

## welcome

Welcome to our 60th and final Newsletter before our traditional summer break.

Before we go we have an update for you about the TREAT-NMD Advisory Committee for Therapeutics (TACT) which is scheduled to have its kick-off meeting in Newcastle with core members gathering in early October. We'd like to wish Cristina and all the other committee members every success in this exciting initiative.

We also include a report about the recent Cure CMD meeting which was held in late June in Atlanta, Georgia. Details of the DMD Non Ambulatory Workshop that was held last month in Paris also features in this edition of our newsletter.

We'd like to remind you that the abstract submission deadline for posters to be displayed at our International Conference is today at midnight (local time). If you have any last minute ideas that you wish to include feel free to submit them via the conference website.

Best wishes from,  
Katie, Volker, Hanns, Steve, Emma, Rachel, Samantha and Michael,  
the Newcastle TREAT-NMD team.

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## at a glance...

[09-12 Sept 2009 IDMC-7  
International Myotonic Dystrophy  
Consortium](#)

[09-12 Sept 2009 14th International  
Congress of the World Muscle  
Society, Geneva, Switzerland](#)

[21-23 Sept 2009 Muscle Study  
Group Annual Meeting, Buffalo, New  
York](#)

[25-26 Sept 2009 SMA 'at the Eve of  
the Cure' conference, Warsaw,  
Poland](#)



05-06 Oct 2009 6th UK SMA  
Research Conference, Edinburgh,  
UK

23-24 Oct 2009 Action Duchenne  
International Conference Holiday Inn  
Bloomsbury London

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

## TACT update - July 2009

Since the launch of the TACT (TREAT-NMD Advisory Committee for Therapeutics) on the 22nd May 2009 ([www.treat-nmd.eu/research/TACT](http://www.treat-nmd.eu/research/TACT)) the committee has been busy working in the background on the next steps. We understand many of you are keen to hear an update and we are grateful for the comments and suggestions we have received since the inception of the committee. We have also received extremely valuable feedback from the TREAT-NMD community at large.



The original idea of the TACT was to have a 'pool' of experts from which members with the most appropriate expertise for each specific compound and disease would be asked to contribute their assessment. In order to guide the effort, ensure continuity of the process and integrate this input we felt that it would be important to establish a core committee that would, along with the chair, be involved in the review of all compounds and essentially help drive the TACT forward. In the process, we will take into consideration the suggestions made so far, as well as the expectations and concerns of the many audiences vested in our work.

The core committee chaired by Cristina Csimma (Viridante Pharmaceuticals, Cambridge, USA) will be comprised of members with expertise in key aspects of drug development:-

Preclinical:

- Raju Nagaraju (Children's National MC Washington, USA)
- Dominic Wells (Imperial College, London, UK)

Drug Discovery / Medicinal Chemistry

- John McCall (PharmMac LLC, USA)

Regulatory:

- Didier Caizergues (GENETHON, France)
- Elizabeth McNeil (Food and Drug Administration, USA)

Clinical:

- Petra Kauffman (Columbia University, USA)
- Jerry Mendell (Ohio State University, USA)
- Thomas Voit (Institut de Myologie, France)

This core committee will meet for the first time in Newcastle on the 3rd-4th October 2009 to review and refine the draft terms of reference; agree on the evaluation process, criteria and working rules for the core as well as the larger TACT group. The TACT will then be in a position to start accepting drug candidates for review in late 2009. We are currently compiling a list of potential drug candidates and would welcome additional suggestions. We anticipate holding two TACT meetings during 2010, the first in February and the second in June, TACT members have been informed of these dates and we are looking forward to helping to facilitate and accelerate the drug review process.

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## Cure CMD Meeting Report 2009 - Atlanta

"Therapeutic Targets in the CMDs" was a conference uniquely devoted to the identification and development of opportunities for translational research in the field of congenital muscular dystrophies (CMDs). The primary goal of the workshop was to address, evaluate and achieve consensus on therapeutic targets in the CMDs by bringing together expertise ranging from basic science to clinical trial design in rare disorders.



The conference led to the outline of a CMD roadmap and preliminary prioritization of efforts based on the identification of short term, mid term and long term scientific targets and their development into treatment strategies with strong translational potential.

