Note of the MCMB strategy workshop discussions – July 2017

Introduction

A workshop was convened during the afternoon of 4th July to explore key science needs and opportunities that fall within the Molecular & Cellular Medicine Board's (MCMB's) science areas. The purpose of this was three-fold:

- to identify important priority areas that will inform the MCMB's decision-making and broader strategic thinking within the MRC;
- to identify challenges areas that could be further development for targeted intervention; and
- to communicate MCMB's interests and priorities to the research community to help inform their work and stimulate demand in key areas.

The workshop included MCMB members and representatives from relevant MRC Institutes, Units, and Centres. The meeting discussed the three existing 'highlight notices' in the areas of Environmental exposure and chronic disease, Radiation oncology & biology, and utilising the facilities at the Research Complex at Harwell and considered whether to retain these as priorities and, if so, whether any changes were needed.

This note aims to capture the key messages from this meeting.

Understanding dynamic biological systems

The development and application of state-of-the-art technologies and quantitative, systems-level approaches provided exciting opportunities to understand and integrate complex and dynamic biology at different scales (genotype-to-phenotype, single cells, tissue, organism, including human and model systems) in health and disease. This will allow a much more sophisticated understanding of the functional interplay between genetics, signalling pathways and networks, and the spatial and temporal organisations that drive physiology/pathophysiology, and the design of more intelligent approaches to develop and target treatments. More specifically, these developments will allow researchers to:

- better understand fundamental cellular states, including the relationship between genotype and phenotype and the impact of the normal and compromised environment on these states;
- develop better experimental systems (cell, tissue, animal models), including tissue models that go beyond current approaches and introduce stroma, connective tissue, vasculature etc. Developments in genetic engineering and synthetic biology will play a crucial role;
- apply (and further develop) quantitative tools for integrating and interrogating different data types (multi-'omics, including protein, metabolites, genome/transcriptome/epigenome) with a focus on understanding the behaviour of single cells and the relationships between them within cellular populations;
- develop improved approaches to image across scales (bidirectional studies from molecular/structure-function, macromolecular, cellular, and physiology/in vivo). New biomarkers, chemical tools, probes, sensors and reporters (including genetically-encoded) will facilitate integration across platforms;
- employ bioinformatics, mathematics, artificial intelligence/machine learning, and computational modelling to analyse biological systems, and understand biological complexity and pathological readouts. This should link strongly with the broader HDRUK ambitions;
- apply knowledge to develop: gene and cell therapies; and cell and tissue engineering systems biology for drug target discovery/validation/development and understanding drug action, toxicology and mechanisms of resistance.

These challenges align well with the current MRC/BBSRC/EPSRC initiative Technology Touching Life (TTL) which aims to foster interdisciplinary research into innovative, and potentially disruptive, technological capabilities that will drive world-leading basic health and life sciences discovery research.

Action: Beyond communicating the needs and opportunities to the research community and stimulating ambitious new proposals, MCMB should explore opportunities to take this challenge area forward as an MRC priority, with the prospects of targeting significant investment. In this regard, TTL offers an excellent opportunity that should be explored (also ambitions in target discovery/validation).

Specialist infrastructure and technology

As analytical technologies become evermore sophisticated, mid-range equipment costs (ca £100k - £1.2m) continue to rise and it is becoming increasingly difficult for researchers to gain access to the collection of platforms needed to remain at the cutting-edge of their fields. Keeping up with the compute and data storage demands is also a growing challenge.

There is the need for the research community to strengthen coordination, cooperation and communication (3Cs) to build collaborative interfaces and maximise efficient use of specialist equipment and research impact.

Action: The MRC plays a crucial role in supporting UK equipment needs and should continue to seek new sources of capital investment to enhance UK infrastructure. There are also opportunities to invest in the linkup of data, data-rich assets and analysis systems (include specialist IT hardware) across the UK research landscape to maximise the utility and value of important assets and analytical technologies, and support broader and alternative analysis; MRC Institutes/Units could be used as a test bed.

There is also the need for improved support mechanisms for technology development. The current cross-Research Council TTL initiative offers one exciting opportunity to tackle this need and the MRC and partners should explore opportunities to expand these ambitions into a major funding initiative to deliver long-term impact. The development of the £100m Rosalind Franklin Institute[1] (RFI) as an innovative multi-disciplinary science and technology research centre offers another outstanding opportunity for technological innovation in the biomedical sciences. The overlapping interests of the RFI and Research Complex at Harwell (RCaH) at the interface of life and physical sciences highlights the need for strong connectivity between the two which could add renewed interest in utilising the RCaH's facilities.

Skills development

There remains the need to enhance quantitative and computational skills in biomedical research with integrative training in wet and dry lab research. This is critical to deliver against the vision for understanding dynamic biological systems but also more broadly across future biomedical research. This should include improve engagement with mathematicians, computational scientists, and physicists to attract important skills and new tools.

Action: The MRC should explore how these training needs might be tackled through future specialist studentships/fellowship investments, including through any future cross-disciplinary training partnerships under UKRI and the Government's recently announced National Productivity Investment Fund[2] (NPIF).

[1] The RFI will draw on expertise from across the UK. Its central hub will be based at Harwell in Oxfordshire, with linked sites at partner universities including Cambridge, Edinburgh, Manchester, Oxford, Imperial College, King's College London, and University College London. Initial technology foci are: x-ray sciences; correlated imaging (x-rays, electrons, photons); photoacoustic imaging; biological mass spectrometry; next-generation chemistry for health.
[2] A new £4.7 billion National Productivity Investment Fund (NPIF) was announced in the 2016 Autumn Statement. This will add an extra £2 billion a year for research and development by Summer 2020.

