Institution: University of Manchester
Unit of Assessment: Biological Sciences (UoA5)
1. Unit context and structure, research and impact strategy

1.1 Overview

The strategic research aims of this Unit of Assessment at the University of Manchester (UoM) are:

> *To conduct the highest quality basic research that advances understanding of biological organisms, tissues and systems, via their molecular and cellular mechanisms, using interdisciplinary approaches to facilitate translation to allied areas.*

Our research structures reflect our REF2014 forward strategy, building on two major research challenges ***'Understanding Life'*** and ***'Disease Biology'***, with 148 staff (143.05 FTE) working under five thematic areas of *Research Strength* (Molecular and Cellular Function; Cell Matrix Biology; Infection, Immunology & Inflammation; Biological Timing; Evolution, Genomics & Development).

To drive the effectiveness of our research in the current REF cycle we have:

- Enhanced the interdisciplinary interface between fundamental and translational science, creating a new single Faculty of Biology, Medicine and Health (FBMH) in 2016.
- Strategically developed our interdisciplinary research portfolio using internal funding and cross-cutting structures (4.1), to expand existing Centres (e.g. Wellcome Centre for Cell-Matrix Research, WCCMR, 1.3.2) and develop new ones (Lydia Becker Institute for Immunology and Inflammation, 1.3.3).
- Exploited our outstanding research infrastructure to enable cutting-edge science, with capabilities boosted by £28m in external funding involving UoA5 researchers, leading to >1,000 research outputs acknowledging our core facilities (3.5).
- Ensured our staff and students are supported and valued (2.1), with enhanced Equality Diversity and Inclusion (EDI) activities, fair promotions and recruitment, attracting 22 externally-funded independent fellows and Early Career Researchers (ECRs) to Manchester (4.3.2), with a supported track onto tenured positions (2.3).
- Produced a robust base for generating impactful research and encouraging innovation, leading to significant healthcare, policy, economic and public engagement outcomes (1.6).

As measures of their success, we highlight:

- Successful renewal of the WCCMR in 2016 for £4.9m, complemented by a £4.6m BBSRC sLoLa award, and externally funded cryo-EM and mass spectrometry infrastructure (£1.1m).
- External support from industrial partners (£2.4m since 2016 from GSK) to the Manchester Collaborative Centre for Inflammation Research, which has catalysed the formation of the Lydia Becker Institute of Immunology and Inflammation with internal funding (4.1).
- Over £41m in funding to support Doctoral Training in biological and biomedical science from UKRI and Wellcome, including a £5.4m interdisciplinary Wellcome award: ImmunoMatrix in Complex Disease (2.5).
- Highly cited outputs: 338 original articles published in the census period in top 5% (Web of Science), 64 with >100 citations.
- Recruitment and support for 36 new fellows/personal awards in this cycle, creating a dynamic base in areas of strategic importance (2.2 and 4.3.2).

1.2 RESEARCH STRATEGY

Our UoA5 research strategy is to undertake discovery science, and develop effective translation, which benefits all society. This builds on the University Strategy (REF5a) which embraces interdisciplinarity as a key driver to address significant research challenges. We have developed two of our REF2014 strategic themes of ***'Understanding Life'*** and ***'Disease Biology'***; researchers at the interface drive these forwards in five major *Research Strengths* in key areas of biology (**Figure 1**). These ambitions necessitate a multi-disciplinary and integrative approach to tackle major cross-cutting themes and we have developed operational strategies to further develop our interdisciplinary science (4.1). Specifically, these ambitions are facilitated by strategic *Research Domains*, which promote cross-cutting research themes that span UoAs and Faculties, and *University of Manchester Research Institute (UMRI)* and Wellcome Institutional Strategic Support Fund (ISSF) internal awards (4.1) to pump-prime and boost targeted areas and promote cross-Faculty interdisciplinary activity.

1.3 RESEARCH STRENGTHS

Spanning our two umbrella areas of ***'Understanding Life'*** and ***'Disease Biology'***, all five *Strengths* encompass fundamental studies of biological processes that inform mechanistic understanding of health and disease that govern the functioning of living organisms.

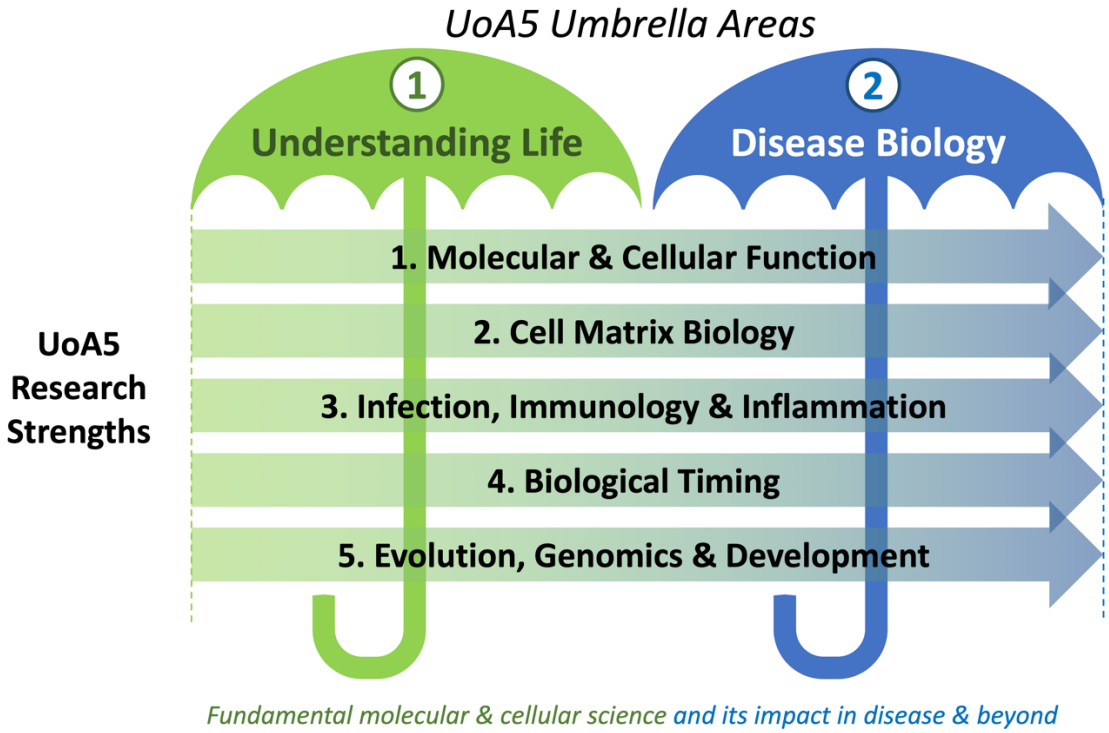

Figure 1. *UoA5 Research Strengths span research challenges developed in REF2014.*

Like the University strategy, we seek to combine foundational and applied science to drive outputs and impact (1.4). Notable research highlights are discussed in the next sections, including those involving other UoAs, such as UoA1 (Clinical Medicine), where joint research has made significant advances. Indeed, 30% of our returned outputs in UoA5 are co-authored with colleagues from the other four Panel A UoAs. We also highlight exemplar studies that address fundamental bioscience (***'Understanding Life'*** ①), or research mechanisms and processes in health and disease (***'Disease Biology'*** ②) *via* numbered hyperlinks, as well as those that do both (① + ②).

1.3.1 Research Strength 1: Molecular & Cellular Function

Staff use a wide range of eukaryotic model systems and state-of-the-art technologies to investigate fundamental aspects of cell behaviour, including gene expression, molecular signalling pathways, RNA and protein fate, and cellular dynamics. Collaborations with other groups frequently consider how these processes impact on disease, linking research to that in UoA1.

Researchers tackle fundamental bioscience topics in cell dynamics, cell matrix biology (linked to the WCCMR; 1.3.2), gene expression, chromatin and signalling, and protein and RNA fate. The grouping includes four Wellcome Trust Investigators (**Ashe H, High, Sharrocks, Woodman**) and has obtained significant RCUK funding (e.g. >£14m of BBSRC funding). Single cell biology is jointly led by **Sharrocks** and Hanley (UoA1), demonstrating reach across fundamental and clinical science. This has been recognised as a fast-moving area of interdisciplinary bioscience where the University has growing strengths; kick-started by an MRC Clinical Research Infrastructure award in 2015 (£4.9m, including **Rattray, White** from UoA5), a further £27.7m in awards has been leveraged using this technology. A key highlight is two successful projects contributing towards the International Human Cell Atlas (HCA) initiative (£0.9m total). Additional UMRI and Wellcome ISSF internal funding is driving collaborative research programmes and implementing cutting-edge approaches to single cell research, to generate novel techniques and analysis protocols (4.1).

Important insights have been made into fundamental elements of molecular and cellular function (***'Understanding Life'*** ①); these include studies of the core principles of signalling, gene regulation and cell dynamics:

- Identifying key transcription factors that control embryonic stem cell gene networks (**Sharrocks**: Cell-Reports-2019①; Cell-Reports-2014①; **Piper-Hanley** Nat-Commun-2020①).
- The effects of cellular stress on modes of mRNA translation, *via* stress granule and P-body formation (**Ashe M, Grant**: Cell-Reports-2014①; Genome-Biology-2017①).
- Definition of the supramolecular organisation of eIF2 translation factors, advancing core understanding of protein synthesis (**Pavitt:** Nat-Commun-2014①).
- The identification of a CLK1 pathway that controls mitochondrial stress (**Whitmarsh:** Nat-Cell-Biol-2015①).
- Definition of a role for 'cytosensor' cellular projections known in attenuating the response to extracellular signalling molecules (**Ashe H**; Dev-Cell-2019①).
- The identification of post-translational modifications of cellulose synthase that regulate its membrane localisation and activity, ultimately contributing to biomass formation (**Turner**: Science-2016①).
- Uncovering the function of Dynein light chains in the formation of bipolar spindle complexes, necessary for cell division (**Allan, Woodman, Woolner**, J-Cell-Biol-2014①).

Our fundamental molecular and cellular science impacts on the understanding of disease (***'Disease Biology'*** ②). This has helped elucidate pathways in genetic disease, for example in developmental disorders:

- Defects in small nuclear RNAs involved in ribosome biogenesis have been shown to lead to leukoencephalopathy (**Pavitt**: Nat-Genet-2016①② see also 1.3.5) whilst disrupting protein trafficking leads to Lowe syndrome and gerodermia osteodysplastica (**Lowe**: Nat-Commun-2019①②).

Similarly, molecular and cellular science in this grouping has impacted on the understanding of cancer**.** This has revealed:

- How oncogenic transcription factors influence cell fate commitment during mitosis (**Taylor**: Cancer-Cell-2015②) and the development of oesophageal adenocarcinoma (**Sharrocks**: Genome-Res-2019②).

- How chromatin remodelling proteins contribute to breast cancer (**Nagarajan:** Nat-Genet-2020②).
- The intricacies of receptor tyrosine kinase (RTK) signalling and the differential response to different ligands (**Francavilla**: Nat-Struct-Mol-Biol-2016①), as well as how oncogenic RTK-driven signalling pathways are rewired in cancer cells (**Francavilla:** Cell-Reports-2017②), and in pancreatic cancer, how these pathways operate during communication with the cancer stromal cell population (**Jorgensen**: Cell-2016②)**.**

This latter research links the molecular cancer work to the Cell-Matrix area (1.3.2) by showing how key intracellular signalling molecules, integrins, are involved in cellular cross-talk.

Research in *Research Strength 1* drives impact, exemplified by three of our returned impact cases. For example, work on protease inhibitors against HIV has revealed a useful off-target action, and basic work on protein engineering led to the development and clinical use of Adoptive Cell Therapy, whilst fundamental developmental neuroscience has primed public engagement cases.

Linked impact cases **Figure 3**: Hampson #5; Thistlethwaite-Hawkins #6; **Prokop #2**

Future research directions: Quantitative single cell technologies will become increasingly influential in our research, enhancing our understanding of cellular heterogeneity and bringing fundamental understanding of the regulation of gene expression into application areas; this will build on our £4.9m MRC infrastructure award plus institutional UMRI backing (3.1 & 4.1), to map processes underpinning genetic disease and cell function. Notable areas of future focus include: chromatin biology (new recruit **Nagaragan**); molecular quantitation (**Francavilla, Jorgensen**); and RNA biology (**Pavitt, Ashe**). We will strengthen links with computational and physical scientists to bolster interdisciplinary work and enhance our ability to handle 'big data' and implement robust quantitative approaches (e.g. *via* **Rattray, Papalopulu,** and new Turing Artificial Intelligence Fellow, **Yao**). This will benefit from links to the Pankhurst Institute and our Digital Futures initiative (4.1.1).

1.3.2 Research Strength 2: Cell-Matrix Biology

Staff address fundamental questions on the role of extracellular matrix and its receptors in the construction, function, and repair of tissues. This includes molecular and cellular studies to uncover mechanisms underpinning interactions with matrix that govern cell cycle progression, motility and tissue development, through to clinical applications in inflammation and cancer. The integration of basic scientists with clinical and translational colleagues engenders a multi- and interdisciplinary environment encouraging advances across UoA boundaries.

