We hope you found your first TREAT-NMD newsletter interesting and enjoyable. This week’s newsletter includes some exciting new developments from PTC Therapeutics regarding their new drug PTC124 – see section 6 below.

Again, we’d like to take this opportunity not only to thank you for your interest and support, but also to encourage you to become actively involved in the network. Communication and working together is at the heart of this network and we're keen to hear from you. Visit our website at www.treat-nmd.eu to find out more about us, or write to us at info@treat-nmd.eu.

Best wishes,

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

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1. 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

2. TREAT-NMD website

The TREAT-NMD website, www.treat-nmd.eu, is developing to become a complete communications platform for the network: an “intranet” for partners and a valuable tool for disseminating information to the wider community. It will be updated on a regular basis over the coming months, so please keep visiting it for news.

3. 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/. Please feel free to visit this website section, read Christophe’s letter, and send your comments via the online form.

4. 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

5. ‘Fact-finding Questionnaire – deadline 27th April 2007

Most partners have already completed and returned their questionnaires- thank-you!

The deadline for submission is today - 27th April. We would therefore be very grateful if partners who have not yet returned their questionnaires could do so as soon as possible.

The questionnaire has been designed by partners to help streamline data collection between partner organisations, saving time and duplication of efforts. Results will be used to keep partners updated and meet network deliverables. Once all the questionnaires have been returned the TREAT-NMD Coordination Office will consolidate and summarise the answers and then we will distribute the results to all partners in May.
6. Latest news / research

New drug to treat genetic disorders due to nonsense mutations

This week a study was published in Nature regarding the preclinical development of PTC124, a potential new treatment for genetic disorders due to nonsense mutations. In response to the media exposure surrounding this study we asked Cláudia Hirawat, Senior Vice President for Corporate Development at PTC Therapeutics, Inc., to give us her perspective on this exciting development and the way the TREAT-NMD network can help accelerate such developments in the future.

Targeting Nonsense Mutations Reveals Promising New Approach to Treating Genetic Disorders: Preclinical Data Published in Nature

Article written specially for TREAT-NMD by Cláudia Hirawat, Senior Vice President, Corporate Development, PTC Therapeutics, Inc.

On the 22nd of April, an article was published in the journal Nature about the preclinical development of PTC124, our drug to treat genetic disorders due to nonsense mutations, currently in Phase 2 clinical trials for the treatment of Duchenne muscular dystrophy and cystic fibrosis. The Nature data demonstrate that PTC124 allows dystrophin to be made in cells in which it was previously absent, to be delivered to the proper cellular location, and to induce restoration of muscle function.

Because PTC124 specifically targets the mechanism of reading through nonsense mutations, it has the potential to treat many genetic disorders. We have categorized at least 1,800 genetic disorders in which a percentage of cases is due to a nonsense mutation. Nonsense mutations are known to cause anywhere from five to 70 percent of the individual cases of most inherited diseases, such as Duchenne muscular dystrophy (13%), cystic fibrosis (40%) and Hurler’s syndrome (70%).

PTC Therapeutics has a strong commitment to neuromuscular disorders. In addition to Duchenne muscular dystrophy, we are considering the clinical applications of PTC124 in several other indications such as spinal muscular atrophy. We also have drug discovery efforts in Duchenne muscular dystrophy and in spinal muscular atrophy. In Duchenne muscular dystrophy we partnered with Parent Project Muscular Dystrophy (PPMD) to create Project Catalyst addressing a number of targets believed to be relevant to all patients with Duchenne muscular dystrophy and potentially other types of muscle-related conditions. In spinal muscular atrophy we are collaborating with the SMA Foundation and Fight SMA. In total there are nine distinct neuromuscular drug discovery or development programs at PTC.

It is wonderful to have our efforts recognized through the Nature paper, but as everyone in the rare disorders community knows, great science is only the beginning in the development of new treatments. The process is lengthy and expensive, and the greatest challenges are often related to information. What is the natural course of the disorder? What would be meaningful endpoints for clinical trials? How could we identify patients who could benefit from a potential treatment? How could we enrol these patients in clinical trials?

