



## TREAT-NMD Partner Newsletter No. 19 and Club of Interest Newsletter No. 13

13<sup>th</sup> July 2007

Welcome to the thirteenth newsletter for the TREAT-NMD Club of Interest. This week's edition features three excellent reports following 10 days of meetings regarding progress in translational research and outcome measures in experimental studies in muscular dystrophies.

We hope you enjoy the newsletter and look forward to hearing your comments – please write to [info@treat-nmd.eu](mailto:info@treat-nmd.eu) with anything you'd like to say. Feel free to forward this newsletter to anybody you think might find it of interest, or invite them to sign up to receive the newsletter directly by visiting our website.

Best wishes,

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

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## 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 the back-issues. If you have received this 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.

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## 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. 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)

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## 3. TREAT-NMD news and reports



Association  
Monégasque  
Contre les  
Myopathies

Clinical trials in DMD- from phase 1 trials to clinical benefit  
Association Monégasque contre les Myopathies &  
Duchenne Parent Project France, Round Table  
June 23rd 2007, Monaco  
by Katie Bushby



This meeting was the 6<sup>th</sup> Round Table organised by the Association Monégasque contre les Myopathies & Duchenne Parent Project France, and was attended by 21 scientists and industry representatives and 10 patient organisation representatives. The remit of the meeting was to discuss the progress from early phase 1 trials in DMD to the development of therapies in clinical use. Presentations covered the current state of the art with respect to ongoing or completed phase 1 trials, including myostatin inhibition, stop codon read through, the sarcoglycanopathy AAV trial and trials of antisense oligonucleotide induced exon skipping. Ongoing preclinical studies related to AON, AAV U7, high throughput drug screening for drugs which might enhance exon skipping and the use of muscle precursor cells were also presented. General discussion focussed on the issues surrounding the large scale production of clinical grade AAV and AON, and the potential long term toxicity or immunogenicity of these agents. There was also a short discussion about the requirements for the execution of clinical trials, and the TREAT-NMD network was presented.

Participants at the meeting recognised the exciting stage that preclinical and early clinical studies in DMD have reached. Some basic methodological questions in common with many of the trials were relevant to the TREAT-NMD objective of accelerating trials in DMD. Some of these were very basic and could begin to be answered as the experience from the early trials accumulates. In terms of measuring dystrophin expression, sharing of Western blotting protocols for standardisation and cross comparison could be useful through the designation of SOPs and/or reference laboratories, while the lack of correlation of dystrophin levels to physiology and function also remains poorly understood. In planning a muscle biopsy, the variability of response of different muscles to systemic treatment seen in animal models is very important for biopsy outcomes including choice of muscle and timing of biopsy, and this could be helped by further definition of non-invasive methods for determining the response of different muscles to treatment. Equally, it needs to be determined how large animal studies might contribute to the understanding of bioavailability and dosing data



for the different compounds. There remains a requirement to define and agree clinically significant and disease specific outcome measures.

Several issues were identified as particularly important for dialogue with the regulatory authorities. As this is a relatively new area for clinical trials, there was a feeling that there was a need for the regulatory authorities to understand the implications of studies in these diseases. Given the untreatable and progressive nature of the disease, can there be any systematic approach to reduce the regulatory timelines? In any specific situation, what preclinical evidence is going to be needed and when will intermediate steps between for example mouse and human be required? The species in which it will be mandatory to perform toxicology studies remain to be defined. A major issue as so many new therapies with mutation specificity are on the horizon is the limited patient numbers- how does this impact on regulatory issues as there will be only small patient cohorts for each targeted therapy, with the potential need for innovative trial design. Another issue we need to understand is whether if one therapy is shown to be effective will it de facto be regarded as the gold standard and other modes have to be compared. Approaches to therapy are required which will be applicable to all boys with DMD, at different stages of the disease.

This meeting was the first of a series of meetings on related topics which have taken place over the past ten days in which TREAT-NMD has been represented and these will be reported in successive newsletters. The need for dialogue amongst all the stakeholders from patient organisations to industry is particularly important, and the Monaco meeting as always allowed the development of fruitful discussion. Many thanks go to Luc Pettavino and Christine Dattola for their hospitality.



