DEPARTMENT *of* NEUROLOGY

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UNIVERSITY *of* ROCHESTER MEDICAL CENTER

CONFIDENTIAL

MRC Centre for Translational Research in Neuromuscular Diseases
First Scientific Advisory Board Review
20th November 2009

Present:

Dr John Porter, Program Director, National Institute of Neurological Disorders and Stroke National Institutes of Health, USA

Dr Louis J. Ptáček, Professor, Department of Neurology, University of California, San Francisco, USA

Professor Michael E. Shy, Co-Director, Muscular Dystrophy Association Clinic at Wayne State University School of Medicine, USA

Professor Vincent Timmerman, Peripheral Neuropathy Group Leader, VIB Department of Molecular Genetics, University of Antwerp, Belgium

Professor Thomas Voit, Scientific-Medico Director, Institut de Myologie, Paris, France

Professor Stephen G Waxman (by teleconference), Bridget Marie Flaherty Professor of Neurology, Neurobiology and Pharmacology. Chairman, Department of Neurology. Director, Center for Neuroscience & Regeneration/Neurorehabilitation Research, Yale University School of Medicine & VA Connecticut, USA

Dr Robert C. Griggs – SAB Chair, Professor of Neurology, Medicine, Pathology and Laboratory Medicine and Pediatrics at the University of Rochester School of Medicine and Dentistry, USA. President of the American Academy of Neurology.

Apologies:

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I. Introduction

The Scientific Advisory Board had the opportunity to review extensive written materials prior to the meeting. At the 20 November 2009 review the Board met with each of the key London and Newcastle leaders and heard presentations from students and trainees in the Centre. The review session was notable for the spirited participation of virtually all program participants with a lunch-time poster session that gave opportunity for informal discussions about the many projects ongoing in the Centre (34 projects presented).

The Centre has made remarkable progress in a short time in establishing an outstanding infrastructure, in developing productive collaborations, in recruitment of talented investigators and in establishing a highly successful training program. The Centre has effectively fused interests and programs from both Newcastle and London to achieve synergies in research and training. Key recruitments and success in securing other grant support have moved both institutions into a leadership position in the experimental therapeutics of neuromuscular disease.

Among the specific achievements of the Centre are the merging of the interests of potential competitors into productive collaborations to the benefit of investigators, trainees and in the very near term, to patients with neuromuscular diseases. Specific areas of translational research achievement include Duchenne muscular dystrophy, mitochondrial myopathies, congenital myopathies, limb girdle muscular dystrophy, channelopathies, and inherited neuropathies.

II. Scientific productivity

In the past 2 years Centre Investigators have demonstrated high productivity and major output in top-tier journal publications. The research on channelopathies, muscular dystrophies, mitochondrial diseases and inherited neuropathies has established the Centre as a leader in these areas. Although the training program has not yet graduated trainees, the poster session gave ample evidence of a high level productivity as well as the integration of trainees in virtually all aspects of centre research.

Suggestions:

1. There should be continued efforts to link the resource groups between the two centers.

2. As clinicians at the MRC CND have impressive expertise, it should be possible for them to assist the scientists in developing outcome measures for the animal models (examples shown were GARS-ENU mutation and PMP22-C3 over expression) to link with the human condition (in this case CMT neuropathy).

3. The MRC CND should continue to integrate the science between Newcastle and London. Possible approaches would be organizing common meetings, courses, seminars, journal clubs and science clubs. We discussed having joint video conferences, or having meetings on alternate locations between Newcastle and London.

III. Imaging

MRC funding has provided only seed money to create active collaborations between neuroradiology and neuromuscular research groups. The imaging initiative has been fostered by: Excellent machine (hardware) infrastructure; dedicated software and methodological development for nerve and muscle imaging; a new Chair for an MR physicist has been created and recruited. Initial studies on LGMD21, inclusion body myositis and Charcot-Marie Tooth have already been initiated.

The potential for imaging to contribute in a major way to the quantitative characterization and longitudinal study of neuromuscular disease will depend upon rigorous assessment of the variability and reproducibility of imaging measurements. While interesting qualitative information can probably be obtained relatively quickly, the true potential of imaging will require more dedicated machine and personnel time. The Centre is well positioned to have a virtually unique position in the field.

A strategic decision has to be taken by the MRC Centre as a group if the future MRI development is going to move towards methodological development (DTI, magnetic resonance transfer, volumetry, perfusion) or clinical applications (patterning, intervention studies). If both alternatives (methodological and clinical orientation) are to be followed even stronger structural and personnel investment has to be provided.

