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MRC Neuromuscular Centre External Advisory Board (EAB) Report

14 November 2014

The EAB was provided with extensive written documentation of the activities of the MRC Neuromuscular Centre for review prior to the EAB meeting. The EAB met with Centre leadership on 14 November 2014. All project and core leaders from both UCL and Newcastle were in attendance. A poster session and meeting with all graduate students and post-doctoral trainees (from both UCL and Newcastle) gave opportunity to assess the quality and work of trainees.

This report considers both: (1) the progress and possible modifications/additions to the current program; and, (2) the proposed evolution of the Centre to a novel focus on the Experimental Therapeutics of Neuromuscular Disease.

Current activities and progress of the Centre:

The previous and current award cycles have been impressively successful. Key to the success was the centralization and harmonization of knowledge, patients, and methodology (experimental, education, biobanks) within the Centre of two world-leading academic centers (UCL, Newcastle). The reports provided to the SAB were impressive, with excellent documentation of outstanding progress made on all projects and aims. The Centre has achieved all stated goals and exceeded targets on each metric and milestone. They have a clear national outreach for nearly all neuromuscular disorders in both children and adults. They have integrated key 'omics technologies into patient characterization, as well as creating strategic investments and research into clinical and imaging outcome measures. The integration of basic science into molecular pathogenesis research of the gene-stratified cohorts is impressive. The group has been central in promoting new areas of therapeutics, as well as proactive recruitment of many patients into multi-site clinical trials.

MRC Centre investigators have been successful in leveraging the MRC Centre grant to secure further sources of support (both UK and EU). They have also been successful in obtaining support from USA NIH and FDA in support of rare disease networks and clinical trials, in both neuropathies and myopathies. They have been successful in influencing NIH policy statements, as well as EU policy. The critical mass of both basic research and clinical investigators seamlessly integrated into translational research programs for neuromuscular disease is an example for rare disease research worldwide. The UCL and Newcastle groups were very tightly inter-digitated and coordinated, with ample evidence of synergism. Previous reports of the SAB noted that integration of the two geographic sites needed improvement, and this has now been accomplished across all five disease-focused groups. This integration has been extended to cover all of the

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UK as well as the EU and the U.S. for all five disease groups. Implementation of the six core support services seems now well-established, with clear evidence of providing expert service to the Centre, and extending this throughout UK, Europe and North America.

Key strengths are the initiation and successful development of global registries, progress on stratified patient cohorts numbering well into the thousands, centralized biobanks, gene identification using next generation sequencing, clinical outcomes research, and the concierge function of targeting stratified patients to clinical trials. Both the PhD program and the MD/PhD training appear to be very well organized, of outstanding quality, with excellent productivity. The post-doctoral fellows also appeared well trained and positioned for retention and future careers in neuromuscular disease research. The posters presented by the students and fellows were polished and well-described and defended by the presenters, with a clear motivation of the role of MRC Neuromuscular Center.

Opportunities for Enhancing the Program:

Education: The program could develop approaches that provide training. in industry practice, alternative careers, rigorous design and reporting of both pre-clinical and clinical trials. Appropriate expertise and coursework is available within the broader university-based curricula at both UCL and Newcastle. The EAB felt that the program could guide and encourage such training systematically. Given the academic success of early trainees and the continuing expectation that most trainees will pursue research careers, the EAB suggests that Centre leadership work to enable young MD investigators to apply for their own grants. The Centre has done an impressive job of funding physicians doing research. However, UK NHS clinical training schemes seem particularly rigid (because of the emphasis on NHS training and inherent difficulties in being released from clinical training to do research training such as a 3-4 year PhD). Sometimes translational research work may not be recognized in the clinical training career path. Centre investigators could provide more influence at the policy level. This will also be important in future to open career perspectives for clinician-scientists with academic ambitions and the Centre could play a major role in this by devising 8 year combined clinical and academic training programmes linked to the Centre in order to generate such future clinician scientists.

It was clear to the EAB that host institutions in NCL and UCL had strongly supported the MRC Centre in the last renewal. This support has resulted in a centre that has matured further in its second funded phase and we consider it arguably the leading centre in the world in neuromuscular translational research. Future success of the Centre beyond the current funding phase will require continuing strong host financial support. The EAB were encouraged by the evidence of robust, continued host support by the formalization of the 'named' Newcastle and London programs (the John Walton Centre and the plans to develop a UCL Department of Neuromuscular Disease in 2015). The EAB strongly endorsed these developments and an excellent way of creating and funding key infrastructure to maintain the Centre at the leading edge and to enable success in the plans to seek external funding to develop into a new experimental therapy centre. The EAB agree that strong host university and BRC support were both critical. This infrastructure will promote the future MRC Centre, as well as leveraging other funding.

Community involvement. The EAB felt that there was a strong international movement towards more active involvement in engaging the patient community in advice and guidance of research Centres. It is clear that both Newcastle and UCL, and many of the international groups they lead or participate in, have active patient involvement. Indeed, the TREAT-NMD network, and many of the EU programs have outstanding stake-holder engagement. However, part of the movement of rare disease groups worldwide is to engage patients/stakeholders in pragmatic advice to the Centre.

Industry involvement. Industry engagement has been a strength of the Centre's research going forward. Industry advisors could be included as part of advice and guidance, much as stake holders could.

Repurposing drugs and Bioinformatics. The stated new goals of the Centre going forward is to bolster and develop bioinformatics research. The EAB agreed that these are important areas of further development. It will be important for the website to reflect the new and developing strengths of the Centre.

