# 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

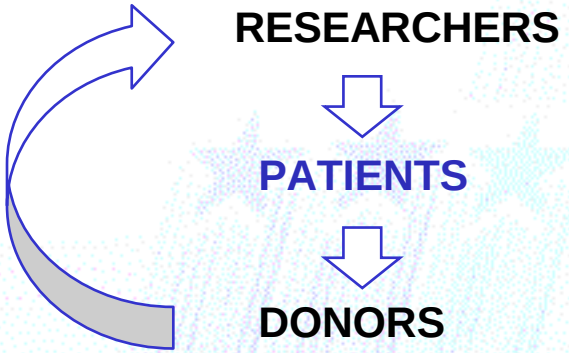
To advance biomedical research towards the cure of muscular dystrophy and other genetic diseases

## 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




## Telethon's responsibility

**Scientific results**
research monitoring and development

**Fund raising**
financial accountability and control of expenses

**Fund allocation**
merit-based selection of research

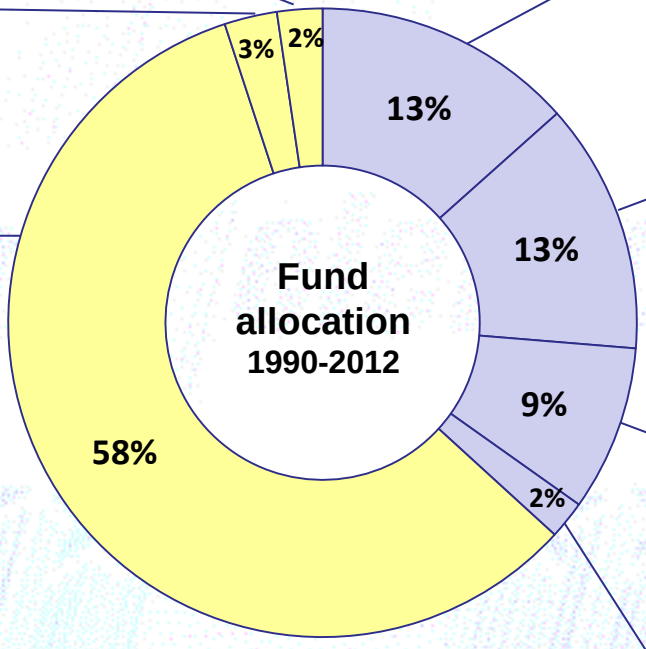
# TELETHON'S RESEARCH PORTFOLIO

## External Research
**MAXIMUM FLEXIBILITY / OPPORTUNITIES**
Telethon's role: **funder → catalyst**

### GENETIC BIOBANKS AND RESEARCH SERVICES

### FELLOWSHIPS
Program terminated in 2006

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




## Intramural Research
**MAXIMUM FOCUS / CRITICAL MASS**
Telethon's role: **developer**