**U.S. National Institutes of Health Workshop on Translational Research in Muscular Dystrophy,  
June 25-27, 2007, Silver Spring, Maryland  
Report for the TREAT-NMD Meeting on Outcome Measures in Early DMD Trials  
by John D. Porter (National Institute of Neurological Disorders and Stroke/NIH)**

This Workshop, organized by the U.S. National Institutes of Health, was attended by over 60 scientists and regulatory agency, governmental organization, and industry representatives from the U.S. and Europe and representatives of 5 patient organizations. The motivation for the meeting was the progress and potential for new therapeutic development in muscular dystrophy and the need for changing mindsets on R&D models among both academia and corporations, the need for changing collaborative models, to ensure that appropriate expertise is brought to bear, and changing funding strategies, given that high development costs preclude any one party from fully funding a novel therapeutic program in rare diseases such as DMD. A variety of mechanisms were incorporated into the Workshop, including keynote talks, a 'lessons learned' case study in therapy development for rare neuromuscular disorders, working groups that reached consensus on a topic prior to the Workshop and presented findings, individual talks from selected experts, and an outside panel of distinguished industry scientists and regulators, seeking to examine the processes and collaborative models used in developing new therapies and to assess the current state of the various therapy development strategies in muscular dystrophy. Particularly at the program launch stage, it was viewed as essential that academia, biotech, and large pharma understand the strengths, weaknesses, and motivations of one another and to begin to formulate partnerships early in the process.

The goals of the Workshop were to: (a) summarize and evaluate the current status of translational research in muscular dystrophy, (b) identify obstacles to ongoing translational research, (c) identify ways to facilitate the rapid progression of therapies in muscular dystrophy based upon experience in this and other diseases, and (d) to produce a summary document for a peer-reviewed journal publication and a summary of the meeting for the U.S. Muscular Dystrophy Coordinating Committee website. The NIH (NIH Translational Research Program in the Muscular Dystrophies), Parent Project Muscular Dystrophy (Project Catalyst), and Muscular Dystrophy Association (MDA Translational Research Advisory Committee) have all launched therapy development funding programs in recent years, just as there has been increasing investment from biotechnology and large pharmaceutical companies in drug development efforts with potential value for muscular dystrophy. This environment called for a Workshop where the field could step back and perform a self-examination, as well as obtain input from a panel of experts in drug development from other fields, in order to increase the efficiency and efficacy of these efforts.



### Therapeutic development processes.

Muscular dystrophy is a target-rich environment—there are numerous potential targets, and it is unclear which of these represent the best therapy development opportunities and how the drugs and biologics that emerge will be best combined to effectively manage patients. In this target-rich environment, with limitations on time, effort, and funding, presenters and participants discussed the critical question as to when enough was known about a target and a candidate therapeutic to enter into a formal therapy development program. This decision involves science considerations (pathology clearly defined, target appropriate, availability of preclinical support to go to the clinic?), drug industry considerations (risk/benefit, regulatory barriers—a clear path to approval, established clinical endpoints, back-up compounds, potential performance of the candidate therapeutic, relevance to multiple populations/diseases, ease, cost, and scalability of the manufacturing?), and issues of the governmental, corporate, and venture capital funders of early stage R&D programs ('experts' comfortable with the target, addresses an unmet medical need, applicability of animal model data to human disease?). A careful overview of animal models and preclinical endpoint measures was motivated by a desire to achieve a 'best practices' consensus to facilitate efficiency and comparability of diverse preclinical development efforts. But it was recognized that we do not yet know enough about the relationship of pathogenesis in dog and mouse models of the human disease, and about the predictability of endpoints in animal models for human efficacy, to yet reach a consensus on models and endpoints. Key principals discussed at the Workshop included the observations that no animal model is perfect (accept what's available, but carefully optimize the experimental design, and recognize that some very good drugs have come from very bad animal models of other diseases), no in vitro/in vivo assay should be used in isolation to avoid misleading results, and quantitative, go/no-go criteria should be used in a milestone-driven research design in order to reach unambiguous decision points in therapy development programs. Emergence of a best practice for preclinical development likely will require successes and failures in clinical trials to validate a specific subset of animal models and endpoints. It was noted that investigators conducting efficacy studies should also be focusing on development of the surrogate endpoints/biomarkers in animals that will facilitate shorter duration clinical trials. Finally, discussions of regulatory and ethics issues that have or will emerge in this field included the need to harmonize local (IRB) and national (EMA/FDA) human studies approval requirements, including coordination between funding and regulatory agencies, the streamlining of bureaucracy at academic institutions, the restoration of common sense into human subject data protection regulations (HIPAA), and eliminating the 'we're here to help you, no matter how long it takes' regulatory burdens.