Critical points:

- Newcastle has not received funding for positions (vs. UCL, two positions), but has a substantive opportunity for contributions (LGMD2I study) and methodological knowledge (spectroscopy of muscle)
- Excellent machine facilities (9.4 T magnet) need to be linked to the various groups using disease-specific animal models
- the MR studies address adult NMD but do not yet focus on paediatric NMD in spite of a very strong paediatric NMD patient volumes and knowledge
- If the 'hardware potential' is to be used and exploited to its full potential, the MRC Centre will need additional dedicated faculty positions --- by UCL or other resources.

IV. Animal models:

The budget for animal models is limited: (£50,000/5 years). Thus, the SAB focused attention on if, and what, the Centre may consider future development of animal models. Development of a greater effort of modeling in training (what models are available? what are the strengths and weaknesses of each organism? proper controls? phenotyping? (pathology, behavior, etc.)) needs to be considered. Such work is truly translational and would augment translation of new observations in humans and to hypotheses that can be tested in mice. Discoveries *in vitro* and in animal models, in turn, can lead to novel therapeutic strategies. Translation of science into animal models should be emphasized as important and a real interest despite lack of funding from this grant.

Clearly, there are outstanding investigators involved in such work but whether the Centre could play a more transformative role, and if so, how?, is a question worth thinking about. While funding at the current levels will not allow implementation of any major effort in this direction (e.g. graduate program in *in vivo* modeling, resources for pilot project to initiate new mouse projects to get preliminary data, core lab for phenotyping neuromuscular phenotypes, etc.), new initiatives of this sort might really synergize with the current Neuromuscular Centre and would be very attractive to many reviewers. Furthermore, the cost to the MRC may result in significant savings more globally since the current model requires that investigators in many different areas and working on different diseases (even within neuromuscular) independently 'reinvent the wheel' with regard to making animal models and characterizing them.

There is a great need to develop a mouse "phenotyping core". Expertise in certain areas is available in labs of collaborating mouse experts and high throughput mutagenesis centers. There is insufficient funding to develop a "phenotyping" core with the current funding but this is an attractive area for potential future funding that could benefit greatly from the Centre. Closer contact/involvement of scientists (PhD students, MD-PhD students and postdocs) from labs with the clinical staff of labs with such expertise would help the translational component of projects. A training course to train "mouse phenotyping doctors" would be attractive but again, would require additional funding. There are strong groups in cell biology as well, and also here a closer link with the clinical staff would be helpful, this would result in better integration within the center, enhance translation research and result in high impact papers. However, it is important to note that impetus for such interactions with such investigators would only exist in funded research already in the area of those investigators' work. To broaden the potential for phenotyping animal models of human neuromuscular diseases will require additional resources.

V. Clinical Trials

The Centre has exceeded or met the targeted milestones for natural history studies and for designing and implementing clinical trials. In fact, investigators in both London and Newcastle are at the forefront internationally in clinical trials in both muscular dystrophy and the channelopathies. This leadership position has clearly been fostered by the recruitments, the collaborations and the infrastructure

of the Centre. Considering the work of trainees and the teaching programmes of the Centre, it is clear that expertise in experimental therapeutics has become a cross-cutting theme of the programme.

Given that translation of basic discoveries into clinical reality with improvement in patient outcomes a number of additional emphases could be considered:

1. Additional expertise in clinical trials infrastructure is needed since existing staff are already handling a maximum load with the prospect of many more studies soon. Clinical coordinators, clinical evaluators, project leaders bring both technical skill and intellectual input into trial conduct and design and recruitment is essential.

2. Expertise in biostatistics and study design have been obtained from industry and other partners. Bringing such expertise into the Centre itself could be of great benefit in terms of improving trial design and for training.

3. The Centre could link existing resources in assessing patient outcomes with the widely-recognised UK and National Hospital leadership in evidence-based resource utilisation for cost : benefit analyses, comparative effectiveness, quality of life/years investigations.

4. Regulatory approval of treatments by EMEA authorities has to be a goal of clinical trials. Incorporating EMEA expertise into the programme could improve training and foster the goals of the Centre.

5. While much can be gained by engagement with industry and participation in industry-sponsored clinical trials, there should be every effort made on having “free and unrestricted access” to all data from all clinical trials.

