

# TREAT-NMD Neuromuscular Network



7<sup>th</sup> September 2007

Newsletter No. 16



Welcome to the re-launch of the TREAT-NMD Newsletter- we hope you had an enjoyable summer.

Partners have been busy since the last newsletter. This edition includes news on current FP7 applications involving TREAT-NMD partners, clinical trial feasibility studies, and the publication of a consensus statement for standards of care in SMA. AFM, who is a partner of TREAT-NMD, supported a 10-year follow-up study of boys with DMD treated with perindopril, which is now published, and demonstrates reduced mortality in these patients. This is an important development for standards of care in DMD. We hope you enjoy our new look!

Best wishes,

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

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## About this newsletter

This is a bi-weekly newsletter sent to all members of TREAT-NMD's "Club of Interest" worldwide. Earlier editions of the newsletter can be found online at [www.treat-nmd.eu/news/newsletter/index.htm](http://www.treat-nmd.eu/news/newsletter/index.htm). If you would like to subscribe directly, please visit our website at [www.treat-nmd.eu/](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.

## 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. 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](mailto:info@treat-nmd.eu). The coordination team in Newcastle will be happy to put you in touch with the person most relevant to your particular interest.

### Feasibility Questionnaire to Identify Clinical Trial Sites in Europe

The TREAT-NMD Clinical Trials Coordination Centre (CTCC) is preparing a feasibility questionnaire to identify potential sites for clinical trials in neuromuscular diseases. The questionnaire will be web-based and will be sent out to our clinical contacts across Europe using information provided by partners. This information will help us to work more efficiently and effectively with companies developing new treatments and therapies for patients with neuromuscular disease and who want to conduct multi-centre trials in Europe and we are actively working with PTC Therapeutics in this area. We appreciate the involvement of the clinical community in helping us to streamline the clinical trials process in Europe by their participation in the fact-finding questionnaires which will be launched soon.

### FP7 Projects

Some of the partners within TREAT-NMD are involved in developing two major applications for EU funding under the FP7 programme. The first, called NMD-Chip, aims to develop targeted DNA chips for high throughput diagnosis of neuromuscular disorders. The second, is a collaboration aiming to construct a comprehensive, dynamic, and systemic cartography of the muscle protein network in normal and pathological condition. Both applications will be submitted this month and if successful will begin sometime in mid-2008.

### Consensus Statement for Standards of Care in Spinal Muscular Atrophy

Following two years of work in collecting and compiling data the Consensus Statement for the Standards of Care for SMA has been published in the August issue of the Journal of Child Neurology (article available from <http://jcn.sagepub.com>). The members of the Standard of Care Committee for SMA who produced this document included a number of TREAT-NMD partners. The lead author, Ching Wang, is currently working with TREAT-NMD to create a brief version of the article in order to facilitate the easier usage for families and physicians. This précis, along with other helpful information, will be posted to the TREAT-NMD web site in the coming weeks.

### Working with the TREAT-NMD Network

The TREAT-NMD Network is only 9 months old but so far we have generated a lot of interest from a number of individuals, organisations and national networks who want to work more closely with us. One of the initial aims of the network was to address the issue of becoming more inclusive and to this end we are currently drafting a Members' Charter that we hope can be used to more formally define our working relationship with the wider neuromuscular community. The Charter will define what TREAT-NMD can offer you as well as what TREAT-NMD would like to see from its members. If you are interested in becoming a member of TREAT-NMD please contact us at [info@treat-nmd.eu](mailto:info@treat-nmd.eu)

### Perindopril reduces mortality in Duchenne muscular dystrophy



Supported by the AFM (one of the TREAT-NMD partners), a team of researcher-clinicians coordinated by Professor Denis Duboc (Cochin Hospital, AP-HP, René Descartes University Paris V) and Doctor Henri-Marc Bécane (Myology Institute, AFM) have published the results of a study into the 10-year follow-up of children affected with Duchenne muscular dystrophy (DMD) treated with perindopril. The study shows a significant reduction of mortality in these children. Moreover, the results seem to underline perindopril's overall protective role.

In DMD cardiac muscle is inevitably affected, and is responsible for the fatal outcome in approximately half the cases. Thus, fighting this cardiac damage is essential in maintaining patients' life expectancy. It was in this context that this long-term clinical research project was undertaken in 10 clinical centres in France. The study involved 57 children aged from 10 to 13 years and lasted a total of ten years, of which the first three

were blinded against placebo. In the treatment group 26 out of the 28 patients are still alive as against 19 out of 29 in the control group.