The emergence of a global registry that facilitates 'one-stop-shopping' for those conducting clinical trials was viewed as essential in the development of Genzyme's Pompe disease drug and represents necessary infrastructure for therapeutic development in the muscular dystrophies. In the case of clinical trials for DMD, where the subjects are minor children, a balance must be sought among the regulatory and ethical concepts of scientific necessity, parental permission, child assent, enrolment of healthy children controls, and an appropriate balance of risk and benefit for the subject. The inability to reach consensus on clinically meaningful outcome measures in the muscular dystrophy field also might be a consequence of the need to first learn from success/failures in more early stage trials. While there is broad international agreement on the core ethical principles to guide pediatric research, there has been resistance in moving from an academic to an industry model in the design and conduct of clinical research. Such a shift has been critical for fields with more experience in drug development and likely would aid the muscular dystrophy field.

### Therapy development collaborations.

Participants in the Workshop heard advice from an academic director of corporate alliances who is responsible for facilitating academic-corporate drug development partnerships at a major U.S. medical school. The need to build strong relationships between academic and corporate partners was viewed as essential in helping overcome the variety of barriers to collaboration (time, space, cultural, access, attention, priorities, long-term plans, etc.). Emphasis was placed on the need to broker relationships, not simply 'deals,' and to base academic-corporate relationships on both science and project management. Just as it was viewed as important that disease registries offer 'one-stop-shopping' for clinical trialists, academic institutions need to minimize internal barriers and provide both a single interface point and a well-honed process for facilitating academic-corporate partnerships in therapeutic development. The TREAT-NMD partnership model also was presented and praised as essential infrastructure to facilitate new treatments for muscular dystrophy.



### Therapy development strategies.

The major strategies currently being pursued in muscular dystrophy were evaluated by working groups of 3- to 4-members, with their findings presented at the Workshop. Separate panels looked at Gene Therapy & Repair/RNA Targeted Therapies, Cell Based Therapies, Muscle Regeneration Therapies, Anti-Inflammation/Fibrosis Therapies, and Membrane Repair/Compensatory Membrane Proteins Therapies. Summaries of these discussions are too lengthy to present here but will be made available on the Muscular Dystrophy Coordinating Committee website and in a peer-reviewed publication.

### Overall assessment.

An expert with experience from both large pharma and a venture capital firm commented that there has been a palpable increase in collaboration and respect among the key partners in the muscular dystrophy field and that maturation of such partnerships is essential to the achievement of effective new therapies for muscular dystrophy. The field has a clear recognition of the value and limitations of available animal models and can best move forward by understanding the caveats and designing careful, statistically rigorous studies to identify not just any candidate, but the best candidates to move forward into the clinic. Again, tendencies to promote personal favourite candidates need to be replaced by pragmatic decision making. An outside industry representative pointed to data that as many as 50 projects need to be launched to produce a drug. The notion was raised that a critical mass of efforts needs to be initiated for muscular dystrophy with a fail early/fail often and move on philosophy. Put another way, muscular dystrophy researchers need to learn how to objectively and dispassionately triage candidates both at the preclinical and clinical trial launch stages—while bets have to be placed on a wide array of targets and therapeutic candidates, available resources are not without limit at any stage of the therapy development pipeline making triage critical. Although potentially 'curative' strategies such as antisense-mediated exon skipping are attractive, and require attention, focusing on common downstream pathways that may be conserved among the different muscular dystrophies allows marshalling of knowledge and resources that might lead to more timely development of new therapeutics.

A regulatory agency participant emphasized the need to understand why a therapeutic candidate fails and, conversely, to appreciate the problems that arise from declaring success too early in clinical development. The regulatory perspective also included the observation that the attractiveness of repositioning existing approved drugs to muscular dystrophy (i.e., off-label use) should be, in part, tempered by the not inconsequential issues in approval of a drug for a new indication and patient population (e.g., lack of knowledge of dosing and patient group-specific toxicity). While there was recognition that agreement on preclinical and clinical endpoints is critical, and that earlier consensus would enhance comparability of different therapeutic strategies, there was an appreciation that the predictive value of endpoints will be validated only by experiences in clinical trials that complete the bench to bedside and back loop. Finally, it was noted that both the pharmaceutical industry and venture capital firms are shifting support toward late-stage therapy development, where risk/benefit ratios are more favourable, and thereby are creating a gap in the earlier stages of drug development that needs to be addressed by alternative funding paradigms. Collectively, the muscular dystrophy field needs to take a broad view of therapy development and begin to identify and focus on the key 'solvable' issues in the field that may lead to effective drugs and biologics in a shorter time frame.