The launching of the TREAT-NMD network is extremely timely to help the community address these challenges and support the development of new therapies. TREAT-NMD provides a critical infrastructure for communication to support drug discovery and clinical trials. Because of the collaborative structure, lessons learned from TREAT-NMD partners will be shared in order to support the advancement of a broad portfolio of therapies in neuromuscular disorders. We are encouraged by the early results from our ongoing Phase 2 studies with PTC124 and look forward to working with the TREAT-NMD network to accelerate the process of identifying new treatments.

For more information about PTC Therapeutics and PTC124, please visit our website at www.ptcbio.com.
PTC124 targets genetic disorders caused by nonsense mutations

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Abstract

Nonsense mutations promote premature translational termination and cause anywhere from 5–70% of the individual cases of most inherited diseases. Studies on nonsense-mediated cystic fibrosis have indicated that boosting specific protein synthesis from <1% to as little as 5% of normal levels may greatly reduce the severity or eliminate the principal manifestations of disease. To address the need for a drug capable of suppressing premature termination, we identified PTC124—a new chemical entity that selectively induces ribosomal readthrough of premature but not normal termination codons. PTC124 activity, optimized using nonsense-containing reporters, promoted dystrophin production in primary muscle cells from humans and mdx mice expressing dystrophin nonsense alleles, and rescued striated muscle function in mdx mice within 2–8 weeks of drug exposure. PTC124 was well tolerated in animals at plasma exposures substantially in excess of those required for nonsense suppression. The selectivity of PTC124 for premature termination codons, its well characterized activity profile, oral bioavailability and pharmacological properties indicate that this drug may have broad clinical potential for the treatment of a large group of genetic disorders with limited or no therapeutic options.

http://www.nature.com/nature/journal/vaop/ncurrent/full/nature05756.html

Orphanet’s European Commission RD Portal contract renewed for 3 years

The Orphanet EC contract with DG Public Health is renewed from 1 April 2007 for a period of 3 years. Total EC funding of €960,000 towards a global budget of €2,674,911 will be shared by 21 of Orphanet’s partners from mainly European countries. These funds will contribute towards Orphanet’s mission of providing accessible, free information to users Europe-wide, to include concrete objectives. During the course of this contract, the data collection on expert services is expected to expand from 22 countries to 35. Basic information will be provided about all rare disorders (2,000 currently) and many new features will be included in the database and the website. The classifications of rare diseases will be included, making it possible to query the database by broad categories of diseases and even by medical specialty. The orphan drugs database will be totally restructured to give visibility to the drug’s stage of development from designation as an orphan drug up to availability on the EU market. The new website will integrate the AAA disabled access classification and will look more like a portal to provide a direct access to all the services already developed by Orphanet. These services are expected to improve the accessibility of available information and provide all European citizens with validated information about rare diseases and specialised RD services in Europe and beyond.

Useful website: The Council for Responsible Genetics

The Council for Responsible Genetics (http://www.gene-watch.org/index.html) aims to stimulate public debate about the social, ethical and environmental implications of genetic technologies. The Council works through the media and interested citizens to distribute accurate information as well as representing the public interest on emerging biotechnology issues. Founded in 1983, CRG is a non-profit, non-governmental organization based in Massachusetts, USA.

A histone deacetylase inhibitor improves survival of spinal muscular atrophy model mice

Spinal muscular atrophy is a neuromuscular disease characterised by motor neuron degeneration in the anterior horn of the spinal cord, responsible for muscular deficiency associated with atrophy. These are due to deletions or, even more rare, missense mutations of the SMN1 gene, which encodes a small ribonuclear protein. All patients possess at least a copy of its centromeric homologue SMN2 that encodes a protein which is very close, functional but unstable. Avila et al. administered trichostatin A, an inhibitor of histone deacetylase, to disease transgenic model mice. They observed a slight increase in the level of SMN2 expression in the neuronal and muscular tissues as well as a better assembly of small ribonuclear proteins. In addition, the treatment improves the lifetime, weight gain and motricity of mice.


