Neurosciences and Mental Health Board (NMHB) Scientific (QQR) Review of the MRC Prion Unit, London Director: Professor John Collinge

Report of the NMHB Visiting Subcommittee

Subcommittee Visit 19th & 20th March 2015

Introduction

The MRC undertakes scientific reviews to be assured of the strategic justification, scientific excellence and value for money of the work being carried out within its Units and Institutes. These reviews take place every five years and are known as quinquennial reviews (QQRs). The process is designed to assess the Unit overall through an evaluation of the quality of its individual scientific programmes, Unit-wide research-related activities, and the added value of the whole. The process enables clear and strategic decisions to be taken about the value of the MRC investments within the national and international landscape.

The Prion Unit Director submitted the Unit Report in July 2014. A Subcommittee (SC) of national and international experts was convened under the Chairmanship of Professor Hugh Perry (Chair of NMHB), to assess the Unit's past performance since the last review in 2009 and to assess the proposed future programmes and strategy. All members of the SC were requested to declare any of conflicts of interest and these are recorded at **Annex 1**. The SC provided an expert assessment of the quality, impact and productivity of the Unit and research programmes in line with the Terms of Reference for the review, which, along with the Subcommittee Membership, can be found at **Annex 2**. The views of the SC were also informed by comments received from expert reviews of each scientific programme and the Unit overall, and the Director's written response to these.

The SC met twice: an initial advisory meeting was held at MRC Head Office (London) on 2 October 2014, followed by the site visit to the Unit on 19-20 March 2015. Additional members attended the site visit, with written comments obtained from original members who were unable to attend.

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The Subcommittee's feedback to the Unit following its first meeting is available on request. Prior to the second meeting, the Director provided a written response to both the reviewers' comments and issues raised by the Subcommittee at its first meeting, together with an update on the Unit's activities/achievements since submitting its report.

During the site visit, the Director and Programme Leaders introduced the key features of their programmes and any notable updates since the submission of the report. The SC led a 'Question and Answer' session with each Programme Leader to clarify issues including any

concerns. Discussions were also held between the SC and senior staff from UCL[1] to probe the strategic and financial support for the Unit from the University.

Alongside reports on the scientific programmes, the Unit also submitted a breakdown of resources for both the past and future programmes and the Unit as a whole. To help the SC assess the Unit-wide research related activities (resources and value for money; training, career development and capacity building; knowledge transfer, and public engagement), MRC Head Office staff provided comments and identified some issues that required further clarification.

This report is not intended to be a verbatim transcript of the visit; rather, it focuses on the criteria the Subcommittee were asked to assess and key issues that emerged from the discussions that have a bearing on the final conclusions and recommendations.

The initial, summary feedback document handed to the Director at the end of the visit is superseded by this report, which adds further detail to the feedback provided on the day and additional commentary to be considered by the Director.

Subcommittee Conclusions and Recommendations

UNIT OVERALL

Score – Unit Overall	
Past work (4 years):	**9**
Future proposals (incorporating proposed cuts)	**8**

Past

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Across the field of prion research, the Subcommittee observed that the Unit's research had made novel and important contributions to describing clinical aspects of prion disease in humans. However, the Unit had not taken a leading role, or integrated substantially, what were widely considered to be the two most important developments over the past five years, namely, the methodology for amplifying misfolded proteins and studies of prion-like transmission of misfolded proteins in other neurodegenerative disorders.

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The benefits of collaborative working within the Unit were acknowledged. However, the large number of co-authored publications, the majority in co-authorship with the Director, made it

[1] President & Provost (Professor Michael Arthur), Head of UCL NIHR Biomedical Research Centre (Professor Bryan Williams)

difficult for the Subcommittee to distinguish either the individual intellectual contribution of each Programme Leader or their career development/trajectories.

While the focus of the Unit was primarily on prion disease, its valuable role in major consortia addressing the genetics of other neurodegenerative disorders was recognised. In addition, the Subcommittee noted that the Unit had developed work on potential links between underlying mechanisms in Alzheimer's and prion disease for example on PrPc as a receptor for toxic A-beta.

Future

A programme of work was presented for the future that, for the most part, was scientifically strong and of very high quality. Many elements of the work were internationally competitive but some programmes or elements of programmes were less so, and could not be recommended to the Board for support by the Subcommittee.