This area is underpinned by the **Wellcome Centre for Cell-Matrix Research (WCCMR),** an externally funded centre of excellence which examines the cross-talk between cells and matrix to provide insights into the mechanisms that underpin tissue assembly and function (***'Understanding Life'*** ①) and identify why matrix dysregulation is a major factor in most chronic diseases (***'Disease Biology'*** ②). Led by **Kadler**, our Centre has received continuous Wellcome funding since 1995, and has been renewed in the REF period (£4.9m in 2016), with a recent £1.7m short-term extension in 2020. The most recent award (to the end of 2023) continues support for nine Centre-based research staff who are also allied to Faculty core facilities, plus maintenance and service contracts for major capital equipment. The Centre Group Leaders collectively hold £37m of funding from Wellcome, other charities, MRC, and BBSRC. Research focusses on three key themes: circadian rhythms (chrono-matrix); the immune system (immuno-matrix); and mechanical stresses (mechano-matrix). The WCCMR is a productive, interdisciplinary research centre, hosting 23 research groups and 145 staff and postgraduate students, with world-leading experts including **Allen** (Wellcome Investigator), **Humphries** (CRUK programme grant), **Kadler** (Wellcome Investigator and BBSRC sLoLa lead), Lennon from UoA1 (Wellcome Clinical Senior Fellow), **Meng** (Versus Arthritis Senior Fellow), and **Grencis** (Wellcome Investigator). The Centre is also home to many excellent early career researchers: **Swift** (BBSRC Sir David Philips), **Dyer** (Wellcome Henry Dale), **Zacharchenco** (UoM Presidential Fellow) and **Woolner** (Wellcome Henry Dale).

Allied strategic Research Domains (4.1) and University structures have helped leverage capital infrastructure for molecular and cell-matrix science challenges. For biomolecular analysis and

structural biology, WCCMR staff have contributed to successful bids for cryo-EM (BBSRC £750k), and mass spectrometry (Wellcome £390k), and linked with the Lydia Becker Institute of Immunology and Inflammation to secure a new £5.4m Wellcome-funded PhD programme in ImmunoMatrix in Complex Disease (1.3.3 & 2.5), as part of a joint ImmunoMatrix Theme.

This grouping has made important advances in the ***'Understanding Life'*** area on how cells communicate with, and respond to, the extracellular matrix (ECM). For example:

- Proteomic studies have demonstrated the complexity and function of integrin-mediated signalling complexes (**Humphries:** Nat-Cell-Biol-2015①),
- Links identified between integrin-mediated complexes and the intracellular cytoskeleton (**Ballestrem:** Nat-Commun-2015①).

These basic discoveries have led to applied findings in the ***'Disease Biology'*** context:

- Demonstrating the importance of the ECM in kidney and liver disease (**Piper-Hanley:** Nat-Commun-2016②) linking our research to that in UoA1.
- Characterising the critical role that integrin signalling plays in T-cell-mediated inflammation (**Travis:** Immunity-2015②).
- Showing how interactions between the ECM in the lung and alveolar macrophages are critical to macrophage metabolism during inflammation (**MacDonald:** Nat-Commun-2014②).
- Similarly, ECM interactions are important in regulating cytokine availability for combatting whipworm infections (**Grencis:** Nat-Commun-2019②).

Future Research Directions

The recent WCCMR renewal focussed on three ongoing interdisciplinary themes, linking the cell-matrix with:

- Circadian biology (1.3.4),
- Mechano-matrix (e.g. **Kadler** BBSRC sLola),
- Immuno-matrix (*via* the Wellcome PhD award, 1.3.3).

We will develop a new theme, Disease Matrix, focused on cancer and fibrosis. Wellcome ISSF support (£285k to **Gilmore**, 4.1) has enabled collaboration with the Manchester Cancer Research Centre, and a subsequent £3.4m award to become part of the **CRUK International Alliance for Early Cancer Detection (ACED**). **Piper-Hanley** will lead on expanding basic scientific studies in matrix biology towards understanding the pathophysiology underpinning fibrotic diseases. We aim to understand how matrix tension drives the profibrotic phenotype of myofibroblasts, and will apply proteomic methodologies developed with our core facilities to determine the pathological "signature" of fibrosis. These studies will target biomarker discovery and digital health (*via* new appointments in artificial intelligence (AI), including **Yau** in UoA5). This links the fundamental science to the new £25m Christabel Pankhurst Institute for Health Technology Research and Innovation (4.1.1), assisted by £2.4m from InnovateUK and £2.1m leveraged from Roche Diagnostics and GE Healthcare.

1.3.3 Research Strength 3: Infection, Immunology & Inflammation

Staff study how immunity and inflammation are regulated across the life course in health and disease. The biology of infection is studied, including microorganisms (virus, bacteria, fungi, parasites) at the molecular and cellular level, through to their behaviour in communities (e.g. the microbiome) and interactions with the infected host, both in health and disease. In both cases, research crosses UoA activities and outputs highlight interdisciplinarity.

This area is underpinned by two Centres/institutes, the **Manchester Collaborative Centre for Inflammation Research (MCCIR)** and the recently established **Lydia Becker Institute of Immunology and Inflammation (LBI)**, both led by Hussell (UoA1). Originally founded in 2012, the MCCIR is a multi-disciplinary research centre that performs exploratory research, in collaboration with industry, investigating the molecular basis of immune health and its dysregulation in

inflammation. Established with initial investment from the University, GlaxoSmithKline and AstraZeneca, MCCIR has grown since the last REF period, with major ongoing funding from GSK (£2.4m since December 2016). The MCCIR sits within the **LBI,** established *via* an UMRI award in 2018 (4.1), and tackles wider immune complexity in major themes. Many are led by UoA5 staff: **Grainger:** barrier immunology, **Davis:** cellular immunology, **Travis:** immune tolerance, **Grencis:** pathogens, parasites and commensals, and **Allen:** immuno-matrix. The LBI embraces cutting-edge technology, such as super-resolution microscopy and deep phenotyping of single cells (4.1, Single Cell UMRI award), uniting 176 PIs and research fellows from across the whole university. LBI themes bridge to other UoAs: cancer immunology (linking with Manchester Cancer Research Centre and CRUK-MI), immuno-informatics (links to UoA10 (Mathematical Sciences)) and neuro-immunology (UoA4 (Psychology, Psychiatry and Neuroscience)). The 30 UoA5 PIs in this *Strength* have secured £31m of external funding in the current REF cycle.

The MCCIR and LBI have made key advances in our ***'Understanding Life'*** umbrella area in molecular immunology, including:

- Discoveries of novel mechanisms underlying macrophage activation in tissue repair, demonstrating that tissue-specific signals are essential for type 2 immune responses (**Allen & Sutherland**: Science-2017①) and uncovering the molecular basis of gut macrophage replenishment (**Allen, Konkel, Grainger:** J-Exp-Med-2018①).
- A new epigenetic mechanism established between the chromatin binding protein Mbd2 and T cell responses, (**MacDonald, Allen, Sutherland, Cook, Grainger:** Nat-Immunol-2019①), identifying Mbd2 as a target for therapeutic manipulation of allergic inflammation and anti-helminth host defence.
- Mapping the molecular details underlying cytokine signalling and how tissue architecture helps constrain TNF-α levels, thereby maintaining a localised inflammatory response (**Paszek, White:** Sci-Signal-2018①).

Often with industrial partners, fundamental studies also describe how cells and systems respond to infection and inflammation, impacting on ***'Disease Biology'***:

- In collaboration with Celgene, **Davis** (Blood-2015①②) helped establish how immunomodulatory drugs augment the activity of natural killer (NK) cells**,** and in collaboration with GSK, discovered how NK cells detach from target cells, which is now being exploited by Fate Therapeutics in a new cell therapy for acute myeloid leukaemia (called FT516) (**Davis**: J-Cell-Biol-2018①②).
- Also with GSK, discovered novel immune system functionality in clearing extracellular molecules from intercellular contacts (**Davis**: Nat-Commun-2014②). This has consequences for drug clearance, leading to further mechanistic investigations for drug design. Davis has joined GSK's Immunology Network to advance this and other issues.
- How chemokine binding proteins inhibit immune cell migration and thence inflammation, suggesting novel therapeutic strategies based on the key binding protein TSG-6 (**Day**, **Milner:** *J-Biol-Chem-2016*①②), which have leveraged knowledge exchange (MRC, £200k) and other external funding (1.6.1).

In the LBI's immune tolerance sub-theme, the use of antibiotics has been shown to perturb mucosal macrophages, leading to long-term immuno-defects (**Mann, Travis, Grencis**: Sci-Trans-Med-2018②).

Many studies integrate expertise from other *Strengths*, such as Cell-Matrix Biology (1.3.2) including:

- Studies showing how the extracellular matrix influences immune responses during lung infection, where the environment controls macrophage metabolism (**Thornton, Grencis, Sutherland, Allen:** Nat-Immunol-2019①②).
- Parasitic infection has been linked with the gut microbiota, characterising the novel interplay between a whipworm parasite and its host, showing how the parasite exploits the host's microbiota, both to achieve infection and promote its long-term survival (**Roberts, Grencis:** Sci-Adv-2018①②).

Infection biology also links with UoA1, notably in the area of mycobiology. Fundamental aspects of genome biology relate to Aspergillus colonization, where a genetic variation in a key transcription factor ZNF77 has been identified as a risk-marker for stratification (**Bowyer**, Denning (UoA1): Nat-Commun-2018②), underpinning ImpactCase#4.

Linked Impact Cases **Figure 3***:* **Cruickshank** #1; Denning, **Bowyer** #4; McBain #6

Future Research Directions: The LBI has recently focused on the COVID-19 pandemic, forming a cross-disciplinary consortium and new objectives allied to respiratory medicine (UoA1). The team, involving immunologists, bioinformaticians and clinicians from four local hospitals, followed patients longitudinally from admission, through to outcome and 12-week follow-up. This revealed critical components of disease pathogenesis that will influence therapy in subsequent infection waves. Led by Hussell, with UoA5 collaborators (**Mann, Menon, Konkel, Rattray, Grainger**: Sci-Immunol-2020①②), the study characterises a biomarker profile that can identify admitted patients at risk of severe disease trajectory. As a reflection of external esteem, the Institute was selected to lead the largest theme in the UKRI-funded Coronavirus Immunology Consortium (UK-CIC) which unites 17 immunology research centres across the UK (£6.4m). Future plans will link COVID-19 research to primary care records to understand the impact of medication, lifestyle and multimorbidity on disease severity.

We will expand the immunology-cell matrix interface, building on the recently awarded Wellcome PhD Programme in Immuno-matrix in complex disease (£5.4m), a joint venture with the WCCMR and the Manchester Cancer Research Centre (1.3.2).

We will build a cross-UoA network of infection biologists using UMRI funding (4.1), to refresh the pipeline for antimicrobials and develop new non-drug-based treatments, as part of a wider University-driven strategy in antimicrobial resistance (AMR). Leadership of the network has been boosted by recruitment of a specialist in the evolutionary microbiology of AMR (**Brockhurst**) alongside existing staff in UoA1 (Bromley, Fenton), as well as synergy with staff in Research Strength 5 (1.3.5).

1.3.4 Research Strength 4: Biological Timing.

Using model organisms, in vitro and computational approaches, staff are uncovering mechanistic links between the circadian clock and animal/human physiology to reveal new, exciting approaches for drug development and therapy. Specific research strengths include inflammation, metabolic and cardiovascular disease, diabetes, and tissue fibrosis, seeking to rapidly progress basic research breakthroughs into a clinical setting.

FBMH has the largest community of circadian researchers in Europe, in the **Centre for Biological Timing (CfBT)**, featuring 27 principal investigators, unified in their goal "to determine, understand and exploit timing as a new dimension in biology and medicine for enhancing human and animal health and wellbeing." CfBT PIs have secured £52m of external funding in the current cycle, as measured by internal UoA5 credit share. Led by Director Lucas (UoA4), their research spans basic biology, neuroscience, many clinical disciplines, mathematics, and engineering. Research is organised across three complementary areas, two led from UoA5: i) Brain, behaviour and environmental response (**Brown**), ii) Internal homeostasis and clock mechanisms (**Bechtold**), iii) Clinical translation and multi-morbidity (Rutter, UoA1).

A core component of research focuses on the entrainment of circadian rhythms by external cues:

- A pioneering discovery is that the mammalian circadian system responds to the blue-yellow colour axis that changes at twilight and provides a more reliable control to the system than light intensity alone (**Brown**: PLoS-Biol-2015①;Curr-Biol-2019①). This has revolutionised appreciation of the effects of artificial lighting on circadian health and led to the production of new international lighting guidelines (**Figure 3**, *ImpactCase#8*).
- New mechanistic insights into how feeding entrains the circadian clock, demonstrating that insulin and IGF-1 signalling rapidly upregulate translation of clock proteins, and that mistimed insulin release creates circadian disruption (**Bechtold**: Cell-2019①②), leading to metabolic and cardiac dysfunction (**Bechtold**: Nat-Commun-2017②).

- New understanding of the molecular mechanisms of casein kinase (CK1ε) as a potential target for alleviating the detrimental effects of chronic shift work and jet lag (**Bechtold**: Curr-Biol-2014①).

Related work with UK Biobank data has identified genetic loci that influence our chronotype and sleep disturbance, sharing pathways with neuropsychiatric and metabolic diseases (**Loudon**: Nat-Commun-2016①; Nat Genet-2016②).

