Translational research in myotonic dystrophy and international networks

Professor Hanns Lochmüller
Institute of Genetic Medicine, Newcastle University, UK
Myotonic dystrophy type 1 (DM1)

- Dominant inheritance
- Unstable CTG repeat expansion
- Severe congenital form
- Relatively frequent in Quebec
DM1 is also a muscle disease: Multi-system disease

- Gastrointestinal tract
- Heart
- Lungs
- CNS
- Eyes
- Endocrine system
- Urogenital system
- Muscle
- Skin

“Progeria”
Why do some neurologists have problems with myotonic dystrophy (patients)?

• **Disease** is ‘difficult’
  - Variable
  - Multi-system
  - ‘What is the best treatment?’

• **Patient** is ‘difficult’ (not just a muscle disease)
  - Cerebral features
  - Initiative ↓, spontaneous complaints ↓
  - Communication, facial weakness, dysarthria ↓
  - Cognitive problems/ behavioral problems
Aim: To evaluate the effect of a tailored behavioural change intervention comprising CBT and physical activity on participation (as measured by the DM1-Activ scale) for severely fatigued patients with myotonic dystrophy type 1 compared to standard care.
Coordinated by Professor Baziel van Engelen at Radboud University, Nijmegen, Netherlands.

€3 million funded by the European Commission through the FP7 funding stream.

Developing a unique non-pharmacological intervention

Cognitive Behavioural Therapy combined with graded physical activity

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697
Study rationale, using CBT and exercise training to improve overall health status.
Optimistic study design based on previous FSHD trial

- Prof Baziel van Engelen previously carried out a study in FSHD
- 3 armed study - control, CBT and exercise (note: not combined CBT and exercise).
- Total of 57 patients included from 300 screened.
- CIS fatigue dropped from 42 to 30 in both exercise and CBT group against standard care.
- More than 70% kept exercising after end of intervention period.
- Also showed improvement in fatty infiltration on MRI
Aerobic exercise training

- **Sub MAX Test**
- **Muscle MR Creatin Kinase NMR spectrosc.**

**Month 0**

**Month 4**

- **16 weeks training**
  - 30 minutes
  - 3x/week
  - 50–65% of VO$_{2\text{max}}$

**Month 7**

- Download of pulsewatch data

**Month 10**

Randomized clinical trial:
- 16-week aerobic training
- Sub MAX Test
- Muscle MR Creatin Kinase NMR spectrosc.
Assessed for eligibility (n = 377)

Not willing to participate (n = 199)
No reaction (84)

Screened n = 94

Excluded (n = 37)
• No severe fatigue (n = 25)
• Wheelchair-bound (n = 8)
• Illiteracy (n = 2)
• Other reasons (n = 2)

Included n = 57

Randomisation 2x

AET (n = 28)
UC (n = 24)
CBT (n = 25)
CIS Fatigue: effect of AET and CBT

The graph shows the effect of Usual care, AET, and CBT on CIS Fatigue over time (T0, 16 wks, 28 wks). Usual care remains relatively stable, AET shows a decrease and then stabilization, while CBT shows a decrease followed by an increase.
The Optimistic Trial

• Double armed (treatment vs. standard care)
• Assessor blind
• Randomised
• 10 month intervention
• Assessment at 4 time points: baseline, 5, 10 and 16 months
• Will involve 286 patients from four clinical centres
• Caregivers/Significant others will also be invited to participate
Four Clinical sites: each recruiting 72 patients, total 286.
Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetically confirmed DM1</td>
<td>Severe depression</td>
</tr>
<tr>
<td>Over 18 years old</td>
<td>Participation in another clinical trial</td>
</tr>
<tr>
<td>Ability to walk independently</td>
<td>Unable to complete study questionnaires</td>
</tr>
<tr>
<td>Ability to provide informed consent</td>
<td>Use of psychotropic drugs (with the exception of modafinil and Ritalin)</td>
</tr>
<tr>
<td>Score &gt; 35 on the checklist Individualised Strength (CIS) fatigue</td>
<td></td>
</tr>
</tbody>
</table>
Secondary Objectives:

• Creation and introduction of evidence based clinical guidelines on exercise and cognitive behavioural therapy in DM1

• Identification of individual (serum, DNA) or composite biomarker profiles as surrogate outcome measures and moderating or mediating factors of the efficacy and safety of the clinical response

• Create clinical trial infrastructure for European DM1 trials, including the collection of natural history data from a large cohort of DM1 patients

The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697
Outcomes

Primary Outcome
- The primary outcome measure will be the DM1-Activ measured at the end of the 10-month intervention period.

