Telethon and Shire: a Public-Private Partnership to Translate the Results of Basic Research to Therapies for Patients

Lucia Monaco
Chief Scientific Officer

International Rare Diseases Research Consortium Conference 2013
INTERDISCIPLINARY TRACK – Ensuring the Collaboration

Dublin, 16 April 2013
ABOUT TELETHON

The Telethon Foundation is a major Italian charity founded in 1990

**Mission**
To advance biomedical research towards the cure of muscular dystrophy and other genetic diseases

**Vision**
To convert the results of excellent, selected and sustained research into available therapies

We give priority to rare genetic diseases that are neglected by major public and private investment

**Our stakeholders**

- RESEARCHERS
- PATIENTS
- DONORS

**Telethon’s responsibility**

- Scientific results: research monitoring and development
- Fund raising: financial accountability and control of expenses
- Fund allocation: merit-based selection of research

We give priority to rare genetic diseases that are neglected by major public and private investment.
External Research
MAXIMUM FLEXIBILITY / OPPORTUNITIES
Telethon’s role: funder → catalyst

Intramural Research
MAXIMUM FOCUS / CRITICAL MASS
Telethon’s role: developer

GENETIC BIOBANKS AND RESEARCH SERVICES

EXTERNAL RESEARCH PROJECTS
- General projects
- Neuromuscular clinical projects
- Program projects
- Exploratory projects

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• General projects
• Neuromuscular clinical projects
• Program projects
• Exploratory projects

FELLOWSHIPS
Program terminated in 2006

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KEY FIGURES 1990-2012
- 371 M€ research investment
- 2,431 research grants
- 1,510 principal investigators
- 445 genetic diseases studied
- 8,698 scientific publications

Telethon Institute of Genetics and Medicine
Naples

HSR-Telethon Institute of Gene Therapy
Milan

Dulbecco Telethon Institute
Telethon’s career program

Tecnothon
Sarcedo (Vicenza)
Development of aids for the disabled

Fund allocation 1990-2012
- 58%
- 13%
- 13%
- 9%
- 3%
- 2%

Source: database Telethon TRic, January 2013
AT A GLANCE

The Institute

- Founded in 1994, based in Naples
- Director: Andrea Ballabio, MD
- 12 independent research groups
- 180 employees including administrative and technical staff
- 4 competitive training programs
- 8 internal research facilities/cores
- Scientific/grant office
- Significant funding from external sources

Expertise

- Specific disease types
- Viral gene delivery
- Cell biology of genetic diseases and advanced microscopy
- Systems biology and functional genomics
- Cellular and animal models of human diseases

Mission

Understand the pathogenetic mechanisms of genetic diseases and develop preventive and therapeutic strategies

Integration of research approaches

molecular genetics ↔ cell biology ↔ functional genomics ↔ systems biology ↔

Source: TIGEM, March 2013
TIGEM PAPERS IN PRESS
March, 2013

Indieri et al.
The impairment of HCCS leads to MLS syndrome by activating a non-canonical cell death pathway in the brain and eyes
EMBO Mol Med

Pastore et al.
Gene transfer of master autophagy regulator TFEB results in clearance of toxic protein and correction of hepatic disease in alpha-1-antitrypsin deficiency
EMBO Mol Med

Sorrentino et al.
A highly secreted sulfamidase engineered to cross the blood-brain barrier corrects brain lesions of mice with mucopolysaccharidoses type II A
EMBO Mol Med

Ferriero et al.
Phenylbutyrate Therapy for Pyruvate Dehydrogenase Complex Deficiency and Lactic Acidosis
Science Transl Med

Settembre et al.
TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop
Nature Cell Biol

Spampanato et al.
Transcription factor EB (TFEB) is a new therapeutic target for Pompe disease
EMBO Mol Med

TIGEM’S SCIENTIFIC PUBLICATIONS BY MAJOR RESEARCH AREA

No. of papers
TOTAL 547 PAPERS
1994-2012

- not indexed
- MEDICAL SCIENCES
- BASIC SCIENCES
- APPLIED SCIENCES/TECHNOLOGIES
- GENETICS

Granting Period
*as of Dec 2012

0%
20%
40%
60%
80%
100%


5 10 8 44 61 10

5 10 7 41 61 18

5 10 7 47 39 9

1 10 11 3 10 1

TIGEM goes translational!
TIGEM STRATEGIC RESEARCH PROGRAMS

**Cell Biology of Genetic Diseases**
- Basic disease mechanisms
- Biological assay development and analysis

**Systems Biology and Functional Genomics**
- Gene network identification
- Drug re-positioning
- Drug discovery

**Molecular Therapy**
- Vector development
- Vector delivery
- Small molecules/chaperones

**NEW THERAPIES**

Telethon-Shire Alliance/IRDiRC Conference 2013/Dublin/16 April 2013/Sci/LM
MAIN DISEASE TYPES