Our international reputation helped attract **Fustin** from Kyoto University on a UKRI Future Leaders Fellowship, whose ground-breaking work has demonstrated the importance of mRNA methylation on molecular timekeeping (**Fustin**: PNAS-2018①). Understanding this evolutionarily conserved mechanism could offer new therapeutic approaches for treating methylation deficiencies (**Fustin**: Commun-Biol-2020①).

Underpinned by an MRC Programme Grant and a Wellcome Investigator Award totalling £2.7m, and in collaboration with colleagues from the **LBI**, CfBT researchers have deciphered pathways mediating clock regulation of the immune system. They have shown that:

- Responses to bacterial lung infections, and the therapeutic effects of the glucocorticoid dexamethasone, depend on an epithelial cell clock (**Loudon**: Nature-Med-2014②).
- In the liver, the clock protein REVERBa exerts time of day-specific control of the spectrum of target genes engaged by glucocorticoid receptor, and that timed administration of glucocorticoids can alleviate their serious metabolic side-effects (e.g. hepatic steatosis) (**Hunter, Iqbal, Rattray, Loudon**: J-Clin-Invest-2018②).

Collaborative studies with researchers in the WCCMR have shown the highly circadian nature of matrix regulation, including:

- The fibrotic response to oxidative damage in the lung (**Meng**: Genes-Dev-2014②) with the targeting of REVERBa possibly presenting a new strategy to reduce collagen deposition by fibroblasts in idiopathic pulmonary fibrosis patients (**Blaikley**: PNAS-2020②).
- Identification of key clock gene regulating cartilage homeostasis, identifying a major risk factor for osteoarthritis (**Meng**: J-Clin-Invest-2020②)
- Further corroboration revealing the circadian control of collagen secretion in normal physiology, and day-night segregation of collagen degradation and synthesis (**Kadler**: Nat-Cell-Biol-2020①).

Linked Impact Cases **Figure 3***:* **Brown, Allen, Bechtold,** Lucas (UoA4) #8

Future Research Directions: We will build on our strengths in basic biology and model systems to unravel the constituent molecular pathways underpinning circadian rhythms, engaging across UoAs with mathematicians and engineers to model and rationalise the findings. With researchers from the Henry Royce Institute - advanced materials, UoA12 (Engineering) - and in a joint venture with the Health & Safety Executive, we will generate new wearable devices to measure the effects of our interactions with the modern environment on our biological rhythms and health. This will complement our recent population level genetic studies with UK Biobank, and in combination with advanced computational approaches (**Rattray, Iqbal**) – again bridging to Digital Futures/Pankhurst Institute (4.1.1) - link between circadian disruption and disease susceptibility, moving towards experimental medicine studies.

1.3.5 Research Strength 5: Evolution, Genomics and Development

Researchers address developmental and evolutionary biology problems that are unified by the concept of the genome as a platform from which biological function and dysfunction can be understood. This frequently integrates computational biology, and spans all scales, from molecules (gene expression at the transcriptional or translational level, underpinning cell fate), via cells (how genetic lesions lead to Mendelian disease), via whole organisms (how adaptive processes change phenotypes), through to how populations adapt (e.g. how antimicrobial resistance arises in bacterial populations).

UoA5 researchers in this *Strength* have been awarded £37.1m in the current REF cycle, again based on percentage credit split. Our genomics work unites clinical geneticists in the Manchester Centre for Genomic Medicine with basic scientists using computational and molecular characterisation of genetic lesions, often in model systems, to bring understanding to human genetic disease and pathology. Our restructure, along with internal funding mechanisms (UMRI, ISSF awards totalling ~£300k, led by **Lovell** and Black (UoA1), 4.1) have helped develop a pipeline from fundamental genome variant characterisation back to translational/clinical leads. Manchester hosts one of seven NHS Genomic Laboratory Hubs and involvement with Genomics England's 100,000 Genomes project provides data for analysis. Such integration of clinical data with fundamental biology helps underpin impact (**Figure 3**, *ImpactCase#3*) at the interface of ***'Understanding Life'*** and ***'Disease Biology'***. Example outputs include:

- Research explaining how genetic variants can produce mechanistic defects in the processing of essential ribosomal rRNAs, leading to developmental disorders (**O'Keefe, Pavitt, Griffiths-Jones**: Nat-Genet-2016②) with co-authors in UoA1 (Crow).
- Studies describing how a genetic variant in the transcription factor STAT2 leads to a type I interferonopathy, with supporting computational molecular modelling data (**Lovell**: Sci-Immunol-2019②) with co-authors in UoA1 (Briggs).
- Mechanistic studies describing an *in cis* 5'UTR variant that causes epigenetic silencing of the *BRCA1* gene, which is associated with familial breast and ovarian cancer in independent families (**Smith M**: Am-J-Hum-Genet-2018②) with co-authors in UoA1 (Newman, Evans).

Computational biology often underpins genome science, including in developmental biology. Examples include:

- The international microRNA database, miRbase, led by **Griffith-Jones**, is central to major genome projects (e.g. the house spider BMC-Biol-2017①), and can also be used to demonstrate conserved evolutionary principles, such as how non-coding RNA drives developmental biology gene expression programmes in arthropods (**Ronshaugen, Griffiths-Jones:** Genome-Res-2016①). miRbase also has wider impact, supporting product design for wide use across the biomedical sciences (**Figure 3**, *ImpactCase#9*)
- Underpinning methods development, such as in single cell biology and gene expression (**Rattray:** Nucleic-Acids-Res-2019①). Multi-disciplinary approaches involving advanced statistical modelling of time-series data to explain how a key transcription factor determines cell fate decisions in the developing mammalian spinal cord (**Rattray, Papalopulu**: Nat-Commun-2019①), part of a broader interdisciplinary theme led by **Papalopulu** characterising the importance of oscillatory regulatory networks in controlling cell fate decisions (e.g. EMBO-J-2020①).

Major insights have been made into fundamental principles controlling developmental pathways, including:

- An integrated zebrafish *in vivo* and computational model demonstrated how asymmetric cell division can drive cell migration in angiogenic development – a hitherto unknown role (**Herbert:** Nat-Cell-Biol-2016①).
- A direct link between cell polarity and cell cycle has been shown in neurodevelopmental pathways, stemming from a localised kinase which phosphorylates a cell cycle inhibitor (**Papalopulu:** Dev-Cell-2014①).

- A new mathematical framework to understand how cell shape and mechanical forces influence cell division has been developed by **Woolner:** Cell-Rep-2019①, whilst others have shown how endocytic signalling pathways are robust to temperature fluctuations in Notch pathways (**Baron:** Cell-2014①).

Evolutionary biology has been strengthened, with new leadership in the area of microbiology (**Brockhurst**) supported by outstanding ECRs (**Lagator** Wellcome Henry Dale Fellow; **Krasovec** UKRI Future Leaders Fellow; **Gifford** UKRI Rutherford Fellow; **Coyte** Presidential Fellow). The group has uncovered novel adaptive mechanisms in microbial populations that drive antibiotic resistance, as well as the dynamics of microbiomes, all underpinned with theory and models:

- Whole-genome sequencing has shown how cross-resistance against multiple phages develops in bacteria, with implications for effective phage therapies (**Brockhurst**: PLoS-Biol-2018①②).
- Ecological theory has been applied to rationalise community phenomena observed in the gut microbiome (**Coyte**: Science-2015①; Sci-Transl-Med-2018②), and shown that possession of certain genes permits bacteria to evolve antibiotic resistance at faster rates, whilst blocking this evolutionary pathway by co-administering other drugs can hinder evolution of antibiotic resistance (**Gifford**: Nat-Ecol-Evol-2018①②).

Linked Impact cases **Figure 3***:* **Griffiths-Jones** #9; Black #3

Future Research Directions: We will enhance genomics research links to the NHS *via* the Genomics Laboratory Hub (led by Black, UoA1). Clinicians finding unexplained genetic variants are matched with UoA5 academics, bioinformaticians and core facilities to generate an integrated pipeline. Supported by internal UMRI funding (4.1), we will use stem cells, model systems, and 'omics techniques to explore the consequences of these mutations, linking to FBMH's Stoller Centre for Biomarker Discovery and UK Biobank.

We will develop a new, cross-Faculty approach to address AMR, building on an UMRI-funded network (4.1) of 127 staff led by Bromley (UoA1). The network bridges infection biologists (1.3.3), evolutionary biologists (1.3.5), clinicians (*via* a £4.5m NIHR award to Felton), public health staff (UoA2), and synthetic biologists (UoA8 (Chemistry)) in the Faculty of Science and Engineering. This has also benefitted from the UoM's Wellcome ISSF (4.1) which helped **Krasovec** deliver key papers and bridge to his UKRI Future Leaders Fellowship (PLoS-Biology-2017①).

1.4 UNIVERSITY STRUCTURE AND CONTEXT

98% of staff in our *Research Strengths* (1.3) work in FBMH. First constituted in 2016, FBMH is one of three large, multi-School Faculties that make up the UoM. This restructure followed a review in 2015 that recognised that modern bioscience research is increasingly multi- and/or inter-disciplinary. Accordingly, we merged our previous Faculties of Life Sciences and Medical and Human Sciences to generate a revitalised platform for multi-disciplinary research, bringing strengths in fundamental biosciences closer to the clinical and translational sciences (4.1 and **Figure 2** below).

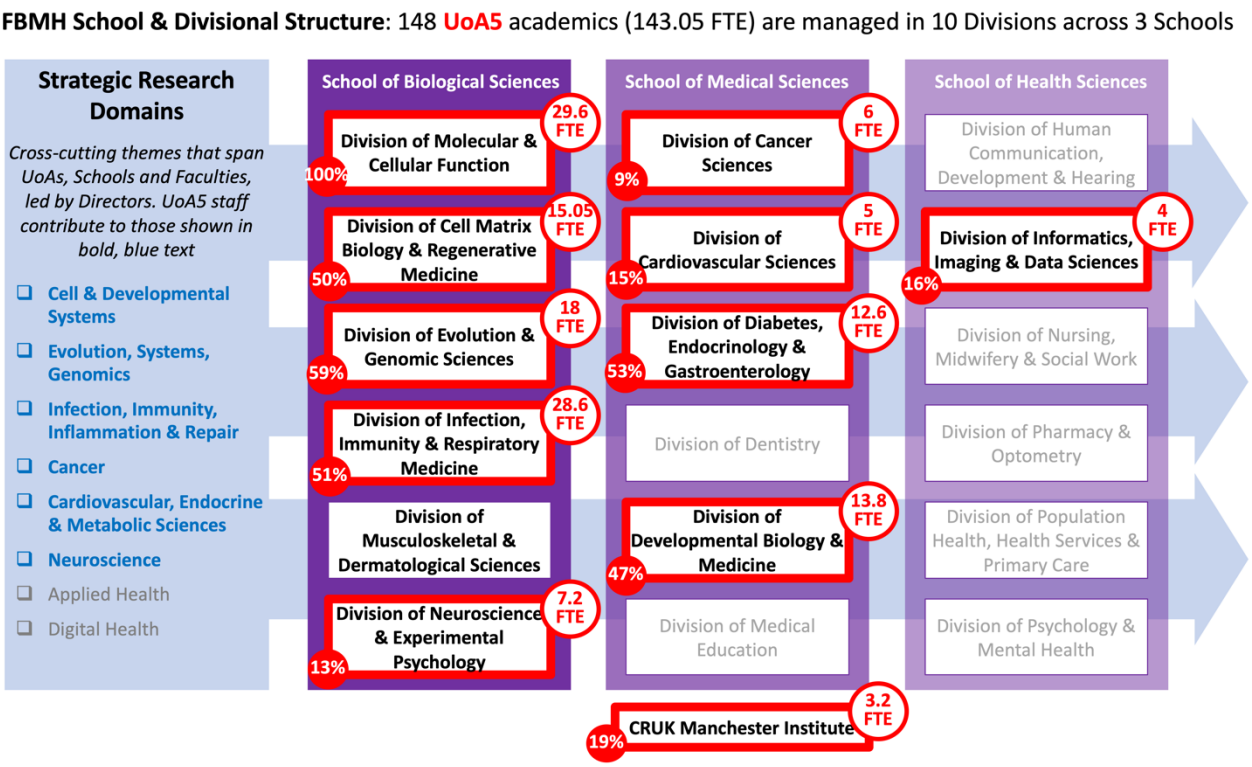

Figure 2. *Faculty and School Structure. Strategic Research Domains (left) are cross-cutting themes to promote and coordinate research activities targeted at major research challenges. For each Division the number of UoA5 staff is shown as FTE (circle, top right), and as % of total FTE in that Division (bottom left).*

FBMH comprises three Schools: Biological Sciences (SBS), Medical Sciences (SMS) and Health Sciences (SHS). Each contains six Divisions (**Figure 2**), the primary operational unit providing direct line management. UoA5's 148 staff (143.05 FTE) are concentrated across SBS and SMS.