To read more about proximal spinal muscular atrophy see
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=70.0

Journal of Clinical Investigation; 117(3):659-71; Mar 2007

ASC-J9 reduces muscular atrophy in Kennedy disease model mice

Kennedy disease is a spinal and bulbar muscular atrophy in which the degeneration of motor neurons causes weakness and muscular atrophy. This degeneration is due to the aggregation of the androgen receptor following an expansion of glutamin repetitions. Yang et al. have shown in vitro that the 5-hydroxy-1,7-bis (3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one (ASC-J9) increases the cellular survival in inhibiting the interactions between the muted receptor to the androgens and its coregulators as well as reducing its nuclear aggregation and increasing its degradation. In addition, the intraperitoneal injection of ASC-J9 in model mice of the disease reduces the muscular atrophy


To read more about "Kennedy disease", see:
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=481.0

Nat Med; 13(3):348-353; Mar 2007

New biotech company to commercialize novel UD gene-repair technology

OrphageniX

5:43 p.m., April 23, 2007--OrphageniX Inc., a new biotechnology company founded by University of Delaware researchers, has been established in Wilmington to develop and commercialize UD-patented technologies for repairing genes that cause rare, hereditary diseases such as sickle cell anemia and spinal muscular atrophy.

The announcement was made in a news release issued by the company on April 13.
Eric Kmiec, professor of biological sciences, and Hetal Parekh-Olmedo, senior research associate, both in the UD College of Arts and Sciences, co-founded and incubated OrphageniX at UD's Delaware Biotechnology Institute in the Delaware Technology Park in 2005.

Kmiec holds 14 UD patents for gene-editing technologies and is widely regarded as a pioneer in the field.

There are more than 5,000 rare or “orphan” diseases, so named because each affects fewer than 200,000 people nationwide. A number of these diseases are caused by a single-point mutation in a gene—which is like a spelling error, a single “letter” out of place, in its DNA code. The DNA nucleotide adenine (A), for example, might be replaced by guanine (G), cytosine (C) or thymidine (T).

Kmiec and Parekh-Olmedo discovered a way to introduce a tiny fragment of DNA into a diseased cell to replace the defective portion, triggering the cell to heal itself.

This method, which focuses on correcting a patient’s genes to make their own proteins, offers a safer approach than treating a patient’s genes with foreign genes or protein replacements, and eventually may lead to cures for rare diseases, according to Michael Herr, president and chief executive officer of OrphageniX.

Herr previously was the director of science and technology at the University City Science Center of Philadelphia.

Sickle cell anemia and spinal muscular atrophy are among the diseases that OrphageniX is targeting, according to Herr.

Sickle cell anemia affects an estimated 72,000 Americans, mostly African Americans. Those afflicted with the disease produce sickle- or crescent-shaped blood cells instead of smooth, round blood cells. These “sickle cells” tend to get stuck in the blood vessels, blocking the flow of blood to the limbs and organs, often causing pain, organ damage and anemia in the process.

Spinal muscular atrophy is a genetic disease caused by the progressive degeneration of motor neurons in the spinal cord, resulting in weakness and wasting of the voluntary muscles. Weakness is often more severe in the legs than in the arms. The disease affects approximately one in 6,000 babies, and about one in 40 people are genetic carriers, according to Families of Spinal Muscular Atrophy.

Herr said the company’s immediate strategy is to advance the new technologies to clinical trials, assemble a leadership team around its UD founders, and identify strategic partners.

7. 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!

A nice example of this can be seen below where our partners from MD-NET recently acknowledged that they were part of TREAT-NMD in the following paper:

The myopathic form of coenzymeQ10 deficiency is caused by mutations in the electro-transferring-flavoprotein dehydrogenase (ETFDH) gene

