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**MRC Centre for Translational Research in Neuromuscular Diseases  
Second Scientific Advisory Board Review  
21<sup>st</sup> November 2011**

**1. Introduction:** The Scientific Advisory Board reviewed extensive written material prior to the meeting. At the 21 November 2011 review the Board met with key London and Newcastle leaders and heard presentations from the Ph.D. and M.D., Ph.D. trainees in the Centre. The Centre Director and other leadership were admirably responsive to the previous SAB criticisms and advice. The SAB was unanimous in the opinion that the Centre has made outstanding progress and that the Centre is arguably the world's leading program for translational research in neuromuscular disease. Examples of specific strengths and accomplishments include:

- Integration of multiple experts and many investigative teams into interdisciplinary programs.
- Well-coordinated and synergistic collaboration across geographically-separate UK locations: Newcastle, London and recently Oxford.
- Similarly synergistic program development with international groups in the EU and USA.
- Established world leaders in each major area of research enterprise with the recent recruitment of additional highly-visible, internationally recognized expertise.
- Development of state-of-the-art infrastructure for phenotyping patients with neuromuscular disease.
- World leadership in developing prospective registries that have genotyped/phenotyped extraordinary numbers of patient with many neuromuscular diseases.
- A biobank that has already become both larger and more productive than other comparable facilities.
- Linkage of Centre institutions with outstanding facilities for animal model development and study.
- Development of a large portfolio of clinical trials under the leadership of Centre faculty.
- Creation of an outstanding training program with an astonishing applicant pool (50/slot)
- Establishing a successful prototype for addressing them many challenges of translational research in a subset of rare diseases
- Strong administrative leadership.

The SAB agreed that continuing the success of the Centre will require:

- Prioritizing amongst the many opportunities to target a limited number of diseases most susceptible to successful treatment .
- Similarly prioritizing amongst diseases for those most susceptible to stratified (personalized) care.
- Developing the systematic approach and bioinformatic expertise to capitalize on data from next generation sequencing.
- Building upon their expanded expertise in imaging for rigorous biomarker development and application.
- Continued fostering the careers of trainees to position them for leadership in translational research in the years ahead.

The SAB agreed that continuing the success of the Centre will require: (Continued)

- Developing/recruiting senior colleagues within the major areas of scientific enterprise.
- Continuing to link with international clinical trial networks --- in particular the recently-funded NIH NeuroNEXT infrastructure.

The SAB reviewed and discussed many key aspects of the Centre including:

**Cell therapy:** Using myogenic progenitor cells or myoblasts with or without *ex vivo* correction is a translational research focus of the MRC Centre. The goal is to repair chronically diseased skeletal muscle and to foster regeneration by replenishing an (exhausted) stem cell pool, possibly in combination with the transfer of therapeutic genes or gene repair approaches such as lentivirus-U7-mediated exon skipping. There is strong and internationally recognized expertise in this field (Muntoni, Morgan), and this will be further strengthened from January 2012 by the arrival of a world leader, Giuglio Cossu. His plan to transfer artificial chromosomes into stem cells in order to repair missing genes is innovative and requires proof of concept. The cell therapy approach is transformative to the field of muscular dystrophies. It ties in with MRC Centre competencies such as biobanking (Lochmueller), viral platform (Thrasher) and GMP-compliant cell therapy facilities (London, Newcastle) for future translation into clinical trials. The goal of setting up a first in human phase 1 trial for Duchenne muscular dystrophy within the next 5 years is ambitious but fits with the translational role of the Centre.

**NextGen sequencing:** MRC Centre investigators have already found 7 new causative genes using exome sequencing methods. Due to the unpublished nature of the data, the SAB did not learn details of the approach and data analysis but commends the Centre for heading in this innovative direction. The collaborative work on phenotyping and outcome measures will serve the investigators well in dissecting the genotype/phenotype correlations in newly identified disease genes. In subsequent studies, the investigators must have a 'pipeline' regarding prioritization of patients selected for exome sequencing, and then prioritization and validation methods for variants identified by NextGen sequencing.