**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**

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



*Source: database Telethon TRic, January 2013*

# AT A GLANCE

## Mission

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

## 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

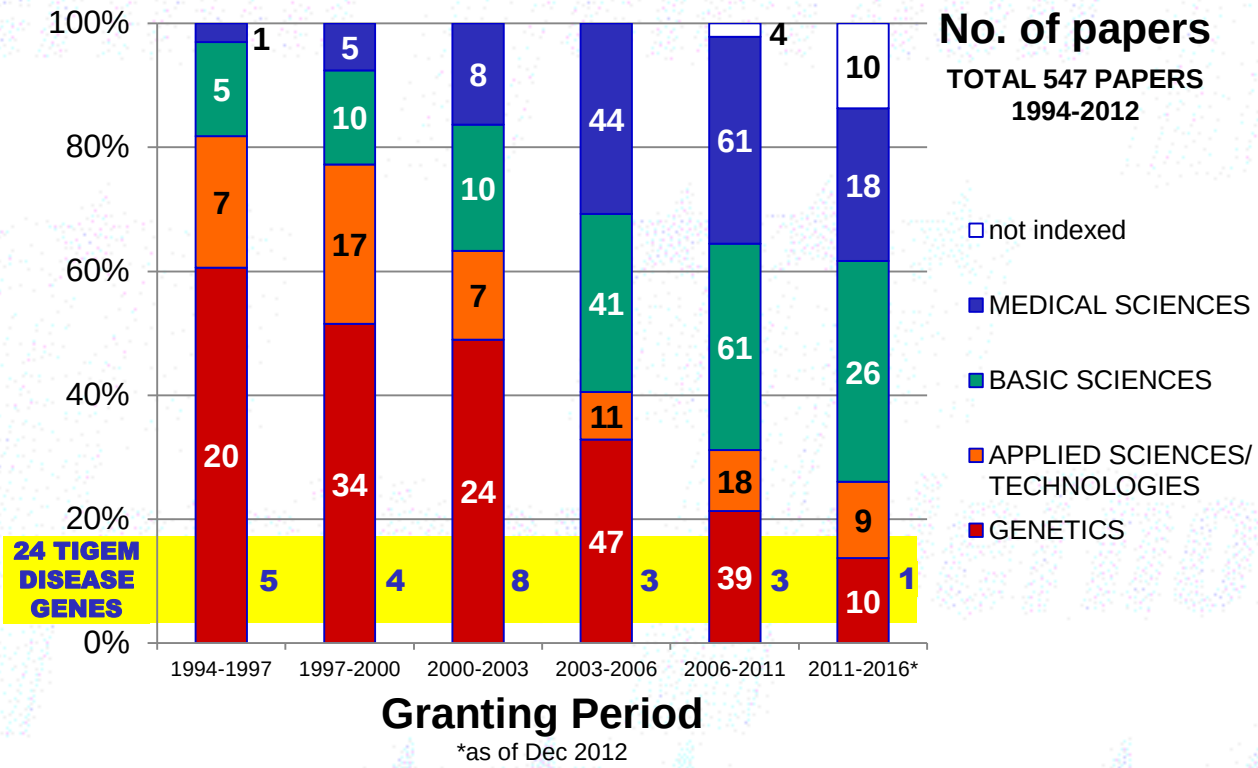
- **Specific disease types**
- **Viral gene delivery**
- **Cell biology** of genetic diseases and **advanced microscopy**
- **Systems biology** and **functional genomics**
- **Cellular** and **animal models** of human diseases

**Integration of research approaches**

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

*Source: TIGEM, March 2013*

# TIGEM'S SCIENTIFIC PUBLICATIONS BY MAJOR RESEARCH AREA




*TIGEM goes translational!*

## TIGEM PAPERS IN PRESS
### March, 2013

Indrieri 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-anti-trypsin 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 IIIA
**EMBO Mol Med**