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Dok ('downstream-of-kinase') family of cytoplasmic proteins play a role in signalling downstream of receptor and non-receptor phosphotyrosine kinases. Recently, a skeletal muscle receptor tyrosine kinase (MuSK)-interacting cytoplasmic protein termed Dok-7 has been identified. Subsequently, we and others identified mutations in DOK7 as a cause of congenital myasthenic syndromes (CMS), providing evidence for a crucial role of Dok-7 in maintaining synaptic structure. Here we present clinical and molecular genetic data of 14 patients from 12 independent kinships with 13 different mutations in the DOK7 gene. The clinical picture of CMS with DOK7 mutations is highly variable. The age of onset may vary between birth and the third decade. However, most of the patients display a characteristic ‘limb-girdle’ pattern of weakness with a waddling gait and ptosis, but without ophthalmoparesis. Respiratory problems were frequent. Patients did not benefit from long-term therapy with esterase inhibitors; some of the patients even worsened. DOK7 mutations have emerged as one of the major genetic defects in CMS. The clinical picture differs significantly from CMS caused by mutations in other genes, such as the acetylcholine receptor (AChR) subunit genes. None of the patients with DOK7 mutations had tubular aggregates in the muscle biopsy, implying that ‘limb-girdle myasthenia (LGM) with tubular aggregates’ previously described in literature may be a pathogenic entity distinct from CMS caused by DOK7 mutations.
In 1965, an adult-onset, autosomal dominant disorder with a peculiar scapuloperoneal distribution of weakness and atrophy was described in a large, multi-generation kindred and named ‘scapuloperoneal syndrome type Kaeser’ (OMIM #181400). By genetic analysis of the original kindred, we discovered a heterozygous missense mutation of the desmin gene (R350P) cosegregating with the disorder. Moreover, we detected DES R350P in four unrelated German families allowing for genotype-phenotype correlations in a total of 15 patients carrying the same mutation. Large clinical variability was recognized, even within the same family, ranging from scapuloperoneal (n=142, 12%), limb girdle (n=410, 60%) and distal phenotypes (n=43, 18%) with variable cardiac (n=47,41%) or respiratory involvement (n=47, 41%). Facial weakness, dysphagia and gynaecomastia were frequent additional symptoms. Overall and within each family, affected men seemingly bear a higher risk of sudden, cardiac death as compared to affected women. Moreover, histological and immunohistochemical examination of muscle biopsy specimens revealed a wide spectrum of findings ranging from near normal or unspecific pathology to typical, myofibrillar changes with accumulation of desmin. This study reveals that the clinical and pathological variability generally observed in desminopathies may not be attributed to the nature of the DES mutation alone, but may be influenced by additional genetic and epigenetic factors such as gender. In addition, mutations of the desmin gene should be considered early in the diagnostic work-up of any adult-onset, dominant myopathy, even if specific myofibrillar pathology is absent.

9. 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](http://www.eurordis.org/article.php3?id_article=1248)

**Microarray and Microfluidics Training Courses**
**14 May 2007**
Edinburgh, Scotland
Advances in Microarray Technology, Lab-on-a-Chip World Congress and SEONSYNTech (Advances in Nucleic Acid Sequencing & Synthesis).

**European Human Genetics Conference 2007**
Date: 16-19 June 2007
Venue: Nice, France

**17th Meeting of the European Neurological Society**
Rhodes, Greece, June 16-20, 2007

**Rare Diseases Research: Building on Success, a European Conference**
Date: 13 September 2007
Venue: Charlemagne building- Brussels, Belgium

**4th European Conference on Rare Diseases (ECRD 2007)**
Date: 27-28 November 2007
Venue: Lisbon, Portugal
More details: [http://www.eurordis.org/article.php3?id_article=1351](http://www.eurordis.org/article.php3?id_article=1351)
10. 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. What else would you like us to include in the newsletter? Write to Emma with your feedback. 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.

11. 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.

12. TREAT-NMD link from your website

In an effort to increase the profile of TREAT-NMD we are asking partners to add a link to the TREAT-NMD website from their existing website. Many of the partners have already done this – thank you! For those of you who have not, we would be very grateful if you could arrange for a link to be created. Supporters and members of the Club of Interest are also warmly invited to link to us – please let us know if you do! 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 on the website at http://www.treat-nmd.eu/private/ for you to create your own hyperlink. Those without a partner login should write to r.h.thompson@newcastle.ac.uk if they would like a copy of the logo.