### TREAT-NMD workshop on outcome measures in experimental trials for DMD, Naarden. 30th June- 1st July 2007, with the kind support of DRCI (UPPMD, PPMD, MDA, AFM)

As part of the TREAT-NMD Network of Excellence, 45 participants met to assess the current situation with respect to outcomes for early trials in DMD. Participants included academics, clinicians, industrial representatives, and patient representatives. The deliverables of the meeting were to determine ways to inform the future planning of the many therapeutic trials on the horizon for DMD.

### Session 1: Preclinical studies

Several speakers presented experience of using animal models for DMD (the *mdx* mouse and the GRMD and beagle dog models) and how preclinical studies can inform the development towards clinical trials.



Four separate issues were highlighted as useful outcomes of preclinical studies with a translational emphasis- will the data be sufficient to convince a company to invest, will the regulatory authorities allow things forward, will ethics approval be available based on the evidence, and will clinicians be convinced to put the compound into their patients.

For development of new therapies in the preclinical stage, working together with the regulatory agencies is important early with an idea of the protocol, use of animals is useful for efficacy, risk benefit analysis, but there is a danger that research interests can unnecessarily overcomplicate the issues. Some relative usefulness of the different measures can be useful, but there will always need to be a degree of target specificity. It is important to distinguish between treatment and protection effects- need to be treating animals where there is already disease and not only rely on data which look at transgenic models. A TREAT-NMD activity led by the University of Basel and Santhera will produce recommendations on the strengths and weaknesses of available models and the assessment procedures available and how they can be standardised.

We are awaiting the results from studies which do move into trial and have to learn from them as much as possible. One issue which could be exploited more is learning from studies of animal models treated with corticosteroids, as here the clinical value of the treatment is known. These data will be gathered from the literature and from amongst the workshop participants. The role of the dog model in the progression of therapeutic compounds to the clinic is yet to be fully determined- this valuable and scarce resource has value in different distinct situations but variability of model and availability issues can lead to problems in interpretation of the data. Careful prioritisation of the work and co-ordination of efforts between the colonies is going to be important.

### Session 2: Learning from completed and current early trials

Early studies of new therapies in DMD are now in progress or complete. Prosensa's experience with direct injection of antisense oligonucleotide shows that this kind of human trial can be very well controlled. Lessons from the trial include the finding that in vitro studies of exon skipping did not perfectly correlate with muscle expression. MRI showed poorer muscle in some patients: they had poorer restoration of dystrophin. No safety problems were encountered or any practical problems with product delivery or rebiopsy of the site of injection. PTC's experience in early trials of PTC 124 has generated questions about the variance in biopsy measures and choice of biopsy site for systemically administered therapies. These include age considerations, relation to disease progress and variability. The lack of early surrogate biomarkers was highlighted. These early studies have a clear aim of testing the relevant hypothesis first, ensure adequate drug exposure, and explore endpoints for future pivotal studies. The outcomes for these first in man trials are very different to larger scale later studies.

Each of these early trials provides useful information which can inform future developments. TREAT-NMD will begin to collect this kind of information systematically as a resource for the community in collaboration with the teams performing these studies.



### Session 3: Specific trial design issues: gene therapy and stem cells

Planning trials of gene therapy agents or cell based therapies raises issues additional to those involving small molecules. Planning AAV phase 1 trials needs consideration of major issues of immune tolerance, not only to the capsid but also possibly to the restored dystrophin. The dog model may be useful to give some idea of possibly effective immune suppression regimes. Proceeding through the process of moving to therapeutic trials will need to be cautious on the basis of immune response. There are a limited number of studies which should need to be done intramuscularly and the data generated to inform the next steps should be carefully monitored and the data shared.

Myoblast transfer has gone through phase 1 studies: negotiations with the regulatory authorities were difficult. Systemic delivery will not be appropriate for myoblast transfer: this therapy is only viable if there is a perspective for local therapies for DMD patients. Data are needed on the kinds of efficacy measures which will relate to local treatment. Other kinds of muscle stem cells may be more amenable to systemic delivery, such as the mesangioblast cell population. Design of these studies includes the intramuscular injection of a small



number of patients as proof of principle followed by a proposed intra arterial delivery protocol. Clear distinction between the issues of safety and efficacy is important.

