8.2.12
Email Holm Graessner: „War‘s das jetzt?“
„Was that it for now?“

After about 1000 emails
After more than 100 telephone calls
After many weeks grant proposal writing
After close to 100 concept meetings

NEUROMICS –
Integrated European Project on
Oomics Research of Rare
Neuromuscular and
Neurodegenerative Diseases

Olaf Riess, University of Tübingen
Overview

- Co-coordinators: Brunhilde Wirth (Cologne)
  Gert-Jan van Ommen (Leiden)
- **19 partners** (14 academia, 5 SMEs)
- Duration: 60 month, Start: 1st October 2012
- **14 work packages**
- 30% industry contribution (budget)
- Total budget: €16,848,604; €12 million EU contribution
- Total project effort: 1,689 person month

HEALTH.2012.2.1.1-1-B:
Clinical utility of -Omics
for better diagnosis of rare diseases
Omics technologies

- Analysing the genome
- Analysing RNA
- Analysing the proteins made
- Analysing metabolites

- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
Deep phenotyping – extending phenotypes into much greater detail

- In Neuromics, Omics approaches will be combined with deep phenotyping
- This is a detailed, comprehensive and precise description of a patient’s phenotype, describing its different components
- Allows more sensitive and useful sub-grouping of patients
Rare but they affect >500,000 patients in Europe

Few effective therapies, lack of genetic diagnoses, little investment by pharmaceutical companies

Extensive genetic heterogeneity

Wide clinical yet partially overlapping phenotypes

Overlapping clinical expertise of specialists

Extensive patient DNA and tissue collections

Possible common therapeutic strategies
### Estimates of prevalence of NDDs/NMDs in Europe

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
<th>Patients in Europe*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTLD</td>
<td>3-10 per 100,000</td>
<td>15,000-50,000</td>
</tr>
<tr>
<td>HD</td>
<td>3 - 7 in 100,000</td>
<td>35,000</td>
</tr>
<tr>
<td>Ataxias</td>
<td>20 in 100,000</td>
<td>200,000</td>
</tr>
<tr>
<td>HSP</td>
<td>2-10 in 100,000</td>
<td>10,000-50,000</td>
</tr>
<tr>
<td>SMA/LMND</td>
<td>5-10 in 100,000</td>
<td>20,000-40,000</td>
</tr>
<tr>
<td>HMN</td>
<td>1 in 2,500</td>
<td>200,000</td>
</tr>
<tr>
<td>CMS</td>
<td>1 - 10 in 1 Mio</td>
<td>500 – 5,000</td>
</tr>
<tr>
<td>CMD</td>
<td>7 - 12 in 100,000</td>
<td>40,000</td>
</tr>
<tr>
<td>D(B)MD</td>
<td>1 in 20,000</td>
<td>25,000</td>
</tr>
<tr>
<td>Dysferlinopathies</td>
<td>1 in 50,000</td>
<td>10,000</td>
</tr>
<tr>
<td>FKRP</td>
<td>0.5 in 100,000</td>
<td>2,000</td>
</tr>
<tr>
<td>MCP</td>
<td>0.5 to 1 in 40,000</td>
<td>6,000-12,000</td>
</tr>
</tbody>
</table>

*Patient numbers are estimated from numbers of single countries and extrapolated to the EU, or are calculated from heterozygote frequencies.
Aims of Neuromics (1)

- **Aim 1**: Screening more than 1,100 patients with unknown genetic cause by **Whole Exome Sequencing (WES)** using next-generation technologies, thereby increasing the **number of known disease genes** for the most heterogeneous diseases from approximately 50% to 80%.

- **Aim 2**: Increasing patient cohorts by **large-scale genotyping** using 3 **gene panel enrichments** for overlapping disease groups (NDD, NMD, SMA/LMND) combined with NGS of so far unclassified patients and subsequent phenotyping.

