TREAT-NMD Partner Newsletter No. 9 and Club of Interest Newsletter No. 3

4th May 2007

This week's newsletter contains information about TREAT-NMD's plans to develop training and exchange programmes for neuromuscular specialists, plus an update from PTC on their promising new therapy PTC124.

The TREAT-NMD Club of Interest is growing on a daily basis – thank you all for your interest and support!

Best wishes,

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

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Newsletter contents

1. About this newsletter

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

2. Working with us

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

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

3. TREAT-NMD training and exchange programme

One of the important aims of the TREAT-NMD network is to promote the integration of different teams and disciplines in the area of neuromuscular disease. The network also aims to stimulate an integrated and multidisciplinary approach by physicians and researchers in the development of new diagnosis and treatment options that will lead to more optimal care for patients.

Training and exchange programme

The TREAT-NMD network aims to stimulate and enable cooperation between various partners in different countries and of different disciplines. To reach this goal a training and exchange programme will be set up, which will help researchers and physicians to exchange knowledge, expertise and techniques on site in a multidisciplinary way.
As well as summer schools, training courses and dedicated workshops, we will set up an exchange programme for participants from both within and outside the consortium.

Candidates willing to participate in the programme, as well as institutes willing to host visitors, can apply to evers@enmc.org or call Pauline Evers on +31 35 548 0478.

The TREAT-NMD website will soon host a kind of online "clearing house" for training programmes and exchange visits. **If you have any vacancies at your department / institution relevant to the network, even if they appear to fall outside the scope of this exchange programme, please advertise them on the TREAT-NMD website.**

Young scientists training visits

Aim: Training and education
Time span: 2 months maximum

Young scientists are defined as those in the first four years (full-time equivalent) of their research careers.

These training visits are reserved for those who wish to work for a short period in a laboratory or a clinic in another country with the goal to:

- learn or develop new techniques
- use equipment or technology not available in their own lab
- gain experience with certain diagnostic tools
- gain experience with certain treatment methodologies

Candidates can submit their proposal, including CV and aim of their stay, to the proposed institution or to evers@enmc.org.

Senior scientists, exchange visits

Aim: exchange and networking
Time span: 1-2 weeks maximum

Experienced researchers are defined as those who, at the time of recruitment, (i) are in a possession of a doctoral degree, or (ii) have at least four years of full-time equivalent research experience.

During the short stay dialogue can be started between laboratories / industrialists / clinical centres / agencies with complementary expertise in order to accelerate cooperation. Visits can be used to exchange know-how or technical issues or to give training on site to the personnel of the host institution.

Candidates can submit their proposal, including CV and aim of their stay, to the proposed institution or to evers@enmc.org.

Senior scientists, developmental visits

Aim: exchange, stimulating research
Time span: 1-3 months

To facilitate the development of new theories or techniques or to transfer knowledge between partners, while aiming at a longer term collaboration programme between the institutes. Also be used as an impulse to start collaborative research or to expand on existing joint programmes.

Candidates can submit their proposal including CV's and aim of their stay, to the proposed institution or to evers@enmc.org. A detailed budget and work plan is required.

PhD fellowships

The TREAT-NMD consortium will look for funding of 4 PhD Fellowships. The Fellowships will be granted for the years 2-5 of the project. Vacancies will be published on the TREAT-NMD website.

Visiting Professorships

Aim: Bring in top-level education in a multidisciplinary setting to the host institution.
Time span: 4 weeks maximum

This programme facilitates in-depth, educationally focused visits by prominent medical or research experts. Medical schools, teaching hospitals and or research institutes in the area of neuromuscular diseases can express their interest to host a visiting professorships aiming at:

- General education in the field of neuromuscular diseases for institutions, which are planning to or in the early phase of setting up a specialised unit for neuromuscular diseases. Priority will be given to institutions in the former Eastern European countries or the accession countries
- Specialised education in a new area of neuromuscular research or treatment that is not yet available at the institution concerned
- Contribution to a broader training programme (e.g. summer school) for a larger audience (including people from outside their own institution)
- Hosting institutions from Eastern European countries are encouraged to apply

Professors are cordially invited to express their interest in a Visiting Professorship to share their knowledge with colleagues working at institutions abroad.
Visiting professors should be internationally known experts in the field of neuromuscular diseases, either in the research area or as a treating physician.
There may be a possibility for candidates outside the consortium to participate in certain parts of the educational programme given by visiting professors.

Both candidates for visiting professorships as well as institutes willing to host them can apply to evers@enmc.org or call Pauline Evers on +31 35 548 0478.