As well as its role of protector of the cardiac muscle, perindopril seems also to have an effect on the diaphragm and the inter-costal muscles.

The results give weight to the recommendation – made by the AFM and Professor Denis Duboc to the specialist authorities – that perindopril be used preventively in children with DMD from the age of 10 years.

### Publication reference

**Périmopril preventive treatment on mortality in Duchenne muscular dystrophy : 10 years follow-up.** Denis Duboc, Christophe Meune, Bertrand Pierre, Karim Wahbi, Bruno Eymard, Annick Toutain, Carole Bernard, Guy Vaksman, Simon Weber, Henri-Marc Becane.

American Heart Journal, September 2007, Vol. 154, pp 596-602 ([www.ahjonline.com/home](http://www.ahjonline.com/home))

## Other News

### EMA bestows its 40th positive opinion for orphan drugs



The European Medicines Agency ([www.emea.europa.eu/home.htm](http://www.emea.europa.eu/home.htm)) last month bestowed its 40th positive opinion recommending marketing authorisation for an orphan medicinal product since regulation came into effect in 2000. Since that time, over 700 applications for orphan designation have been received by the EMA, of which 470 received favourable recommendations, 11 were refused and the rest were withdrawn or are still in process. Upon receipt of an orphan designation status, the sponsor is eligible for incentives to develop and market the product, financed through a special EC fund totalling 6 million euros in 2007. The incentives scheme to develop orphan products has resulted in a steady number of submissions applications: 19 more applications for marketing authorisations for orphan-designated medicines are currently under review, according to a recent EMA press release.

### European Quality Assurance (QAU) Database released

TREAT-NMD would like to encourage all NMD diagnostic laboratories to register in the Quality assurance database for genetic testing labs via the link below.



EuroGentest, ([www.eurogentest.org](http://www.eurogentest.org)) the FP6 EU-funded network of excellence (contract nr LSHB-CT-2004-512148) devoted to genetic testing, has just released in collaboration with Orphanet ([www.orpha.net](http://www.orpha.net)) the first version of the Quality Assurance database (QAU) for genetic testing laboratories. It is expected that the database will quickly become a necessary resource for geneticists and other professionals around the world in order to provide accurate and reliable test results to patients and their families. The QAU database includes all laboratories offering any form of genetic testing (molecular, cytogenetic, biochemical). To participate in the QAU database follow the link below, select 'clinical test' and then choose a country.

[www.orpha.net/form/formGB.html](http://www.orpha.net/form/formGB.html)

### Switzerland eligible to participate in FP7



Following the signature of a scientific agreement with the European Union, Switzerland has gained eligibility for full participation in the Seventh Framework Programme. Swiss researchers may participate "on an equal footing" with EU scientists in all calls for proposals, including those open since the start of the year.

### **COST - European Cooperation in Science and Technology**

COST invites researchers from across Europe to submit proposals to establish research networks and use this unique opportunity to exchange knowledge with other European researchers.

COST invites proposals for new COST Actions contributing to the scientific, economic, cultural or societal development of Europe. Proposals playing a precursor role for other European programmes involving young groups' ideas are especially welcome. On average financial support in the form of a grant for € 90.000 p.a., normally with a duration of 4 years, can be expected.

The next date for Preliminary Proposals is 30 September 2007.

Further information is available at the following link: [www.cost.esf.org/index.php?id=721](http://www.cost.esf.org/index.php?id=721)

### **FDA grants for rare disease medicine clinical trials available**

The Food and Drug Administration (FDA) Office of Orphan Products Development (OOPD) is pleased to announce the availability of funds for fiscal year (FY) 2009 and FY 2010 in the form of grant awards to support clinical trials on the safety and effectiveness of products for rare diseases and conditions. For FY 2009, the application receipt date is 6 February, 2008, and for FY 2010, the application receipt date is 4 February, 2009. The complete text of the FDA request for applications is available online.

[www.fda.gov/orphan/grants/2009RFA.html](http://www.fda.gov/orphan/grants/2009RFA.html)

### **Grants for Global Health rare disease programs available**

Support for the creation of new multidisciplinary global health educational and research programs is available from the Fogarty International Centre of the National Institutes of Health in the US. Many international and multinational collaborative research efforts have been developed with a focus on rare diseases, including cancers and neurological disorders. The grant aims to increase interactions among global health researchers in diverse fields, and to encourage new investigators to consider working in global health. A major component of the grant is the development of new multidisciplinary curricula and associated activities. Opportunity is restricted to certain low and middle income countries as described by the World Bank.