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

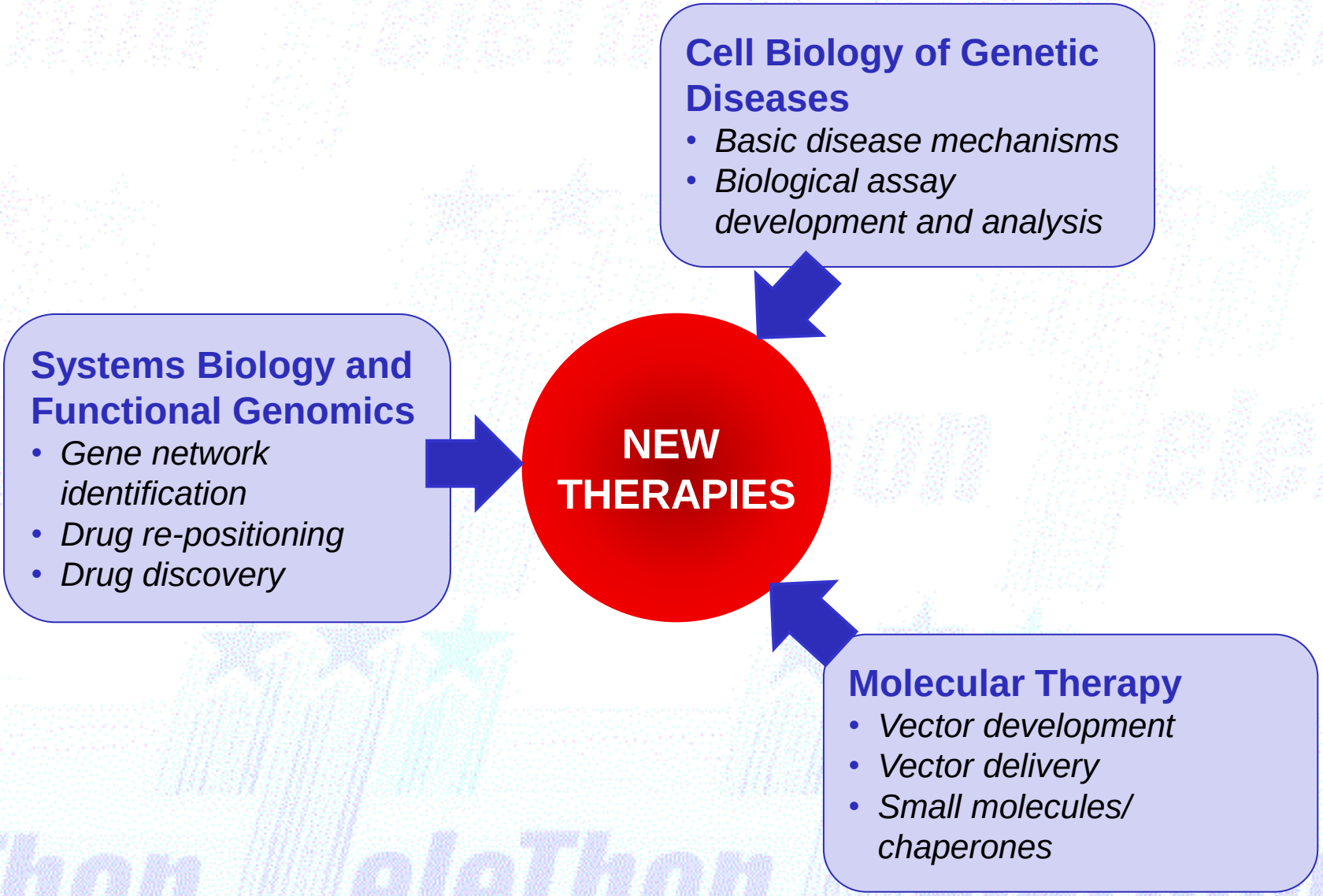
Settembre et al.
TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop
**Nature Cell Biol**