VI. Training

The education and training program was originally designed for six trainees at the PhD degrees separable into basic and clinical tracks. Over 110 candidates applied for these positions and all the positions have been filled. Additional funding has been obtained so that there are 9 trainees in the program; seven in the basic and two in the clinical tracks. All the students have active, mentored research projects. All participate in a structured translational curriculum in which basic students attend clinics and in which clinical students interact with basic research laboratories. The MRC Centre elected to recruit all students within the first two years of the program to ensure that the students would finish their three or four year programs within the five year cycle of the Centre and also to ensure that there would be a “critical mass” of students in classes and clinics.

The SAB was extremely impressed with the rapid development of the program, its structure and with the exceptional quality of the students. In fact our major concern was how the training program

might be expanded to include more trainees since less than one in 10 applicants were chosen for the limited slots and many well qualified applicants were therefore not offered positions. Since these trainees will likely become leaders in translational neuromuscular disease the SAB believed that expanding the training program would add to the impact of the MRC Centre on translational neuromuscular disease without markedly expanding the budget of the overall program.

A second concern of the SAB was how to increase interactions between the training at UCL with that of Newcastle. We recognized that there are interactions between the two sites at present and that the training program is still in its early stages. Nevertheless we think it beneficial to institute some modifications in the current program to make it easier for students at each site to take advantage of events happening at their sister institute. For example teleconferencing might be provided when relevant speakers give lectures at one or the other institution or when students at either institution present journal clubs. We also discussed the potential of "sandwich trainees" in the next cycle of the Centre to further foster interactions between the two institutions. In this type of slot a student would spend one portion of their training program at UCL and the remaining portion at Newcastle.

Other issues were how best to facilitate the transition of the students into high quality postdoctoral fellowships after they finish the program and how best to obtain feedback from the students while they are in the program. The site visit presentations and posters showed that current students are exceptional and a program designed to ensure that they continue to receive high quality mentorship after graduation would be to the Centre and the students' benefit. A program designed to obtain feedback from students during their training would permit ongoing improvement in the training program and mentorship.

Specific Suggestions:

1) Double the size of the training program either by taking twice as many students in the first two years or by continuing to recruit in years 3-5 although we recognize that if the latter approach is taken mechanisms will need to be introduced to support training of students whose last years may occur after the Centre's funding cycle is finished.
2) Add teleconferencing capabilities for the two institutions so that relevant lectures, journal clubs and other related activities can be shown concomitantly to all the students at both institutions.
3) Provide a formal mechanism by which mentors or Centre faculty facility the transition from student to postdoctoral fellow. Since obtaining external funding will be an important part of the students' futures we would also suggest that a grant writing program or course be included into the curriculum.
4) Provide a formal mechanism for student feedback on how best to improve the education and training program

The Burden of Bureaucracy:

There was discussion amongst the SAB and PIs involved in the Centre concerning the growing burden of regulatory bureaucracy. There have been improvements recently in the US in decreasing regulatory

paperwork (at a federal level) without compromising protection for research subjects. Regulation is complicated at many levels (University, Institute, Department, etc.) because of the concern about potential liabilities associated with doing research in humans. This results in multiple layers of review where Institutes/Departments give contradictory reviews. This creates several problems. First, it cuts the "purchasing power" of the funds since the cost of the bureaucracy is becoming a larger and larger relative cost to all research funding. Second, the time spent on dealing with bureaucracy (for PIs, trainees) is time *not* spent accomplishing the research. Third, young, intelligent, energetic students and post docs find the paperwork daunting may turn potential leaders in translational research away from the field.

An example of bureaucracy interfering with accomplishment of stated goals is the difficulties of contracts between Universities. The SAB feels that the cooperative work between UCL-Queen's Square and Newcastle University (and Harwell and other Institutions too) is an attractive element of the Centre. Fostering more interaction and cooperation is creating exciting synergies. However, There has been difficulty in setting up certain agreements between UCL and NU.

VII. Summary

The MRC Centre for Translational Research in Neuromuscular Diseases has achieved impressive results in terms of scientific productivity, the recruitment of senior translational scientists and the collaborative ties to build effective bridges and synergies amongst investigators. The research on channelopathies, Duchenne muscular dystrophy, mitochondrial disease and peripheral neuropathies have placed the Center at the leading edge of translational research --- with the potential for truly breakthrough science in clinical discovery. There are promising interactions between the geographically separated scientific communities in London and Newcastle. Both groups have been the driving-forces behind new networks of cooperating clinical investigators and clinicians throughout the UK and Europe and extending to North America, Africa and Asia. The combined expertise within the Centre has placed the programs at the forefront of translational research broadly and specifically on rare disease research and neuromuscular disease research.

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