Amongst drugs with potential to enter into clinical trials relatively soon, the anti-apoptotic agents Debio 0025 (Debiopharm) and omigapil (Santhera) were discussed with potential applicability in the collagen VI and MDC1A CMD forms, recognizing that they treat secondary effects not target primary pathways and therefore at best will decrease rate of disease progression. The antioxidant N-acetyl-L-cysteine (NAC) has shown potential in SEPN1 patient cells and is expected to proceed to clinical trials in SEPN1 patients within the next 2 years. Anecdotal evidence suggests that prednisone may have a beneficial effect in the alpha-dystroglycanopathies similar to its effect in dystrophinopathies, suggesting another immediate clinical trial possibility. The antihypertensive and antifibrotic agent losartan could be of potential use in MDC1A as there is evidence for upregulated TGF beta signaling in human biopsies and the mouse model.

Midrange targets on the translational map included protein therapy with laminin 111 for use in MDC1A patients, either alone or in combination with strategies directed at upregulation of alpha 7 integrin expression. Several screens are directed at upregulation of glycosylation of alpha-dystroglycan are currently actively pursued. Long range targets include stem cell therapy the pharmacological manipulation of regenerative capability of muscle, gene delivery to muscle and gene corrective strategies such as the knock-down of dominant negative mutations in collagen VI.

The conference also explored a number of additional potential targets related to muscle atrophy, necrosis, mitochondrial function, growth factor signaling including myostatin inhibition and the regulation of fibrosis formation.

To help establish an inventory of currently available tools and models, a working group within the conference delineated current parameters used in physiologic assessment of *dyw*, *dy3k* and *col6a1* knockout mouse ([www.curecmd.org/scientists](http://www.curecmd.org/scientists)). In addition, a list of dystroglycanopathy mouse models, CMD zebrafish and CMD drosophila models was established ([www.curecmd.org/scientists](http://www.curecmd.org/scientists)).

Discussions concerning the readiness for clinical trials in the CMDs centered around innovative clinical trial design and support for the CMD International Registry, to be launched in August 2009 and modeled after the DMD patient initiated database curated by Emory Genetics. Discussions included experiences and lessons from previous trials in rare neuromuscular disorders, consideration of innovative trial designs, as well as perspectives provided by the FDA and representatives of pharmaceutical companies with an active investment in neuromuscular disease.

A CMD Toolkit panel led by Dr. John Porter and Dr. Glen Nuckolls from the NIH summarized currently available scientific and clinical resources, including those at the NIH and the CDC. Dr. Volker Straub presented the TREAT-NMD neuromuscular global resources and discussed the TACT committee which is focused on preclinical therapeutic candidate review. Currently available genetic resources were highlighted, including high throughput genetic testing for the CMDs currently being validated at Emory Genetics. Amongst the high priority items necessary for the CMD Toolkit was the development of immortalized cell lines and assays suitable for high throughput screening assays and a continued effort to make standard CMD mouse models available at Jackson Laboratories.

Postdoctoral candidates applied for travel grants supported by the conference organisers. The list of the 5 successful young scientist can be viewed at <http://curecmd.org/scientists/winners>.

The conference organizers, Dr. Carsten Bonnemann and Cure CMD would like to thank NINDS, NIAMS, ORD and MDA for conference support through dedicated conference grants. Additional non-restricted educational grants were made by Debiopharm and PTC Therapeutics.

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## DMD Workshop Report

On the 17th June 2009 28 participants from Europe and the US attended a TREAT-NMD workshop, also supported by the Foundation to Eradicate Duchenne [www.duchennemd.org](http://www.duchennemd.org), in Paris to discuss the selection of outcome measures for Duchenne Muscular Dystrophy (DMD) clinical trials involving non-ambulatory patients.



There are currently several groups in the process of developing non-ambulatory protocols in DMD for submission to the regulatory authorities. The aim of the workshop was to help harmonise existing efforts as well as plan for future trials. The invited workshop participants included clinicians, academics and physiotherapists as well as representatives from patient organisation and industry..

