



# TREAT-NMD

## Neuromuscular Network

5<sup>th</sup> October 2007 · Newsletter No. 18



This is a feature-packed edition of the newsletter that includes a report on the EAMDA meeting in Warsaw, details of the TREAT-NMD feasibility study for clinical trial centres, the first of our "Focus on" sections which this week features TREAT-NMD partners LUMC, plus a report on the Bulgarian delegation visit to Newcastle.

Please forward any items that you would like to be included in future editions of the newsletter to [info@treat-nmd.eu](mailto:info@treat-nmd.eu).

Best wishes,

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

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### About this newsletter

This is a fortnightly 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.

### TREAT-NMD Clinical Trial Coordination Centre Feasibility Questionnaire – Online Now!

As you are aware, there are multiple cutting-edge therapies at the end of the preclinical phase or in the early clinical development phases. These include different therapeutic approaches including nonsense mutation suppression, gene-therapy, stem-therapy, cell therapy and exon-skipping. We hope and expect that in the near future, a number of clinical trials will be carried out in patients with neuromuscular disorders (NMD), including Duchenne muscular dystrophy (DMD), and spinal muscular atrophy (SMA).

Through WP 5.1 TREAT-NMD has established the TREAT-NMD Clinical Trials Coordination Centre which has the facilities and capabilities to assist in the planning, organization, conduct and evaluation of clinical trials in NMD throughout Europe. Different kinds of trials from small-scale 'proof of principal' studies (Phase I) to large multi-centre Phase II/III trials will be supported.

As NMDs are very rare, clinical benefit trials must recruit patients at multiple centres so as to achieve large enough sample sizes and have sufficient statistical power to address important clinical questions. To facilitate and accelerate clinical trial development, TREAT-NMD is establishing a database to register potential investigational sites. As part of this process, we have prepared a feasibility questionnaire for completion by medical centres that treat patients with NMDs and could potentially participate in a clinical trial. This questionnaire is designed to collect information on the potential eligibility of a centre to host a future clinical trial rather than collect feasibility information regarding a specific clinical trial.

Therefore, if you are an investigator interested in the study of NMDs we would invite you to complete our feasibility questionnaire online in order to determine your interest and capability for potential participation in upcoming clinical studies. The information that you provide in response to this survey is invaluable for maximizing the potential that your centre has in participating in future clinical trials.

Please use the following link to access the TREAT-NMD Clinical Trial Feasibility Questionnaire:

<http://skl14e.ukl.uni-freiburg.de/eu.treatnmd.fq.web/register.jsf>

A number of investigators have been contacted personally and we would therefore encourage you to communicate with other investigators within your institution to see if they have already completed the questionnaire. We would ideally like one survey per institution. If you have any queries please feel free to contact us via e-mail at [emma.heslop@treat-nmd.eu](mailto:emma.heslop@treat-nmd.eu) or [angela.stanescu@uniklinik-freiburg.de](mailto:angela.stanescu@uniklinik-freiburg.de)

### EuroBioBank seeks new biobanks

The **EuroBioBank network** of DNA, Cell and Tissue Banks for Rare Disease Research aims to expand and include new neuromuscular biobanks. Membership is free of charge. Some of the benefits of membership include gaining better visibility and displaying biological sample collections in the online network catalogue.

If you know of any muscular biobank who would be interested in joining EuroBioBank, please let us know or request more information about membership at : [contact@eurobiobank.org](mailto:contact@eurobiobank.org)

Please visit our website: [www.eurobiobank.org](http://www.eurobiobank.org)

### Starting a discussion forum on Gender issues in relation to TREAT-NMD

The text below was written as a draft suggestion for TREAT-NMD policies on gender issues by Carina Wallgren-Pettersson [Carina.Wallgren@helsinki.fi](mailto:Carina.Wallgren@helsinki.fi)

- Comments are invited on the policy declaration itself
- How can we best achieve these goals?
- Do Network participants feel there are further issues that need to be raised or addressed in this context and would they be willing to be involved in Gender issues discussion forum?

The action plan for gender equality aims for making itself redundant, in that women and men from the beginning of Network activities have equal opportunities of engaging in its work on all levels. In fact, looking at the proportions of women and men involved already, the overall participation of women is 43 %, i.e. close to 50%. Among younger researchers, women are "overrepresented", and among senior scientists and network leaders they are slightly "underrepresented", probably reflecting the common trend at European Universities of equality development over time.