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



*Source: database Telethon TRic and Thomson Reuters, January 2013*

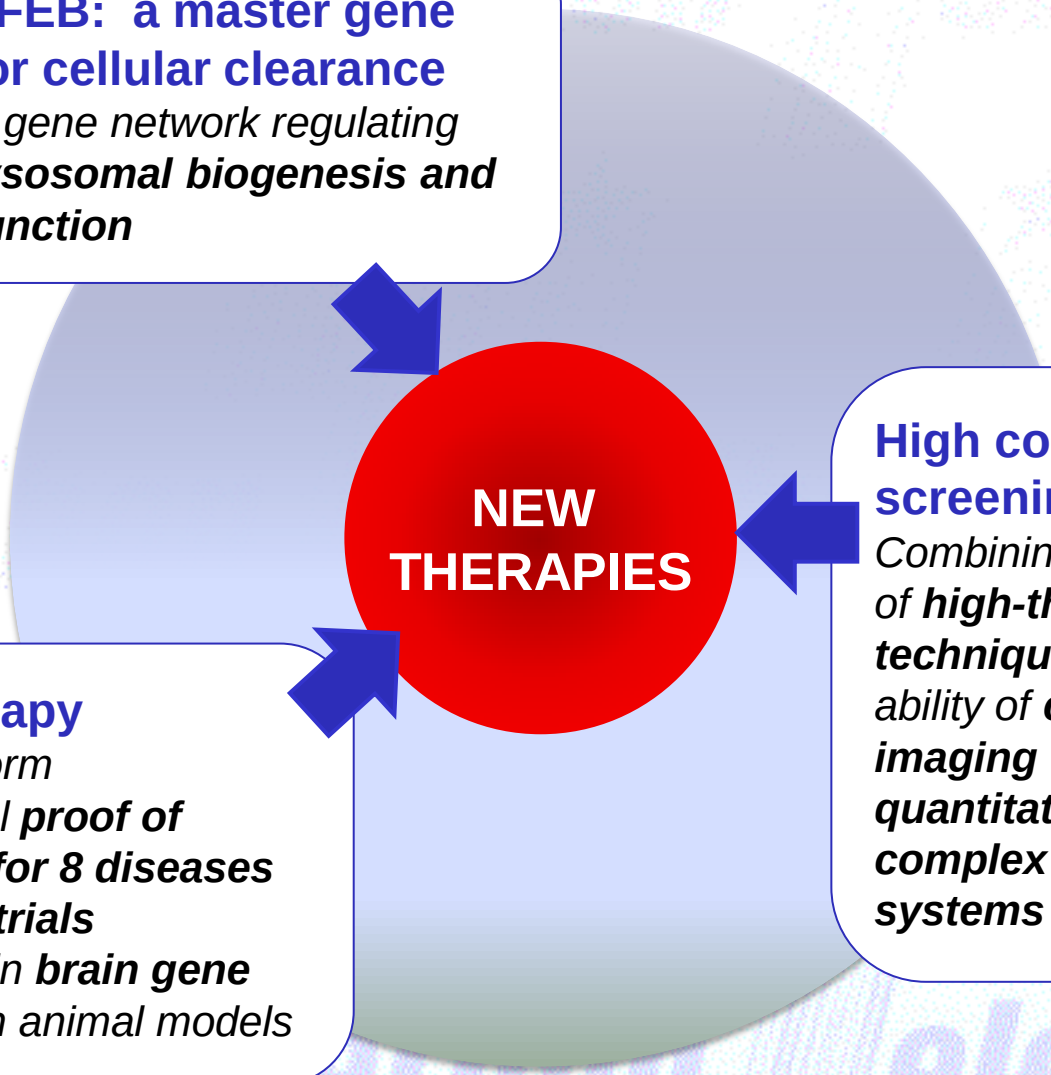
# TIGEM STRATEGIC RESEARCH PROGRAMS



# 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

# TIGEM'S THERAPEUTIC APPROACHES




**TFEB: a master gene for cellular clearance**

*A gene network regulating* ***lysosomal biogenesis and function***

**High content screening**

*Combining the efficiency of* ***high-throughput techniques*** *with the ability of* ***cellular imaging*** *to collect* ***quantitative data*** *from* ***complex biological systems***

**Gene Therapy**

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

# 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**

## Basic Research

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

Translational graduation

## Clinical development

**Shire** will eventually **license the most interesting results** and **guarantee their development into effective therapies** to be delivered to patients around the world