Secondary Outcomes
- **Activity:**
  - 6-minute walk test (6MWT), Myotonic Dystrophy Health Index (MDHI)
  - Physical activity measured with actometer.
- **Fatigue and sleepiness:**
  - Fatigue and Daytime Sleepiness Scale (FDSS), Checklist Individual Strength (CIS) fatigue
- **Quality of life:**
  - Individualised Neuromuscular Quality of Life Questionnaire (InQoL)
- **Mood:**
  - Beck Depression Inventory for Primary Care
- **Cognitive:**
  - Apathy evaluation scale (AES), Stroop test

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement no 305697.
Visit 1 and 2 combined where possible

Around 10 CBT sessions will have taken place by month 5.

The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697.
The intervention: Cognitive Behavioural Therapy

Aim: To develop a novel protocol to implement and assess CBT as a treatment to stimulate an active lifestyle in DM1 patients and reduce fatigue, through an innovative approach with exercise fully integrated as a module in CBT.
The intervention: Cognitive Behavioural Therapy

• The CBT consists of three phases.

• **Phase I:**
  • Working on the conditions to become more active (sessions 1-5)

• **Phase II:**
  • Becoming Active (sessions 6-10)

• **Phase III:**
  • Staying active (Sessions 10-14)

• Phase I and II take about 5 months, followed by five months Phase III.
• We anticipate a maximum of 20 sessions, with at least 5 face to face.
## Modules involved in CBT.

<table>
<thead>
<tr>
<th>Module</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensation for reduced initiative</td>
</tr>
<tr>
<td>Regular sleep/wake rhythm</td>
</tr>
<tr>
<td>Helpful thoughts about fatigue and DM</td>
</tr>
<tr>
<td>Activity regulation and increase</td>
</tr>
<tr>
<td>Managing Pain</td>
</tr>
<tr>
<td>Optimising the interactions with the direct environment</td>
</tr>
</tbody>
</table>

The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement n°: 305697.
Phase I: Meet the conditions to become more active (sessions 1-5)

- All patients complete:
  - Goal Setting
  - Compensating for reduced initiative.

- Then based on baseline assessment a selection of:
  - Optional modules which target factors that sustain fatigue
  - Sleep-wake pattern
  - Even distribution of activities
  - Helpful thoughts about fatigue and MD
  - Managing pain
  - Optimising social interactions
Phase II: Becoming Active (sessions 6-10)

Graded Activity Programme

- Slowly and steadily increasing walking or cycling
- From 4 x 1 minute a day to 2 x 30 minutes a day.
- Working towards the physical goals set at the start of treatment.

Or

Graded exercise programme

- Tailor made exercise programme supervised by physiotherapist.
- This incorporates regular activities of the patients choice and support to achieve them.
**Phase III: Staying active (Sessions 10-14)**

- **Evaluation of the treatment:**
  - Have goals been realised,
  - Which strategies were helpful?
  - Plans to stay active
  - What to do in case of relapse?

- “booster sessions.”

The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697.
Measuring activity: GeneActiv

• Worn after each assessment visit for 2 weeks (14 days)
• Lightweight watch-like device worn on the non-dominant ankle.
• The device is waterproof. But advise removal when bathing as the strap is not.

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697
Data Management: Cloud internet

Security

Processing

Storage

Provenance / Audit

eScience Central
Measuring activity: GeneActiv

- Each 14 day period will generate around 1.2 GB of data.
- This will be uploaded to the MoveEcloud.
- The data is analysed in the cloud and a report generated.
  - Includes overall levels of activity
    - Pervasively passive: at most two active days
    - Fluctuating Active: more than two active days and less than two inactive days
    - Pervasively active: at most two inactive days
  - Daily report of activity, showing peaks and troughs throughout the day
- This report can then inform the direction of the CBT
Sub-Studies: Muscle and Cardiac MRI

Muscle Imaging
• A subset of 100 patients, 25 at each site.
• Upper and lower leg images
• Protocol based on FSHD study

Cardiac imaging
• Subset of less than 30 patients
• Newcastle only
Registries and Recruitment

• Recruitment and retention are identified challenges in the study.