An explicit goal of the Network is to eventually involve everyone working in the field of neuromuscular disorders across Europe, which means taking the aim of equality beyond simple gender issues.

The same policy of course applies to patients with neuromuscular disorders, including those who participate in Network policy-making, those who wish for their data to be entered into the Network Databases, and those who wish to take part in forth-coming treatment trials. In the context of patient care, the Work package on Standards of Care will address issues related to pregnancy, delivery and child care.

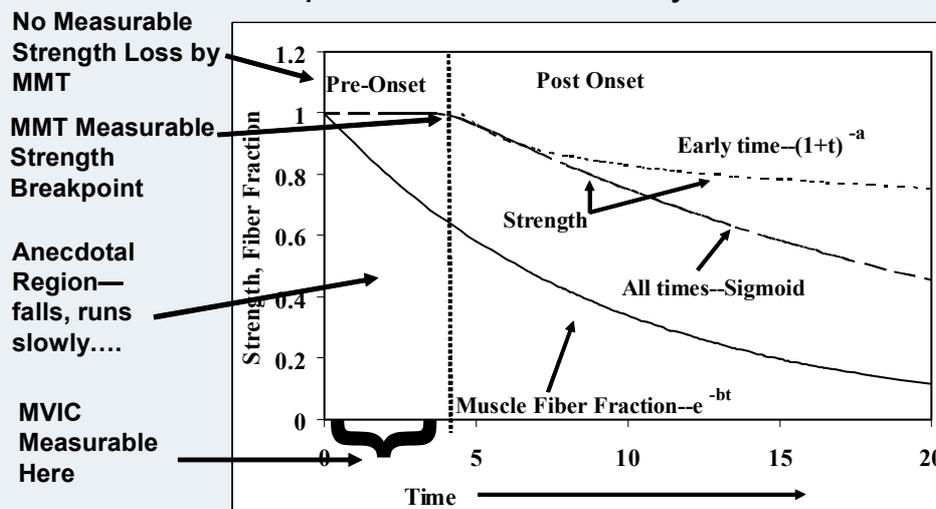
If you have any comments/suggestions please contact [carina.wallgren@helsinki.fi](mailto:carina.wallgren@helsinki.fi) or [emma.heslop@treat-nmd.eu](mailto:emma.heslop@treat-nmd.eu)

### A Predictive Method for Assessing Treatment Effectiveness in Neuromuscular Disease Clinical Trials – by MW Munn

There is a near term potential for application of gene therapy methods for treatment of a number of neuromuscular diseases. In order to determine the degree of success of the treatment, it is useful to be able to predict, with reasonable accuracy, the normal course of the disease for each individual for comparative purposes. This ability reduces the number of patients required for clinical trials as well as the duration of the trials. To this end, we have developed such a model which has been successfully applied to DMD, LGMD, and ALS patients. Existing databases such as the CIDD Duchenne Dystrophy database, published LGMD data, and privately provided data (Michelle Eagle) were used to develop and validate the predictive model. Predictive ability relies on use of a quantifiable variable with physical meaning. Qualitative variables, such as manual muscle testing (MMT) results, are inadequate. We have chosen muscle fiber fraction (MFF) as the basic variable. Published research provides a way to transform existing MMT data to the more physically meaningful MFF. As a side effort, we have also created transformations between many

muscle related evaluation schemes. We have found that a sizeable fraction (30% or more) of the CIDD cases possess an MFF which decays exponentially with a fixed decay constant, i.e.  $MFF = e^{-at}$ , where "a" is the decay constant and "t" time after conception—zero time. This is analogous to radioactive decay where the MFF half-life is  $t_{1/2} = 0.69/a$ —i.e. half of the muscle fibers are lost in that time. To date all longitudinal cases of LGMD available also show this pattern as well as a very limited number of ALS cases (ALS cases have a zero time which is derived from the model). Once the decay constant, "a", is known, the entire MMT strength loss curve can be calculated by use of a modified Richard's equation. Interventions are also modeled by use of a damped Richard's growth curve. Because the physical parameter, MFF, is used, it can also be related to factors which could modify "a", such as body temperature. The decay constant "a" holds within it the underlying physical forces which generate neuromuscular disease. For example, the distribution of discrete values for "a" follows the probability distribution for base pair separation in DNA. The CIDD database reveals two other decay modes which are not exponential and further research is required to determine a method for prediction of progression for those cases. The accompanying figure shows the basic form for the model with the exponential decay of MFF and the Richard's sigmoid for manual strength testing results.