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4. Patient databases: online discussion/ comment facility

Hanns Lochmüller and Christophe Beroud, the leaders of the TREAT-NMD work on creating international patient databases, are inviting comments from specialists via an online comment form at http://www.treat-nmd.eu/biobanks/. A number of useful comments and documents have been received and can be viewed at the aforementioned address. Please feel free to visit this website section, read Christophe's letter, and send your comments via the online form.

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5. Extending the network

From the very start the TREAT-NMD network has planned to expand to include new countries. Over the past month or so we have been approached by organisations from the Czech Republic, Bulgaria and Ukraine who are keen to become involved in the network. We are in the process of drawing together draft rules for integration. These 'rules' will be discussed and finalised at the Governing Board Meeting in Naarden this July. If you have any thoughts on this subject, please e-mail us at the TREAT-NMD Coordination Office.

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6. Cochrane Group

Randomised trials in NMD
As part of their TREAT-NMD work KCLSM are required to keep a register of all randomised trials in NMD. They are therefore interested to know if you are undertaking or planning to undertake a randomised controlled trial for a neuromuscular disease, and if so what is the title of the trial. If you are please e-mail details of your trial to cochranenmd@kcl.ac.uk

Cochrane Reviews
Preparing and keeping up to date systematic reviews of all interventions for neuromuscular disease is a major task and its accomplishment will require the whole-hearted collaboration of many members of the TREAT-NMD programme.
Please let us know of any intervention which you think would benefit from a Cochrane Systematic Review at cochranenmd@kcl.ac.uk. If you would like to know more visit our website www.kcl.ac.uk/cochranenmd or contact us.

If you would like to author a new review, we would be very pleased to hear from you. We do provide training and support in systematic reviewing. This includes literature searching, detailed methodological advice and instruction in meta-analysis. We support reviews through the editorial process until they are acceptable for publication in the Cochrane Database of Systematic Reviews, part of The Cochrane Library, an electronic information resource containing systematic reviews of effectiveness of interventions. This resource is widely available in academic and health institutions and disseminated internationally.

7. PPUK and TREAT-NMD will work together on UK patient databases

One of TREAT-NMD's major goals is to create harmonised international patient databases for DMD, SMA, and in the future for other neuromuscular disorders, so that when any new treatment becomes available, researchers can gain access to the patients who might benefit. Some countries have already done much valuable work in this area, and where a national database of suitable quality exists, together with a functioning legal framework for patient consent and so on, it is clearly very important to build on the existing work and not reinvent the wheel.

In the UK, a registry for Duchenne muscular dystrophy has been created by the patient charity PPUK, and at a meeting at the Newcastle Centre for Life on 19 April, PPUK representatives Nick Catlin (CEO) and Robin Sharp met with representatives from Treat-NMD Kate Bushby, Stephen Lynn, Rachel Thompson, Emma Heslop, Hanns Lochmüller and Elaine Scott to discuss working in partnership on the further development of the registry and its harmonisation with the international registry to be created by TREAT-NMD. The two groups agreed that there was much to be gained from this concerted approach.

For further information please contact emma.heslop@ncl.ac.uk or nick@ppuk.org or visit our websites:
www.treat-nmd.eu
www.dmdregistry.org/
www.ppuk.org

8. Latest news / research

PTC Therapeutics Announces Additional Positive Interim Phase 2 Results of PTC124 in Duchenne Muscular Dystrophy

Following on from the article in newsletter 8 (27 April 2007), PTC Therapeutics, Inc. (PTC) today announced positive interim data from a Phase 2 clinical trial of PTC124 in patients with Duchenne muscular dystrophy (DMD) due to a nonsense mutation. This data was presented today at the 59th American Academy of Neurology Annual Meeting in Boston, MA. The results from the first two cohorts of the three-cohort study show that treatment with PTC124 was associated with increases in muscle dystrophin expression and reductions in serum creatine kinase values in at least 50 percent of evaluable patients.

"These data provide clinical evidence that PTC124 treatment may address the underlying cause of DMD," said Dr. Richard Finkel, Director of the Neuromuscular Program, Children's Hospital of Philadelphia, PA, who presented these results today at AAN as one of the trial's lead investigators. "Development of PTC124 offers the potential for a new therapeutic option for patients with DMD due to a nonsense mutation."

Langdon Miller, M.D., Chief Medical Officer of PTC, added, "We are very pleased with these additional pharmacologic proof-of-concept data from our short-term Phase 2 clinical trial of PTC124 in patients with DMD. Based on the growing body of Phase 2 clinical data, we plan to initiate longer-term clinical trials to evaluate the clinical benefit of PTC124 in patients with DMD."

