Post-Board/Panel Report

Name of Board/Panel: Molecular and Cellular Medicine Board
Date of Meeting: 12th/13th October 2016
Commitment Budget for this meeting: £12.5m
Volume of applications considered (Post- Triage): 41
Value of applications considered (Post-Triage): £34m
Number of awards made: 13
Funds committed: £12.6m

Notable decisions and discussions:

MRC-PHE Centre for Environment and Health (CEH) mid-term review.

The Board welcomed the mid-term report from the Centre Directors (Professors Paul Elliott and Frank Kelly, Imperial and KCL respectively), congratulating them on establishing the UK's preeminent investment in environmental exposures and human health, that remained strategically important for the MRC and continued to deliver very good value for money (from the core 5 year MRC - £3m, and PHE - £2.4m investment).

The Director had presented his ambitions to develop the Centre into a University Unit. However, the Board was not persuaded - the current Centre structure had some distance to go before establishing a clearly defined and coherent set of internationally-competitive research programmes (in particular drawing together epidemiology into mechanisms of exposure and disease causality); the current very broad portfolio of work, funding and geographic split-site better aligned with the looser centre model.

Nevertheless, in terms of national leadership, key stakeholder interactions (in particular regulatory / policy), and skills and capacity building in a strategically important area for the MRC, members agreed there was a case for exceptional centre funding beyond the normal 10 year timeframe. Any future application would need to clearly demonstrate sharper scientific focus and strengthen the use of the MRC-NIHR National Phenome Centre in analysing biological samples to improve our molecular understanding of how exposures affect public health.

MR/P010105/1 Graham Jackson, MRC Prion Unit, 48 months, Value: £929k, Title: *Development of enhanced methods for the screening and diagnosis of prion disease*
This work was **declined** by MCMB after first being considered as part of the recent MRC Prion Unit QQR in 2015. The primary objective was to further develop existing methods to ultimately refine the applicability of a diagnostic test for human prion disease. The main concerns for the Board were: a lack of feasibility data regarding the assays involved in the research proposal, limited clinical need, and a lack of novelty. Furthermore, the justification for the high level of resources requested had not been made. The Board recognised potential to apply similar assay strategies to other neurodegenerative diseases, which could have greater clinical utility given higher prevalence levels.

MR/P010555/1 Paul Elliott, Imperial College London, 5 years, Value £2.2m, Title: Mechanistic pathways linking ambient air pollution exposure to atherosclerosis and cardiovascular disease.
Paul Elliott is the director of the MRC-PHE Centre for Environment and Health, and Chair of PSMB.

Declined. The programme of research to investigate the mechanistic links of exposure to atherosclerosis / cardiovascular disease was suitably ambitious, from a very strong group and supportive environment, and in a strategically important area. It drew on a range of short- and longer-term exposure studies, including the recent Newton-funded award to the Centre as part of the MRC-NERC 'Atmospheric pollution and human health in a China megacity' programme.

However, there were notable the risks in delivering meaningful outcomes from analysing the complex and heterogeneous array of data inputs- proof-of-principle analysis to help demonstrate definitive links between exposures and biomarkers to mechanisms and disease

was missing. Whilst the programme was interesting, ambitious and in a priority area, the Board was not sufficiently confident that the plans would be fully realised.

Wellcome Trust MRC Cambridge Stem Cell Institute, University of Cambridge, Director: Professor Tony Green. Centre renewal; Cost to MRC: £3.3m; Score 9.

Overall Assessment: This award secures the second tranche of 5 year Centre funding available under the MRC Centre Scheme. The Board agreed that under the refreshed leadership of Professor Green and with long-term university commitment, the Institute would continue to deliver excellent science and was well positioned to pursue the translational opportunities (key themes – stem/progenitor cell biology in health; stem/progenitor cells in disease – malignancy and regenerative failure; disease modelling; and cellular therapeutics). With this success, CSCI would be seen not only as an internationally leading centre of excellence in stem cell biology, but also in its application to human health needs. This offered excellent value for money for MRC, and the Board was strongly supportive of continuing strategic investment in CSCI.
Training: The award includes renewed support for the "MRC Physical Biology of the Stem Cell" doctoral training grant which specifically targets interdisciplinary training opportunities across physical and biological sciences in the stem cell field which had been very successful to date.
Mid-Term Review: Given previous challenges in the Institute being able to demonstrate delivery against the Institute's translational agenda, and some uncertainties around the new Director's bottom-up translational strategy and new management structure needing refinement, the Board mandated the second Mid-Term Review should focus on this aspect of the Institute's work and ensuring leadership structures were fit for purpose.
Sustainability beyond MRC Support: The CSCI will move into the University-funded £55m new build "Capella" building, occupying 55% of the footprint in 2018. The University demonstrated the longer term strategic importance of CSCI to their research strategy, providing additional support to the Institute's early career researchers (tenure track scheme, posts) and infrastructure (especially to manage capital needs with the move to Capella) when challenged. Whilst it is unclear what the future of Wellcome Trust support will look like in five years time, the Board were reassured that the longer-term future of the Institute was secure.
Addendum: *Since the Board, The Wellcome Trust has made their (separate) decision (as part of their wider Centres Competition) to also renew their support at a cost of £9.8m; a further £2.5m is likely to be secured from renewing WT support for their PhD Studentship programme in the Institute. This represents excellent leverage for MRC. The Award will be administered by the Wellcome Trust on behalf of both funders, excepting the MRC DTG.*