## Dystrophic Time Evolution—Megascoring Exponential Fiber Decay



If you would like to participate in an e-mail discussion forum to help forward the work in this area, please e-mail [Emma.Heslop@treat-nmd.eu](mailto:Emma.Heslop@treat-nmd.eu) who will be happy to add you to the discussion list. We suggest that TREAT-NMD partners involved in assessment tools and outcome measures may be interested to participate as well as people from the wider neuromuscular community.

## Bulgarian visit to Newcastle University

On the 6<sup>th</sup> and 7<sup>th</sup> of September a Bulgarian group consisting of Prof. Dr. Ivailo Tournev, Dr. Velina Guergueltcheva and Dr. Violeta Mihaylova from the Clinic of Neurology in Alexandrovska University Hospital and Dr. Albena Jordanova, a molecular geneticist from the Molecular Medicine Centre and the National Genetic Laboratory, Sofia visited the Institute of Human Genetics and the TREAT-NMD coordination centre in Newcastle. The visit aimed at exchanging ideas on best practice guidelines in investigating and dealing with neuromuscular disorders and strategies for harmonizing efforts in different parts of Europe. It coincided with a visit by Professor Thomas Sejersen from the Swedish Karolinska Institute, leader of the TREAT-NMD work on standards of care.

A tour around the Institute of Human Genetics and the muscle immunoanalysis unit in Newcastle University provided information on the diagnosis and research of NMD – histological analysis including immunohistochemistry, genetic studies and experimental myology. There was a discussion on care of NMD patients, clinical and genetic consulting, physiotherapy, assisted ventilation and social care.

The TREAT-NMD coordinators explained the activities in the different workpackages of the TREAT-NMD project. There was a special discussion on how to contribute to the development and management of supranational patient registries. The Bulgarian team presented the current structure of healthcare for NMDs in Bulgaria, the available diagnostic tools in the Alexandrovska University Hospital and the Molecular Medicine Centre in Sofia. There was a short review of the NMDs diagnosed in the country with some epidemiological data and genetic profiles. The team also presented their major research interests and achievements. A special emphasis was placed on their experience in community-based activities in high-risk groups, the current state of NMD patient care in Bulgaria, future directions in their work and integration into the TREAT-NMD network. They presented their NMD project “Contemporary approach to the diagnosis and research of hereditary neuromuscular disorders in Bulgaria – translation of the scientific achievements to the patient’s care”, funded by the Bulgarian Ministry of Education and Science, 2007-2010, for which the TREAT-NMD coordinators provided a letter of support. The project focuses on the clinical, genetic and epidemiological investigation of newly identified forms of NMD in Bulgaria, as well as the development of unified patient databases as a prerequisite for scientific collaboration and providing most appropriate care for the patients.

“It is our belief that harmonizing the efforts on a supranational basis will assure and promote best practice of caring for people with NMDs, including future novel treatment opportunities”.



## EAMDA 37<sup>th</sup> GENERAL MEETING, 27-29 September, Warsaw, Poland



From 27-29 September 2007 the 37th annual general meeting of the European Alliance of Neuromuscular Disorders Associations (EAMDA) took place in Warsaw, organised together with ENMC and TREAT-NMD and focussing on TREAT-NMD.

EAMDA is the European umbrella organisation for neuromuscular disease patient organisations and has a membership covering more than 20 countries. Patients and physicians from 15 different countries were present in Warsaw.

**Patients went to a lot of trouble to attend the meeting: paying for their own travel costs, travelling by plane with their wheelchair or, where air travel was not possible, coming in adapted cars – the group from Malta travelled more than 3200 km! Helpers accompanying the patients also attended the meeting.**

The program on Friday was devoted to *the role of patient organisations in the roadmap to therapy and better standards of care*. Peter Streng (ENMC / TREAT-NMD) presented on the subject, after which the participants worked in groups to identify bottlenecks on the roadmap as well as solutions. The main problems identified included lack of knowledge of (para)medics on treatment and co-morbidity, lack of centres of excellence (diagnosis, care, rehabilitation and clinical trial centres), low government and insurance support, and (use of) registries. Patient representatives subsequently came up with possible actions for their own organisations to tackle these problems.

