Working together to accelerate treatments for Neuromuscular Disorders -
The TREAT-NMD model
A unique opportunity

• EU call for applications for a “Network of Excellence” aimed at accelerating therapies for rare inherited neuromuscular disorders
• “Durable restructuring of the research environment” leading to harmonisation
• Application led by Newcastle University (Straub and Bushby)
• 21 partners, 5 years’ duration, 10m Euros infrastructure budget
• Funding commenced 1st January 2007
Selection of partners: excellence, representation

Backup from international scientific advisory board
TREAT-NMD co-ordination office

- Guide integration and harmonisation
- Ensue financial durability of the network
- Create the network ICT infrastructure

www.treat-nmd.eu
Email: info@treat-nmd.eu
Partners and the wider world: Network communication

- Outreach to > 2500 via newsletter
- Website (soon to be revamped) provides information to a global audience
- Ready to admit new members via Charter
- Interaction with NOEs, interest groups (DRCI, MSG, ICC, Wellstone Centres, CDC...)
- Training and educational programme
Activities address the infrastructure to harmonise the pathway from lab to trials

- Standardisation of assessment of animal and cell models
- Protocols for molecular diagnosis
- Production, toxicology and systemic delivery methods
- Assessment of patients in clinical trials
- Standards of diagnosis and care
- Organization of registries and biobanks
- Design and organization of multi-centric clinical trials
- Integration of support groups
- Ethical environment
Standardised assessment of animal models

• Review of available models leading to creation of standardised operating procedures in different areas of assessment:
  ▪ Calcium homeostasis, CK measurement, force generation, echo, electrophysiology…

• Excellent example of convergent programme!
  ▪ Wellstone initiative, AO7 (Santhera)

• Initial workshop Nov 2007 (Wellstone), follow-up meeting planned summer 2008 in Zürich

• Next challenge is achieving international acceptance of this gold standard (journals, funding bodies…….)
High Throughput Screening Models

- Cell lines have been made and evaluated as a tool for drug screening
- These cell lines have been distributed to various laboratories for further evaluation
- To date, the models will be used to assay exon skipping and utrophin upregulation
Therapeutics 1 (AFM)

• Tests have been developed to control therapeutic vectors using the baculovirus system
  ▪ Titration of baculovirus stocks using real-time quantitative PCR
  ▪ Genetic stability and insert identity of baculovirus stocks
  ▪ Detection of contaminant baculoviruses

• Review of existing European GMP facilities has been initiated
  ▪ AFM will co-fund two GMP production facilities in France
Therapeutics 2 (LUMC)

• Optimisation of systemic delivery of AONs in \textit{mdx} mice
  - Ongoing toxicology studies to test for most efficient exon 44 and 51 AONs
  - Ongoing toxicology and bio-distribution assays for exon 51
  - Studies with exon 44 AON have been initiated

• Report on initial findings on route of administration and short-term AON treatment studies is in preparation

• Functional studies in untreated \textit{mdx} mice and wild type mice have been initiated
  - Functional test protocols will be optimised and implemented (working with UNI BASEL group on appropriate animal model studies and SOPs)
Trial readiness: outcome measures

- Development of online registry of outcome measures (Michael Rose, KCL)
- Assessment of available tools in clinical situation (Eugenio Mercuri, Rome)
- Identification of gaps in knowledge
- Dialogue ongoing with industry and regulatory agencies (to establish unified and accepted OMs for different trials)
  - Flexibility, training (e.g. to physiotherapists in OMs), education
Trial readiness: standards of care

• Why?
  ▪ To address inequalities in treatment today
  ▪ To provide a level playing field for access to new treatments tomorrow
  ▪ Provide tool for lobbying

• How?
  ▪ Consensus development
  ▪ Cochrane Collaboration

Activity of Karolinska Institute, KCL in collaboration with ICC and CDC
DMD standards of care

- TREAT-NMD is working with the US CDC on the major publication (autumn 2008) of a comprehensive set of standards for DMD care.

- TREAT-NMD has published an interim document detailing recommendations for diagnosis, neurology, GI/nutrition, respiratory care, cardiac care, orthopaedics, psychosocial, rehabilitation and oral care.
Trial readiness: Patient registries

• Many benefits to patients of registries
  ▪ Feedback on standards of care and new developments
    o Broader educational role
  ▪ Feeling a sense of “belonging” to a broader community
  ▪ Not being left behind as trials develop
  ▪ A link to the research community

• Many benefits to industry of registries
  ▪ Easy access to patient community
  ▪ Clear concept of target market
Patient registries: objectives

- **Clinical trials:**
  Feasibility, Planning, Recruitment of patients

- **Research:**
  Epidemiology; Genotype-phenotype; Natural history of disease; Disease modifiers; Influence of treatments

- **Health care:**
  Planning, Providing services and products

- **Politics:**
  Lobbying, Decision making
Patient registries: content

Items must be

• simple and short enough to ensure participation.
• detailed enough to be useful.
• harmonized internationally.
• standardized to allow a computerized data analysis:
  - a list of answers is proposed,
  - free text is limited as it is difficult to standardize and therefore difficult to analyze.
• versatile enough to work with different modes of data collection: professional report, patient report.
Patient registries

- Existing registries
  - Mand/highly enc. items
- New registries
  - Mand/highly enc. items

Global database
(UMD software)
Registries for DMD: harmonized items

- Personal data of patient (name, birth date, address)
- Diagnosis (DMD, BMD, IMD, SCcarrier, not determined)
- Mutation/Deletion
- Motor function: ambulation
- Medication: steroids
- Scoliosis surgery
- Cardiac involvement
- Ventilatory function (Ventilator use)
- Muscle biopsy