MR/P010008/1 Kamil Kranc, University of Edinburgh, 36months, Value: £476k. Title: Therapeutic targeting of HIF prolyl hydroxylases in acute myeloid leukaemia.
Awarded. This was an ambitious proposal from a very highly regarded researcher building on recent important observations on the differences between normal haematopoietic and leukemic stem cells. The proposal brought together complementary expertise from other institutions (Oxford, Manchester, Heidelberg) to usefully combine mouse and human research which could unlock new therapeutic opportunities in an area of on-going clinical need.

MR/P010156/1 Anthony Carr, University of Sussex. External Scientist Staff (ESS).
Declined. The application was looking to take forward a new strand of work, after the core interests of the lab following on from the previous programme grant had recently been supported through a Wellcome Trust Senior Investigator award. This application was not competitive due to concerns over how translatable the recently published yeast findings would be to the human systems. The applicant was invited to submit an amended application for funding within 6 months.

MR/P010016/1 Roberts Stefan, University of Bristol, Value: £1m. Strong proposal, that couldn't be funded, because of financial constraints and was thus held over to the February 2017 meeting.

Intramural discussions / decisions (if applicable):

QQR of the CRUK/MRC Oxford Institute for Radiation Oncology, Oxford
The Institute represented a unique investment in the UK and there were clear signs of the added value that long-term core investment provided and it was important to continue supporting the Institute in Oxford at this time. In the next QQ the Institute should aim to improve the overall quality of the radiobiology science, build on the interface between basic and clinical research and treatment, and develop of a larger cadre of excellent clinical programmes led by clinician scientists and increase the scale of external funding. In turn the University and NHS Trust needed to deliver urgent and significant infrastructure investment to sustain the OIRO as an internationally leading research institute in radiation oncology and improve cancer treatment. The MRC, CRUK and University should start recruitment plans in early 2017 for a new Director to succeed Professor McKenna when he steps down at the end of September 2019. The next five years would be crucial in determining the long-term success of the Institute. The Board agreed to support the Institute at the level of **£17,221k (92% level funding**) over the next QQ, which included **£2,187k** financial headroom to establish the new Director's programme.

Pre-QQR strategy discussion for PPU
The current Director had taken over directorship in 2012 and the upcoming QQR provided a timely opportunity to reflect on the evolution of the Unit and the recent changes to the Division of Signal Transduction Therapy (DSTT) programme.

Members agreed that the PPU continued to occupy an excellent research niche, with a coherent set of programmes. An impressive aspect of the Unit was its ability to identify and prioritise signalling pathways relevant to human diseases. The current Director had also reinvigorated aspects of the Unit's research following departure of some key personnel at the last QQR.

The future vision presented by the Director indicated exciting new opportunities applying Unit skills in a range of medically-relevant areas, for example expanding the Unit's on-going focus in unravelling signal pathways of parkinsonism with good plans to access mouse models at MRC Harwell. The Unit had clearly built an excellent set of academic and industrial partnerships that would continue to complement and capitalise on core Unit strengths.

A particular strength of the Unit is the on-going Division of Signal Transduction Therapy (DSTT) industry partnership that provides a model for the early, highly iterative stages of translation in the pre-competitive space. Members noted that the DSTT partnership was being renewed with some modifications, the QQR would be an opportunity to clarify any potential impacts.

Members acknowledged the continued progress in rebalancing of junior versus senior programme leaders, and that the QQR would be an opportunity to further consider difficulties in recruiting to clinical positions at the Unit, in conjunction with discussions with the University. However, members drew particular attention to gender balance, noting currently there was only one female programme leader. It would be important in the QQR to understand any issues related to this (e.g. staff recruitment process and outreach to the research community).

