



TREAT-NMD Partner Newsletter No. 11 and Club of Interest Newsletter No. 5

18th May 2007

This week's newsletter contains a report from the EuroBioBank/TREAT-NMD meeting and information about an upcoming discussion on patient perspectives on outcome measures.

We have a number of other reports in the pipeline for the coming weeks and have been receiving interest from Japan to Brazil – we're delighted to hear from you, so please do keep in touch.

Best wishes,

Katie, Volker, Stephen, Emma, Arron and Rachel – the TREAT-NMD coordination team

Newsletter contents

1. About this newsletter
2. Working with us
3. TREAT-NMD news and reports – Eurobiobank meeting and outcome measures discussion
4. Latest news / research
5. Calls for proposals
6. Upcoming conferences, meetings and workshops
7. Partner-specific items
8. Send us your news and views!



1. About this newsletter

This is a weekly newsletter sent to all members of TREAT-NMD's "Club of Interest" worldwide. We are receiving new subscriptions all the time, so if you've missed the earlier editions of the newsletter and would like to catch up, please visit our newsletter archive online at <http://www.treat-nmd.eu/news/newsletter/> where you will find all back-issues. If you have received this letter from a friend or colleague and would like to subscribe directly, please visit our website at <http://www.treat-nmd.eu/> where you will find a subscription form at the bottom of the homepage. You can also use the same form if you no longer wish to receive this newsletter – just select the unsubscribe button.

2. Working with us

TREAT-NMD aims to be an inclusive rather than an exclusive network, and you do not have to be based in Europe or be a partner to be involved. Much international collaboration with experts from all over the world is already taking place, and new links are being developed.

If you are involved in any of TREAT-NMD's areas of interest and have something you'd like to say or a suggestion of where we could work together, we encourage you to get in touch by writing to us at info@treat-nmd.eu

3. TREAT-NMD news and reports

Patient perspectives on outcomes for trials – opening a debate

Kate Bushby, UNEW

Last weekend TREAT-NMD organised a workshop alongside an ENMC meeting on plans for trials in spinal muscular atrophy (SMA). A full report will be presented in the next couple of weeks. The debate was predominantly around outcomes for SMA, but the participants took advantage of the assembled expert group also to discuss briefly the state of the art for outcome measures in DMD trials. It is clear that many ways exist for measurement of change in muscle strength and function but that there is a gap in the measures that we know can detect change and an understanding of what we really can determine is "life altering" or of fundamental importance to daily life and function. This is a major issue when it comes to regulatory approval of new compounds.

For this reason, we are planning to work together with patient organisations to develop more of a perspective on what "life altering" outcomes really are – how parents and patients might want to define these so that the definition does not come entirely from the regulatory authorities, industry or clinicians.

We have drafted a questionnaire for patients and parents designed to elicit responses on what they themselves consider the most important outcome measures and will launch a discussion group for the workshop participants at the beginning of next week. If you have a particular interest in the patient perspective on this issue and would like to join this discussion, please let us know by writing to rachel.thompson@treat-nmd.eu.

EuroBioBank/TREAT-NMD meeting report

Hanns Lochmueller and Sarah Baumeister, MD-NET

On May 10-11 2007, the 5th annual EuroBioBank meeting, in conjunction with TREAT-NMD, took place at the Eurordis headquarters in Paris. The meeting was attended by representatives from all participating member biobanks and representatives of patient organizations including Eurordis, AFM and the ENMC.



EuroBioBank (www.eurobiobank.org) is a European network of DNA, cell and tissue banks founded in 2002 and coordinated by the European Organization for Rare Diseases (Eurordis). Among the founding members are 11 biobanks from 7 European countries, most of them focused on the field of neuromuscular research.

The objective of EuroBioBank is to further improve and extend a network of European biobanks where scientists are encouraged to deposit biomaterials and are also welcome to obtain specific material they need for their research. Within TREAT-NMD, the special focus is on neuromuscular diseases and translational research. Work package WPO4.1 is headed by Eurordis with the goal of improving and adapting the existing EuroBioBank structures to the objectives and needs of TREAT-NMD, in particular to facilitate the exchange of neuromuscular biomaterials.

In the course of the meeting, EuroBioBank members were informed about TREAT-NMD objectives and deliverables such as regular update of the online catalogue and specific training sessions. Furthermore, EuroBioBank members, along with re-elected Scientific Coordinator Prof. Hanns Lochmüller and newly elected Deputy Scientific Coordinator Prof. Corrado Angelini, agreed upon an effort to attract additional European biobanks as members to the EuroBioBank network. Interest was expressed by representatives from Israel (Dr Zelina Ben-Gershon, Senior Scientific Director from the Israeli Ministry of Health) and the UK (Dr. Rita Barresi, University of Newcastle) who both attended the meeting.