Mandatory:
- Medication: steroids

Highly encouraged:
- Ventilatory function (Ventilator use)
Registries for DMD: optional items/modules

- Availability of biomaterial at biobank
- Other outcome measures (scales, etc.)
- Quality of life
- Standard of care
- Socio-economic burden of disease

- To be developed in cooperation with the relevant TREAT-NMD activities and work packages
Patient registries: **national curators**

- Collect the data in each country
  - from the professionals (geneticists, physicians)
  - from the patients (self-report)

- **DMD**: mutational spectrum of dystrophin gene
- **SMA**: mutations of SMN1 gene & copy number of SMN2 gene
  (use the international mutation nomenclature: standardization)

- Validate the genetic & clinical data in order to maintain high-quality / accurate data
  national curators

- Feed the data into the database
Patient registries

- Professional report (geneticist, physician)
- Patient report (self-report)

Curator

National database/registry
  - Mandatory items
  - Highly encouraged items

TREAT-NMD global database

Pseudonymised (encrypted) data
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Patient registries

- Patient report (self-report)
- Professional report (geneticist, physician)
- Curator
- National database/registry
- Mandatory items
- Highly encouraged items
- TREAT-NMD global database
- Pseudonymised (encrypted) data
Originally planned national TREAT-NMD registries on DMD & SMA (2006)
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Currently planned national TREAT-NMD registries on DMD & SMA (April 2008)

Associated Registries:
- Australia
- Canada
- Japan
- USA

UK partnership with Action Duchenne
Currently planned national TREAT-NMD registries on DMD & SMA (April 2008)

- 20 countries around the world planning to set up TREAT-NMD registries for patients with DMD/BMD or SMA
- Patients from countries not listed here can register in countries that use a self-report system (e.g., in the UK or in Germany)
- Patients are encouraged to register only in one national registry
Examples for active national TREAT-NMD registries on DMD & SMA (April 2008)

Website for Bulgarian DMD/BMD and SMA registries

Website for Czech and Slovak DMD/BMD registries

Website for German DMD and SMA registries
Legal/ethical best practice for registries

• Feed-Back to the patients
• Possibility of data withdrawal
• Informed consent
• Pseudonymised (encrypted) data
• Frequent updates of data
• Extension to other diseases

TREAT-NMD registries will adhere to these principles via the TREAT-NMD registry charter
TREAT-NMD global databases: charter

- Was developed and revised Jul-Dec (2007) with the help of partners, lawyers, ethicists, patient organizations
- Sets the framework for the cooperation between the global database, national registries and third parties
- Defines best practice for global database and for national registries
- Shall be adopted by national registries and TREAT-NMD
- Shall be part of contracts and agreements with third parties
- Is publicly available on the website (reference doc)
Third party access and participation

Global database

Local Ethics Board Approval

TREAT-NMD Oversight Committee Approval

TREAT-NMD

Third parties (industry, academia)
Steps for integrating existing / setting up new national registries: the registries toolkit

- Plan for technical implementation on the national level
- Information and involvement of national patient organizations, clinicians
- Amend/seek IRB (ethic’s board) approval for existing/new registry; respect national data protection laws
- Translation and adaptation of informed consent, patient information, questionnaire and other documents
- Hire curator personnel; curator training
- Secure additional funding on the national level
- Adopt registry charter; nominate representative for TGDOC
Trial readiness: site feasibility and clinical trial co-ordination

- University of Freiburg (MD-NET)

- Planned services:
  - Project and data management
  - Monitoring
  - Study assistance
  - Training
  - Bioinformatics
  - Trial site identification
  - Guidance on European regulations
  - EMEA/FDA contacts
CTCC Feasibility Questionnaire

In the near future we will:

• Identify Clinical Trial Centres across Europe capable of performing Phase I, II and III Clinical Trials in DMD patients

• Engage and liaise with Industry

• Facilitate training and education workshops to promote harmonisation of trials across Europe

• Develop standard protocols
CTCC Feasibility Questionnaire: trial site identification

As of March 2008:

- 95 sites currently registered (~37% of total contacted)
- in 27 countries worldwide
- at least 56 sites have been identified as having previous or current experience in conducting clinical trials
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CTCC Feasibility Questionnaire: overall patient population

[Graphs showing overall patient population distribution by diseases and age groups]
TREAT-NMD Network in Action

• Close collaboration with industry

Industry is interested but, more importantly, involved in the research and integration activities that are being developed in TREAT-NMD.

Their interest is broad:
design of clinical trials, access to well characterised and standardised patient groups, pre-clinical testing, and production of therapeutic agents.

Current collaborations include:

- PTC Therapeutics,
- Acceleron Pharma,
- AVI BioPharm,
- Summit,
- Genosafe

- Trophos,
- Prosensa,
- Santhera,
- Genethon,
TREAT-NMD Network in Action

- DMD and SMA “flagship” projects of network:
  - Progress includes
    - Collaboration with PTC therapeutics
    - Ongoing co-ordination of AON trials
    - Advisory board for TROPHOS in SMA
    - Regulatory discussions ongoing
Priorities in next year

- National and international implementation of first year’s results
  - Registries
  - Standards of care
  - Mouse model SOPs
- Direct trial activity/ experience
- Develop training programme
- Enhance patient outreach
- Plan International meeting for 2009

• Consider the sustainable outcomes of the network after five year funding period
For further information…

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