**Animal models:** Even though the Animal Studies Core was given only limited support in the original MRC award (50k over five years) the Core has established a neuromuscular phenotyping lab for animal models and has piloted studies using MRI through use of other institutional resources. The animal studies core has also established a broad phenotypic screen that can readily be applied to a spectrum of disease models. In so doing the core is exceptionally strong in preclinical research that provides rationale and proof of concept in support of clinical trials. As examples, Francesco Muntoni plays a leading role in development of animal models of dystroglycanopathy, Martin Koltzenburg has developed important models of neuropathic pain, and Lizzie Fisher and their Harwell collaborators play a leading role in the International Mouse Phenotyping Consortium, including the MRC Neuromouse effort. A considerable strength in the MRC Centre is the cross-talk between basic and clinical researchers on designing preclinical studies that are based upon considerations of clinical feasibility. With their application of NextGen sequencing and discovery of new disease genes in patients, the Centre will be poised for decisions as to which mutations should be prioritized to develop animal models and move forward to understand mechanisms and to develop therapy. Although the MRC is not providing major support, the Animal Studies Core is essential to identify area(s) where UCL/NCL can lead toward better

preclinical studies that assess candidate therapies and reduce the failure rate of phase 2 clinical trials. Through rigorous design and conduct, and thorough reporting of preclinical proof of concept data that link basic and clinical scientists to ensure that only carefully triaged candidate therapeutics go to clinical trials. The MRC Centre can play a leading role by facilitating best practices through conferences, publications, and examples of their own choices as to what goes to clinical trial.

**Biobank:** The MRC Center for Neuromuscular Diseases has successfully created a national neuromuscular biobank: Human muscle and nerve tissues and cell cultures, with currently almost 2000 human cell lines that have been used in more than 20 scientific projects. The establishment of the biobank has allowed both Center investigators and also external centres to receive cell lines for their own research. The MRC has recruited biomaterials (20%) from external labs in the biobank. More than 600 samples were given out for research to 50 scientists, and there are already 13 research publications and 4 grant applications funded using the biobank (3 are joint applications between London and Newcastle). The MRC biobank is now linked to international rare disease biobanks via the Eurobiobank. The Centre has enabled structural support to create a national biobank for neuromuscular diseases with planned further integration into the Eurobiobank, including a certification for biobanking.

**Imaging:** The goal of MRI imaging in neuromuscular disease during the first cycle was to increase the use of strong MRI infrastructure to develop better biomarkers for neuromuscular diseases. They have applied quantitative MRI in IBM and CMT. Manuscripts are in preparation for test-retest reproducibility in healthy volunteers, cross sectional, and longitudinal studies. The Newcastle site took the lead on the first systematic, multi center study in LBMD2I. Twelve month follow up measurements are underway. The center has developed novel approaches to using existing hardware and software to systematically make quantitative measurements and apply them as a biomarker of patient phenotype. Such implementation will be important for ongoing and future clinical trials. One of the strengths of the Center is that the sites are using different hard and software. In this way, it is a model for future multicenter clinical trials in neuromuscular disease. Thus, data regarding intersite and test-retest reliability will be important for such future studies.

**Clinical trials:** The Centre infrastructure has made possible an increase in the number of experimental trials in from 8 to 30 --- many directed by Centre investigations. There are already 19 manuscripts based on these studies. The MRC Neuromuscular Centre has a unique resource for leadership in trials: First, world leadership and expertise in many diseases including the muscular dystrophies, channelopathies, mitochondrial diseases and inherited neuropathies. Second, the extensive registries maintained by the Centre facilitate trials because the patients are well characterized and are available for rapid recruitment. Registries within the Centre for Duchenne Muscular Dystrophy (DMD), channelopathies, mitochondrial diseases and inherited neuropathies are among the best in the world. The SAB was impressed by the successful rapid recruitment of patients for many of the trials, particularly since many trials in other centres fail because of inadequate recruitment; third, these registries position the Centre for participation in trials supported by industry and for international studies since both industry and other sites can count on well characterized patients that will be recruited. Examples include the internationally recognized antisense oligonucleotide trials to promote exon skipping in DMD that is funded by industry and the ascorbic acid trial in CMT1A in which investigators in Italy sought out and