For more information: <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-o8-001.html#SectionI>

### **MDA Research Grants Programs**

The MDA is now accepting applications for its 'Spring Review' and request for applications need to be submitted by 15th December 2007 with final applications submitted by 15th January 2008. Further information is available from [www.mdaua.org/research/guidelines.html](http://www.mdaua.org/research/guidelines.html)

### **AFM Call for Proposals 2008**

The AFM has launched its Call for Proposals with two review sessions — the deadlines are 5th October 2007 (first session) and 29th February 2008 (second session). Please visit the AFM web site for further information ([www.afm-france.org](http://www.afm-france.org))

**The DMD Genetic Therapy Group website has been updated** ([www.dmd.nl/gt](http://www.dmd.nl/gt))

The website gives a brief introduction of the exon skipping strategy and an explanation of how exon skipping can be applied for different types of mutations. The primary mission of the DMD Genetic Therapy Group at the Department of Human Genetics (chaired by Prof. Dr. Gert-Jan B. van Ommen) of the Leiden University Medical Center (LUMC) is the development of a genetic therapy for Duchenne Muscular Dystrophy (DMD). The project started in 1998 and is currently supervised by Dr. Annemieke Aartsma-Rus. In a joint effort the DMD genetic therapy group and Prosensa are developing antisense oligonucleotides (AONs) as small synthetic molecule drugs for DMD.

**Telling Stories, Understanding Real Life Genetics** ([www.geneticseducation.nhs.uk/tellingstories/index.asp](http://www.geneticseducation.nhs.uk/tellingstories/index.asp))

This is an innovative new electronic resource developed for healthcare professionals employing the real-life stories of patients and their families living with genetic conditions. The user-friendly website is intended to help health professionals, especially nurses, midwives and health visitors, understand and appreciate the relevance of genetics and the impact a genetic illness can have on the daily life of patients. The site is also intended as educational support. A "Catalogue" of stories can be sorted by various themes, such as genetic condition, inheritance, or genetic intervention. With a spectrum of storytellers describing how their condition first emerged, the response of general practitioners and caregivers to symptoms that had often never before been seen, and the often long road to specialised care and treatment, "Telling Stories" provides a powerful testimony of the needs of rare disease patients in the context of the general medical milieu.

**New neuromuscular disease web resource** ([www.neuromuscular.deusto.es](http://www.neuromuscular.deusto.es))

This website was developed at Deusto University (Spain) and contains a lot of information about neuromuscular diseases for Spanish speakers.

## Upcoming Conferences, Workshops, Meetings and Summer Schools

**Sixth International Conference: Improving the use of Electromyography in Paediatrics**

**22 - 24 October 2007**

Institute of Child Health, London

[www.ich.ucl.ac.uk/education/short\\_courses/courses/2T\\_19](http://www.ich.ucl.ac.uk/education/short_courses/courses/2T_19)

This course provides a unique opportunity for all those who ever have to perform EMG in children to learn how to achieve the best for their patients. The aim has been to go from the basics of the examination to some of the most advanced techniques that can be performed to stretch those who are already doing Paediatric EMG. The course will consist of lectures, practical demonstrations and discussion of case studies.

## RNA

### Antisense-mediated exon skipping: A versatile tool with therapeutic and research applications

Annemieke Aartsma-Rus and Gert-Jan B. van Ommen (LUMC)

Antisense-mediated modulation of splicing is one of the few fields where antisense oligonucleotides (AONs) have been able to live up to their expectations. In this approach, AONs are implemented to restore cryptic splicing, to change levels of alternatively spliced genes, or, in case of Duchenne muscular dystrophy (DMD), to skip an exon in order to restore a disrupted reading frame.

The full text (PDF) can be freely downloaded at [www.rnajournal.org/cgi/content/abstract/rna.653607v1](http://www.rnajournal.org/cgi/content/abstract/rna.653607v1)



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NEUROLOGY

### GNE protein expression and subcellular distribution are unaltered in HIBM

S. Krause, A. Aleo, S. Hinderlich, L. Merlini, I. Tournev, M.C. Walter, Z. Argov, S. Mitrani-Rosenbaum, H. Lochmueller (MD-NET)

Mutations in *GNE* encoding UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE) cause hereditary inclusion body myopathy (HIBM). To define the role of *GNE* mutations in HIBM pathogenesis, GNE protein expression was analyzed. GNE protein is expressed at equal levels in HIBM patients and normal control subjects.