• Three of the four clinical centres using national registries, UK, Germany, France (DM-scope collaboration with Quebec)

• All collecting the core dataset agreed in the Marigold/TREAT-NMD workshop in 2009.

• This data is also being collected as part of the OPTIMISTIC trial.

• The use of the registries is important for the creating an infrastructure for future DM1 trials in Europe.
Mandatory data items:  
- Personal Data: name, address, DOB, sex, phone number, email.
- Clinical Diagnosis: Congenital DM, DM1, DM1 asymptomatic carrier, other, unknown.
- Genetic test result: DM1 mutation (triplet repeat expansion, other mutation), result pending, not tested.
- Current best motor function: ambulatory (unassisted), ambulatory (assisted), non-ambulatory.
- Wheelchair use: no, part-time (age at which first started using), full-time (age at which started using full-time).

Highly encouraged data items:  
- Myotonia: severe, mild, none, medication.
- Cardiac: heart condition, ECG, echocardiogram, cardiac medication, device.
- Pulmonary: non-invasive ventilation, invasive ventilation, pulmonary function test.
- Digestive: dysphagia, gastric/nasal tube.
- Other: cataract surgery, fatigue/sleepiness, fatigue medication, age of onset, genetic details/repeat size, positive family history, ethnic origin, other registry.
UK Myotonic Dystrophy Patient Registry

- Online patient driven registry, funded by patient organisations and supported by TREAT-NMD
- Clinical and genetic data entered by a nominated medical professional
- Over 400 people currently registered (since May 2012)
- Information about OPTIMISTIC sent to about 200 people meeting the eligibility criteria
## DM Registries Worldwide (2013)

<table>
<thead>
<tr>
<th>Country</th>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulgaria</td>
<td>DM1 and 2</td>
<td>-</td>
</tr>
<tr>
<td>Canada</td>
<td>DM1 and 2</td>
<td>168 DM1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31 DM2</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>DM1</td>
<td>277</td>
</tr>
<tr>
<td>France (Including Quebec)</td>
<td>DM1</td>
<td>1500</td>
</tr>
<tr>
<td>Germany</td>
<td>DM1 and 2</td>
<td>200</td>
</tr>
<tr>
<td>New Zealand</td>
<td>DM1</td>
<td>67</td>
</tr>
<tr>
<td>Poland</td>
<td>DM1 and 2</td>
<td>100 DM1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 DM2</td>
</tr>
<tr>
<td>Serbia</td>
<td>DM1 and 2</td>
<td>300 DM1, 30 DM2</td>
</tr>
<tr>
<td>UK</td>
<td>DM1 and 2</td>
<td>370 DM1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 DM2</td>
</tr>
<tr>
<td>US (Rochester)</td>
<td>DM1</td>
<td>~ 850 DM1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~ 150 DM2</td>
</tr>
<tr>
<td>US (Myotonic Dystrophy Foundation)</td>
<td>DM1 and 2</td>
<td>&gt; 900</td>
</tr>
<tr>
<td>Italy</td>
<td>DM1 and 2</td>
<td>Just Launched</td>
</tr>
</tbody>
</table>
The aim of OPTIMISTIC: Improve clinical practice for patients suffering from myotonic dystrophy type 1 (DM1)

We hypothesize that a comparable but DM1-specific CBT intervention, aimed at the fatigue maintaining beliefs and behaviours, tailored to the individual DM1 patient, will lead to a significant reduction of fatigue and improved quality of life.

Organisations
Here you will find local organisations that provide assistance and information to people affected by DM1 and their families

Registries
Here you will find your national patient registry, being part of a registry may give you the opportunity to take part in clinical research like OPTIMISTIC.

OPTIMISTIC study launched
Preparations for myotonic dystrophy trial underway.