# TELETHON'S RESEARCH DEVELOPMENT

## From bench to bedside through industrial partnerships

**IP MANAGEMENT**

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

**REGULATORY AFFAIRS**

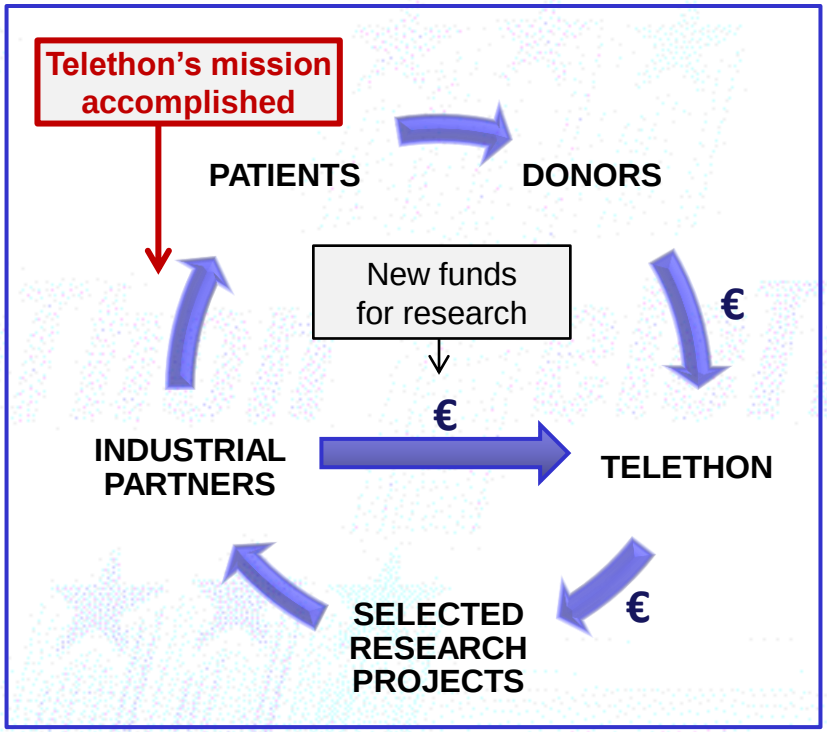
- 9 **orphan drug designations** (ODD) for 6 products:
  - 5 ODD at EMA
  - 4 ODD at FDA