The full text of this article is available online: [www.neurology.org/cgi/content/full/69/7/655](http://www.neurology.org/cgi/content/full/69/7/655)

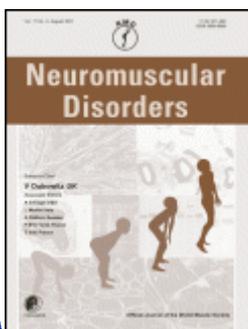


### Distal myopathy caused by homozygous missense mutations in the nebulin gene

C. Wallgren-Pettersson, V-L Lehtokari, H. Kalimo, A. Paetau, E. Nuutinen, P. Hackman, C. Sewry, K. Pelin, B. Udd (UH.HI)

A novel, recessively inherited distal myopathy was caused by homozygous missense mutations in the nebulin gene, in which other combinations of mutations are known to cause nemaline myopathy.

The full text of this article is available online <http://brain.oxfordjournals.org/cgi/content/abstract/130/6/1465>



### Cap disease caused by heterozygous deletion of the $\beta$ -tropomyosin gene *TPM2*

V-L Lehtokari, C. C. Groote, P de Jonghe, M. Marttila, N.G. Laing, K. Pelin, C. Wallgren-Pettersson (UH.HI)

First published report of the identification of a causative gene for cap myopathy.

Neuromuscular Disorders 17 (2007) 433-442

Journal web site

[www.elsevier.com/wps/find/journaldescription.cws\\_home/973/description#description](http://www.elsevier.com/wps/find/journaldescription.cws_home/973/description#description)

## Partner Publications

Please inform the TREAT-NMD Coordination Office of any upcoming or recent publications that you may have so we can highlight these in future editions of the newsletter.

### Adult Stem Cell Population Identified with Potential to Repair Muscle in Disease or Injury

Scientists at the Children's Hospital of Pittsburgh of UPMC have discovered a unique population of adult stem cells derived from human muscle that could be used to treat muscle injuries and diseases such as heart attack and muscular dystrophy. The results of the study led by Johnny Huard and Bruno Péault is published in the September issue of the journal Nature Biotechnology.

[www.nature.com/nbt/journal/vaop/ncurrent/abs/nbt1334.html](http://www.nature.com/nbt/journal/vaop/ncurrent/abs/nbt1334.html)

### FDA Grants Tikvah Therapeutics, Inc. Orphan Drug Status for Sodium Phenylbutyrate for the Treatment of Spinal Muscular Atrophy

Tikvah Therapeutics, Inc., a biopharmaceutical company focused on new treatment options to better manage central nervous system diseases, announced that the U.S. Food and Drug Administration (FDA) has granted Tikvah Therapeutics orphan drug status for sodium phenylbutyrate for the treatment of spinal muscular atrophy (SMA).

Sodium phenylbutyrate, a histone deacetylase (HDAC) inhibitor, currently approved to treat urea cycle deficiency, has been identified in in-vitro systems and in various animal models as an agent that can increase the level of SMN protein. Findings from in-vitro studies as well as pilot clinical work suggest that phenylbutyrate treatment in SMA patients may improve motor function.

Tikvah Therapeutics will be working in conjunction with the FDA, and collaborative clinical trial groups focused on SMA to develop well-controlled multi-centre trials to fully evaluate sodium phenylbutyrate in the treatment of SMA.

Further information can be found at [www.tikvahtherapeutics.com](http://www.tikvahtherapeutics.com)

## Partner-specific items

### Welcome to Newcastle Hanns!

Professor Hanns Lochmuller (MD-NET) has moved from the University of Munich to Newcastle University to take up the position of Professor of Experimental Myology.

Hanns can now be contacted via;  
e-mail: [hanns.lochmuller@newcastle.ac.uk](mailto:hanns.lochmuller@newcastle.ac.uk)  
Telephone: +44 (0)191 241 8602

### Industrial Liasion Council Meeting

October 2007 Basel, Switzerland

### Database Curators' Training Course

7-9th November 2007 Inserm, Montpellier, France

Invitations will be sent out shortly to attend this hands-on training course as part of the development of the TREAT-NMD European Patient Database.

## Job and Training opportunities

Current job and training opportunities are advertised on the TREAT-NMD website.

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

[www.treat-nmd.eu/activities/training\\_educ.htm](http://www.treat-nmd.eu/activities/training_educ.htm)

## Send us your news and views!

We strongly 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](mailto:emma.heslop@treat-nmd.eu)