The Subcommittee recognised the collaborative nature of the work in the Unit, however the case for overall Unit support was considered to be poorly structured. The future plans were weakened by the lack of clarity and distinctiveness between the programmes. Within each programme the long term aim was often unclear, with many programmes presented as a series of experiments lacking cohesion or a distinct 'narrative thread'. This aspect had increased since the last QQR. For the Unit's future success, it is strongly recommended that individual programme leaders are able to demonstrate their intellectual freedom in driving their own research programmes within the overall framework of the Unit's mission.

The strategy to include structural work in the Unit's portfolio was endorsed strongly by the Subcommittee. Although indicative plans were set out in the Report, the relevant programme was not considered to be viable in the absence of a dedicated Programme Leader from the Unit. Future plans for structural biology would therefore need to be assessed by MRC at such time as a high calibre, independent individual had been identified by the Director.

It was evident during the visit that the Unit as a whole lacked areas of expertise that could benefit the Unit, for example, a full appreciation of the complexities of the behavioural and cognitive tests necessary for neurodegenerative diseases research, or to pursue functional neuroscience in areas such as live cell imaging.

The strategic rationale for establishing the Unit in the 1990s arose because of the public health threat from prion disease. In 2015 it was clear that the level of risk had changed. Good public health measures were in place and there were no longer diseased cattle within the UK food chain. In this context, members discussed the balance of MRC funding across the neurodegenerative diseases portfolio. Prion disease was a relatively rare disorder, yet received a higher, and possibly disproportionate, level of MRC funding compared with much more common conditions such as Alzheimer's and Parkinson's disease. Over one quarter of the MRC's neurodegeneration budget (£209.3m from 2009/10 to 2013/14) was spent on prion disease research (£56.2m; 27% by value), with less spent on Alzheimer's disease (£45.0m; 22% by value or Parkinson's disease; £48.5m; 23%).

In this regard, an important consideration was whether greater insight might be gained from overlaps between prion and other neurodegenerative disease genetics and biology in mouse or human work, giving rise to new routes of investigation. The extent of such insights was as yet unknown and the Unit's plans for investigating or influencing other neurodegenerative disease areas are still not extensive. Apart from Programme 1 (genetics), the Unit's outreach to external groups within and outside the prion community was viewed as overly selective. The Subcommittee advised that the wider neurodegenerative diseases community could benefit from increased interaction with the excellent scientists in the Unit, which would also provide mutual benefit.

Resources and value for money

The Unit had requested a budget of £35m (including £1m for additional studentships) representing an increase of 10% on level funding at £31.7m (adjusted for inflation). The Subcommittee concluded that this was not justified, given that the future programmes were not of uniform quality.

The Subcommittee also raised concerns regarding the value for money of the Unit as presented. For example, several of the programmes contained uncompetitive elements, while a number of posts lacked clear justification, e.g. the large number of animal technicians (particularly in light of potential reductions in the number of animals required) and the full-time graphics manager post for the production of high quality images for all areas of publication, including videos, the website and audio-visual assistance.

Accordingly a reduction in resources was recommended on a programme-by-programme basis, as further detailed in comments on each programme.

In the area of training, the Subcommittee recommended that eight MRC studentships should be allocated to the Unit over the quinquennium, representing a reduction from the present level of two per annum ie a reduction to one per programme. However the length of these awards should be extended from three to four years as proposed, representing a small overall increase in resource allocation (see section below on Research training, career development & capacity building). The allocation of studentships to programmes should be more transparent.

It was noted that the Unit was unique among MRC Units in that it did not have a broad portfolio of external income and relied almost entirely on MRC core support, supplemented by MRC strategic awards. The clinical programmes were supported by additional NIHR BRC funding. The Subcommittee recommended that more external awards should be sought in the next quinquennium to add scientific diversity, as well as value, to MRC core funding.

The Subcommittee provided advice on the capital equipment requests for the future, as well as for the additional requests for capital and support staff in light of the proposed move to the Courtauld Building. These are summarised in Annex 3. The future location of the Unit and associated issues such as removal and refurbishment costs were matters for consideration by MRC Management Board and Council alongside the final outcome of the quinquennial review. Proposals for transition to a University Unit would be considered by MRC and UCL once the outcome of the quinquennial review was known.

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Ethics and Research Governance

The Subcommittee did not identify any ethical issues requiring detailed consideration.