MCMB highlight notices

1. Environmental exposure and health

The introduction of the highlight notice in October 2012 has delivered a modest increase in demand across MRC's Boards and Panels but this has delivered only a marginal increase in MRC investment, especially within MCMB's area of interest in mechanistic and system-based approaches to explore the causal pathways between exposure and chronic disease. Since 2015, however, ODA-associated investments have increased through Newton and Global Challenge Research Fund (GCRF) initiatives.

Understanding the effects of environmental exposures on human health continues to be an important priority area for MCMB and the MRC more broadly. The key challenge is to understand the biological mechanisms of response to external insults (including mixtures) over time and how they lead to pathology.

Research should look to integrate complex exposure data with biomarker readouts of exposure and effect and explore the relationship between genotype and exposure effects on different cells and physiological systems. This requires strong partnerships with organ specialists e.g. respiratory, cardiovascular, hepatic, auditory (noise pollution) etc. New experimental challenge models need to be developed to investigate experimental exposures as do improved approaches to quantify exposures.

There is strong alignment in ambitions and challenges between environmental exposures and health, mechanistic toxicology and drug/chemical safety communities. There is, therefore, value in bringing complementary skills and interests together under collaborative programmes.

With major new funding available through the Newton/GCRF initiatives, there remain excellent opportunities to attract significant sustained investment over the coming years and it will be important that the UK research community capitalises on these.

Action: MCMB should retain a highlight notice that encapsulates the important needs and opportunities in environmental exposures and health. However, there is value in extending this into 'Exposures, biological mechanisms and disease' thereby addressing a broader set of interlinking research needs across the environment, toxicology and drug safety sciences:

- analysing multi-dimensional data;
- studying insults and the molecular/cellular/physiological readouts to disease, and the influence of genotype on these;
- developing computational models and experimental challenge systems to study exposures, biological effects and causal pathways;
- establishing robust translational pathways to policy, clinical setting, and industry.

Given PSMB's interests in environmental epidemiology, the join-up in priorities and messaging will be important. Future activities in TTL, including community engagement (e.g. workshops) and consortia-building should be used to outreach to complementary disciplines (e.g. personal exposure devices).

2. Radiation oncology and biology

Whilst notable efforts have been made over the last 10 years or so, the UK still lags behind leading industrialised countries in both radiation oncology research and medicine. A strong and vibrant research base is required to drive developments in cutting-edge clinical care.

Radiation oncology has been a priority area for MCMB since 2010 and a refreshed highlight notice was published in Autumn 2013. Whilst the highlight notice conveys clear commitment from MCMB in supporting research in this area, the increase in demand (and corresponding investment) observed shortly after its publication has not been sustained.

MCMB is keen to see hypothesis-driven research that moves beyond descriptive/correlative studies and explores the mechanisms underlying biological responses to radiation in malignant and healthy tissues, including through combination with drugs. Integrative approaches that explore the role of stroma, vasculature, and host immunological responses should be encouraged, together with a stronger link-up between UK excellence in DNA damage/repair and clinical studies.

Action: The current highlight notice should be revised to better communicate the new challenges and the need to apply cutting edge science and infrastructure (including imaging, molecular/cell analytical technologies). It is important that the MRC draws from the insights that will emerge from the forthcoming CRUK review of radiation oncology and aligns interests and activities where appropriate. MCMB should consider developing a workshop to engage important research communities and explore new approaches to tackle the major challenges in the field.

The MRC should also explore opportunities for training and capacity-building (e.g. through initiatives such as NPIF).

3. Research Complex at Harwell (RCaH)

Established in 2010 as a partnership between the MRC, BBSRC, EPSRC, NERC, STFC and Diamond Ltd., the RCaH serves as a research hotel to support life and physical science research that capitalises on the large facilities on the Harwell campus (Diamond synchrotron, ISIS neuron source and the Central Laser Facility).

Interest form the biomedical research community in locating research activities at the RCaH had fallen away since its establishment, resulting in under-use of MRC's space allocation; this trend was also seen by BBSRC. Diamond's development of high-throughput, automated sample-loading and remote access to crystallography data over the intervening years had been a principal driver for this reduced need for onsite working.

There were however, important new developments on the Harwell campus that could revitalise the need for use of the RCaH – including:

- the recent appointment of Professor Jim Naismith through the University of Oxford as the new RCaH Director in 2017. Professor Naismith is keen to enhance the utility of the RCaH for the biomedical sciences and will present his new vision for the RCaH at its forthcoming QQR in 2018/19;
- establishment of the National Electron Bio-Imaging Centre (eBIC) and XFEL Hub, and perhaps even a new generation of beamlines at Diamond; the RCaH could play an important role in developing new approaches to sample preparation;
- establishment of the hub of the new Rosalind Franklin Institute (2016-21) (and possible 'University quarter' at Harwell); There is significant complementarity in the interests of the RCaH and RFI in supporting the interface between the life and physical sciences and capitalising on cutting-edge and emerging technologies which offers important opportunities to develop strong future connectivity and possible joint working

Action: It was important for MCMB to continue to promote the opportunities and value of the RCaH through the website at the current time; this would not be positioned as a formal MCMB science priority. The Office should liaise with Professor Naismith to update the wording of the notice to improve the messaging around the scientific opportunities and the available facilities/technologies. The forthcoming QQR and RFI development will inform longer-term plans.

Annexes

1. Summary of MCMB's formal priorities

Annex 1

Summary of MCMB's formal priorities

The following will be used to help prioritise investments during Board ranking discussions:

1. Understanding dynamic biological systems
2. Exposures, biological mechanisms and disease
3. Radiation oncology and biology

These will be used in conjunction with the following corporate MRC priorities:

1. New investigators
2. Experimental medicine – using humans for discovery research
3. Advanced therapeutics