On Saturday many Polish patients and physicians attended the meeting, bringing the total to over 100 participants. Amongst them were guests of honour Professor Hausmanova-Petrusewicz and Mr Bielak, chair of the Polish Neuromuscular Patient Association. Professor Kwiecinski, the national consultant in neurology, read a letter received from the Polish Minister of Health. The minister stressed the importance of the meeting, where physicians committed to improving the life of patients are working together with these patients towards development of better treatment and care.

Professor Kate Bushby, TREAT-NMD coordinator, presented on the recently published *Consensus Statement for Standard of Care in Spinal Muscular Atrophy* (Wang et al. *J. of Child Neurology*, 2007; 22; 1027). A user-friendly précis of this paper will be launched on the TREAT-NMD website next week. Prof. Hanns Lochmüller stressed the importance of patient registries, both to follow the natural course of the disease and to achieve the main goal of registering patients for potential recruitment in upcoming clinical trials. Physicians and patients from several countries were eager to be added to the TREAT-NMD databases.

Judith van Deutekom from Prosensa showed that clinical trials with exon skipping in Duchenne patients are on the horizon. However, at the start this will only include a very limited number of patients. Dr Ryniewicz and Dr Marchal presented on best practices in Poland with regard to standards of care in DMD and prevention of cardiomyopathy. Dr Praznikar (Slovenia) and Dr Carlier (France) showed us how gait and MRI can be used to assess disease status in patients. Dr. Hervé Laouenan from AFM France concluded the

day with an overview of the bottleneck meeting organised by AFM in January 2007 and a presentation on the use of stem cells in neuromuscular disease. It became clear that this treatment might be an option, but it will take years before we can expect benefits. In a TREAT-NMD network meeting physicians were able to discuss their expectations and needs directly with the TREAT-NMD team. The issues of training and education were addressed and again the registries were discussed in detail.

### Achievements of the meeting:

- The Polish Minister of Health stressed in a letter to the Board of the Polish Neuromuscular Patient Association the importance of good care for patients with neuromuscular diseases. Official backing like this is of great value in terms of gaining future governmental support for improvements in NMD treatment.
- The Polish Patient Association for NMD succeeded in establishing contacts with the Ministry of Health and attracted media attention during the conference.
- Representatives (patients and physicians) from 15 different countries from both Eastern and Western Europe discussed progress in treatment and care for NMDs and their possible contributions for paving the road to better care.
- Several countries expressed their interest in setting up national registries and taking part in the TREAT-NMD initiative.
- TREAT-NMD will facilitate dissemination and implementation of the recently published Standards of Care in SMA by 1) supporting the translation of the précis of the publication into various languages, and 2) organising training sessions in various countries on request.
- Several suggestions were made to TREAT-NMD for training and education (summer schools for physiotherapists, hands-on training in scoliosis surgery, hands-on training in the use of outcome measures like the Hammersmith scale). The TREAT-NMD team responsible for developing training programmes will work on this further.

The 38<sup>th</sup> EAMDA annual conference will be in Sofia in Bulgaria on 12-14 September 2008.



## Focus on the Leiden University Medical Center (LUMC)

The LUMC is leader for work package 8.2 (Optimization of systemic delivery and improvement of quality and safety standards for treatment of patients with muscular dystrophies and spinal muscular atrophy). Main objectives of WP8.2 involve genotoxicity and in vivo toxicology studies, optimization of delivery methods, dose and treatment regimens and determination of the delivery efficiency required for therapeutic effect in animal models (improvement of muscle function and endurance).

The work performed in the LUMC for this work package mainly focuses on the development of a systemic delivery method for antisense oligonucleotides (AONs) as tools to induce exon skipping in Duchenne patients. This approach was pioneered by Judith van Deutekom at the Department of Human Genetics (Leiden University Medical Center, the Netherlands), Steve Wilton (University of Western Australia, Australia) and Masafumi Matsuo (Kobe University Graduate School of Medicine, Japan). The strategy aims to restore the disrupted dystrophin open reading frame in Duchenne patients to allow generation of partly functional, Becker-like proteins by hiding an exon from the splicing machinery with an AON (for more information see [www.dmd.nl/gt](http://www.dmd.nl/gt)). Proof of concept has been obtained in patient-derived cultured muscle cells and the *mdx* mouse model. In collaboration with Prosensa Holding we recently obtained clinical proof of concept through an exploratory study in which four DMD patients received a local dose of a 2'-O-methyl phosphorothioate (2OMePS) AON targeting exon 51. In close collaboration with Prosensa B.V, current research focuses on safe and efficient systemic delivery.