The Phase 2 clinical trial is being conducted at three sites in the United States: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Cincinnati Children's Hospital Medical Centre, Cincinnati, Ohio; and the University of Utah, Salt Lake City, Utah. In the study, patients have received 28 days of PTC124 treatment at one of three dose levels. All clinical trial participants are boys with a nonsense mutation in the dystrophin gene, substantially elevated serum creatine kinase levels, and symptoms associated with DMD. The analysis presented today includes data from 26 patients with DMD who received PTC124 at the low-dose and medium-dose levels. Completion of accrual and analysis of data from a higher dose level are ongoing.

The primary endpoint of the trial has been the proportion of patients having an increase in dystrophin expression in muscle during 28 days of treatment with PTC124. Pre- and post-treatment muscle biopsies were

available from all 26 patients for analysis. *In vitro* treatment of patient muscle cells with PTC124 showed evidence of a dose-dependent increase in dystrophin expression in all of the evaluable patients. Preliminary review of the data indicate that, at both dose levels evaluated in this analysis, approximately half of the patients demonstrated visible improvement in the staining for muscle dystrophin *in vivo*. Overall, four of the six, or 67 percent, of patients treated at the lower dose level and 10 of the 20, or 50 percent, of patients treated at the medium dose level demonstrated an increase in the expression of dystrophin post-treatment. Response did not appear to be dependent on type of nonsense mutation.

Additionally, statistically significant reductions in the concentrations of muscle-derived creatine kinase levels in the blood were observed during PTC124 treatment. Several parents and teachers reported that boys participating in the study had improvements in terms of greater activity level and increased endurance during treatment. Individual subjects at both dose levels demonstrated some improvements in upper and lower muscle strength however in the overall analysis the magnitude of change was not statistically significant.

PTC124 was well tolerated among the 26 patients included in the study. Adverse events were infrequent, mild to moderate in severity, and did not result in therapy interruptions or discontinuations. There were no safety concerns based on physical examinations, vital sign measurements, electrocardiograms or laboratory parameters. Compliance with PTC124 treatment was excellent at both dose levels.

Stuart W. Peltz, Ph.D., President and Chief Executive Officer of PTC Therapeutics, stated, "In addition to the clinical proof-of-concept data we disclosed late last year, these new insights provide us with further evidence supporting the potential of PTC124 in genetic disorders due to a nonsense mutation. The findings in the DMD trials are consistent with the results observed in Phase 2 clinical trials of PTC124 in patients with cystic fibrosis and with preclinical results in the DMD mouse model that were recently published in *Nature*. We are eager to extend testing of this concept into other nonsense-mediated genetic disorders."

Insmed Announces Promising Results from IPLEX Phase II Myotonic Muscular Dystrophy Clinical Study

Insmed Inc. (Nasdaq: INSM) today announced positive results from a Phase II investigator-sponsored study of the company's drug, IPLEX™, in patients with myotonic muscular dystrophy (DM1). Preliminary results of the clinical study, being conducted at the University of Rochester School of Medicine and Dentistry, showed that six months of treatment with doses of IPLEX up to 1 mg/kg/day in six patients met the primary study endpoints of being safe and well tolerated. In addition, IPLEX treatment was associated with improvements in muscle mass, cholesterol and triglycerides. During the six months of treatment, 5 out of 6 patients experienced an improvement in lean muscle mass. Patients also reported improvement in gastrointestinal function, endurance and cognitive function during treatment with IPLEX.

"We are very encouraged by the results from this preliminary study of IPLEX in myotonic dystrophy. The results not only indicate IPLEX was safe, well tolerated and had a positive effect on muscle and lipid metabolism, they also suggest IPLEX may have a positive effect on aspects of the disease that affect patients' daily living," said Dr. Geoffrey Allan, president and CEO of Insmed.

Study Description: The primary objectives of this ongoing open-label, Phase II dose escalation study are to examine the safety and tolerability of once-daily, subcutaneous injection of IPLEX in up to 15 patients with DM1 and to identify the maximum tolerated dose. The next cohort of patients will be treated for six months with a dose of IPLEX which will be titrated up to 2 mg/kg/day. The study is funded by the National Institutes of Health and the Muscular Dystrophy Association, with supply of IPLEX drug provided by Insmed. A Phase II, placebo-controlled study to further investigate the safety and efficacy of IPLEX in a larger number of patients with DM1 is being designed based on the preliminary results of this study.