Within Divisions, UoA5 staff work in interdisciplinary teams alongside staff from other panel A UoAs. This promotes collaboration between applied and basic scientists. For example, all bar one contain staff from other UoAs, and 30% (106) of our returned outputs are co-authored by academics from at least one other Manchester UoA. Similarly, 31% of awards to UoA5 staff have co-applicants from UoAs 1-4. Several staff from UoA5 work in hospital labs alongside clinical colleagues or are embedded with chemists, physicists, informaticists, computer scientists, mathematicians, and environmental scientists to foster greater interactions, in the Manchester Institute for Biotechnology, which houses our University strengths in industrial biotechnology and synthetic biology. This epitomises our cross-cutting interdisciplinary ethos and our Faculty's future research strategy, which is embodied in three grand challenges:

i. Discovering novel biological, psychological and social mechanisms

ii. Developing new approaches to prevention and early detection of disease

iii. Developing next generation person-centred therapies, interventions and care pathways

We will develop this strategy further in the next REF cycle, where fundamental bioscience discoveries (***'Understanding Life'***) are the foundation of challenge (i), and bridge to applications (***'Disease Biology'***) addressing (ii) and (iii) above. These will link discovery science to University

institutes/Centres with a focus on health technology research and translation (e.g. our Pankhurst Institute and Stoller Centre for Biomarker Discovery, 4.1.1). Specific examples include:

- Further development of infection biology understanding and applications in AMR (1.3.3 & 1.3.5, and 4.1), leading to new treatments and practice
- Growth in exploiting genomics sequence and allied 'omics data for characterising genetic disease (1.3.5), leading to novel diagnostics and treatments
- Influence of circadian biology on disease detection (1.3.4 & 1.3.2), leading to experimental medicine studies

which all impact on challenges (ii) and (iii).

1.5 Research support strategy & infrastructure

A broad range of research support is available for staff, from the library, governance, and pre- and post-award grant support teams. We strongly support the open access (OA) agenda, and our University library aids with deposition of outputs and administers the University block grants from UKRI and Wellcome, augmented by the £300k UoM OA fund. They also ensure Author Accepted Manuscripts are deposited in the University's PURE system. Schools also employ a full-time member of staff who assists staff in dealing with OA matters, ensuring our high OA compliance rate (98%). Manchester has also played an important role in promoting OA compliance in the biomedical sciences from the President (**Rothwell**) down. UoM was a partner on the UKPMC/EuropePMC project with the British Library and the EBI, with **Hubbard** sitting on the project board during the REF period and promoting OA compliance more widely.

The Faculty Research Governance Team supports all researchers undertaking biomedical, clinical and health-related research. All staff undertake mandatory annual research integrity training, and each Division contributes staff to our ethics committee structure. The Faculty team acts on behalf of the University as Research Governance Sponsor, to drive forward the University's Research Integrity agenda (REF5a, section 2v). This includes the University-wide Open Research Working Group who arrange training events and workshops around Open and Reproducible Research.

Research support at the School level is administered *via* dedicated Research Support Managers and Officers (one per Division) who provide direct input in identification of resources, budget construction, and compliance with funder terms and conditions, and University policy. In addition, Research Support Managers provide input towards School research goals, including provision of management information on research activity, and participation in statutory returns for external organisations. For major awards, programme grants and similar, FBMH's Strategic Funding Team (SFT) provides comprehensive support (3.3).

1.6 Impact strategy

Our institutional statement (REF5a section 2) outlines our focus on impact, where we were ranked first in Europe in the 2018 THE University Impact Rankings. The University and FBMH research strategies aim to have an impact beyond academia and yield economic, health and social benefits. UoA5 research spans fundamental discovery science (***'Understanding Life'***), *via* mechanistic work with implications for disease (***'Disease Biology'***), through to therapeutic targets and impact on clinical treatment, leading to impact in three main themes: (i) health – including translating research into new practices and products to deliver improvements in health and wellbeing; (ii) environmental and social – engaging with the public, education and promoting public health messages, stimulating policy debate and influencing policy decisions; and (iii) economic and commercial, including the establishment of profitable spin-out companies, creation and commercialisation of new products, industry investment in innovative research. Harmonising with the FBMH impact strategy, UoA5:

- Supports and develops researchers to achieve their goals, enhance research partnerships and stakeholder engagement, including industry,
- Builds productive partnerships, and
- Delivers positive societal impact by maximising translation and implementation of research.

The following sections describe our methods to achieve this.

1.6.1 Mechanisms promoting impact

Oversight and governance of the University's impact activities are ensured by the overarching University Research Impact Group, chaired by the Vice-President for Research. Our structures facilitate joint research between UoA5 staff and others in the Faculty in areas including cancer, inflammation and genomics, thereby maximising translation and impact (**Figure 3**).

School-level Knowledge Exchange & Impact Officers (KE&IOs) provide one-to-one support for writing impact sections of funding applications and planning for, monitoring, evidencing and evaluating the resulting impact. Since 2014, they have contributed to 87 draft impact sections on grants. KE&IOs also signpost researchers to other University support teams such as the Business Engagement Team, UoM Innovation Factory (the University's commercialisation arm), as well as the Library and Press Office and other specialist academic networks. Each School in the Faculty has a dedicated academic Director of Social Responsibility, with Social Responsibility leads in each Division. The University Academic Lead for Public Engagement with Research, **Cruickshank**, is from UoA5. She led the UoM's first Gold award from the National Co-Coordinating Centre for Public Engagement, and awards from the BBSRC for her immunology research on parasitic worm infections and public health (Worm Wagon) - see also ImpactCase#1 (1.3.3 & **Figure 3**). Recently, Cruickshank's citizen science research on asthma and hay fever symptoms has linked into Computer Science (UoA11) to develop a novel app in the Britain Breathing project.

Further impact support is provided by an institution-level team which unifies activities, administering impact awards made to the University, including a £300k BBSRC Impact Acceleration Account, MRC Confidence in Concept funding, and Wellcome Institutional Translational Partnership Award (iTPA). Eighteen UoA5 academics have received a total of £1.1m from these awards, to accelerate the transition from discovery research to translational development by supporting preliminary work or feasibility studies. The Wellcome iTPA funds two Translational Research Facilitators, who lead the following two schemes: Access to Expertise Award (£250k) and Projects for Translation (£220k). Six UoA5 researchers have received awards from these schemes, allowing them to leverage additional external funding. For example, **Day/Milner** received a total of £232k overall, including £57k of iTPA support, which was targeted at TSG6, a biologic for degenerative immunological conditions. This in turn lead to a Versus Arthritis Programme Grant (£1.23m) to identify osteoarthritis patients who are most responsive to the developed biologic. The MRC also funded development of a diagnostic assay for anti-TNF drug treatment response in rheumatoid arthritis which confirmed that immunoprofiling can predict clinical outcome, leading to a patent application in preparation, and £96k of proof of principle funding from UoM Innovation Factory. Other notable examples include two Knowledge Transfer Partnership (KTP) awards to commercialise yeast strains in brewing (**Delneri**, CloudWater Brew Co. £190k) and algal-based omega3 oil biosynthesis (**Day Anil**, Algaecytes Limited, £293k).

1.6.2 Recognising and rewarding impact

As part of our strategy to instigate a culture change in impact awareness, we started the 'Making a Difference Awards' (May 2015) to recognise the contribution made by staff and students to society. This included awards for 'Outstanding Benefit to Society through Research' which recognises success in collaborative working and knowledge exchange activities, and 'Outstanding Public Engagement'. Success in working with industrial partners or generating IP is recognised at Faculty or School-level annual Research Symposia, with awards for 'Best new industrial collaboration' and 'Most promising new innovation' awarded, with accompanying presentations to inspire enquiries to the Business Engagement team. Our annual Performance and Development Reviews require all academic staff to detail their contributions to business development and public engagement. This scheme allows line managers to recognise and encourage impact achievements, and use the evidence for promotions.

Led by **Hubbard**, UoM was a finalist in BBSRC's 2016 Excellence with Impact competition, and was awarded two commendations; for outreach in collaboration with the Manchester Museum and

effectively embedding impact across our staff development programmes. The bid featured prototype REF2021 impact cases from **Cruickshank, Prokop,** and **Griffiths-Jones** (**Figure 3**).

The Faculty has funded impact activities during the current REF cycle. For example, funding for an Experimental Officer to resource "droso4schools" and to support production of educational YouTube videos for the Fly Facility (**Prokop**, **Figure 3**) and to **Cruickshank**, for the development and delivery of English to Speakers of Other Languages classes and the #BritainBreathing app for allergy tracking and monitoring. Similarly, the University matched the £25k won in the 2013 BBSRC Activating Impact competition, to support a variety of activities linked to disclosures requiring further development. One such award (to **Hentges**) primed research on the role of Med31 in bone ossification, helping secure a BBSRC CASE award with Syngenta in 2017.

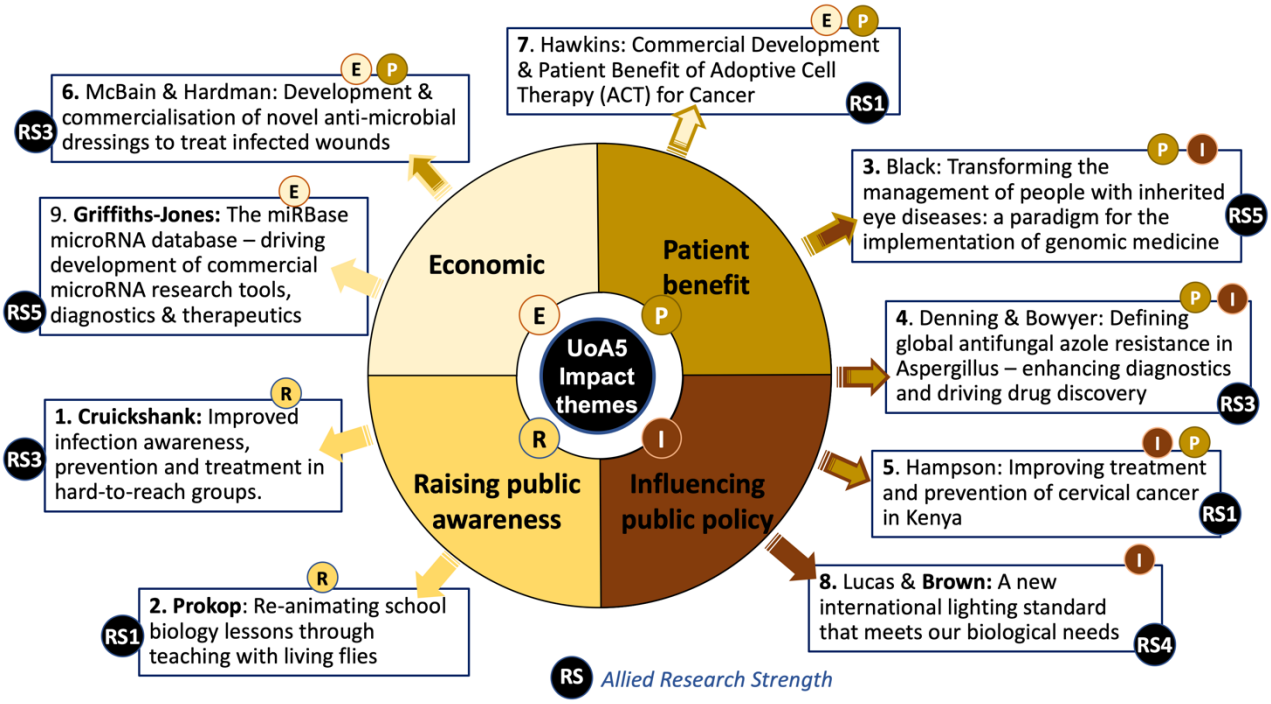

Figure 3. *Impact cases supported by our strategy*

1.6.3 Training, mentoring and capacity building

The University and Faculty have developed a range of training materials and resources for staff and students on the importance of impact at all stages in the research cycle, including dedicated sessions on our compulsory New Academics Programme. We have developed an extensive set of 'how to' guides and training modules on 'Pathways to Impact' guidance and 'Impact Pipelines', available *via* the University intranet. For students, we have delivered workshops and competitions at the Manchester Enterprise Centre with our Business Engagement team acting as judges/mentors, offering an insight into the life science industry. Supported by BBSRC Knowledge Exchange & Commercialisation Seminar Funds, over 200 postgraduate students have attended Faculty Industry workshops, where industry representatives share advice on making the transition to industry and collaborating with industrial partners. Similarly, we also promote student impact activities *via* the professional internships for PhD Students (PIPS) scheme as part of our BBSRC DTP programmes.

1.6.4 Strategic partnerships, IP and business engagement

Partnerships are critical to impact and we have strategic links with several major partners including GSK and Boots UK Ltd (4.1.3). The role of the University is described in REF5a, section 2iv. Over the seven-year REF period, the entrepreneurial activity of staff from UoA5 has resulted in > £6m in total grant income associated with IP, and a total number of 40 patents. Examples of impact cases

relating to commercialisation are the microRNA database (#9 **Griffiths-Jones**) and dressings for wound healing (#6 McBain), as shown above.

1.6.5 Social responsibility and influencing policy development

One goal of UoA5 research is to influence the public and change policy (1.6). Examples of success are provided by two of our impact cases:

- #8 Lucas, resulting in novel guidelines to regulate the wavelengths of light used for illumination (1.3.4).
- #5 Hampson, where drug repurposing to treat cervical cancer was used in the debate on the Medical Innovation Bill (2014), informally known as the Saatchi Bill (1.3.1).