### People involved in WP8.2 (Department of Human Genetics)

**Dr. A. Aartsma-Rus** Annemieke Aartsma-Rus is a senior postdoc at the Department of Human Genetics and leader of the DMD genetic therapy group. She is the scientific representative of the LUMC in the TREAT-NMD governing board. During her PhD research she was involved in the development of therapeutic antisense-mediated exon skipping for DMD. She successfully defended her thesis titled "Development of an antisense-mediated exon skipping therapy for Duchenne muscular Dystrophy – Making sense out of nonsense" in February 2005 and now continues to work on the further optimization of the exon skipping therapy.

**BASc. C.L. de Winter** Christa de Winter has been working as a research technician on antisense-mediated exon skipping since November 2003. Her work mainly involves comparing different systemic delivery methods and AON dosing regimes in dystrophic mouse models.

**MSc. J.A. Heemskerk** Hans Heemskerk started working as a PhD student in May 2005. His project focuses on the development of safe and efficient antisense formulations for systemic treatment of muscle tissue in DMD patients.

**MSc M. van Putten** Maaïke van Putten started as a PhD student in September 2007. Her project will focus on the assessment of the levels of exon skipping and dystrophin that are required for functional improvement in dystrophic mouse models.





**Prof Dr G-J.B. van Ommen** Gert-Jan van Ommen is head of the Department of Human Genetics at the LUMC. Amongst others, he has supervised research on neuromuscular and neurodegenerative diseases (with a focus on DMD and Huntington Disease). In addition he was involved in the development and application of genome research and diagnostic technology for disease study, diagnosis, therapy and prevention, including the societal aspects of genetic advances. The antisense-mediated exon skipping therapy approach for DMD was pioneered in the department under his supervision, and brought into a first clinical trial in the LUMC on his initiative and guidance.



**Dr. P.A.C. 't Hoen** Peter-Bram't Hoen works as a senior postdoc at the Department of Human Genetics. He has set up high-throughput RNA and protein profiling studies for muscle diseases, established a muscle gene expression databases containing data from all studies published and supervises research on the identification of biomarkers that correlate with disease severity in several mouse models for muscular dystrophies. These biomarker profiles can be used to assess therapeutic effects after (AON) treatment.

### LUMC personnel involved in other TREAT-NMD Activities



**Dr. H.B. Ginjaar** The Laboratory for Diagnostic Genome Analysis (LDGA) (Clinical Genetics; [www.lumc.nl/klingen/dna](http://www.lumc.nl/klingen/dna)) in Leiden performs mutation analysis for many disorders nationally and internationally. Ieke Ginjaar is a staff member at the Department of Clinical genetics. She is responsible for DNA/RNA and protein diagnostics of DMD/BMD and LGMD in the Netherlands. She set up dystrophin analysis in muscle tissue and still performs immunological analysis for D/BMD/LGMD patients. Her mutation database, which includes all mutations found in Dutch B/DMD patients will be instrumental in setting up a Dutch DMD patient registry that includes clinical data as well.



**Dr. J.T. den Dunnen** Johan Den Dunnen is a staff member at the Departments of Human and Clinical Genetics. He has a long standing interest in research and diagnosis of DMD and is the original autor intellectualis of the exon skipping approach. He initiated the Leiden Muscular Dystrophy pages ([www.DMD.nl](http://www.DMD.nl)), curates the DMD mutation database, storing all DMD mutations published and submitted worldwide, and he has established and maintains the LOVD system, which will be employed to set up the Dutch DMD patient registry. Finally, he has supervised the generation of the hDMD mouse model, containing a full copy of the human DMD gene in the mouse genome. This human dystrophin functionally compensates the lack of mouse dystrophin in the *mdx* mouse, so hDMD/*mdx* mice are healthy. This mouse models allows testing human specific AONs in vivo.

