

welcome

This edition of the TREAT-NMD newsletter is devoted to our conference in Brussels. The eight sessions and 134 accompanying posters cover the major topics in translational research and unite many of the leaders in the field, who have come together to address the current barriers to therapy development, determine where consensus is available, and ultimately drive forward the future collaborative agenda between scientists, clinicians, industry and patients. The sessions will discuss the latest results from ongoing projects and demonstrate the current consensus in these different areas. The conference will also highlight the areas in which further collaborative efforts are needed and will call for action in these areas.

We'd like to thank all session chairs, panel members and participants for their hard work making this conference a reality, and look forward to seeing many of you in Brussels!

at a glance...

14-18 Nov 2009 Mechanisms Involved in Muscle Atrophy and Hypertrophy, Carmona, Spain.

17-19 Nov 2009 TREAT-NMD / NIH International Conference

27 Nov 2009 King's College London Neuromuscular Symposium

26-27 Feb 2010 Towards a Brighter Future - Sydney, Australia.

10-17 April 2010 American Academy of Neurology Annual Meeting - Toronto, Canada.



TREAT-NMD / NIH conference begins Tuesday!

The last registrations are still coming in and there is still time to register either [online](#) or at the start of the conference itself at the registration desk which will open at 9am on Tuesday 17th November.



The conference itself **begins at 2pm** in the **ballroom** with a welcoming address by Kate Bushby followed by a keynote speech by Gert-Jan van Ommen. The eight highly interactive sessions with panel discussions and audience participation are described in brief in this newsletter. Full details of the programme can be found on the [conference website](#).

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Session 1: Making Clinical Trials in Neuromuscular Diseases a Reality

This session starts the conference with an exploration and discussion of the models that would best guide therapy development programmes, including the industry standard of label-based design, and will address novel partnering models

to ensure that appropriate expertise and funding is recruited to projects. We will also discuss the important and controversial issue of triaging both repositioning candidates as well as novel therapeutics for neuromuscular disease - seeking input from drug developers, academics, advocacy groups, and patients. In a focussed discussion session, the views of patient organisations representing small patient numbers, as well as the larger patient organisations and the FDA, will be discussed.



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Session 2: Target and Candidate Identification

We will review the kinds of cell assays one can use for initial screens to identify potential therapeutic starting points for possible future development. For this, one needs to consider a number of related themes such as:



- What cell types are to be used? e.g. primary cells, immortal cell lines, stem cells
- Any trade off between throughput vs. target relevance? e.g. compound collection size, assay complexity, disease relevance
- Are the assay end points appropriate for screening?

Once 'hits' have been identified using the screening assay the next requirement is to confirm the hit can manipulate the cellular processes believed to gain a therapeutic advantage in order to develop a candidate for consideration in animal models i.e. the concept of hit validation in vitro. Questions that need to be asked when considering this include:

- Is the 'hit' mechanism known?
- Is there a valid in vitro therapeutic endpoint? e.g. increased target RNA, relocalisation of target protein.
- Is the 'hit' toxic in cells?

It is only after iteration and refinement of the therapeutic repetitively through the assay and in vitro validation that a compound should be considered a therapeutic candidate and moved to testing in vivo for proof of concept.

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Session 3: Animal model assessment

Testing of candidate drug and biologic therapeutics in animal models is an essential step to provide the proof-of-concept needed for moving new treatments into clinical trials. Although animal models are, by definition, specific to single neuromuscular diseases, it is critical to collectively learn from the experiences in individual diseases. We will describe common lessons from the shared experience and pitfalls from a diverse range of therapy development efforts in neuromuscular disease. Topics to be addressed include: bringing adequate rigor to animal efficacy testing, seeking the 'ideal' animal model for therapeutic testing, rodent versus "large animal" models, outcome measures to define whether a candidate is a 'go' or a 'no-go', ensuring consistency from lab-to-lab and company to company in neuromuscular therapy development.



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Session 4: Therapeutic Misconception and Ethical Considerations

It is absolutely necessary to conduct clinical trials involving adults and children with rare diseases. It is also mandatory that participation in clinical trials is based upon voluntary and adequately informed consent. However there is a growing body of evidence that those with parental decision making responsibility may be unable to distinguish between research and treatment, the so-called "therapeutic misconception".