These kinds of therapeutic strategies represent an area at a different stage of development to the previous drug based therapeutic strategies where the time scale from phase 1-2-3 can be envisaged being relatively short- here there will be sequential steps asking specific questions about immune tolerance in particular and the time scale to clinical application is much longer. This is an important issue for dissemination and communication when informing patients of the prospects of treatments in this area coming into the clinic.

#### **Session 4: Assessment of muscle biopsies**

There are crucial issues related to the interpretation of small amounts of dystrophin which can be expected as a result of early therapeutic interventions. Quantification of immunolabelling can be improved by image analysis systems and controlling with another protein (spectrin/ laminin alpha 2). This technique has been independently developed in at least three labs. Quantification of low levels of dystrophin down to 2-5% can be shown by Western blotting but the technique is labour intensive and requires careful controls, both in terms of the amount of total protein in the sample and the amount of actual muscle protein. Experience of the various labs in this area will be shared to develop standardised operating procedures.

A question which remains is the need for a pre-treatment biopsy for early trials. There is some evidence that there is no increase in revertant fibres with time, but how generally referable this is, is not yet clear. This can be an issue for ethical review, but also for trial design and the validity of the ultimate results of early studies.

#### **Session 5: Surrogate measures**

As a non-invasive method for monitoring treatment efficacy, MRI has promise: progression can be demonstrated with time and regions can be identified and quantified relative to fat and water phantoms. There are areas for more work in terms of benchmark data, standard operating procedures and consensus for data analysis. Strengths of the technique include the possibility to look at distribution of pathology, pathophysiology, anatomical correlation and monitoring of therapies. Blood RNA profiling is at an early stage and greater numbers are needed to validate early studies. Serum protein profiling is another approach where results are being generated. A biomarker development programme in France may generate leads which should be pursued on a collaborative basis.



#### **Session 6: Definition of clinically relevant endpoints**

The role of TREAT-NMD in assessing and harmonising clinical endpoints is in establishing the value and limitations of the existing scales with or without adaptation, and training in the available techniques. Initial efforts have concentrated on the assessments of functional

scales as a monitoring tool for gain and maintenance of skills. This has highlighted the interrelationships between the different scales as well as the specific value of different scales in specific trial settings. For example, the North Star ambulatory assessment is useful and valid for ambulant children with DMD but less useful for children who may lose ambulation during the period of the trial, and is not appropriate following loss of ambulation. MFM has the advantage of being able to follow patients for longer term studies. Functional scales have a role- they are clinically relevant: cross validation with timed tests is in progress. Ultimately we need to identify a correlation with "life changing events". Functional tests may be influenced by standards of care- and this TREAT-NMD activity needs to feed in here urgently to assuage these concerns. We should recognise that we need to capture the possibility of stabilisation of disease as this is important for the long term. This will most likely require placebo control and longer term studies.

Data from the CINRG group shows that muscle strength measurement is a relevant surrogate measure for DMD trials and results from Pompe disease show that quantitative muscle testing correlates with disease duration, loss of muscle function, and physical function correlated with quality of life. Correlation with DXA data and other measures is in progress.

There is a growing interest in the use of activity monitoring and tests such as the 6 minute walk test. Activity monitoring has had some work done in DMD and should ultimately be useful to measure activity levels and



intensity of activity. Correlation with other measures and longitudinal data are necessary. Variability is an important factor- day to day and seasonal and there also appear to be difficulties in measuring very small children. A TREAT-NMD meeting on the use of activity monitors was held on July 11<sup>th</sup>.

For the identification of trial design to satisfy regulatory authorities, endpoint selection is crucial. One multi-centre trial may be an alternative to two studies to be more time efficient. Clinically meaningful endpoints have to have obvious value to the patient and define how the patient feels, functions or survives. Surrogate measures are a substitute for clinical benefit and may not have an immediate value to the patient. FVC could be an example of this. Pharmacodynamic endpoints might include dystrophin expression: exploratory endpoints would be relevant to future studies. An ideal pivotal trial will have a mixture of these kinds of endpoints. Prior use in pivotal studies can be an advantage at the regulatory level.

#### Session 7: Regulatory perspective

TREAT-NMD could have an important role in talking to regulators and also talking to the people who fund therapies once approved. This is something which needs to be built into the planning of therapies at an early stage - learn from the Genzyme model.