partnered with the Centre for their project. Fourth, the excellent research in cell biology of neuromuscular diseases at UCL and Newcastle, facilitates a move into clinical trials since the infrastructure for trials is in place. Finally, the Centre is well-positioned to take the lead in developing new approaches to trial design and outcome measures because of its strong imaging expertise. (Examples include the use of MRI outcome measures for inclusion body myositis (IBM) and neuropathies as well as trials to measure the benefits of physical exercise in the neuropathies and mitochondrial disorders.)

**Exercise:** Newcastle has a long tradition of exercise science investigators and interventions in other (non-NMD) populations, and the MRC Centre proposes to leverage this expertise to the MRC neuromuscular centre. There is increasing international acknowledgement that exercise interventions are greatly needed in neuromuscular diseases. This will become increasingly important as combinatorial therapies are assessed in translational studies. An NIH NIAMS consensus panel made exercise interventions in neuromuscular diseases a top priority. Exercise interventions in neuromuscular disease becomes especially important in the context of combinatorial therapeutic modalities. Recent published studies from this MRC Centre (Becker muscular dystrophy) and other centers (polymyositis) have uniformly shown functional benefit from exercise as a therapeutic modality in neuromuscular disease. Bridging the exercise science and neuromuscular interventions areas within the context of the MRC Centre is a logical and appropriate extension of the Experimental Clinical Trials section. While outcome measures will need to be clarified in neuromuscular exercise interventions on Centre patients, the endpoint research in the context of natural history studies, coupled with the imaging surrogate endpoint research, will provide outstanding synergism between these three subsections of the Experimental Clinical Trial section. Centre investigators should highlight their previous research in Becker, and propose integrating exercise into prospective clinical trials with clear methods and end points to show the relevance and significance of their approach.

**Training:** The MRC Centre is training 7 graduate students and 2 clinical students for a Ph.Ds that are directly funded by the MRC Centre grant. The 9 students are concluding their training. These students were recruited from a vast number of applicants (~50/slot) reflecting the Centre's ability to attract outstanding trainees. The training program provides strong clinical perspective to Ph.D. candidates and an equally strong and broad basic science familiarity to M.D. clinician trainees. The presentations of the Centre's trainees were uniformly outstanding. In addition to the Centre-funded trainees, a much larger number of non clinical and clinical PhD trainees funded are integrated into many of the Centre' training venues. The SAB considers that this program has been highly successful justifying an expansion in the number of trainees (if possible) as well as continued mentoring and career launching of trainees who are finishing their program.

**Host institution's commitments:** Both UCL and Newcastle have made a substantial financial matching contribution (£3 million host support in total to match the application to the MRC). The fruits of the existing host commitment are broadly evident: major space commitments; outstanding facilities for phenotyping patients; major recruitments of new faculty in areas that have strengthened the Centre; establishment of a highly productive biobank; new imaging capability coming on board; expansion of training activities of the Centre to a much larger group of non-Center trainees. Furthermore, while not necessarily a by-product of the Centre, the appointments of Centre leadership and investigators into

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senior academic positions at the National Hospital (Prof. Hanna) and at Newcastle (Prof. Chinnery) inspires confidence that both institutions will maintain their high level of commitment to the Centre as well as reap broad benefits from the Centre's contributions.

The Scientific Advisory Board:

Eric Hoffman

John Porter

Louis Ptacek

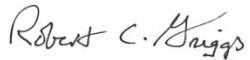
Michael Shy

Vincent Timmerman

Thomas Voit

Stephen Waxman

Robert C. Griggs, Chair,

 (signed for the SAB)