- **Aim 3**: Identifying **disease modifiers** through the characterization of cohorts with extreme early and late age of onset (SMA, HD, CMS, SCA).
Aim 4: Developing biomarkers with a focus on pre-symptomatic implementation, for application in diagnosis and clinical trials.

Aim 5: Combine Omics approaches to better understand pathophysiology guiding therapeutic approaches.

Aim 6: Developing target-driven therapies for muscular dystrophies such as DMD, LGMD2B, CMD, other NMD, and polyQ expansion diseases, subsequently to be translated to other disease groups using the expertise of the consortium.

Aim 7: Improving infrastructure and ontologies towards their application for NDD/NMD and to support translational research and networking with A and C projects.
**Subprojects and work packages (1)**

**SP1**: Deep phenotype analysis and OMICS-based identification of novel genes, modifiers and biomarkers

- **WP1** – Deep phenotype analysis in presymptomatic and symptomatic NDD/NMD patients
- **WP2** – Identification of novel disease genes in NDD/NMD patients
- **WP3** – Identification of modifying factors in patients with extreme disease severity
- **WP4** – Identification of hypothesis-driven biomarkers for disease progression
SP2: Clinico-genetic diagnostics and Omics biomarkers

- WP5 – Development and implementation of disease group spanning NGS-based diagnostic tools
- WP6 – Diagnostic readouts for predicting disease modification
- WP7 – Omics-based biomarkers for progression and therapy monitoring based on disease pathways
- WP8 – Bioinformatic tools for diagnostic prediction
SP3: Omics to elucidate pathogenesis and guide therapy

- WP9 – Omics-assisted therapy development
- WP10 – Elucidation of pathogenesis and monitoring of treatment
- WP11 – Modifier gene identification and study in proteinopathies
Subprojects and work packages (4)

Innovation, Impact and Communication

- WP12 – Impact and Communication
- WP13 – Research Infrastructure

Project Management

- WP14 – Management
Who is involved? 15 Academic partners

- University of Tübingen, Germany
- Leiden University Medical Centre, Netherlands
- University Hospital Cologne, Germany
- Newcastle University, UK
- German Centre for Neurodegenerative Diseases, Germany
- UCL - Institute of Child Health, UK
- UCL-Institute of Neurology, UK
- Aix-Marseille University Medical School, France
- INSERM, France
- University of Antwerp, Belgium
- Università degli Studi di Milano, Italy
- University of Ferrara, Italy
- Cambridge University, UK
- University of Western Australia
- University Hospital Freiburg
Who is involved? 5 Industry partners

- deCODE Genetics, Iceland
- Ariadne Diagnostics, USA
- Profilomic, France
- Agilent Technologies, Sweden
- Bio-prodict, Netherlands
Who is involved?
Non-European associated partners

- Guy A. Rouleau (Ste Justine Hospital Research Center, Quebec Montreal)
- Eric Hoffmann (Children’s National Medical Center, Washington)
- Michael Shy (University of Iowa)

Interested to participate in NeurOmics:
- Sharon Hassin-Baer (Department of Neurology and Sagol Neuroscience Center, Chaim Sheba Medical Center)
- Zoran Gucev (Medical Faculty Skopje, Macedonia)
- Daniel MacArthur (Massachusetts General Hospital)
- Antoni Matilla-Duenas (Health Sciences Research Institute Germans Trias i Pujol (IGTP))
- Bela Melegh (University of Pecs)
- Manuel Posada (Institute of Rare Diseases Research (IIER), Institute of Health Carlos III)
- Bart Van de Warrenburg, UMCN, The Netherlands
### SAB member