Furthermore, EuroBioBank members were pleased to hear that EuroBioBank has itself been a research subject. The study was presented by Michaela Mayrhofer, a PhD student from the Political Science Department at the University of Vienna, and will be published in the near future.

4. Latest news / research

Possible New Treatment Target Found for Muscular Dystrophy

By Ohio State University Medical Center
May 15, 2007

(HealthNewsDigest.com) - COLUMBUS, Ohio – Scientists have identified a potential therapeutic target in muscles for the treatment of Duchenne muscular dystrophy, the most common form of the progressive disease.

The researchers focused on the role of a protein involved in the body's inflammatory response named nuclear factor kappa B (NF-kB). The study confirmed that this protein is responsible for the chronic inflammation and muscle-cell death that are hallmarks of Duchenne muscular dystrophy.

The research also showed that activation of the protein is required to block the ability of skeletal muscle cells to regenerate the cells destroyed by that very same inflammation.

This dual role makes the protein particularly attractive as a target for therapy, said Denis Guttridge, assistant professor of molecular virology, immunology and medical genetics at Ohio State University Medical Center and senior author of the research.

"NF-kB is driving the inflammation – but that's only half of the story. It also plays a role in skeletal muscle cells by blocking their ability to regenerate," said Guttridge, also a researcher in Ohio State's human cancer genetics program.

Guttridge and his colleagues also found that inhibiting the protein reduced inflammation and allowed muscle tissue to regenerate in animals with a disease similar to muscular dystrophy, suggesting that a drug against NF-kB could one day serve as therapy to prevent progression of the disease in humans.

The work was published in the April issue of the Journal of Clinical Investigation.



Duchenne muscular dystrophy affects about one in 3,500 boys, who show early symptoms of muscle degeneration and typically lose the ability to walk between age 6 and 12. With progressive disease, most patients die of respiratory failure or cardiac dysfunction in their 20s. Girls can carry the gene that causes the disease, but most have no symptoms.

In muscular dystrophy, the immune system attacks muscle cells, which causes cell death. The muscle tissue can regenerate because stem cells replenish them when the muscle is injured. But, in general, humans have a limited pool of muscle stem cells. Researchers believe that the constant action of muscle degeneration and regeneration eventually expends all available stem cells, tipping the balance toward progressive muscle degeneration.

Previous research has shown that the immune process becomes heightened in muscular dystrophy, contributing to chronic inflammation that kills muscle cells. NF- κ B is implicated in that process, suggesting that blocking the protein should stop the inflammation. But to date, anti-inflammatory medications used to treat Duchenne muscular dystrophy do not appear to be effective in slowing progression of the disease.

So Guttridge and colleagues took that theory a step further, demonstrating that the process that activates NF- κ B also affects muscle cells' ability to regenerate. The researchers used mice lacking the dystrophin gene, which is essential for the structure, function and integrity of muscles. Mutations in the dystrophin gene are the primary cause of Duchenne muscular dystrophy.

When the researchers raised mice that also lacked I-kappa-b kinase (IKK), the enzyme that turns on the NF- κ B protein, they found a noticeable increase in cell regeneration in muscles of mice carrying the disease that mimics Duchenne muscular dystrophy.

Guttridge and his colleagues then used a chemical inhibitor to block the protein's activation. They introduced an experimental peptide, engineered to block the enzyme's activation of the protein, into muscles of mice lacking the dystrophin gene.

"Blocking NF- κ B led to improved muscle function," Guttridge said. "Validating the role of this protein in disease progression with a drug-based inhibitor suggests that NF- κ B is a viable target in this disease."

Guttridge said any drug developed to block NF- κ B might slow the degeneration-regeneration cycles in Duchenne muscular dystrophy patients or might even reduce the initial inflammation, which would delay onset of that cyclical process.

The researchers plan to conduct additional studies of the peptide under different conditions before trying to prove its usefulness for clinical application in humans.

The compound, known as a NEMO-binding domain peptide, was discovered at Yale University and developed by TheraLogics Inc., a North Carolina-based company.

This research was supported by the National Cancer Institute and the Muscular Dystrophy Association.

Ohio State co-authors are graduate student Swarnali Acharyya (lead author), with graduate student Nadine Bakkar, research scientist Micheal Carathers and associate professor Michael Weinstein of the human cancer genetics program; postdoctoral researcher Tepmanas Bupha-Intr and assistant professor Paul M. L. Janssen of physiology and cell biology; professor Zarife Sahenk of neurology; and graduate student Katherine L. Gardner and associate professor Jill A. Rafael-Fortney of molecular and cellular biochemistry.

Stat3 constitutive activation restores the SMN deficit observed in spinal muscular atrophy

Spinal muscular atrophy is a neuromuscular disease characterised by motor neuron degeneration in the anterior horn of the spinal cord, due to SMN₁ gene mutations. **A therapeutic approach** involves increasing the expression of the SMN₂ gene expression, a SMN₁ homologue encoding a functional but unstable SMN protein. By treating the human and murine cells with sodium vanadate, trichostatin A or aclarubicin,



researchers observed an increase in the SMN2 expression induced by Stat5 activation. Complementary experiments suggest that Stat5 signalling regulates the transcriptional activity of the SMN2 promoter, making this signalling pathway a new potential pharmacological target for the treatment of spinal muscular atrophy.