Publications
Contact
Downloads

www.optimistic-dm.eu
OPTIMISTIC as part of networked translational research - why do we need networks?

• Rare diseases - no one country is enough

• To tackle issues that can be settled more effectively collaboratively than alone

• To provide a platform to support and accelerate translational research with opportunities for collaboration and cooperation

• To add value to the research aims of individual groups
Three year work plan

2007-2011
EU funded Network

2012 onwards
Alliance funded through multiple streams with global partners & membership

Governance
Chair – Annemiek e Aartsma-Rus
Vice – Eric Hoffman

Executive Committee
Supported by academic advisory board (“task force”) of NMD leaders
Global networking

New Rare Disease Initiatives from 2012:
IRDiRC, RD-Connect and Neuromics

Strong emphasis on collaborative research!
Harmonised research funding initiative launched by the European Union and US NIH – other countries invited to join

Goals: Diagnosis for all rare diseases and 200 new therapies for RD – by 2020

Governed by Executive Committee made up of representatives from each member organisation

Now has 35 committed members from across Europe plus Australia, Canada, China, USA (+ others joining)

Each member commits to spending min. 10 million USD over 5 years on research projects contributing to IRDiRC objectives

Scientific input via 3 scientific committees (diagnostics, therapies, and interdisciplinary) and working groups consisting of experts from funded projects
<table>
<thead>
<tr>
<th>Country</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Western Australian Department of Health</td>
</tr>
<tr>
<td>Canada</td>
<td>Canadian Institutes for Health Research</td>
</tr>
<tr>
<td></td>
<td>Genome Canada</td>
</tr>
<tr>
<td>China</td>
<td>Beijing Genomics Institute</td>
</tr>
<tr>
<td></td>
<td>Chinese Rare Disease Research Consortium</td>
</tr>
<tr>
<td>EU</td>
<td>European Commission</td>
</tr>
<tr>
<td>Finland</td>
<td>Academy of Finland</td>
</tr>
<tr>
<td>France</td>
<td>French Association against Myopathies</td>
</tr>
<tr>
<td></td>
<td>Agence National de la Recherche</td>
</tr>
<tr>
<td></td>
<td>Lysogene</td>
</tr>
<tr>
<td>Georgia</td>
<td>Children’s New Hospital Management Group</td>
</tr>
<tr>
<td>Germany</td>
<td>Federal Ministry of Education and Research</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian Higher Institute of Health</td>
</tr>
<tr>
<td></td>
<td>Telethon Foundation</td>
</tr>
<tr>
<td>International Consortium</td>
<td>E-RARE 2 Consortium</td>
</tr>
<tr>
<td>Netherlands</td>
<td>The Netherlands Organization for Health Research and Development</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>Korean National Institute of Health</td>
</tr>
<tr>
<td>Spain</td>
<td>National Institute of Health Carlos III</td>
</tr>
<tr>
<td>UK</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>USA</td>
<td>Food and Drug Administration Orphan Products Grants Program</td>
</tr>
<tr>
<td></td>
<td>National Human Genome Research Institute (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Center for Advancing Translational Sciences(NIH)</td>
</tr>
<tr>
<td></td>
<td>National Cancer Institute (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Eye Institute (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Neurological Disorders and Stroke (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Child Health and Human Development (NIH)</td>
</tr>
<tr>
<td></td>
<td>National Eye Institute (NIH)</td>
</tr>
<tr>
<td></td>
<td>NKT Therapeutics</td>
</tr>
<tr>
<td></td>
<td>Office of Rare Diseases (NIH)</td>
</tr>
<tr>
<td></td>
<td>PTC Therapeutics</td>
</tr>
<tr>
<td></td>
<td>Sanford Research Institute</td>
</tr>
<tr>
<td></td>
<td><strong>International Pharma Companies</strong></td>
</tr>
<tr>
<td></td>
<td>Genzyme (Sanofi)</td>
</tr>
<tr>
<td></td>
<td>Shire</td>
</tr>
</tbody>
</table>
EC-funded IRDiRC omics projects

Other IRDiRC projects

RD-Connect platform

Combined repository for linked data

EURenOmics

NeurOmics

RD-Connect
An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

Overarching objectives:

- Contribution to the IRDiRC objectives of delivering 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020

- Development of an integrated, quality-assured and comprehensive platform in which complete clinical profiles are combined with -omics data and sample availability for rare disease research, in particular IRDiRC-funded research.
**RD-Connect additional objectives**

- **Patient registries**: developing best practice for registries used for research – establishing interoperability standards, common data elements => feeding into central platform

- **Biobanks**: developing interoperability standards, common MTAs, searchable online catalogue of sample availability (building on EuroBioBank and BBMRI) => feeding into central platform

- **Bioinformatics tools**: developing and integrating clinical bioinformatics tools and making them accessible through the central platform and via APIs and web services

- **Ethical, legal and social issues**: addressing data sharing and informed consent for omics research, proposing a regulatory framework for linking RD medical and personal data, integrating patient perspective
<table>
<thead>
<tr>
<th>WP1: Coordination</th>
<th>WP2: Patient registries</th>
<th>WP3: Biobanks</th>
<th>WP4: Bioinformatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanns Lochmüller</td>
<td>Domenica Taruscio</td>
<td>Lucia Monaco</td>
<td>Christophe Béroud</td>
</tr>
<tr>
<td>Newcastle and TREAT-NMD</td>
<td>ISS and EPIRARE</td>
<td>Fondaz. Telethon &amp; EuroBioBank</td>
<td>INSERM Marseille</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WP5: Unified platform</th>
<th>WP6 Ethical/legal/social</th>
<th>WP7: Impact and innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivo Gut</td>
<td>Mats Hansson</td>
<td>Kate Bushby</td>
</tr>
<tr>
<td>CNAG Barcelona</td>
<td>Uppsala</td>
<td>Newcastle and EUCERD/ EJARD</td>
</tr>
</tbody>
</table>
RD-Connect’s central platform will make the data generated by IRDiRC projects rapidly available to the wider rare disease research community. Raw genomic data from collaborating projects is securely deposited in the European Genome-Phenome Archive (EGA) then reprocessed through a standard pipeline to ensure cross-compatibility of data from multiple projects. The processed data is held in the central RD-Connect database, where it is combined with other omics data types plus phenotypic and biomaterial information. Researchers approved by a data access committee will access data through a data coordination centre that enables comparison of datasets across projects and analysis with sophisticated bioinformatics tools.
Data flow within RD-Connect

- Source data
  - Biomaterial data
  - Omics data
  - Other IRDRC project data
  - Phenotype and registry data

- Secure, permanent raw data archive
  - European Genome-phenome Archive

- RD-Connect platform
  - Combined repository for linked data
  - Directly integrated bioinformatics tools
  - Access to additional tools via webservices/APIs
Linked with omics research projects

- **HEALTH.2012.2.1.1-1-B**: Clinical utility of -omics for better diagnosis of rare diseases
- **TWO projects**, EU contribution EUR 12 million per project
- Duration: 5 years

**EUREN Omics**

- European Consortium for High-Throughput Research in Rare Kidney Diseases (Franz Schaefer, Universitätsklinikum Heidelberg, Germany)

**Neuro Omics**

- Integrated European Project on Omics Research of Rare Neuromuscular and Neurodegenerative Diseases (Olaf Riess, Institute of Human Genetics, University of Tübingen)
Diseases and disease groups

- Huntington disease (HD)
- Front-temporal lob dementia (FTLD)
- Hereditary spastic paraplegia (HSP)
- Ataxias (ADCA, ARCA, CA)
- Spinal muscular atrophies & lower motoneuron diseases (SMA, LMND)
- Hereditary motor neuropathies (HMN)
- Congenital myasthenic syndrome (CMS)
- Congenital dystrophies & myopathies (CMD, CMY)
- Muscular dystrophies (DMD, BMD, FSHD, LGMD)
- Muscular channelopathies (MCP)
Aims and objectives

• Use the sophisticated -omics technologies
• Revolutionize diagnostics
• Develop pathomechanism-based treatments for ten major NDD and NMD groups
• Combine -omics approaches with deep phenotyping
• Identify biomarkers and disease modifiers
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 305697.