• Lysosomal storage disorders (LSDs)
  – mucopolysaccharidosis (MPS) type I, MPSII, MPSIIIA, MPSVI, MPSVII, multiple sulfatase deficiency, Pompe disease, Fabry disease

• Retinal degenerations
  – retinitis pigmentosa and allied disorders

• Liver metabolism
  – primary hyperoxaluria type I, Crigler-Najar disease, alpha1-anti-tripsin deficiency

• Neurodegenerative diseases
  – Huntington disease, Parkinson disease

• Membrane trafficking
  – cystic fibrosis, renal Fanconi syndrome, spondyloepiphyseal dysplasia, Wilson disease

• Organelle biogenesis
  – ciliopathies
TFEB: a master gene for cellular clearance
A gene network regulating lysosomal biogenesis and function

Gene Therapy
• AAV platform
• Pre-clinical proof of principle for 8 diseases
• 2 clinical trials
• Expertise in brain gene delivery in animal models

High content screening
Combining the efficiency of high-throughput techniques with the ability of cellular imaging to collect quantitative data from complex biological systems
THE TELETHON-SHIRE ALLIANCE

1 October 2012 - Telethon entered into a research collaboration and license agreement with Shire to identify new treatments for lysosomal and neurodegenerative diseases.

Research programs selected from the existing independent research at TIGEM:

- **Modulation of cellular clearance** via the TFEB pathway in LSDs and neurodegenerative diseases
- **Small molecule approach for LSDs** (high content screening)
- **Development of new gene therapy** approaches for the CNS

5-year research programs economically supported by Shire

Shire will eventually license the most interesting results and guarantee their development into effective therapies to be delivered to patients around the world.
From bench to bedside through industrial partnerships

**IP MANAGEMENT**
- 39 patent families filed
- 20 active patent families
- 56 active patent applications
- 8 patents granted

**MARKETING AND NEGOTIATION**
- 8 sponsored research contracts
- 15 license and option agreements
- 20 biotech and pharma partners

**ALLIANCE MANAGEMENT**
- 3 strategic alliances
  - **GSK**: ex vivo gene therapy of 7 genetic diseases at **HSR-TIGET**
  - **BioMarin**: high content screening at **TIGEM**
  - **SHIRE**: basic research on lysosomal and neurodegenerative diseases at **TIGEM**

**REGULATORY AFFAIRS**
- 9 orphan drug designations (ODD) for 6 products:
  - 5 ODD at EMA
  - 4 ODD at FDA

**Telethon’s mission accomplished**

New funds for research

Source: Telethon Research Development Office, March 2013
Imagining New Therapies for Patients with Rare Diseases: Shire and TIGEM Translate the Future

Phil Vickers, Ph.D.
Senior Vice President  R&D
Background to Shire

Shire is named as the Marketing Company of the Year in the United Kingdom and our UK marketing team is recognized as the Marketing Team of the Year by PharmaTimes in their annual Marketer of the Year competition.

Angus Russell named CEO of the Year at the annual Scrip Awards.

Shire named one of the top charitable contributors in the Boston area by the Boston Business Journal.

Sylvie Gregoire named one of the Top 10 Women in Biotech by FierceBiotech.

Dr. Norman Barton recognized by Penn State as Distinguished Alumni.

Shire is honored with the 2012 EURORDIS Company Award for its work with patient groups to provide access to medicines throughout Europe.

*As of 16 January 2013

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Market capitalization: $18.26 billion*

2012 revenues of $4.68 billion

Top 40 biopharmaceutical company worldwide

Top 15 biopharmaceutical company in Europe

Third largest pharma company in UK FTSE100

~5500 employees globally

Stock exchange listings

February 1996 (SHP LN)

March 1998 (SHPG)

To be as brave as the people we help.
# Current HGT Portfolio: Global Development

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Animal POC</th>
<th>Pre-Clinical IND Tox</th>
<th>Phase I/II</th>
<th>Phase II/III</th>
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<tbody>
<tr>
<td>ACE-Induced Angioedema</td>
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<td><em>Hunter CNS</em></td>
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<td><em>Retinopathy of Prematurity</em></td>
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<td>MLD</td>
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<tr>
<td>Sanfilippo A</td>
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<tr>
<td>DMD (clinical hold)</td>
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<tr>
<td><em>Sanfilippo B</em></td>
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<tr>
<td>Dystrophic EB (DEB)</td>
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<td><em>IgA Nephropathy (IGAN)</em></td>
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<tr>
<td>Research</td>
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Legend:
- **Green**: AE Peptide
- **Yellow**: IT Platform
- **Purple**: Protein
- **Red**: Research