**BASc L. van Vliet** Laura van Vliet started as a research technician in June 2007 and is involved in the generation of hDMD deletion mouse models. The deletion models would allow testing the therapeutic effect of human AONs in a mouse model.

**Dr. J.J.G.M. Verschuuren** Dr Jan Verschuuren is a neurologist at the Department of Neurology of the LUMC, where he heads the neuromuscular section. He was the PI on the recent trial on intramuscular treatment of Duchenne patients with antisense oligonucleotides in Leiden. He was one of the initiators of the Dutch ALADIN (All against Duchenne in the Netherlands) consortium, which aims to standardize Duchenne patient care in the Netherlands. He is involved in setting up a patient registry for Dutch DMD patients.



**Dr C. Straathof and Dr WCG Overweg-Plandsoen** Dr Chiara Straathof and dr. Truus Overweg-Plandsoen are neurologist/neuromyologist and child neurologist, respectively, at the LUMC Department of Neurology. Within the ALADIN consortium they aim to standardize patient care in the Netherlands. They are responsible for the organization of the LGMD outpatient clinic with emphasis on DMD and SMA. During their (half) day visits patients are seen by a multidisciplinary team consisting of a neurologist, pediatrician, pediatric cardiologist, orthopedic surgeon, rehabilitation physician and neuromuscular nurse.

**Dr. J.C. van den Bergen** Dr Janneke van den Bergen started working at the Department of Neurology in October 2007 as an AGIKO (Dutch term for physician who combines a PhD study with a neurological training). She will be involved in the clinical assessment of Dutch DMD patients and implementing this information in the Dutch DMD patient registry.

**Prof. Dr. Egbert Bakker** Bert Bakker, professor of Molecular genetics at the LUMC, leads the Laboratory for Diagnostic Genome Analysis (LDGA) at the department of Clinical Genetics; [www.lumc.nl/klingen/dna](http://www.lumc.nl/klingen/dna)). Since 1985 when he performed the first prenatal diagnosis for DMD worldwide, genetic tests for neuromuscular dystrophies have been among his major interests. The LDGA is an international reference centre for the molecular diagnosis of DMD/BMD, FSHD, LGMDs.



**Prof. Dr. Silvère van der Maarel** Silvère van der Maarel is Professor of Medical Epigenetics at the Department of Human Genetics of the Leiden University Medical Center. His research focus is on the (epigenetic) disease mechanisms underlying facioscapulohumeral muscular dystrophy (FSHD). Other research themes include oculopharyngeal muscular dystrophy (OPMD) and the limb girdle muscular dystrophies (LGMD). By means of intracellularly expressed antibody domains he aims to uncover disease mechanisms in muscular dystrophy.



### Prosensa BV (Leiden, the Netherlands)

**Dr. J.C.T. van Deutekom** Judith van Deutekom pioneered the antisense-mediated exon skipping strategy at the Department of Human Genetics starting in 1998. As Head of Research of Prosensa Holding she is now further exploring the field of RNA modification technology for application to DMD and other hereditary NMDs.



For further information or to contact one of the individuals mentioned above please contact

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If you would like to write a piece for the 'focus on' section on your institution, please e-mail

[Emma.Heslop@treat-nmd.eu](mailto:Emma.Heslop@treat-nmd.eu)

## Novel POMGnT1 mutations define broader phenotypic spectrum of muscle–eye–brain disease

Ute Hehr & Goekhan Uyanik & Claudia Gross & Maggie C. Walter & Axel Bohring & Monika Cohen & Barbara Oehl-Jaschkowitz & Lynne M. Bird & Ghat M. Shamdeen & Ulrich Bogdahn & Gerhard Schuierer & Haluk Topaloglu & Ludwig Aigner & Hanns Lochmüller & Jürgen Winkler