Another example comes from **Cruickshank**, who developed a phone app to capture symptoms of allergy and asthma sufferers to correlate with measurements of pollution and other environmental triggers. The results have influenced politicians at both regional and national levels, with Cruickshank invited to present her work at the Greater Manchester Council. She was subsequently invited on to the Council's Air Quality Task and Finish Group to inform strategy on air quality in the region. She also presented the project at Parliament to MPs and interested parties as part of Evidence Week in 2019. To start addressing concerns around air quality and health directly, a UKRI funded-community based project was initiated in collaboration with a city council housing group, S4B.

2. People

2.1 Staffing strategy and staff development

The organisational structures reflect our strategy to promote work at interdisciplinary boundaries, particularly at the biomedical interface. Consequently, many of the areas identified as *Research Strengths* in Section 1.3 comprise staff from different organisational areas and, indeed, different UoAs. This adds dynamism as we encourage new links to forge.

The 148 staff returned to UoA5 include a diverse mix of bioscientists contributing to our *Research Strengths* (1.3). Our strategy is to target recruitment in areas of existing strength and strategic importance (e.g. to targeted Chairs in immunology (**Allen**), evolutionary microbiology (**Brockhurst**), and AI (**Yao**)). We have also recruited ECRs in these areas to generate critical mass with a view to long-term expansion, major collaborative funding, and Centre bids. Our *Presidential Fellowships* scheme has improved the quality and quantity of our ECRs and fellows (2.3 and 4.3.2), and we have a total of 36 externally-funded personal awards across all career levels in this REF cycle (4.3.1).

2.2 Equality and diversity

As equality, diversity and inclusion are fundamental to success, we seek best practice for all ED&I principles and protected characteristics. The FBMH ED&I committee, chaired by the Associate Dean for Social Responsibility (SR), meets quarterly and includes: an ED&I Partner, postgraduate student, HR partner, the three School SR Directors, Chair of our University's Disabled Staff Network, representative BAME staff and students, Academic Lead for ED&I (Gender Equality), Athena SWAN and Race Charter Marks' Coordinator, and a Student Experience representative. Both SBS and SMS (where most UoA5 staff work) were re-awarded Silver Athena Swan awards following our restructure. SBS has set the tone with a 68% female leadership team including both the original (Worthington) and current (Hoyland) Heads of School. This strongly signals that performance and leadership skills are recognised and promoted regardless of gender.

31% of staff and 24% of Professors/Readers are female. Significantly, 40% of promotions to Chair were female in the most recent round, demonstrating equal progression. UoM champions and has invested £80k in the national Aurora Women's Leadership Programme, launched in 2013 by the Leadership Foundation, AdvanceHE. This has enabled 70 talented UoM women to take part in the programme, including four from UoA5. Three have been promoted since attending, including to Chair (**Cruickshank**) and Reader (**Hentges**).

The University has a Bronze award from Race Equality Charter Mark, retained in 2019, and is signatory to the Disability Confident Scheme and Stonewall Diversity Champions Programme. FBMH launched the pilot flagship Inclusive Advocacy Programme, designed to ensure that high-performing researchers from under-represented groups, including BAME, are supported to reach their full potential. The programme aims to increase diversity in leadership positions and promote inclusivity within academic culture. The proportion of BAME staff in UoA5 is 8.8% (16 staff), of which three (19%) are Chairs, two of whom were promoted in the current REF cycle.

2.3 Presidential Fellows and ECRs

FBMH recognises the importance of strong support for ECRs and have introduced schemes to recruit talented young scientists at the 'stepping stone' phase of their career; 27 (18%) of our returned UoA5 staff are ECRs starting their first independent post. UoA5 has benefitted from internal schemes, notably the University's Presidential Fellowships, to recruit the next generation of researchers. Launched in 2017, the scheme built on the previous Dean's Prize fellowship providing three years' salary, research and travel expenses, access to research facilities and crucially, strong mentoring from line managers to achieve independent fellowship success. This scheme has attracted 10 ECRS to UoA5 in the areas of immunology/infection (**Dyer, Green, Greenhalgh, Menon**), development (**Manning, Wong, Sagner**), cell-matrix (**Zacharenko**), and evolutionary biology (**Coyte, Lagator**). A number have already won external fellowships, including Wellcome Henry Dale (**Lagator, Dyer**)

and MRC Career Development Fellowships (**Wong**). FBMH has also recruited five Henry Wellcome Postdoctoral Fellows, with four sponsored and mentored by academic staff returned in UoA5.

2.4 ECR AND FELLOWSHIP SUPPORT

All ECRs and Fellows are supported by our Faculty Fellowship Academy. Established in 2013, this helps talented researchers to gain externally-funded fellowships, providing support from initial planning through to interview practice, with ongoing mentorship; 22 externally-funded independent fellows were successfully supported over the assessment period to win awards (4.3.2). The Academy's full-time Manager coordinates activities including: 1-2-1 fellowship application advice sessions, bespoke events, and a Fellows network that the fellows themselves run. Advice sessions are popular, with over 500 people attending at least one session since January 2014. Events raise awareness of opportunities, with invited talks from funders including MRC, Wellcome, CRUK, BHF, BBSRC, and NIHR. The network helps fellows to meet informally and share common ideas/problems. Fellows also sit on many of our governing bodies, including School Research Committees, Divisional Leadership Teams, and, importantly, on School Leadership Teams and Promotion Committees. For example, **Francavilla** (Wellcome Henry Dale Fellow), is part of the SBS Leadership Team.

We actively support Fellows towards permanent baseline-funded positions or further externally-funded Fellowships *via* a mid-term Fellowship Review Committee chaired by the Head of School, which reviews progress against objectives set at the outset of the Fellowship. The review provides a supportive environment to discuss any issues arising and agree future plans. Since 2018, we have reviewed 30 Fellows in SBS. Of the 18 who have completed their fellowships, 14 were offered extensions at the end of their Fellowship or are/will be taken on permanently. Within UoA5 specifically, following the completion of their Fellowships, currently six will be taken on to baseline (**Lopez-Castejon, Orozco, Hepworth, Konkel, Das, and Swift**).

2.5 STAFF DEVELOPMENT AND MONITORING

The University is committed to creating an environment where researchers can develop and fulfil their potential (see REF5a, section 3.3). For example, UoM was the first in the sector to introduce an open-ended contracts policy that carries additional benefits for research staff with four or more years continuous service. This includes an extra three months' salary (after external grant funding has ceased) to provide a further opportunity for career development, e.g. undertake specific training, job shadowing. There is also a redeployment scheme where staff are offered preferential consideration for UoM job vacancies for a further six months after external funding ends. Research Staff also benefit from our Extended Access Policy providing access to email accounts and e-resources for a 12-month period beyond their contract end.

Academic and research staff are recognised and rewarded through our annual promotions process, which considers career-breaks, ill-health, and part-time working. Promotion of research staff is independent of funding being available from their current grant, with the cost borne by the relevant School. Support is provided *via* promotion workshops and School/Divisional promotion champions, with successes shared and celebrated through the online research staff handbook. This approach has led to a year-on-year increase in research staff promotions (success rate 88%). During this REF period, 20 UoA5 staff have been promoted to Chair, including six women.

In FBMH, staff development is coordinated by our Centre for Academic and Researcher Development (CARD). CARD is the hub for the delivery of Faculty training, mentoring, and coaching for the personal and professional development of all academics including research staff. It helps build research capability, teaching and learning best practice and accreditation, leadership and management capacity, personal effectiveness, and strategic career management.

CARD convenes the Faculty Research Staff Representatives Forum, a network of >30 research staff representing every Division in the Faculty. In September 2019, a university-wide team led by FBMH research staff celebrated the first University of Manchester Postdoc Appreciation Week, linking with global initiatives to raise awareness and celebrate the achievements of our >2,000 diverse postdoctoral researchers. Led by UoA5's **Hahn**, our efforts were recognised internationally by the

(USA) National Postdoctoral Association and were awarded the 2019 Elsevier National Postdoc Appreciation Week best new event award. Postdoc appreciation week is now an embedded annual event.

2.6 POSTGRADUATE RESEARCH AND SUPPORT

The Manchester Doctoral College oversees the University's doctoral training and research staff development, integrating postgraduate research support with research career development. Multiple Centres for Doctoral Training (CDTs) and Doctoral Training Partnerships (DTPs) have been driven by UoA5 staff, notably from BBSRC, EPSRC and Wellcome. Two BBSRC DTPs have been active during the current REF period (DTP1 £6m; DTP2 £9m) which have been built upon by the award of £12m for DTP3 in 2020. Our size, diversity and research strength allowed UoM to bid successfully as one of the few 'single site' lead institutions. The BBSRC DTP currently recruits 21 standard and five CASE students per year, with 12 fully funded by BBSRC and the rest by the University, demonstrating our financial commitment to PGR research. A cross-Faculty EPSRC/MRC DTC led by **Kimber** from UoA5 in Regenerative Medicine (£4.3m) also illustrates our excellence in interdisciplinary graduate training. UoM also leads the Wellcome 4ward North Clinical PhD Academy (£5m) for Northern England, which brings clinicians to study for PhDs at Manchester. Four are hosted in UoA5 staff labs (**Sharrocks**, **Hepworth/Grencis**, **Luckman/Dunne**, and **Travis**).

We have hosted three Wellcome Doctoral Programmes during the current REF cycle. Each recruits six students per year (one fully Faculty funded):

- Molecular and Cell Biology, £2.5m (MCB **Ashe H, Sharrocks**)
- Quantitative Biology and Biophysics, £2.6m (QBB **Papalopulu, Rattray**)
- Immuno-Matrix in Complex Disease, £5.4m (ICD Hussell, **Allen**).

We also run schemes where students have additional PhD supervisors from other institutions. These are the A*STAR Institute in Singapore, the University of Melbourne, Australia, and the Weizmann Institute of Science, Israel. Collectively, these programmes recruit 8-10 students per year, with funding provided by the University and partner Institutions to strengthen our international links. More recently, our unique BBSRC DTP3 combines with the Universities of Toronto and Melbourne to offer further international collaboration opportunities.

In total, 517 PhDs were awarded in the current cycle, averaging 3.62 graduates per UoA5 FTE, a 42% increase on the like-for-like matched statistics for 2014.

Our Manchester DTP bids focussed on key priority areas. For example, our DTP3 aligns with BBSRC's "Advancing the Frontiers of Bioscience Discovery" strategic theme, in the areas of "Understanding the rules of life" and "Transformative technologies" which map to our *Research Strengths*. All three of our Wellcome-funded programmes are focussed on the fundamentals of molecular, cell and developmental biology. The QBB programme epitomises our interdisciplinary strengths and cross-faculty working (4.1), with all recruited students from a physical sciences background supervised by 'wet' and 'dry' supervisors with complementary backgrounds in biosciences, mathematics, physics, computer science or engineering.

Since 2016, the Doctoral Academy has been responsible for operational support and guidance of all UoA5 postgraduate research (PGR) students, from recruitment to completion. Funding is provided for conference attendance and society membership. We have an extensive student representative network allowing dialogue with Division, School and Faculty research committees. Each student has a primary supervisor and at least one co-supervisor to provide comprehensive interdisciplinary support throughout their research programme. In addition, students are allocated an Advisor, who acts in a pastoral role. All students have access to a designated Divisional-level PGR Tutor who monitors and supports their progress independently of the supervisory team.

2.7 STUDENT TRAINING, SUPPORT AND ENGAGEMENT

Training from The Doctoral Academy ensures generic skills development, timely completion of the degree, and increased future employability. All PGR students undertake an initial skills-needs analysis to identify areas for development and, throughout their programme, undertake research

skills training directly related to their project. This includes generic training on writing, presentation, statistics, and personal effectiveness, as well as bespoke core facility workshops to promote interdisciplinarity, covering technologies ranging from biomolecular analysis, through to bioimaging, genomic technologies and bioinformatics. Our online progression monitoring system, eProg, records progress and encourages supervisory feedback.

PGR student representatives sit on Divisional, School and Faculty-level committees, and also on committees of UKRI-funded programmes, thereby empowering students and helping integration into the research culture. Our PGR student-led Graduate Society hosts public engagement activities and external speakers, enhancing networking opportunities for students. To recognise student achievements, each School has postgraduate prizes, as well as PGR Student of the Year awards at School, Faculty and University level.

The UoM considers student wellbeing a priority. Multiple initiatives operate across both the University and Faculty, including 24/7 mental health and counselling support, PGR student representatives with a remit for advising on mental health and an online 'Pulse-Check' initiative including Wellbeing Apps allowing PGR students to self-check their mental and physical wellbeing. A successful Office for Students-funded bid (£150k) has allowed us to investigate mental health issues and promote self-help through the use of Wellbeing Apps. Furthermore, UoM is partnered with the Greater Manchester Health and Social Care Partnership, to offer an integrated approach to supporting students *via* the university and NHS. In 2018, we established a successful 'PGR Parents Group' that meets regularly to provide peer support, as well as a 'PGR Partners Group' in 2019 that provides a support forum for partners, particularly of international PGR students.