#### 4. Upcoming conferences, meetings and workshops



##### Rare Diseases Research: Building on Success - a European Conference

Date: 13 September 2007

Venue: Charlemagne Building- Brussels, Belgium

This EC conference will focus on increasing the visibility of rare diseases research and raising awareness within the 27 EU Member States and the European Parliament on the research needs in this area, providing the rare diseases community with the opportunity to express their needs in terms of research and the EC with input for future FP7 calls for research proposals.

For more information: <http://cordis.europa.eu/en/home.html>

To register: <https://webgate.cec.eu.int/fmi/iwp/cgi?-db=rarediseases07&-loadframes>



##### EuroGentest Workshop on internal auditing for genetic testing laboratories

Date: 20-21 September 2007

Venue: Leuven, Belgium



Registration is open for this EuroGentest workshop on internal audit for genetic testing laboratories that will feature presentations, role play, video fragments and group discussions on how to prepare, execute and report internal audits.

Registration deadline: **15 July 2007**

For more information and to register now;

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

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## 5. Pick of the press releases

### Comment on PTC Therapeutics Press Release

by John Porter, NIH

The following press release announces the award of a \$15.4M cooperative agreement from the U.S. National Institutes of Health (NIH) to Lee Sweeney (University of Pennsylvania) and PTC Therapeutics for development of small molecule therapeutics for muscular dystrophy. This team has an established track record in the development of PTC124, a stop codon readthrough drug in phase 2 clinical trials for Duchenne muscular dystrophy (DMD), and is now looking at other drug development targets. This award was made through an innovative NIH grant program designed to foster collaborations that are essential to therapy development in rare diseases. Since it is not yet clear which of several therapeutic strategies may ultimately succeed in DMD, research teams and funding strategies need to be available to address multiple candidate therapeutics in parallel.

With support from Parent Project Muscular Dystrophy, Sweeney and PTC Therapeutics identified small molecule scaffolds with sufficient activity, selectivity, and potency for each of four well-validated muscular dystrophy targets and are positioned to launch drug development efforts to optimize at least two compounds through an iterative, rational drug design program to the stage of a U.S. FDA Investigational New Drug (IND) application. Based upon this key pilot data from the Parent Project award, the research team was able to successfully compete in a novel research grant program developed at the National Institute of Neurological Disorders and Stroke.

Funding from this NIH award supports IND-enabling preclinical activities for the four targets, two of which are gene complementation strategies that are specific for DMD and two others that address muscle regeneration with potential applicability for a broad spectrum of neuromuscular disorders. Unlike traditional hypothesis-driven NIH grants, this award uses a milestone-driven research model, with the achievement of annual, quantitative go/no go thresholds required for continued funding. This collaboration between academics, advocacy, corporate, and NIH partners reflects the changing mindsets, collaborations, and funding strategies that are necessary for translational research and not only brings together the requisite scientific expertise, but is essential in dispersing the risks inherent in therapy development for a rare disease.

This cooperative agreement is funded by the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the U.S. NIH.



### Grant Extends Research Originally Supported by Parent Project Muscular Dystrophy

#### PTC Therapeutics Announces \$15.4 Million NIH Research Grant for Duchenne Muscular Dystrophy

PTC Therapeutics, Inc. (PTC), recently announced that the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH) have awarded a \$15.4 million, five-year U54 grant to fund further research into Duchenne muscular dystrophy (DMD). The grant award will support a research collaboration between PTC and the University of Pennsylvania School of Medicine and will build upon previous research and discovery work supported by Parent Project Muscular Dystrophy (PPMD) under an initiative known as Project Catalyst.

"This grant supports promising preclinical research on a number of targets believed to be medically relevant for DMD," said H. Lee Sweeney, Ph.D., Professor and Chairman of the Department of Physiology at the



University of Pennsylvania School of Medicine, Scientific Advisor to PPMD and principal investigator on this NIH grant. “Over the course of this grant, our goal is to have Project Catalyst compounds ready for advancement into clinical trials for patients with DMD.” Ellen Welch, Ph.D., Group Leader, Genetic Disorders at PTC and principal investigator for PTC on this grant, commented, “We are very excited about this grant award as it expands our ability to advance promising programs that we have been developing over the past several years.”