Abstract Muscle–eye–brain disease (MEB, OMIM 253280) is an autosomal recessive disorder characterized by a distinct triad of congenital muscular dystrophy, structural eye abnormalities, and cobblestone lissencephaly. Clinically, MEB patients present with early onset muscular hypotonia, severely compromised motor development, and mental retardation. Magnetic resonance imaging reveals a lissencephaly type II with hypoplasia of the brainstem and cerebellum. MEB is associated with mutations in the gene for protein O-mannose beta-1,2-N-acetylglucosaminyltransferase (POMGnT1, OMIM 606822). In this paper, we report the clinical findings of nine MEB patients from eight families. Eight of the nine patients presented typical features of MEB. However, a broad phenotypic variability was observed, ranging from two patients with severe autistic features to another patient with an unusually mild phenotype, initially diagnosed as congenital muscular dystrophy. Furthermore, severe hydrocephalus was reported in two families during a previous pregnancy, emphasizing the phenotypic overlap with Walker–Warburg syndrome. In addition to three previously reported mutations, we identified six novel POMGnT1 mutations (one missense, five truncating) in the present patient cohort. Our data suggest mutational hotspots within the minimal catalytic domain at arginine residue 442 (exon 16) and in intron 17. It is interesting to note that all mutations analyzed so far result in a complete loss of enzyme activity. Therefore, we conclude that the type and position of the POMGnT1 mutations are not of predictive value for the clinical severity. This supports the notion that additional environmental and/or genetic factors may contribute to the observed broad spectrum of POMGnT1-associated phenotypes.

Neurogenetics DOI 10.1007/s10048-007-0096-y

## Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up.

Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, Berard C, Vaksman G, Weber S, Bécane HM.

BACKGROUND: Duchenne muscular dystrophy (DMD), an X-linked disorder due to lack of dystrophin, is associated with muscle weakness and myocardial dysfunction. Although preliminary data support the efficacy of angiotensin-converting enzyme inhibitors on left ventricular (LV) function, our aim was to examine the long-term impact of a preventive treatment with perindopril on mortality in children with DMD. METHODS: Patients with DMD between the ages of 9.5 and 13 years presenting with normal LV ejection fraction were included in this prospective study. They were randomly assigned for 3 years to perindopril, 2 to 4 mg (group 1), or placebo (group 2) in a double-blind protocol, followed by open-label treatment with perindopril for up to 10 years. Survival rate at 10 years in each group is reported. RESULTS: There were 28 patients assigned to group 1 and 29 to group 2. Baseline characteristics were similar in both groups. At the end of the 10 years' follow-up period, survival status was available for all included patients: 26 (92.9%) of 28 patients in group 1 were alive at 10 years versus 19 (65.5%) of 29 in group 2 ( $P = .02$ ). Kaplan-Meier cumulative survival was significantly lower in group 2 than in group 1 ( $P = .013$ ). CONCLUSION: Early initiation of treatment with perindopril is associated with a lower mortality in patients with DMD with normal LV ejection fraction at study entry.

Am Heart J. 2007 Sep;154(3):596-602.

[http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=17719312](http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17719312)

## FDA issues genetic test guidelines for industry and FDA staff

In the US, the FDA has issued a documents concerning genetic testing- the Pharmacogenetic Tests and Genetic Tests for Heritable Markers (<http://www.fda.gov/cdrh/oivd/guidance/1549.pdf>) guidance was issued in June of this year for the pharmaceutical industry and for FDA staff. This guidance seeks to shorten development and review timelines, facilitate rapid transfer of new technology from research to laboratory use, and encourage informed use of pharmacogenomic genetic diagnostic devices. It also provides recommendations for sponsors and reviewers for preparing and reviewing premarket approval applications and premarket notification submissions. Array-based tests are included in the scope of the document, along with single and multiple marker tests. The recommendations set down a basic framework from which manufacturers and scientific reviewers can operate, and include the preparation topics of applications, intended use, device design, analytical studies, instrumentation, and comparison studies. Evaluation, effectiveness and labelling topics are also covered.

## Partner-specific items

### AFM looking for volunteers to appear in the Telethon



The AFM has decided to organise an event for this year's Telethon to highlight the pan-European fight to deliver treatments for NMD. This will take place in Metz on 7th and 8th December and will consist of workshops, meetings and a round table with a public audience in a "European Gene Café" in the afternoon of 8th December.

It would be fantastic to have TREAT-NMD partners and other people interested in the project taking part in this event especially those from Germany, Luxembourg, Belgium, the Netherlands, Switzerland and the UK.

The objective is to involve a minimum of 30 members from European partners participating in this event which could be the opportunity to communicate through different media (press, radio, TV) first in France, but in other countries involved too.

If you are interested please contact Hervé LAOUEANAN who co-ordinate the event.

[hlaouenan@afm.genethon.fr](mailto:hlaouenan@afm.genethon.fr)

## 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)

