Sanofi Aventis, Oxford Biomedica, Onon Pharmaceuticals, UCB, Vertex Pharma and GSK. Six of our staff were directors of limited companies in the science and technology industry. SITraN has 1

of 15 MRC-AstraZeneca Compound Collaborative Grants (2013). 27 UK companies funded collaborative projects worth £3.8M to UoA1 staff and 28 overseas companies funded £4.9M of research projects. The award of the first MRC-Industry fellowship (Renshaw) and that Johnson holds a joint appointment with UCB Pharmaceuticals also demonstrate active collaboration.

International - 20 Cat A staff were supported by 28 EU funded projects valued at £9.5M to this UoA including: Co-ordination of EU FP7 programme EUHANET (Makris, £470k); 2 EU FP7 Marie-Curie Training Networks, TranCYST and FishforPharma. 2 NIH (USA) project grants (Goodeve and Cox); MRC-China Initiative project with Tongi University (Shaw).

Notable External Committee Posts in the UK Fulfilled by our staff: Chair of MHRA's Commission of Human Medicines, of the Department of Health's Scientific Pandemic Influenza Committee and of the National Biological Standards Board (Sir Gordon Duff); Expert Advisory Group members (Dockrell and Wales); Chair, Expert Advisory Group for Gastroenterology, Rheumatology, Immunology and Dermatology (Wilson). Chairman, NICE Guideline Development Group, Diabetes in Children (Wales); Member, NICE Standing Committee for Guideline Updates (Offiah); Member, HTA Clinical Evaluation and Trials Board (Heller). Reed is on UK Government Advisory Committee Breast Cancer Screening.

Membership of Overseas Funding Committees: Scientific Advisors to the Research Council of Norway (Azzouz, Lewis); Health Research Board Ireland (Azzouz, Dockrell); German Ministry of Education and Research (Bandmann); Cyprus Research Promotion Foundation (Evans); Academy of Science Finland grant board (Shaw); Advisor, European Medicines Agency (Bishop).

Senior Learned Society and Charity Roles: Chair of Medical Schools Council (Weetman); Registrar of Academy of Medical Sciences (Whyte); President, European Society of Pathology and Vice-President, Royal College of Pathologists (Wells); Council Member, Society for Leukocyte Biology FASEB (Whyte); Secretary General of the European Confederation of Neuropathological Societies (Ince); President, Cancer and Bone Society (Washington DC) (Coleman); Breast Cancer Campaign trustee (Coleman); Board of International Osteoporosis Foundation (McCloskey); Vice-President, Royal College of Pathologists, and President, European Society of Pathology (Wells).

Awards: NIHR chair (2013, Wild); Royal College of Radiology Roentgen Professor (2013, Offiah); British Cardiovascular Society Michael Davies Award (2011, Evans); OBE for services to medicine (2009) and British Oncological Association Lifetime Achievement Award (2008, Hancock - retired 2010); European League Against Rheumatism (EULAR) Centre of Excellence Award (2011-2016); European Calcified Tissue Society's Philippe Bordier Clinical Award (2012, Eastell); Royal College of Pathologists Research Medal Award for Haematology (2010, Chantry); The European Association of Urology's Crystal Matula award (2010, Catto); Medical Futures Innovation Award (2011, Wild). MCBR ranked 1st in the UK and was placed in the top six academic centres worldwide for osteoporosis research (Sciencewatch, ISI Thomson) and named a 'Centre of Excellence' by Leukaemia & Lymphoma Research.

Other contributions:

- Examples of our PPI involvement: HIV Lay Expert Advisory Panel (LEAP) is involved in steering research to improve the health and wellbeing of people living with HIV. The Sheffield pulmonary vascular disease unit is closely linked with the Pulmonary Hypertension Association, the only UK charity especially for people with pulmonary hypertension. The Sheffield Motor Neurone Disorders Research Advisory Group (SMND RAG) brings together those affected by MND to inform research.
- The School's M.Sc. programmes include extended original research projects and generate a stream of well-trained candidates for Ph.D. scholarships. Since 2008 over 300 students have graduated with an M.Sc. Over 50 have progressed to doctoral studies.
- Twenty two people have been members of journal editorial boards (for over 50 journals) including four Editors in Chief/Chairman and one founding editor.
- Review of the Organ Donor Register (Sir Gordon Duff, Report to Secretary of State, DoH, 2010)
- Our researchers have authored: 42 clinical/diagnostic guidance articles, averaging 46 citations (total 1945); over 1200 research articles (27603 citations); and 216 reviews (cited over 5144 times) in the REF period as well as over 700 meeting abstracts, 160 letters and editorial pieces.