The overall aim of the workshop was to present and discuss the merits of possible outcome measure for use in DMD trials as a first step towards reaching a consensus among the neuromuscular community. Specifically the workshop aimed to;

- Address the issue of functional measures suitable for trials in non-ambulant DMD
- Consider the special case of single limb delivery where subtle changes in muscle strength will need to be detected
- Work to harmonise efforts in data collection and improve natural history

Introduction and context

The workshop was opened by Kate Bushby and the workshop chairs Francesco Muntoni and Eugenio Mercuri.

Elizabeth Vroom presented the patient and parent perspective. Elizabeth noted that a 'good' outcome measure for patients is one which records a function / measure that matters (is important) to them - a point which was also made by EMEA representatives at a meeting organised by TREAT-NMD in October 2008 to discuss outcome measures for SMA trials.

Eugenio Mercuri, presented the lessons learnt from harmonising efforts in SMA Outcome Measures. Eugenio noted over the last 2 years the community has started to work together to decide which particular scales were the best to use to test a specific hypothesis in a specific population. The community as a whole has also learnt to work with EMEA and FDA in the initial planning stages of trials.

Elena Mazzone discussed the recently developed TREAT-NMD upper limb functional scale which is currently being tested by the SMA groups in Europe (as part of a project funded by SMA Europe) and will be tested by the US groups in the future- such upper limb scales may be adaptable for use in DMD. Tina Duong (CINRG) presented preliminary results from the CINRG/UC Davis DMD

Longitudinal Study on outcome measures in non-ambulatory DMD patients. Elena Pegoraro (University of Padova) presented data on the identification of a validated genetic modifier of older DMD patients and its potential importance as a co-variant in clinical studies.

#### Appraisal of specific measures and harmonisation of efforts

Prior to the workshop a working group of specialised physiotherapists met to discuss the suitability of commonly discussed outcome measures for non-ambulatory DMD trials as well as issues relating to planning training programmes, coordinating training between the different groups (TREAT-NMD, CINRG, MDA) and coordinating efforts to facilitate progress. During the workshop Michelle Eagle (Newcastle Muscle Team) presented the physiotherapist consensus on outcome measures (including respiratory, functional scales / functional timed tests and upper limb evaluations) and fed back the plans for collaboration discussed during the session including the integration of different efforts.

The following sessions were concerned with sharing experience in different measures relevant to non-ambulant DMD and gave several researchers the opportunity to present data on measures they currently use. Michelle Eagle discussed data on Forced Vital Capacity (FVC). Marion Main presented Myometry of upper limbs in non ambulant DMD using the Cytech myometer. Robert Pangalila presented data on Hand function, measured with MFM and its relation to strength and range of motion in adult DMD patients. Laurent Servais presented preliminary data on the quantification of upper limb function in non ambulatory patients using clinical test and actimetry. Jean-Yves Hogrel presented information on grip strength assessment in weak patients. Pierre Carlier and David Bendahan discussed the role of assessment of MRI scans as an outcome measure for DMD. Erik Henricson discussed the NIH NeuroQoL project which has been validated in DMD teens / young adults. The last presentation of the day was given by Leone Atkinson (PTC) regarding the preparation of the PTC non-ambulatory protocol.

The round –up and discussion session was chaired by Eugenio Mercuri and Francesco Muntoni and it gave all the participants the opportunity to discuss the questions raised throughout the day. Many potential outcome measures do exist to collect data in non ambulant DMD from the perspective either of functional studies or the assessment of strength in a single limb. Some of the scales available are known to the regulatory authorities for different diseases. All require further study in the DMD population, and this comparative work is under way via collaborations between the TREAT-NMD, CINRG and MDA groups. TREAT-NMD and CINRG will establish an international working group to help move this work forward and the TREAT-NMD Registry of Outcome Measures (ROM) will be used as a tool to facilitate the collaboration.

**MORE >**

## TREAT-NMD Summer Break

This is our final newsletter before the summer break with our next newsletter scheduled for Friday 4th September. If you have any suggestions or news articles please feel free to [contact us](#), we're always pleased to hear from you.



Our conference website will still be taking bookings throughout the summer break allowing delegates to take advantage of the early booking discounted rates. Programme details of what looks to be a very interesting and exciting conference are available on the [conference website](#).

It just remains for us to wish you all a very enjoyable and relaxing summer break.

See you in September - the TREAT-NMD coordination team.

[www.treat-nmd.eu](http://www.treat-nmd.eu)

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