Unit-wide research-related activities – Assessment and Advisory comments

Knowledge transfer

Overall, the Subcommittee agreed that Knowledge Transfer was satisfactory. Some of the Programme Leaders were noted to be engaged in UK government Advisory Committees as well as international organisations (examples are that Professor Mead is a member of the Department of Health Advisory Committee on Dangerous Pathogens Transmissible Spongiform Encephalopathy (TSE) Subgroup and Dr Wadsworth is on the WHO International Expert Consultation group on tissue distribution of TSE infectivity). An effective relationship between the Programme Leaders and MRC Technology had been maintained over the past quinquennium and this was expected to continue for the future. The Unit had a long-standing collaboration with GSK for the small molecule programme. The Unit provided data on the distribution and sharing of materials and data to the Subcommittee. This included:

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GRO-B There was no overarching Unit policy, nor clear plans to implement a policy. Other types of sharing were reported as being decided on a case by case basis under the guidance of the Director.

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INDIVIDUAL SCIENTIFIC PROGRAMMES

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Programme 8

Programme Leader: Professor John Collinge

Programme Title: Prion kinetics, toxicity and synthesis and its wider relevance

Science

The Subcommittee commended Professor Collinge's past work, which was excellent and of outstanding scientific quality. He was an internationally recognised leader in his field. A major finding during the quinquennium was the discovery of the association between prion proliferation/infection and toxicity. This finding supported an original overarching hypothesis that had acted to stimulate the prion field as a whole. The development of the small molecule work had progressed well and the Unit had received an MRC DPFS award for further studies. The transformation of the Unit's cell-based prion assay through automation (automated scrapie cell assay) was an excellent achievement.

Dr Kloehn had left the programme, to lead Programme 5. He had been promoted from PLT to PL in 2014.

The future programme, while of excellent scientific quality, was not as compelling in terms of coherent scientific vision. The plans were less focused than the past work and lacked a clear narrative. Some significant questions were not answered to the satisfaction of the Subcommittee, for example about how neurotoxicity would be assayed (see also programme 4) or whether the Unit could usefully begin to study biomarkers that were upstream of the prion molecule in the infection process.

The Subcommittee doubted whether the Unit's measure of neurotoxicity was sufficiently well defined in the context of disease progression. This was due to the fact that while infectivity could be measured with precision, neuropathological measures were much harder to quantify (and had not been used in their previous studies), while different populations of CNS neurones vary in their susceptibility to prion infection.

Resources

The effort and costs for the different elements of this substantial programme were unclear. The Subcommittee asked the Unit to prepare a clear breakdown and justification of the costs per project of this programme for the Board.

Score	
Past work (4 years):	10
Future Proposals:	9

Programme 9

Programme Leader: Dr Graham Jackson

Programme Title: Molecular diagnostic strategies in prion disease

Science

Dr Jackson's significant contribution to the Unit across a number of programmes was acknowledged by the Subcommittee.

Past productivity was good and had resulted in the development of a novel human blood-based prototype test for prion protein (DDA test), which was currently being used as a diagnostic tool in a research setting. The DDA test was a major achievement that was recognised to be world-leading compared with the other types of test that were available, although it was recognised that further development work would be necessary if the test were to be used in the future as a screening tool.

The test was 98% specific but at around 71% sensitivity in people with disease it is currently unsuitable for population screening. The sensitivity in infected people without clinical disease was unknown. To date, the Unit had not produced evidence that sensitivity of the DDA test could be improved, although had suggested that there may be variability in prionaemia as a clinical feature of disease with only a subset showing infectivity. The Subcommittee expressed concern that this tool would therefore be inappropriate for screening because of the potential for a large number of false negatives within any population screen.

The emphasis of the future plans was the extension of the work on prion tests to include amplification strategies (the Protein Misfolding Cyclic Amplification Assay (PMCA) and the quaking-induced conversion (QUIC) method combined with matrix capture) as potential ways to improve detection limits and to extend the range of body fluids that could be tested. This work was intended also to better define the range of prion isoforms that are now known to occur following infection. There were also plans for assay automation and on quantitative seeding using the DDA to establish the best molecular markers for disease progression.

The Subcommittee discussed whether and how the DDA test could be developed further and if this work should be within the Unit or outsourced to a commercial partner. However the Unit had explained that attempts by MRCT to find a commercial partner to develop the DDA test had been unsuccessful to date. Dr Jackson had clarified that the Unit had tried to increase the sensitivity of the DDA test but had found that sample volumes needed to be upscaled, leading to the decision to focus in the future programme on prion amplification methods, alone or in combination with the DDA test. He further explained that while human-based biomarker work needed to take place in category 3 containment facilities in the Unit, rodent-based biomarker work could take place outside the Unit provided local ethical and safety committees were satisfied. The Subcommittee noted that this opened the way for working in collaboration with other groups.