In this session we will explore the possible implications of this evidence for the design and conduct of clinical trials for neuromuscular diseases through a formal debate and interactive panel discussion. It is perhaps uncontroversial that those responsible for regulating research and for providing ethical approval have the responsibility to ensure the safety and well-being of vulnerable children. During this session we will explore the extent of this responsibility and its implications for parents, researchers, and regulators. It will be proposed that where parents have unrealistic expectations of benefit it is unlikely that they meet the conditions for a legal and ethical consent. With this in mind, the panel will debate the following motion:

'Parents who express hope in the possibility of therapeutic benefit from clinical trial participation should not be allowed to consent for their children to enter trials'

The audience will be invited to vote on the motion before and after the debate. This session involves people with NMDs, patient advocates, a clinician, an ethicist, a parent and a lawyer. During the debate the panel will:

- deconstruct the concept of the "therapeutic misconception"
- invite audience participation and questions
- provide expert commentary
- conclude with constructive advice using examples of good practice with a view to their dissemination throughout the wider community

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Session 5: Developing Novel, Disease Targeted Therapies and Systemic Delivery

We will highlight novel gene directed therapies for neuromuscular diseases: expected therapeutic benefits, delivery issues, and regulatory challenges. Exon skipping is taken as a model approach for gene-specific therapy. Invited speakers will present the latest results of cutting-edge pre-clinical and clinical trials, including new results from exon



skipping trials, limb perfusion gene delivery, and systemic AAV total body delivery.

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Session 6: Registry Development for Clinical Trials

As clinical trials become a reality in an increasing number of neuromuscular conditions, the need for registries containing well-defined, up-to-date and locatable patient cohorts is

becoming ever more pressing. Many therapies require a precise knowledge of the patient's particular genetic mutation. Other clinical items are important as potential inclusion criteria for a trial. At the same time, data collected must be

streamlined, simple and in many cases self-reportable by patients or carers in order to achieve maximum uptake. Ethical issues around consent, data ownership and data protection must also be carefully considered, and the benefits to patients and families of signing up for the registry clearly defined.



We will draw on the success of the TREAT-NMD global registries for DMD and SMA, which are already being used by pharmaceutical companies to provide trial feasibility information, and extend this with experience from other disease groups, using the example of the National Research Roster for Huntington Disease. The importance of registries from a regulatory perspective in terms of postmarketing/ approval studies and pharmacovigilance will also be considered. The overall aim of the session will be to draw on lessons learned and summarise best practice for registry development for other neuromuscular conditions.

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Session 7: Clinical Outcome Measures

The correct choice of outcome measures for a clinical trial can be critical to its success. Making these choices can be a time consuming and lengthy process and if the process is repeated for every trial may result in a large duplication of effort. Even when the choices have been made there are many practical issues that need to be addressed in order to successfully implement an outcome measure for a trial. The panel participants represent the many stakeholders involved in outcome measures including clinicians and academics who have created, assessed, chosen and implemented outcome measures for trials, industry partners, regulators and patient representatives. We will highlight the factors that may influence the choice of outcome measures and the tools that are being developed to help with making the choice. We will draw on examples from trials planning and implementation for SMA, DMD, Charcot Marie Tooth, myotonic dystrophy, inclusion body myositis and peripheral nerve disease.



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Session 8: Effects of Long-Term Treatment and Combination Therapeutics

We will focus upon the future of long-term treatment. Most approaches currently in development do not cure a disease; however they will slow its progression. Determining long-term net benefit requires different outcomes measures than the ones generally used in short term studies. In addition, of the drugs already used, benefit for long-term treatment has not

been established. Using Pompe disease and Duchenne Muscular Dystrophy as examples basic guidelines for the use of these drugs should be created in the interim period.



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TREAT-NMD resource generation - poster presentations

At the heart of TREAT-NMD's ethos is a commitment to developing the resources that the community needs to accelerate therapy development and delivery. These resources span the research and clinical arenas and are available to scientists, clinicians and patients. Individually they are rarely addressed in single research projects, yet together they form a suite of tools that are essential to rapid progress towards new treatments. Partners have been asked to create and present posters showing the breadth and depth of work being carried out by the network. Further



details of the posters on show can be found [here](#).

These posters will first be presented at the internal TREAT-NMD Governing Board meeting and will then be integrated into the main conference poster sessions for all conference delegates to inspect. After the conference has closed full abstracts of each of the posters will be available on the conference website.

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