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Country</th>
<th>Organisation</th>
<th>Expertise</th>
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<tbody>
<tr>
<td>Harry Orr</td>
<td>Prof.</td>
<td>USA</td>
<td>University of Minnesota Medical School</td>
<td>NDD, SCA1</td>
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<tr>
<td>Thomas A. Rando</td>
<td>Prof.</td>
<td>USA</td>
<td>Stanford Center on Longevity</td>
<td>NMD, Aging</td>
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<tr>
<td>Arthur H.M. Burghes</td>
<td>Prof.</td>
<td>USA</td>
<td>Ohio State University</td>
<td>SMA, NMD, Therapy</td>
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<tr>
<td>Ségolène Aimé</td>
<td>Dr.</td>
<td>France</td>
<td>Emeritus director of research at INSERM</td>
<td>IRDiRC, Coordinator Support-IRDiRC (A-Project)</td>
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<tr>
<td>Hanns Lochmüller</td>
<td>Prof.</td>
<td>UK</td>
<td>Newcastle University</td>
<td>NMD, Coordinator RD-Connect (C-Project)</td>
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## Subproject and WP leaders

<table>
<thead>
<tr>
<th>Subproject title</th>
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<tr>
<td>SP1: Deep clinical and molecular characterisation of patients</td>
<td>UK Cologne</td>
<td>Brunhilde Wirth</td>
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<tr>
<td>SP2: Clinico-Genetic diagnostics and Omics biomarkers</td>
<td>Uni Tuebingen</td>
<td>Olaf Riess</td>
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<tr>
<td>SP3: Omics guiding treatment</td>
<td>LUMC</td>
<td>Gert-Jan van Ommen</td>
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<tr>
<td>1</td>
<td>DZNE</td>
<td>Thomas Klockgether</td>
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<td>Bio-Prodict</td>
<td>Henk-Jan Joosten</td>
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<tr>
<td>2</td>
<td>UK Cologne</td>
<td>Brunhilde Wirth</td>
<td>9</td>
<td>LUMC</td>
<td>Annemieke Aartsma-Rus</td>
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<td>3</td>
<td>UCL</td>
<td>Sarah Tabrizi</td>
<td>10</td>
<td>Uni Milan</td>
<td>Elena Cataneo</td>
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<td>4</td>
<td>INSERM</td>
<td>Alexis Brice</td>
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<td>Uni Cambridge</td>
<td>David Rubinsztein</td>
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<td>Alexandra Durr</td>
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<td>Olaf Riess</td>
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The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 2012-305121 “Integrated European -omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases (NeurOmics)”. 
FP7 funded, 5 year project involving 21 international centres, all experts in their field

Working towards the IRDiRC goals

Operating in close interaction with RD-Connect, EURenOmics and Support-IRDiRC

Overall aim of improving patient diagnosis, care and therapy and facilitating more clinical trials for a group of 10 NMDs and NDDs in line with IRDiRC’s goals

Makes extensive use of the latest, cutting edge Omics technologies

NEUROMICS expertise and findings may be transferrable to a wider range of related conditions
FP7 call context

2.1.1-1 –Omics for rare diseases

„construction of a solid foundation for the molecular characterisation of rare diseases by a systematic application of –omics approaches and technologies. A key success factor will be the establishment and/or harmonisation of databases and bio-resources, including standardisation and quality control aspects, of the data and samples collected“
HEALTH.2012. 2.1.1-1 –Omics for rare diseases

A: Support for international rare disease research
   - Support-IRDiRC

B: Clinical utility of -omics for better diagnosis of rare diseases
   - NeurOmics
   - EURenOmics

C: Databases, biobanks and 'clinical bio-informatics' hub for rare diseases
   - RD-Connect
Approaches include next generation sequencing, array-based technologies, mass spectrometry.

Omics looks at very large amounts of biological data.

Sophisticated bioinformatics software is used to process the data.

The English language neologism omics informally refers to a field of study in biology ending in -omics. The related suffix -ome refers to a totality of some sort; it is an example of a "neo-suffix" formed by abstraction from various Greek terms...

http://en.wikipedia.org/wiki/-ome
Concept of clinical-genetic and basic-applied research