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<th><strong>External Investments Complement our Internal Engine</strong></th>
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<tr>
<td><strong>Clinical Assets</strong></td>
</tr>
<tr>
<td>✓ Jerini (HAE)</td>
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<tr>
<td>✓ Acceleron (DMD)</td>
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<tr>
<td>✓ Premacure (ROP)</td>
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<tr>
<td><strong>Preclinical Assets</strong></td>
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<tr>
<td>✓ Lotus Tissue Repair (DEB)</td>
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<td>✓ IGAN (IgA nephropathy)</td>
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<td>✓ Due diligence ongoing</td>
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<td><strong>Strategic Investment Group</strong></td>
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<tr>
<td>✓ Bluebird Bio (Gene Therapy)</td>
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<td>✓ Ultragenyx (Ultra rare diseases)</td>
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<td>✓ Promedior (Fibrosis)</td>
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<td>✓ Armagen (Novel CNS delivery)</td>
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<tr>
<td><strong>New Technologies</strong></td>
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<td>✓ ArGen-X (Antibody Platform)</td>
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<tr>
<td>✓ Lentigen (Gene Therapy)</td>
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<td>✓ Sophysa (Intrathecal Delivery)</td>
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<td>✓ Ethris (RNA Delivery)</td>
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<td>✓ Sangamo (Gene Therapy)</td>
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<td><strong>Creative Partnerships</strong></td>
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<td>✓ TIGEM</td>
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<td>✓ Boston Children’s Hospital</td>
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<td>✓ Atlas Venture</td>
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To be as brave as the people we help.
Shire HGT Vision

“Through Imagination and Leadership, Transform the World of Rare Diseases and the Lives of Patients around the World Every Day”
A Track Record of Partnership: Research Collaboration to Identify and Clone the Multiple Sulfatase Deficiency Disease Gene

Biochemical Approach

Kurt von Figura

- purified the enzyme to homogeneity
- peptide sequencing via MALDI MS

Genetic Approach

Andrea Ballabio

- genetic complementation using microcell mediated chromosome transfer into MSD cells
- identification of candidate genes within a 3Mb region of chromosome 3

Therapeutic Applications

Mike Heartlein

- demonstrated that co-expression of the FGE gene could restore specific activity to sulfatases
- large scale bioreactor production

FGE cloned within 10 months of establishing collaboration

To be as brave as the people we help.
The Multiple Sulfatase Deficiency Collaboration

- A collaboration that allowed both the company and the laboratories of two academic institutions to walk away with achievements that particularly benefited each party
- Technology underpins multiple therapeutic approaches

- Identified the enzyme and clarified the mechanism of a unique posttranslational modification
- Established the role of a single gene in knocking-down multiple enzyme activities in a genetic disease

- Enabled sulfatase manufacturing
- Opened a pipeline of sulfatase therapeutics
- Generated Intellectual Property
- Translated excellent science into therapeutics

To be as brave as the people we help.
Combining Innovations: Intrathecal Delivery of ERT’s

PET Imaging Data
Shire – Telethon Partnership at TIGEM: Value to Shire

5 Year Partnership; 3 Early Stage Umbrella Programs Initially Focused on 9 Research Projects

- The missions of Shire and TIGEM are completely aligned
  - Translation of research into safe, innovative, effective therapies to treat patients with rare disease
- Access to world-leading scientists with a clear focus on therapeutic areas clearly aligned with our strategic focus
- TIGEM has a proven track record of successful partnerships
  - The uncertainty of science requires flexibility
  - Dynamic, open, collaborative spirit built on trust, respect, and good ‘chemistry’
- Expertise and experience complements internal Shire expertise
  - Focus on gene therapy, proteins, small molecules
  - A natural transition from TIGEM research to Shire drug development
  - Both organizations gain learnings which are useful for the future
- Shire focused on expanding R&D capabilities through strategic partnerships

To be as brave as the people we help.
ACKNOWLEDGEMENTS

Lucia Faccio
Annamaria Merico
Telethon Business Development Office

Andrea Ballabio
TIGEM Director

Antonella De Matteis
Alessandro Fraldi
Enrico Maria Surace
Giancarlo Parenti
Shire program PIs

Graciana Diez-Roux
TIGEM Scientific Office

Arthur Tzianabos
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