New ECR supervisors initially act as co-supervisor, until successful completion of the degree, before holding primary supervisory responsibility. FBMH's compulsory New Academics Programme provides training, with particular emphasis on 'Effective Supervision by the New Supervisor'. Furthermore, as part of supervisors' continuing professional development, the Faculty provides refresher courses on supervisory policy, good practice in recruitment, managing the student/supervisor relationship and supporting career development.

3. Income, infrastructure and facilities

3.1 INCOME

External support: UoM is a major recipient of bioscience funding from UKRI, charities, international and industrial sources (>£185m awarded from the BBSRC and Wellcome during the period), and has been consistently ranked as the first or second highest recipient of BBSRC funding since 2014. UoA5 staff have been pivotal to this success, named on 59% of BBSRC (£57m), 52% of MRC (£66m) and 55% (£48m) of all Wellcome funding to UoM in the current REF.

BBSRC funding in UoA5 covers the key strategic priority areas in World Class Underpinning Bioscience, Industrial Biotechnology (IB) and Synthetic Biology (SynBio). Our promotion of interdisciplinarity has helped leverage funding success in these areas, which often lie at UoA boundaries. For example, we have had interdisciplinary BBSRC grant successes from three sLoLa grants that were active over this REF cycle, totalling ~£13m:

- **Hubbard** Spatio-temporal map of the developmental fly interactome
- **Pavitt** Understanding how RNA interacting proteins modulate the translatability of mRNAs
- **Kadler** Modulating extracellular matrix secretion and assembly for long term health

UoA5 researchers have helped develop the SYNBIOCHEM Centre for synthetic biology (**Delneri**; ~£10m from BBSRC), reinforcing inter-Faculty links to the Manchester Institute for Biotechnology where it is based, along with colleagues in the Faculty of Science and Engineering. These successes are promoted by our structures, which interface core biosciences with physics, chemistry, mathematics, computer sciences, engineering, material sciences, pharmacy, psychological sciences, dentistry and medicine. In addition to excellence in basic bioscience, our work crosses into the biomedical arena, as demonstrated by our extensive Wellcome and MRC funding (£72m in total, based on UoA5 credit-split awarded in this REF cycle). This is exemplified by the Wellcome Centre for Cell-Matrix Research (~£5m) (1.3.2), and our exploitation of graphene technology for 2D Materials for Next Generation Healthcare Technologies (2D Health) (**MacDonald**; ~£5m from EPSRC). UoA5 has contributed to research in the cancer arena through the award of the MAnchester RESearch Transforming Radiation Oncology (MAESTRO) Programme as Part of CRUK RadNet (~£16m). Our work has also contributed to major national and international research efforts including the Human Cell Atlas (**Sharrocks, Rattray**; ~£1m from MRC). In addition to interdisciplinary teamwork, we have secured numerous programme level grants to support individual PIs, exemplified by 12 PIs holding Wellcome Investigator/Senior Investigators awards (>£18m), attesting to our international quality science.

Our work at the frontier of bioscience research is underpinned by access to cutting edge core facilities (3.5) enabled through UoM investment and external funding. Since 2014, we have acquired ~£28m of equipment funding from external sources and typically invest ~£1-2m per year from internal funds. Notable awards include:

- A £4.9m MRC award to harness the single cell capabilities of our genomics and imaging facilities (Systems Microscopy Centre).
- Two awards from BBSRC 18ALERT to augment our live cell imaging with a Lattice Lightsheet Microscope (£463k) and an imaging CyTOF (£440k).
- Development of the Stoller Biomarker Discovery Centre (**Hubbard** from UoA5; ~£12m from MRC) and the recent acquisition in 2019 of an Orbitrap Exploris 480 (Wellcome £390k) to expand our mass spectrometry portfolio.
- A recent BBSRC 19ALERT award (£750k) has modernised our EM capabilities by funding the acquisition of new cryo-EM equipment.

External funders have also supported research interactions by providing income in kind. This totals £2.1m during the current REF cycle, covering access to the National Electron Physical Science Imaging Centre for electron microscopy and the Diamond Light Source for X-ray crystallography/SAXS at Harwell, leading to 38 publications (e.g. **Baldock, Roseman, Derrick,**

Ford) and NIHR BRC funding (**Taylor**). Researchers also make use of the long-read sequencing available at the MRC regional sequencing facility in Liverpool.

3.2 UNIVERSITY SUPPORT FOR RESEARCH EXCELLENCE

The University and Faculty have supported strategic areas of research during the current REF cycle with targeted investment in appointments, support for equipment bids (3.1 above), internal fellowships (2.3), and by financial support for Centre bids. For example, we supported the MCCIR centre directly and Lydia Becker Institute *via* an UMRI award (4.1), focussing on our immunology Research Strength (1.3.3). This has come in the form of major strategic appointments (**Allen, Davies**) and support for ECRs (see also 2.3), particularly *via* underwrites whilst seeking Fellowships. Similar support was provided for the ongoing development of the WCCMR and development of our single cell capabilities (4.1).

3.3 OPERATIONAL INFRASTRUCTURE

As part of UoM's strategic vision of world-leading research, there has been significant investment in infrastructure for securing and managing research funding. The University Research Services team provides cross-Faculty support for research, including a specialist EU office, compliance and risk management, research governance and data protection. Specific research management for UoA5 is provided by the FBMH Research and Business Engagement Team, comprising Research Services, Research Governance, the PGR Doctoral Academy, Business Engagement and Strategic Funding. In Research Services, 28 staff support different elements of the research lifecycle, including advice and guidance on funding opportunities and costing and submitting applications. Attracting funding for initiatives that complement our research strategy, such as Centres and large consortia grants, is supported through the FBMH Strategic Funding Team (SFT). The success of the Team during the REF period is demonstrated by the number and value of the Centres and Consortia bids (3.2).

The SFT is part of our wider Research Strategy and Innovation Team, and comprises a group of Strategic Funding Managers who work not only across the Faculty, but also on pan-university initiatives. Its primary objective is to coordinate the development of strategic grant proposals, and has helped obtain >£250m research funding. The SFT supports our multi-disciplinary research portfolio, coordinating cross-cutting research areas, facilitating themed workshops and large events that help collaborations grow and prosper, performing strategic analysis of outputs and impact from funded research to inform strategy, and developing strong relationships with funders to pre-empt major calls and communicate changes in funding policy and strategic priorities. This has generated many multi-disciplinary collaborations involving UoA5 researchers. An example is **Biological Timing** (1.3.4); the SFT instigated a series of workshops between engineers and circadian biologists, leading to a successful Wellcome ISSF proposal to create novel sensors to capture temporal real-world data on light exposure. SFT support has also provided performance and competitor analysis, targeted development of personal and collaborative award applications, and dedicated efforts to recruit and relocate international researchers (UKRI Future Leaders Fellow, **Fustin**). Another major driver has been to increase the number of collaborations between fundamental biologists and clinicians. This has been achieved through support of our Clinical Genomics and Single Cell Biology UMRIs (4.1), and SFT representation on the Faculty Research Domains and the associated Manchester Academic Health Science Centre. This promotes interactions with our allied NHS Trusts and oversees pump-priming initiatives specifically aimed at new partnerships. This has supported a 65% increase in publications co-authored by UoA5 with UoA1 researchers from 48 in the first three years of the REF period to 79 in the last three years.

The University provides centralised IT support, from routine user support through to data storage and high-performance research computing. At a local level, a dedicated Research Data Manager in our core facilities ensures that data and meta-data are archived according to international standards. Centrally, there is a dedicated Research IT team, comprising ~50 FTEs, which is embedded in central IT and provides support for a broad range of activities, including High Performance Computing platforms, a dedicated research Virtual Machine Service, cloud-based resources and research software engineers that can be assigned to individual projects. Much of our computational

biology work, particularly in the structural biology, bioinformatics and genomics areas, is performed on the Computational Shared Facility (CSF), a platform currently comprising approximately 12k cores. The CSF is tightly integrated with the Research Data Storage platform which provides approx. 8,000 TB of resilient data storage to the UoM research community, across three sites. A user-driven working group, chaired by UoA5 member (**Rattray**) meets regularly with Research IT staff to discuss computing and storage needs, ensuring requirements and user demands are fed into the central team.

3.4 CAMPUS INFRASTRUCTURE

Most UoA5 researchers are located in the Michael Smith and AV Hill buildings on the central University campus, directly connected to the Stopford building and the Core Technology Facility (CTF), allowing easy interaction with other researchers in the Faculty. The CTF also allows interaction with biotech firms co-housed there. Interdisciplinary work is also enabled *via* UoA5 researchers in the Manchester Institute of Biotechnology. Further interdisciplinary and translational research is facilitated by our juxtaposition to the Manchester Foundation Trust, creating a single contiguous Biomedical Corridor. Close connections with the Manchester Cancer Research Centre are facilitated by embedding several UoA5 researchers in the Oglesby Research Building (adjacent to the Christie Cancer Hospital) and the CRUK Manchester Institute. To cement this partnership, the University has recently committed to the building of a new integrated Cancer Research building (~£150m) alongside funding from CRUK and the Christie Hospital.

3.5 RESEARCH FACILITIES

The vision for our research infrastructure is simple: competitiveness requires cutting edge research facilities, maintained and operated by skilled staff to deliver key technologies. Our facilities are located optimally, managed appropriately, and available to all. To ensure that our researchers' current and future needs are met, we pursue both top-down (through Domains/Divisions) and bottom-up (from academic community and user groups) horizon scanning strategies. For example, issues raised by users triggered a review of the electron microscopy research facility, which resulted in strategic investment and the acquisition of ~£2m of EM equipment since 2018. To maximise effectiveness, facilities engage with the research community throughout UoM, and with partner healthcare trusts. To maintain international competitiveness, we invest in emerging technologies. In parallel, optimal utilisation and management of FBMH space allows co-location of cognate research groups and underpins effective research strategy.

The Faculty hosts eight core research facilities: Bioimaging, Biological Mass Spectrometry, Biomolecular Analysis, Electron Microscopy, Flow Cytometry, Genomic Technologies (with integrated Bioinformatics support), Genome Editing, and Histology. To complement these equipment-based cores, we also have a Fly Facility and an extensive Biological Services Facility (BSF) to provide a wide range of model organisms (sheep, rats, mice, African striped mice, gerbils, fish, frogs, tortoises and snails). With 9,000 m^2 of usable space (including ~7,000 mouse cages), a turnover of £2.5m and 42 FTE staff (up from 38 in 2014), the Manchester BSF is one of the largest in Europe. To maintain and grow international competitiveness, there has been £1.9m investment since 2014, including the construction of a germ-free facility. A Management Advisory Group meets quarterly to ensure liaison between the academic community and staff involved with animal care. The BSF also leads on raising public awareness of the use of animals in research and our web site has been recognised for its ease of use by UAR (Understanding Animal Research) and is one of the first establishments to be awarded the "Leaders in Openness 2019–2022" status. The Faculty also provides technical resource for research support services, including a media kitchen, decontamination/sterilisation facility and central stores, infrastructure services, and manages and maintains core communal equipment including centrifuges, molecular imaging systems, and liquid nitrogen storage facilities. These services are supported by a team of 20 technicians.

These core research facilities have expanded over the review period through internal and external investment. Over £42m has been invested in the equipment base (including >£14m from UoM) and staffing has increased from 33 staff in 2014 to 49 in 2020. The increased size and capacity are reflected in turnover (<£2m in 2014 to ~£3.5m in 2019). We operate a transparent and equitable

charging policy with discounted rates applied to support postgraduate student training. Despite our extensive strategic investments, cost recovery has increased annually to over 90%.

Investment in the core facilities is exemplified by our core Genome Editing Unit. Historically, this was focussed solely on creating and rederiving transgenic mouse models. However, in 2014 we made a strategic investment from our Wellcome ISSF fund in an Experimental Officer to develop CRISPR technologies. Since then, the facility has grown from two to seven staff, and now contains a service arm creating both transgenic mice (114 created in the REF period), engineered cells (23 created and 12 in progress since inception in 2019), and recombinant plasmids (>500 in the past 18 months), as well as a research and development arm to establish and implement new cutting-edge technical advances. The facility now contributes to many new research areas, spanning basic, translational and clinical areas in zebrafish and mice through to patient-derived cells, and underpins a rapidly increasing number of outputs each year (from one manuscript in 2015 to 18 in 2020). Novel technical advances from these studies include: the generation of an endogenous gene fusion system in mouse (HaloTag) that transforms the capacity to perform live single cell imaging combined with dynamic ChIP-seq analysis of rhythmically expressed transcription factors (**Hunter**, PNAS-2020); the use of new derivative CRISPR tools within cell lines (CRISPR activation), to analyse the function of putative enhancers identified in GWAS studies linked to different diseases (**Rattray**, Nat-Commun-2020); the establishment of an *in vivo*, virally delivered gene knock-out approach in mice that provides a significant 3Rs advantage (Mol-Metab-2019). The successful application of the above technologies by a core facility has enabled and accelerated dissemination and uptake by other research groups.