NIRGs/Preliminary NIRGS (1 awarded from 1 considered at Board):

MR/P010334/1 Mcintyre Alan, University of Nottingham, 36 months, Value: £435k Title: Defining the role of FOSL2 in molecular adaptation to hypoxia in colorectal cancer

Programme Grants (2 awarded from 7 considered at Board):

MR/P010121/1 Caldecott, Keith, University of Sussex, 60 months, Value: £2m, Title: Cellular and Pathological Responses to Chromosome DNA Single-Strand Breaks

Tissue culture costs pruned by £100k, awarded pending confirmation that there was no overlap with ERC funding held by the applicant. It was confirmed post-board that the application was distinct.

MR/P0502005/1 Oliver Peter, University of Oxford, 36 months, Value: £999,967.61, Title: Investigating Novel Stress Response Pathways in Neurological Disease.
The Mammalian Genetics Unit (MGU) received 90% level funding (£34.2m) following the 2014/15 QQR but was invited to apply for two additional, new core programmes in 2015/16 to take its core funding back to ca 100% (£38m). Professor Fisher's award was approved in February 2016 (MR/N501931/1, "Novel and Bespoke Mouse Models for Dissecting Neurodegenerative Disease", 4 years, £1,766,285.36) but Professor Oliver was asked to reshape and resubmit his application. The resubmission was subsequently awarded and together these two programmes have strengthened the focus on neurological disease and brought total core investment for the current QQ to £36.97m (97% level funding).

Both the Oliver and Fisher awards will be rolled into core MGU support.

Applications with Joint Funders:

MR/P010393/1 Dale, Nicholas, University of Warwick, 48 months, Value: £773k, Title: Structural and biophysical basis of Connexin26 channel mediated disease
A 30% BBSRC co-funding commitment has been adjusted against this application

List of all Grants Awarded

Grant Reference	Applicant/PI	Research Organisation	Grant Title	Fund amount*
MR/P010091/1	Futter, Clare	University College London	The regulation of endocytic sorting and cholesterol transport by PTP1B-mediated ESCRT dephosphorylation at ER-endosome membrane contact sites	£451,622
MR/P010393/1	Dale, Nicholas	University of Warwick	Structural and biophysical basis of Connexin26 channel mediated disease	£772,839
Centre	MRC Cambridge Stem Cell Institute renewal	MRC Cambridge	QQR of the Wellcome Trust-Stem Cell Institute renewal, Cambridge	£3,300,000
MR/P010008/1	Kranc, Kamil	University of Edinburgh	Therapeutic targeting of HIF prolyl hydroxylases in acute myeloid leukaemia	£479,462
MR/P010121/1	Caldecott, Keith	University of Sussex	Cellular and Pathological Responses to Chromosome DNA Single-Strand Breaks	£1,973,108
MR/N030117/1	Brown, Nicholas	University of Cambridge	Making connections with GO: an integrative approach to highlighting medically relevant Drosophila data	£896,172

MR/P009948/1	Surani, Azim	University of Cambridge	Human germline in vitro models for development and the epigenetic program	£632,196
MR/P01058X/1	Norman, Jim	University of Glasgow	The role of the transfer RNA repertoire in generating secretory phenotypes during epithelial homeostasis	£1,315,852
MR/P010423/1	Nichols, Jennifer	University of Cambridge	Defining the prerequisites of naïve pluripotent human embryo cells for self-renewal in culture	£678,292
University Unit	McKenna, G	Oxford Institute for Radiation Oncology, Oxford	QQR of the CRUK/MRC	£321,000
MR/P010334/1	McIntyre, Alan	University of Nottingham	Defining the role of FOSL2 in molecular adaptation to hypoxia in colorectal cancer	£434,938
MR/P009972/1	Gaughan, Luke	Newcastle University	MICA: Characterisation of a novel bromodomain inhibitor AZD5153 in castrate resistant prostate cancer	£311,444
MR/P502005/1	Oliver, Peter	University of Oxford	Investigating Novel Stress Response Pathways in Neurological Disease	£1,008,067
MR/P010016/1	Roberts, Stefan	University of Bristol	The role of Wilms tumour 1 in the mitotic checkpoint	£451,622

* Funds committed are subject to change and are not finalised until RO has submitted start certificate.

Post-Board/Panel Capital

Grant Ref/PI/RO	Capital Requested	Capital Awarded	HEI Contributions
MR/P010393/1/Dale/Warwick	£64,066	£64,066	£32,033
MR/P01058x/1/Norman/Glasgow	£100,000	£100,000	£50,000