[Human Molecular Genetics ; 16\(5\):499-514 ; Mar 2007](#)

5. Calls for proposals

We regularly publish calls for proposals that might be of relevance to TREAT-NMD in this section of the newsletter. The network has ambitious plans in areas such as training and education, and since these are not covered by our initial funding from the EU, we have to seek funds from elsewhere. We strongly encourage anyone outside the network who is interested in developing links with us to look through these calls and see if there is anything of relevance to you. We also encourage partners to consider possibilities for academic exchanges via these proposals.

Attracting additional funding to the network activities is vital if we are to ensure the future sustainability of the network. There are a number of research-based calls for proposals under FP7 that would be suitable for the network, and we would like to ensure that the network has every opportunity to obtain funding through FP7. Therefore, it is important that the Coordination Team at Newcastle (stephen.lynn@treat-nmd.eu) are kept up-to-date on any of your research proposals that are associated with the network activities, as we can offer help and support as well as a united front in which we work together to win European funding either as a single partner or in collaboration with other partners and non-network colleagues.

FP7 Call – Health

Call FP7-HEALTH-2007-B has been postponed until the 11 May 2007 (previously 4 May 2007). Documentation for the call has not been published on the EU website at this time; however, we will receive full details on this from our management partner ACIES next month (after 18th June) at which time we will upload a document onto the TREAT-NMD website. If you are considering submitting a proposal in response to this call (or any other funding calls) we would be grateful if you could contact the TREAT-NMD Coordination Team at Newcastle to discuss your research proposal submission.

6. Upcoming conferences, meetings and workshops

Ethics Matters: 18th Canadian Bioethics Society Conference & 3rd International Conference on Clinical Ethics and Consultation

Organized by the Canadian Bioethics Society

Date: May 30-June 3, 2007

Venue: Toronto, Ontario, Canada

<http://www.utoronto.ca/jcb/ethicsmatters/>

European Human Genetics Conference 2007

Date: 16-19 June 2007

Venue: Nice, France

<http://www.eshg.org/eshg2007/>

1-day Conference: Clinical Research for Rare Diseases: Opportunities, Challenges and Solutions

Date: 5 September 2007

Venue: Washington, DC, USA

<http://rarediseasesnetwork.epi.usf.edu/conference/index.htm>

Rare Diseases Research: Building on Success - a European Conference

Date: 13 September 2007

Venue: Charlemagne building- Brussels, Belgium



EuroGentest Workshop on internal auditing for genetic testing laboratories

Date: 20-21 September 2007

Venue: Leuven, Belgium

Registration is open for this event, which is EuroGentest's next workshop. The aim of this workshop is to train the participants to efficiently and effectively direct and/or participate in a laboratory audit in the spirit of peer review and education. Participants are motivated to exchange ideas and learn from each other and the experts, by general presentations, role play, video fragments and group discussions

Registration deadline: 15 July 2007

<http://www.eurogentest.org/web/db/unit1/event/124/index.xhtml>

8th EPPOSI Partnering Workshop on Orphan Drugs

Date: 18-19 October 2007

Venue: Copenhagen

<http://www.orpha.net/actor/EuropaNews/2007/doc/epposi.pdf>

4th European Conference on Rare Diseases (ECRD 2007)

Date: 27-28 November 2007

Venue: Lisbon, Portugal

NB: Registration is open. Deadline for abstract submission: 30 May 2007

http://www.rare-diseases.eu/home_en.php

The TREAT-NMD meetings advertised in last week's newsletter are now advertised on the TREAT-NMD website – please see the "news and events" section for details.

If there is an event you would like us to publicise in future newsletters and on our website, please send details to rachel.thompson@treat-nmd.eu.

7. Partner-specific items

TREAT-NMD Project Management Manual

ACIES have produced the first version of the Project Management Manual that sets out the main decision-making rules and procedures regarding running the TREAT-NMD project. This manual is designed to help partners better understand the Network management structure and decision rules. The manual will be modified on a regular basis, if necessary, to better address new Network needs and/or requirements.

The manual is available as a pdf document on the private section of the TREAT-NMD website and can be found at <http://www.treat-nmd.eu/private/>.

If partners have any comments on this manual please contact either Bénédicte Charrin (ACIES) at eu-new@acies.fr or Stephen Lynn (UNEW) at stephen.lynn@treat-nmd.eu

8. Send us your news and views!

We encourage all partners and supporters to send their own news and updates and we will be happy to include them in future editions of the newsletter. Please send your contributions to emma.heslop@treat-nmd.eu.