A second area of investment and growth has been in developing our single cell capabilities, which are incorporated into the Bioimaging, Flow Cytometry and Genomic Technologies Facilities. In Bioimaging, there has been a major influx of equipment with the acquisition of super resolution microscopes including STED, STORM, and lattice light sheet systems. This is mirrored by the establishment of CyTOF and Hyperion single cell systems in Flow Cytometry and the acquisition of 10x Genomics and ICELL8 systems for single cell sequencing based analyses. Additional technical resource has been dedicated to the latter two facilities to cover these new technologies. These recent developments have allowed us to apply novel approaches, such as using a Flipper-TR probe and Fluorescence Lifetime imaging to study membrane tension in live cells. This demonstrated that directional persistence and membrane tension is highly coordinated and could explain how cells move rapidly into fibrotic areas and promote cancer invasion (**Caswell**, Dev-Cell-2019). Current projects are probing the lung environment in COVID-19 patients using the CyTOF, and other studies have used the 10x system to reveal profound mitotic heterogeneity within a living biobank of ovarian cancer *ex vivo* models (**Taylor**, Nature-Commun-2020).

Engagement with the research community is ensured through improved web presence, annual workshops and the establishment of regular user group/advisory board meetings as exemplified by the Bioimaging and Biological Mass-spectrometry core facilities. The annual reports on the core facilities show that there has been an upgrade in the quality and impact of research activity in FBMH based on associated publication metrics through the core facilities (from 111 papers in 2013 to 209 during 2019).

The success of our core facilities is exemplified by the high number (1,243 from 2014-2020) of research outputs acknowledging their input over the reporting period. Of these, 295 are co-authored by core facility staff, demonstrating their added value and the utility of their expert input into the projects. Several of these involve multiple core facilities and can be exemplified by the combination of staff in Bioimaging (Spiller), Mass Spectrometry (O'Cualain) and Genome Editing Unit (Adamson) contributing to the discovery that competitive cytokine signaling predicts tissue thresholds for the propagation of macrophage activation (**White**,**Paszek**, Sci-Signal-2018)**.**

4. Collaboration and contribution to the research base, economy and society

4.1 INTERDISCIPLINARITY AND COLLABORATION

4.1.1 Promoting interdisciplinarity and collaboration

As part of our longer-term strategy, we introduced several measures to encourage and increase interdisciplinary science in FBMH:

- **Domains**: These major, interdisciplinary research themes span several UoAs and operate across Schools (**Figure 2**). Domains encourage interdisciplinarity between UoA5 researchers with others from more clinically-oriented or technically-focused areas elsewhere in the University. Domain Directors use a variety of approaches to build research strengths, including focussed meetings, retreats, and workshops. The most relevant Domains (with numbers of UoA5 staff members indicated [ ]) are:

    - **Cellular & Developmental Systems** has ***'Understanding Life'*** as a core theme; the Domain acts as a cross-UoA forum to study how cellular dysfunction causes disease, enhanced by understanding of how alterations affect cells, their behaviour, and their interactions. [62]
    - **Infection, Immunity, Inflammation & Repair** links basic, clinical, and translational innovation with particular strengths in chronic lung conditions, dermatology, musculoskeletal disease and complex wounds. It was integral to formation of the Lydia Becker Institute (1.3.3), which in turn facilitated integrated and rapid responses to the COVID-19 pandemic. [48]
    - **Evolution, Systems & Genomics** encompasses the broad scope of genetic diversity from viruses and bacteria, fungi and protozoans, plants, and animals – including humans. Genetic and genomic work includes neonatal testing through St Mary's Hospital and working with data from millions of completed genomes. The Domain is also linked with the Manchester Centre for Genomic Medicine, and helped catalyse the Genomics UMRI bid (see below). [35]
    - **Cardiovascular, Endocrine & Metabolic Sciences** links mechanistic, cellular and molecular studies of the heart and circulation, the control of energy balance, and endocrine and metabolic systems to disease. Biological timing is a key sub-theme (1.3.4). [26]
    - **Cancer** connects fundamental molecular and cellular cancer biology to the Manchester Cancer Research Centre – a partnership between the University, Cancer Research UK and The Christie NHS Foundation Trust. [20]
    - **Neuroscience & Mental Health** contains a Vision sub-theme, encompassing circadian and inner retinal photoreception, linking Research Strength 1.3.4 to UoA4. [17]

- **UMRI-funded research networks**: The University of Manchester Research Institute (UMRI), funds groups, as part of the Manchester 2020 strategic plan, to establish the University as a major centre for interdisciplinary research. A number are led by or involve significant input from UoA5 staff, integrating researchers from several *Strengths*, and have received a total of £429k (**Figure 4**). One of the first such networks, the **Lydia Becker Institute of Immunology and Inflammation** has already flourished into a mature Centre (1.3.3). The others are:

    - **Centre for Biological Timing -** Promotes cross-Faculty links in areas related to biological timing in public policy, modelling and mathematical analysis of oscillatory systems in complex biological contexts, and enhances clinical translation of biological timing into clinical trials and healthcare.

- **Infection network -** To assemble an integrated community of clinical, academic and industrial partners focussed on antimicrobial strategy in the settings of mono- and multi-morbidity, and with a significant emphasis on respiratory infection and sepsis.
- **Interdisciplinary single cell biology -** Connects cell signalling, nuclear regulation and absolute molecular quantification of protein and RNA at single cell resolution with mathematical modelling to understand 'cell state', facilitating understanding of emergent properties from tissues and systems.
- **Genomics -** A network of experimental and computational biologists using interdisciplinary basic science approaches to improve interpretation of human genomic variation, particularly where biological knowledge is insufficient either to determine pathogenicity or understand its mechanism.

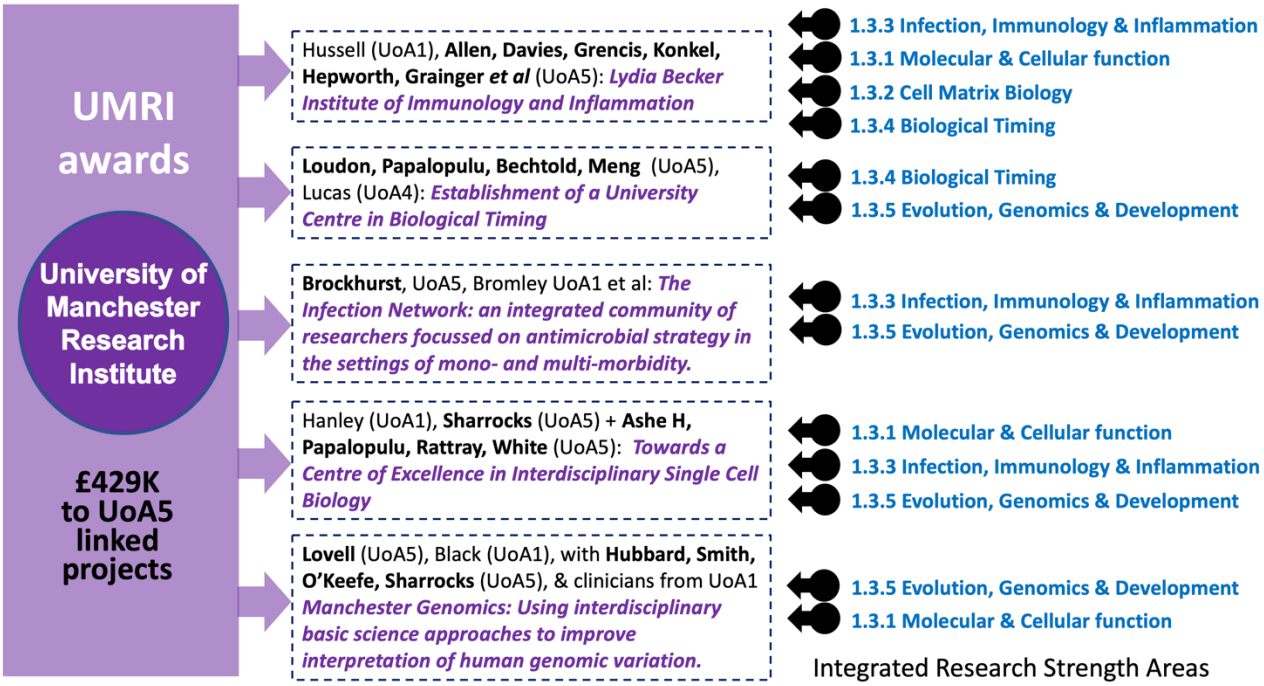

Figure 4. *Competitively awarded interdisciplinary pump-priming awards from UMRI*

- **ISSF awards:** A central Wellcome ISSF theme has been to fund interdisciplinary research teams. During the current REF cycle, we have invested our two awards (total £4.5m) on ECRs, interdisciplinary research projects, public engagement, and infrastructure. UoA5 researchers have been heavily involved in the leadership of four major funded projects totalling £906k (**Table 1**): two 'Cross-Faculty Consortia' bids in 2018 to establish novel project-focussed groupings, and two 'UMRI Consolidator' awards in 2019/20 to synergise with existing UMRI networks.

Table 1. Competitively awarded Institutional Strategic Support Fund awards

Leadership	*Title*	Aims	Value
Lovell, **Gifford (UoA5)**, Felton (UoA1), van Staa (UoA2), Knight (UoA7), House, Galla (both UoA10)	*Tackling antimicrobial resistance by understanding evolutionary landscapes*	Harnessing innovations in sequencing and modelling to further understanding of the fitness consequences of antimicrobial resistance evolution, the accompanying ameliorating mutations, and effects on population dynamics	£250k
Gilmore, **Swift (UoA5)**,	*Modelling the dynamic changes of micro-*	Using novel mass spectrometry techniques and biomaterials to	£285k

Roncaroli (UoA4), Domingos, Saiani (UoA12)	*environment during cancer initiation and progression*	characterise and recapitulate distinct tumour cell environments from patient samples, and provide insight into the complex matrix interactions that drive tumour progression	
Sharrocks, Piper Hanley, Rattray (UoA5), Hanley (UoA1), Jensen (UoA10)	*Towards a Centre of Excellence in Interdisciplinary Single Cell Biology*	To embed technical expertise in our core facilities to generate foundational Spatial Transcriptomics datasets that can benefit multiple researchers in hypothesis generation, and to develop cutting-edge capability for mathematical modelling of dynamic changes at single cell resolution	£198k
Brown (UoA5), Lucas (UoA4), van Tongeren (UoA2), Casson, Johnson (UoA12)	*Bioelectronic monitoring of light exposure and circadian rhythms*	Generating tools and proof of concept data for applying wearable technology to study biological rhythms and contingent aspects of human health. Exploiting the synergy between Manchester's expertise in biological timing, bioelectronics, and occupational health to generate large scale grant funding and improve health	£172k

- **University Institutes and Networks**: The University has several cross-Faculty institutes and research networks where UoA5 staff lead or play pivotal roles, to help transform life and health sciences. Our Digital Futures network contains the Data Science and Artificial Intelligence Institute, led by **Rattray**, which couples methodologists and translational scientists in biomedicine and health, drawing on strength-in-depth in data science (**Rattray, Yau, Iqbal, Causey-Freeman**). Similarly, the Christabel Pankhurst Institute is a new collaboration between UoM, the NHS, business and local government in a £25m initiative to promote and translate needs-led health technology research and innovation into practice. These initiatives will be central to translation of future research in our research themes (e.g. 1.3.1, 1.3.2, 1.3.4), *via* AI/data science, materials and technology.
- **Integrative Doctorial Programmes** - Our major doctoral programmes (2.6) are interdisciplinary, with supervisory teams built from staff with different areas of expertise and backgrounds. Notable examples are the BBSRC DTP and the Wellcome-funded Quantitative and Biophysical Biology PhD programme led by **Papalopulu, Rattray** and Jensen (UoA10), which both involve co-supervisory teams involving mathematicians, statisticians and physical scientists as well as bioscientists (2.6). The effectiveness of these strategies is exemplified by 30% of returned outputs having UoM co-authors from outside of UoA5.

4.1.2 Collaboration with UK and international institutions

Our collaborative networks extend beyond Manchester. UoA5 staff have held honorary professorship positions at four UK and four international institutions. We co-publish extensively within the UK (30% of our papers), with the Universities of Oxford and Cambridge, and Imperial College London, being the most regular partners. Moreover, we continue to drive an international research agenda, and 105 UoA5 staff participate in international collaborations delivering 775 papers since 2014 (~50% of total output), with a broad world-wide distribution (**Figure 5**). The most frequent collaborations were with Harvard University, NIH, INSERM and CNRS (114 papers).