It was relevant that a collaborative study using the Unit's DDA test was being proposed by the National Blood and Transplant (NBT) and National Institute for Biological Standards and Control (NIBSC). The purpose was to increase assay throughput and sample handling with a view in the future to using the assay in a UK population study. This work was being proposed under the auspices of the TSE Subgroup of the Department of Health Advisory Committee on Dangerous Pathogens, following the July 2014 House of Commons Science and Technology Committee Report on blood safety and the risk of vCJD. GRO-B

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The Subcommittee was not persuaded that the Unit's proposals for new work on prion PMCA and QUIC tests in combination with the DDA test were sufficiently novel or of high enough quality to justify continued effort as the main focus of the future quinquennium. This work was resource-intensive and other international laboratories were already well advanced in this area. The plans for biomarker work were also not viewed as cutting edge.

Additionally, in the absence of preliminary evidence that sensitivity could be improved, the Subcommittee could not recommend that core MRC support should be used for continued refinement of the DDA test over the full quinquennium. It was noted that both these issues would require further discussion by both the Board and Management Board.

Resources

The Subcommittee did not support continuation of core support for further work on the prion blood test (DDA test), and did not regard the proposed studies on the PMCA and QUIC tests and biomarker work as internationally competitive. Following the Subcommittee meeting, Management Board was asked to clarify the MRC's position core support of the DDA test reported in the footnote below.[3]

The Director was encouraged to use Dr Jackson's skills through the refocus of other programmes.

Score	
Past work (4 years):	8
Future Proposals:	7

[3] In light of continued work on the blood test since the submission of the Unit's report, Management Board confirmed that core Unit funding for this aspect was appropriate for a further period of up to 12 months maximum. Beyond this, any future support to carry on work on the blood test will need to be submitted to NMHB for assessment.

Annexes

Annex 1	Conflicts of Interest
Annex 2	Membership and Terms of Reference of the Subcommittee
Annex 3	Subcommittee comments on the capital equipment requests for the next quinquennium and on the additional capital and staffing requests in relation to the transfer to the Courtauld Building

Annex 1

Conflicts of Interest

The following specific interests were noted at the Site Visit on 19th & 20th March 2015:

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Annex 2

Terms of Reference and Subcommittee Membership

Terms of Reference for the Scientific (QQR) Review of the MRC Prion Unit

1. To report to NMHB on the Unit in the context of progress, issues and opportunities in Prion disease research worldwide; including both translational progress and the contribution of prion research to wider research in neurodegeneration.

2. To assess the progress of the Unit's work, in both discovery research and translation; (including progress against expectations from the 2009 QQR). Significant issues with accommodation have disrupted the Unit's research during the current QQ period. The overall disruption should be considered equivalent to the loss of at least one year's work and the current QQ should be assessed in relation to a 4 year period of productivity rather than 5 years. This will be formally notified to the referees, QQ panel and Board.

3. To assess the Unit's future strategy overall, including scientific directions; balance between research areas; coherence; external partnerships / coordination; and added value from Unit support with core funding in the UCL environment In addition, to assess the future strategies for translation, external collaboration with public and commercial sectors, and contributions to wider neurodegeneration science.

4. To assess future proposals in each programme / area, relative to competitive funding standards, and taking into account importance, quality and value for money.

5. To assess the Unit's training and career development strategy and achievements.

6. To recommend to NMHB:
   - whether the work of the Unit should continue and if so on what scale and in what form;
   - realistic expectations for the development of the Unit's work over the next five years.

Subcommittee Membership

Name	Institution
Professor Hugh Perry (Chair)	University of Southampton and Chair, NMHB
Professor John Atack	University of Sussex and NMHB member
Dr Rob Buckle	Director of Science Programmes MRC Management Board Representative
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Members unable to attend Subcommittee meeting but are providing written comments	
Name	**Institution**
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MRC Observers and Office Staff	
Professor Jim Smith	MRC Deputy Chief Executive and Chief of Strategy, Director of the National Institute for Medical Research (MRC Council Observer)
Dr Kathryn Adcock	Head of Neurosciences and Mental Health
Dr Catherine Moody	Programme Manager, Neurodegenerative Diseases and Stroke
Mrs Anne-Marie Philp	Head of Scientific Reviews