About IPLEX™: IPLEX was approved in the United States in December 2005 for the treatment of children with growth failure due to severe primary IGF-I deficiency (Primary IGFD). IPLEX (rhIGF-I/rhIGFBP-3), a complex of recombinant human insulin-like growth factor-I (rhIGF-I) and its predominant binding protein IGFBP-3 (rhIGFBP-3). The drug is also being investigated for various other indications with unmet medical needs, including HIV-associated adipose redistribution syndrome, retinopathy of prematurity and amyotrophic lateral sclerosis.

About Insmed: Insmed is a biopharmaceutical company focused on the development and commercialization of drugs for the treatment of metabolic diseases with unmet medical needs. For more information, please visit www.insmed.com.

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9. TREAT-NMD website proforma: please return as soon as possible

To all activity leaders: the TREAT-NMD website proforma deadline has now passed. We would like to thank all who have returned their completed proformas: they have provided valuable content for the website, and this will be appearing online shortly. We realise that the deadline was rather a tight one, so we do understand that some of you required more time. Nevertheless, the website is an important public face for the TREAT-NMD project and providing up-to-date information on it is crucial. We therefore encourage you to complete and return your contributions as soon as possible to r.h.thompson@newcastle.ac.uk

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10. Fact-finding questionnaire

Most partners have already completed and returned their questionnaires: thank you! However some partners are still to return their forms and we would like to encourage you to do this as soon as possible.

The results of the questionnaire will be used to write a short overview report for all partners and interested supporters. Additionally, individual partners will receive feedback on the questions relating to their specific work packages.

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11. Acknowledge TREAT-NMD

We would like to encourage all TREAT-NMD partners to recognise the support they receive from the TREAT-NMD network in papers, on posters and at conferences and workshops, whether that be through direct funding or via the support they receive from its members. It is not only good for the growth of the network but also fulfils one of our deliverables!

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12. Upcoming conferences, meetings and workshops

EURORDIS European Workshop: Gaining Access to Rare Disease Research Resources
Date: 4-5 May 2007
Venue: Institut Pasteur, Paris, France
More details: http://www.eurordis.org/article.php3?id_article=1248
This conference will be attended by Volker Straub and Hanns Lochmüller on behalf of TREAT-NMD. A conference report will follow.

37th annual general meeting of EAMDA (European Alliance of Muscular Disorders Associations)
Date: 27-30 September 2007
Venue: Warsaw, Poland
More details: http://www.eamda.net/poland.html

XVth Annual Congress of the European Society of Gene and Cell Therapy
Venue: Rotterdam, The Netherlands
Date: 27-30 October 2007
More details: http://www.esgct.org/

As new upcoming conferences only appear once in the newsletter we have decided to provide a full overview of all upcoming conferences under the news and events section of the TREAT-NMD website. This will appear within the next few weeks.

If there is an event you would like us to publicise in future newsletters and on our website, please send details to r.h.thompson@newcastle.ac.uk.

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13. Send us your news and views!

We encourage all partners and supporters to send their own news and updates and we will be happy to include them in future editions of the newsletter. Please send your contributions to emma.heslop@newcastle.ac.uk.. Please e-mail us with any information you have on upcoming education and training opportunities including workshops, conferences, funding, exchange programmes, clinical placements, visiting professorships and lectureships.

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14. Publicising TREAT-NMD

If you plan on attending any conferences, workshops or other meetings please download the TREAT-NMD double-sided colour flyer http://www.treat-nmd.eu/assets/documents/TREAT-NMD_Flyer.pdf and hand it out to interested parties. You also have the option of downloading an editable version in Microsoft Publisher format (higher resolution, better for large batch printing) http://www.treat-nmd.eu/public_html/private/docs/TREAT-NMD_Flyer.pub. We have had a limited quantity of flyers printed, therefore if you would like some to be posted to you for a specific event, please write to r.h.thompson@newcastle.ac.uk detailing the event you plan to attend and the numbers you require.

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15. TREAT-NMD link from your website

In an effort to increase the profile of TREAT-NMD, supporters and members of the Club of Interest are warmly invited to link to the TREAT-NMD website. To download a web-friendly TREAT-NMD button for your website please click on the following link and copy the appropriate line of code to your website: http://www.treat-nmd.eu/link.htm
Alternatively the TREAT-NMD logo is available to partners via the website at http://www.treat-nmd.eu/private/.. Those without a partner login should write to r.h.thompson@newcastle.ac.uk if they would like a copy of the logo.