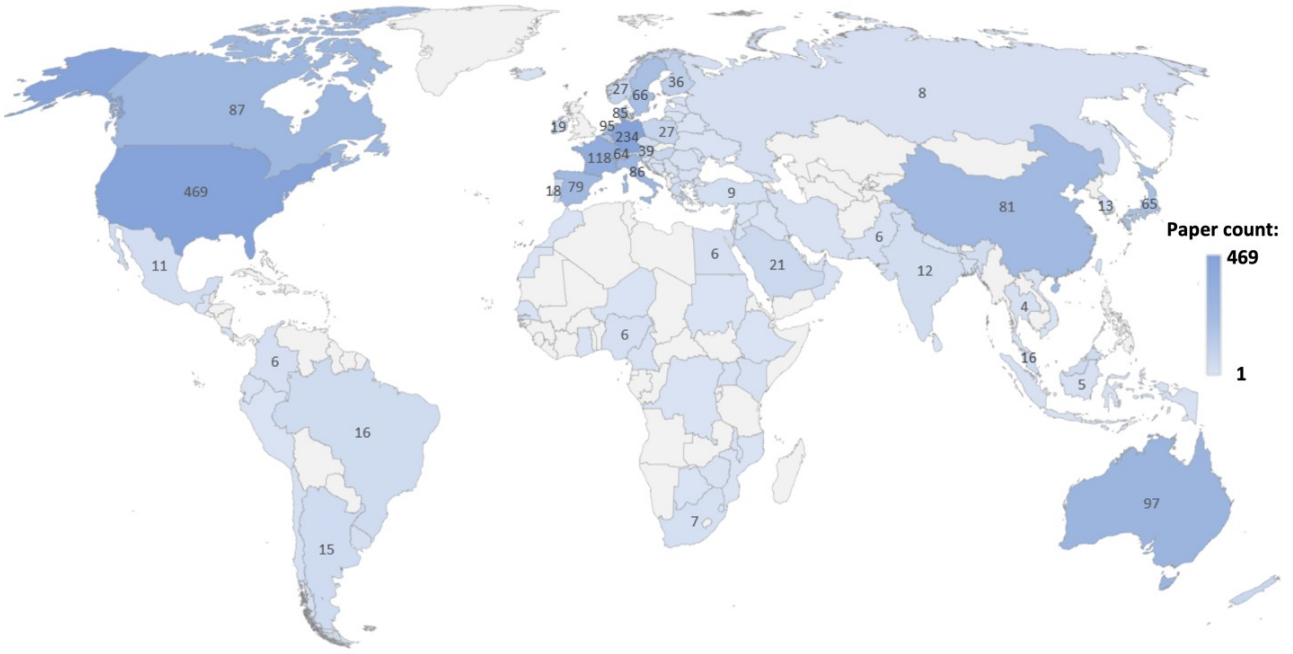

Figure 5. *World-wide distribution of outputs co-authored with UoA5 staff. Numbers correspond to the total number of outputs from that country, also coloured by gradient.*

4.1.3 Collaboration with industry

We develop strategic links with major partners to generate impact:

- MCCIR and Lydia Becker Institute (1.3.3). Renewed in 2016 for £908k in partnership with GSK (**Davis, Travis, Grainger, MacDonald, Lopez-Castejon**), and originally established with joint investment from UoM, GSK and AstraZeneca. Its aims are to harness academic innovation to investigate basic mechanisms and, importantly, advance drug development for clinical needs. Ongoing work between GSK and **Davis** seeks to exploit these targets (1.3.3), where identification of macrophage receptor nanoclusters has led to further funding (GSK, £660k and Bristol Myers Squibb, £960k).
- Similar partnerships with Boots UK Ltd have been renewed (£3.6m overall), involving **Meng** and **Swift** from UoA5, targeted at fundamental bioscience of skin ageing.
- Unilever (**Thornton, Dearman)**: on behaviour of T lymphocytes to skin sensitising chemicals and oral mucins to chemicals (total £600k).
- Eli Lilly (**Luckman, D'Agostino)**: mode of action of natural hormones/transmitters and their effects on appetite and body weight (total £950k).
- ABInBev (**Delneri):** novel yeast strains for brewing and biotech (total £263k). Discovered a new yeast species growing at high altitude with cold tolerance, catalysing further industrial interactions with local brewers (Cloudwater KTP £190k).
- A Manchester consortium was awarded £4.5m from InnovateUK as part of the ID Liver award with £855k to UoM (**Piper-Hanley, Rattray, Martin K**).
- 35 BBSRC/MRC CASE studentships with 32 different companies.

Total funding of £6.9m has been acquired from the commercial sector during the REF period.

4.2 CONTRIBUTION TO COMMUNITY ENGAGEMENT

4.2.1 Peer review and strategic contributions to research strategy

UoA5 staff have performed 142 different journal editorial roles either as editors or editorial board members, including several editorships at prominent journals (*Nucleic Acids Research*, **Sharrocks**; *Journal of Cell Biology*, **Humphries**; *BMC Evolutionary Biology*, **Brockhurst**) and three acting as editor-in-chief (*Parasite Immunology*, **Grencis**; *Frontiers in Cell and Developmental Biology*, **Kouskoff;** *Regeneration*, **Amaya**). Extensive UoA5 staff membership of grant panels includes 29 on RCUK panels (five as chair, **Cruickshank**, **Hubbard**, **Luckman**, **MacDonald, White**), 19 on charity panels (including four Wellcome, **Papalopulu**, **Kadler, Ashe H, Grainger**), and 18 international panels (three as chair, **Sharrocks**, **Ford**, **Travis**). **Humphries** chairs, and is the Senior Independent Member of BBSRC Council. **Hubbard** chaired BBSRC's Institute Assessment Exercise that awarded £70m to its Research Institutes, and **White** served on BBSRC groups, developing their 'People and Skills' and Bioimaging strategies. **Rattray** has served on multiple UKRI advisory panels, most recently the BBSRC Data Intensive Bioscience Review. **Rothwell** has co-chaired the Prime Minister's Council for Science and Technology and is a board member of the Dementia Research Institute. A further nine staff have served on advisory boards for UK or international research institutions and organisations, and 17 UoA5 staff have held directorships/consultancies/advisory board membership in a commercial setting, including major bioproducts/pharmaceutical companies Pfizer (**Bechtold**), Unilever (**Konkel**), AstraZeneca (**Rattray** and **Rothwell**), Eli Lilly (**Luckman**), GSK (**Rothwell**) and Smith and Nephew (**Day P**). **Allen J** is on the UoA5 REF2021 panel.

4.2.2 Contributions to scientific societies and conferences

Twenty UoA5 staff have contributed to the running of Academic Scientific Societies, including two associated with the Academy of Medical Sciences (Vice-President, **Humphries**; Chair of Sectional Committee, **Davis**) and two as presidents of international societies (International Society for Hyaluronan Sciences; **Day A**; Machine Learning for Computational Systems Biology, **Rattray**). **Rothwell** was the Inaugural Chair and President of the (Royal) Society of Biology, Council Member of the Royal Society, **Delneri** is a UK Commissioner on the International Commission on Yeasts.

UoA5 staff have had major roles in organising conferences, with 35 as organisers of 75 national, and 55 of 116 international conferences (including four chairs of Gordon Research Conferences, **Baldock**, **Day A**, **Francavilla**, **Thornton). Lovell**/**Delneri** bid for and won the right to host the Society for Molecular Biology and Evolution international meeting in Manchester in 2019. Staff regularly present their work at scientific conferences and workshops. Fifty-two UoA5 staff have delivered plenary/keynote conference presentations (24 national and 30 international; 175 talks in total). Nine talks have been delivered at elite EMBO run events and 18 at Gordon conferences.

4.3 AWARDS AND RECOGNITION

4.3.1 Prizes and awards

UoA5 staff hold fellowships of prestigious societies (Academy of Medical Sciences, **Allen J, Davis, Humphries, Loudon, Papalopulu, Rothwell**; Royal Society Edinburgh, **Allen J**; Royal Society, **Rothwell**; Academia Europaea, **Day, Humphries, Loudon, Rothwell, Taylor S**). Since 2014, five researchers have been awarded prizes by academic societies, including the lifetime achievement Fell-Muir Prize, awarded by the British Society for Matrix Biology (**Kadler**) and the Fleming prize from the Microbiology Society (**Brockhurst**). **Allen J** was elected as an EMBO member, **Brockhurst** was awarded the Philip Leverhulme Prize for ECRs and **Konkel** a Lister Prize Fellowship. **Cruickshank** has had her work on innovation recognised through winning Project of the Year in the Bionow awards.

4.3.2 Fellowships

A significant number of personal fellowship/awards have been made to UoA5 staff, which span all our *Research Strengths* – first independent fellowships*, ECRs**:

- 10 Wellcome Investigator awards.
- 2 Wellcome Senior Research Fellows
- 1 Versus Arthritis Senior Fellow
- 1 ARUK Research Fellow
- 1 Medical Research Foundation Fellow
- 3 BBSRC David Philips Fellows
- 5 MRC Career Development fellows
- 2 UKRI Future Leaders Fellowships
- 9 Wellcome Sir Henry Dale Fellowships

Cell and developmental biology (*Research Strengths* 1 & 5, 1.3.1, 1.3.5):

- Membrane synthesis (**High** Wellcome Investigator)
- Membrane receptor turnover (**Woodman** Wellcome Investigator)
- Fundamental principles of developmental biology (**Papalopulu** Senior Research Fellowship **Ashe H** and **Rattray** Wellcome Investigators; **Das*** MRC CDA; **Herbert** Wellcome Senior Research Fellow; **Wong**** (MRC CDA)
- Transcriptional control of gene expression (**Sharrocks** Wellcome Investigator)
- Endocytotic recycling of tyrosine kinases (**Francavilla*** Wellcome Henry Dale)
- Microtubule dynamics (**Hahn**** Leverhulme Early Career Fellow)

Cell matrix biology (*Research Strength* 2, 1.3.2):

- Collagen homeostasis (**Kadler** Wellcome Investigator)
- Mechano-stress and ageing (**Swift*** BBSRC David Philips Fellow)
- Cell-matrix and immune cell recruitment (**Dyer**** Wellcome Henry Dale)
- Mitotic spindle and cell environment (**Woolner*** Wellcome Henry Dale)
- microRNAs and wound healing (**Kurinna**** MRC CDA)

Immunology and infection (*Research Strength* 3, 1.3.3):

- Respiratory immunology (**Allen J** Wellcome Investigator)
- Cell surface imaging immunology (**Davis** Wellcome Investigator)
- Pathogen host immunology (**Grencis** Wellcome Investigator)
- Oral immuno-surveillance (**Konkel*** BBSRC David Philips fellow)
- Microbiota and mucosal inflammation (**Mann**** Wellcome Henry Dale)
- Monocytes, infection and inflammation (**Grainger*** Wellcome Henry Dale & Senior Kennedy Trust fellow)
- T-cell responses in inflammatory disease (**Hepworth*** Wellcome Henry Dale & Lister Fellow)
- Deubiquitination and the inflammatory response (**Lopez-Castejon*** Wellcome Henry Dale)
- Inflammation in cerebrovascular disease (**Strangward**** ARUK Fellow)
- Fungal sulphur metabolism (**Amich Elias*** MRC CDA)
- Infection and stroke (**South****, Medical Research Foundation fellow)

Circadian biology, vision (*Research Strength* 4, 1.3.4):

- Clock control in lungs (**Loudon** & Ray Wellcome Investigators)
- Clocks, cartilage and aging (**Meng** Versus Arthritis Senior Fellowship)
- Epigenetic regulation of clock in metabolism (**Fustin**** UKRI Future Leaders Fellow)
- Visual coding and the circadian clock (**Allen A**** Wellcome Henry Dale)
- Vision and clocks *via* the SCN (**Brown*** BBSRC David Phillips)
- Neuroactivation of appetite suppression (**D'Agostino**** MRC CDA)

Evolutionary biology (*Research Strength* 5, 1.3.5):

- Evolution of mutation rates (**Krasovec**** UKRI Future Leaders Fellow)
- Multi-drug resistance mechanisms (**Gifford**** UKRI Rutherford Fellow)
- Evolution of gene regulatory networks in AMR (**Lagator**** Wellcome Henry Dale)

4.4 IMPACTS ON THE ECONOMY AND SOCIETY

In addition to the Impact Cases returned (**Figure 3**), 15 patents have been filed by UoA5 staff, and two spin-out companies have been created (Links Logistics, **Day A;** GeneGini, **Day P**). A notable example is the patents granted for using TSG-6 to treat bone disorders and eye disease, which form the basis of a case to develop a spin-out company (**Milner, Day A**).

There have been multiple inputs into public engagement. Notably, **Davis** has written two books on popular science with the latest on the immune system (*The Beautiful Cure*), ranked as a Book of the Year in The Times, Telegraph and New Scientist, and translated into 15 languages. He has published a variety of articles including in The Times and Wired magazine and has made >50 media presentations over the REF period to discuss science related to his research, including on the BBC, ITV, Channel 4, and Radio 4, and has given a wide range of public talks at literary, science and music festivals in the UK and internationally. Similarly, **Cobb** has made extensive contributions to public engagement, writing two books on the history of science (*The Idea of the Brain* and *A History* and *Life's Greatest Secret: The Race to Crack the Genetic Code*), authoring three major radio programmes (on BBC radio 4 and world service), writing 29 popular science articles and giving 80 public talks. His 'Brain' book was long-listed for the Baillie-Gifford non-fiction prize 2020.

Our work on the fruit fly extends beyond the **Prokop** impact case (stimulating practical biology in schools) with **Hahn** presenting at the Manchester Museum as part of the Manchester Science Festival. This event also saw **Else** raise public awareness of parasitic infections in conjunction with the National Trust at Quarry Bank Mill, Styal, and **Brockhurst** generate an audio-visual interactive installation about disease transmission. **Cruickshank** has contributed to the climate change agenda by raising awareness of air quality issues in partnership with Manchester City Council. **Turner** presented at the BBSRC flagship Great British Bioscience Festival on "The Complex Life of Sugars". Multiple staff have engaged with patients and the general public, either directly or *via* the BBC (*Food: Truth of Scare?*) to explain the scientific basis of cancer (**Sharrocks**, **Nagarajan**, **Bruce**) and heart disease (**Shiels**, **Wang Liu**).