In 2003, PTC and PPMD initiated Project Catalyst, a research collaboration funded by PPMD to identify new treatments for patients with DMD. Project Catalyst leveraged PTC’s proprietary drug discovery technology called GEMS (Gene Expression Modulation by Small-molecules) to search for new potential drugs for DMD patients. The GEMS technology allows PTC to identify small molecules that up- or down-regulate the production of proteins. Utilizing the GEMS technology, promising lead compounds were identified for several targets believed to be medically relevant for DMD.

“We are extremely pleased that the initial progress of Project Catalyst will be extended through this NIH grant award,” stated Pat Furlong, Executive Director and Founder of Parent Project Muscular Dystrophy. “PTC and UPenn have demonstrated a long-standing commitment to research and clinical development for DMD and have made remarkable progress to date. The support of the NIH for Project Catalyst’s efforts offers great hope to all members of the DMD community.”

“This grant is a model of the type of translational research we seek to support,” said John D. Porter, Ph.D., Program Director, Neurogenetics Cluster and Technology Development Program, NIH National Institutes of Neurological Disorders and Stroke. “The strength of this collaboration is that it brings together advocacy groups, academia, industry, and government in order to make an impact on the treatment of rare disorders such as DMD.”

“We are honored to receive this award from the NIH in conjunction with our colleagues at UPenn,” stated Stuart W. Peltz, Ph.D., President and Chief Executive Officer of PTC Therapeutics. “These funds help support our commitment to developing multiple treatments for neuromuscular disorders. With PTC124 in Phase 2 trials for nonsense-mediated DMD, we are establishing the clinical and regulatory path for new treatments for DMD in which the Project Catalyst compounds can follow. Our goal is to help provide treatment options for all DMD patients.”

For more information please contact Jane Baj at PTC [jbaj@ptcbio.com](mailto:jbaj@ptcbio.com)

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## 6. Job opportunities

Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands

1 x Post-doctoral Researcher, 1 x PhD student, 1 x Research Technician

The Department of Human Genetics is looking for a post-doctoral researcher, a PhD student and a research technician for its team investigating new therapeutic strategies for patients with Duchenne muscular dystrophy. The strategies use antisense oligoribonucleotides (AONs) to correct the genetic defect in the gene coding for dystrophin. The current projects aim to analyze the effect of this therapy in more detail and to further improve the efficacy of the therapy by investigating the possible synergistic effects of other therapeutic approaches applied in combination with the gene correction therapy.

We are seeking candidates with BSc, MSc or PhD in Molecular Biology, Biochemistry, Biotechnology or related discipline and preferably a background in muscle physiology. Experience with cell culture and state-of-the-art biochemical techniques is essential and applicants should be qualified to work with laboratory animals.

If you have any questions, or if you want more information about this position, please contact either;



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Closing date - **31st August 2007**.

We have added a job opportunities page to our website, so please visit to view all current job advertisements (<http://www.treat-nmd.eu/jobs.htm>)

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## 7. Partner-specific items

### Discussion forums / lists

Would you like us to set up a discussion forum for you on the TREAT-NMD website?  
If so, please e-mail [rachel.thompson@treat-nmd.eu](mailto:rachel.thompson@treat-nmd.eu).

Discussion lists currently active include:

- Registries and biobanks
- Standardised assessment of animal models
- Outcome measures for clinical trials (especially patient's perspective)
- Standards of diagnosis and care in DMD and SMA
- [New - Tro19622 Steering committee](#)
- [Coming soon- Gender Issues](#)

If you would like to be involved in any of these discussions or if you know someone who would like to contribute, please let the TREAT-NMD office know (by writing to [rachel.thompson@treat-nmd.eu](mailto:rachel.thompson@treat-nmd.eu)).

### Calls for proposals / funding opportunities

Please forward to us at the Coordination Office any calls for proposals and funding opportunities you receive within your institution. We will then advertise these in the newsletter and on the website.

### Deliverable reports

Many partners have deliverable reports due within the next few weeks, could we please encourage you to observe the due course of action for the production of your report as outlined in the e-mail you will have received from ACIES and as detailed below;

1. The work package leader responsible sends the completed deliverable, using the template attached to the e-mail, to the activity leader
2. The activity leader has 2 weeks for reviewing and iterating with the partner responsible.
3. The activity leader then sends the deliverable to the Project Coordinator (+ copy to [eu-new@acies.fr](mailto:eu-new@acies.fr)), who will also check it before sending it to the European Commission.

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## 8. 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)

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