Transition to new 2018 MRC Centre

The transition to the 2018 proposed MRC 'new' grant was a key focus of discussion. The EAB endorses the proposed 'new' focus to a broadly-based program of experimental therapeutics, with the stated goal of developing disease modifiers and treatments to improve patient lives. The EAB considered that the platforms (patient cohorts, biobank, trials and outcomes capabilities and MRI biomarker development) that the MRC Centre has developed will be critical to underpinning a new therapy centre. An initial investment and reasonable ongoing support from the host universities and the host Biomedical research Centres at UCLH, GOS and Newcastle is likely to yield a splendid return on investment in terms of grants, intellectual property and other aspects.

It was clear that the Centre has begun developing the focus, objectives, themes, and organization of the future new Centre. The EAB felt that the conceptualization of the new experimental therapeutics approach was a logical next step, and perfectly appropriate for the 2018 application. The overall infrastructures able to support development of novel therapeutics for orphan diseases drug pipeline will include:

- Drug discovery, chemistry
- Pharmacology, toxicology, pharmacogenomics (particularly in context of stratified medicine), pharmacokinetics, pharmacodynamics
- Orphan drug designation, regulatory infrastructure
- Formalized pre-clinical efficacy trials (proof of concept)
- Clinical trial programs (phase 1, 2a, 2b)
- Biomarker discovery (pharmacodynamics, surrogate biochemical outcome)
- Accelerated approval approaches
- Post-marketing clinical efficacy
- PCORI (patient centered outcomes research, QOL tools)
- Intellectual property approaches traversing all of above.

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- Innovations in financial streams and funding strategies (venture philanthropy, public/private partnerships)
- Data stewardship
- Integration of all programs into TREAT-NMD TACT review and other international study groups.

It is not expected (or even desired) that the new Centre would be well-equipped to carry out all of the above areas. But they need to be acknowledged, with plans for strengthening certain areas that fit well into an overall plan. Many of the above bullets could be discussed in the context of collaborations (formal or informal) with other national or international academic groups, or private companies. Also, the broader UCL and Newcastle universities may have shared interests in co-developing some of these specific areas. Developing such academic and private partnerships could be part of the planning for the Centre from 2018 onward. The goal would be to focus on specific drugs and diseases, where there is clear synergism in the approach to the multiple parallel programs.

Other Steps to Consider:

- Emphasis of TREAT-NMD progress on pre-clinical SOPs and TACT, and systematic extension to other neuromuscular disorders
- Emphasis on pipeline for robust pre-clinical efficacy trials, including mechanisms for validation of studies (by established CROs or other academic sites; using SOPs and sensitive/reliable outcome measures)
- A cornerstone of the current MRC Centre has been training. Building on this success, new training programs should take into consideration the minor suggestions regarding further developments noted above. Other areas could include: informatics training; a new Masters track in translational and clinical research; training that develops skills in biomarker development (e.g., MRI). Their training program is well positioned to become an international source of next generation of neuromuscular investigators. MRI as an endpoint is a cornerstone of their new training programs.
- With a future focus of the Centre on experimental therapeutics, the 'cross-cutting themes' approach could shift into a 'drug development pipeline' as often used by industry (e.g. what drug is at what stage of the pipeline). The 'Core' infrastructures could be placed above the pipeline model, and the specific drug development programs in specific disorders could be placed below the pipeline. Using that model the current core activities could evolve into developing Target Product Profiles (TPPs) for therapies under development by or with the assistance of the Centre; can seamlessly link the activities under the guise of TPP development

    - Advantage: links the therapy development process from preclinical rationale through labelling of the approved drug/biologic
    - TPP element—indication: stratified cohorts across multiple NMDs (activity #1) valuable in indication choice

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- TPP element—preclinical rationale: preclinical/clinical collaboration (activity #6) and pt tissue samples (activity #3) both facilitate the development of 'adequate' rationale for 'go' decision making on clinical trials
- TPP element—pt population: stratified cohorts (activity #1) establish feasibility of trials, natural history studies, etc.
- TPP element—treatment duration/delivery/modality/regimen & safety/efficacy: pt cohorts (activity #1), trial know-how (activity #2), and biomarkers (activity #4) both are essential here
- Discussing this concept of Centre core activities re TPPs with industry may provide further insights into how Centre activities may be shaped to facilitate common goals in drug discovery and development, including identifying gaps in Core Activity coverage in addressing TPPs

Summary

Overall the EAB considers that the MRC Centre has achieved or exceeded all expectations and milestones. It is now considered internationally as one of the leading centres for translational research and training in neuromuscular diseases in the world. It has built impressive cohorts, biobank, MRI expertise and trials capability. The genuine joint working between senior international investigators in NCL and UCL is a notable and impressive feature. The EAB endorse the vision to evolve into an experimental therapy centre to develop therapies that improve the lives of patients. In order to be in the best position to achieve a successful application to external funders additional embedded host financial support from the BRC's and the Universities is essential. We consider that such a national strategic therapy centre would have few if any rivals internationally and would pay rich dividends in terms of benefit to patients and to the host institutions.

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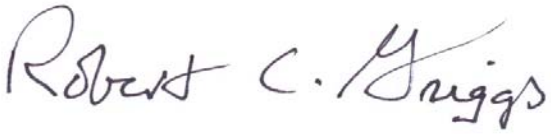

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