**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**






*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

Shire

**Our purpose**
We enable people with life-altering conditions to lead better lives.

# 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 on of the Top 10 Women in Biotech by *FierceBiotech*

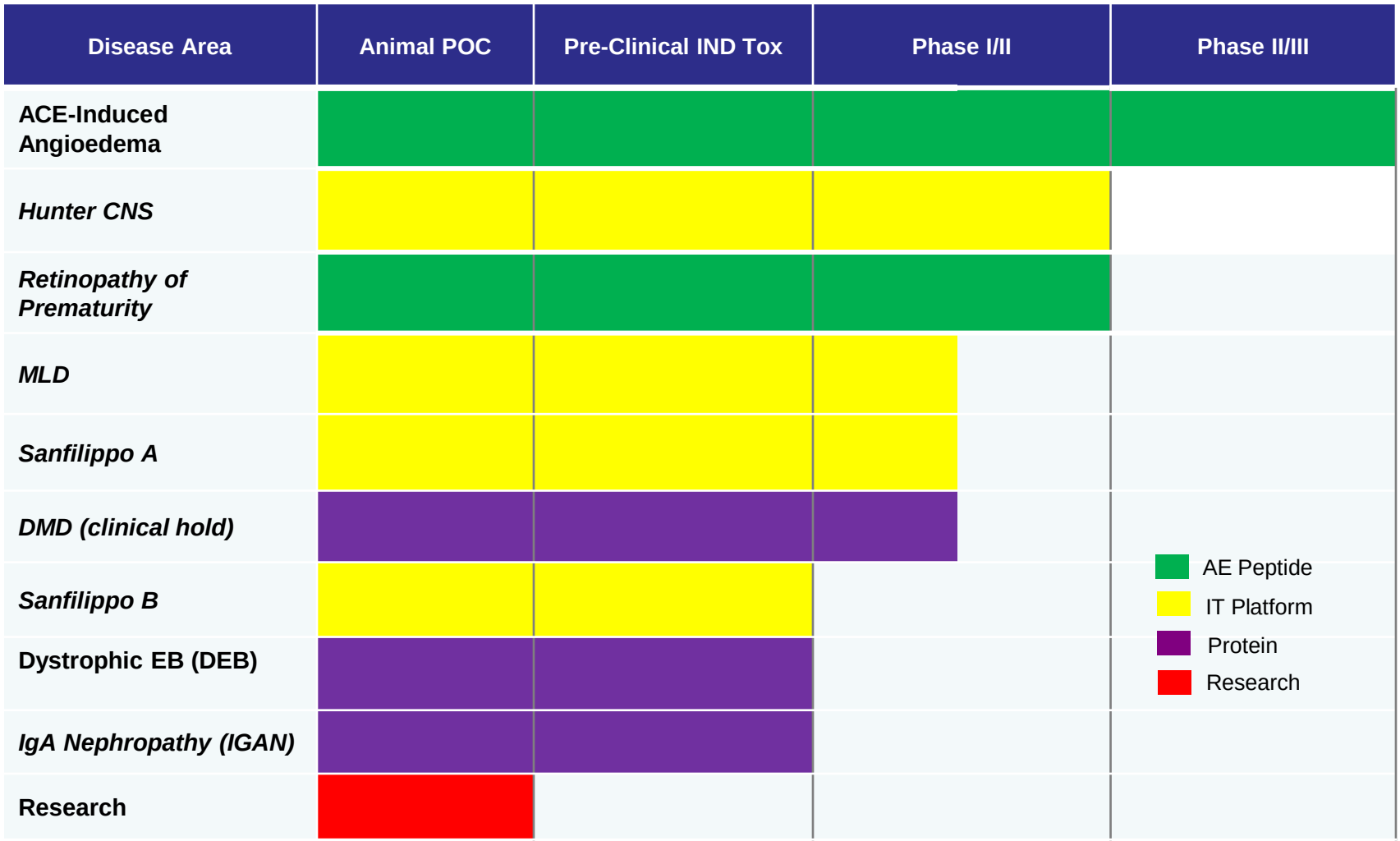
Dr. Norman Barton recognized by Penn State as Distinguished Alumni

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

- 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
  - London Stock Exchange February 1996 (SHP LN)
  - NASDAQ March 1998 (SHPG)

# Current HGT Portfolio: Global Development



# External Investments Complement our Internal Engine

| | | |
|---|---|---|
| Clinical Assets | ✓ Jerini (HAE)<br>✓ Acceleron (DMD)<br>✓ Premacure (ROP) | Jerini · Acceleron Pharma · premacure |
| Preclinical Assets | ✓ Lotus Tissue Repair (DEB)<br>✓ IGAN (IgA nephropathy)<br>✓ Due diligence ongoing | Lotus Tissue Repair · IGAN Biosciences |
| Strategic Investment Group | ✓ Bluebird Bio (Gene Therapy)<br>✓ Ultragenyx (Ultra rare diseases)<br>✓ Promedior (Fibrosis)<br>✓ Armagen (Novel CNS delivery ) | bluebirdbio · ultragenyx · ArmaGen Technologies (Biotechnology for the Brain) · Promedior (therapeutics to treat fibrosis) |
| New Technologies | ✓ ArGen-X (Antibody Platform)<br>✓ Lentigen (Gene Therapy)<br>✓ Sophysa (Intrathecal Delivery)<br>✓ Ethris (RNA Delivery)<br>✓ Sangamo (Gene Therapy) | arGEN-X · Lentigen · SANGAMO · ethris (Enabling Therapies) · SOPHYSA |
| Creative Partnerships | ✓ TIGEM<br>✓ Boston Children's Hospital<br>✓ Atlas Venture | tigem (Telethon Institute of Genetics and Medicine) · Children's Hospital Boston (The first place for children) · ATLAS VENTURE |

# Shire HGT Vision

"Through Imagination and Leadership, Transform the World of Rare Diseases and the Lives of Patients around the World Every Day"

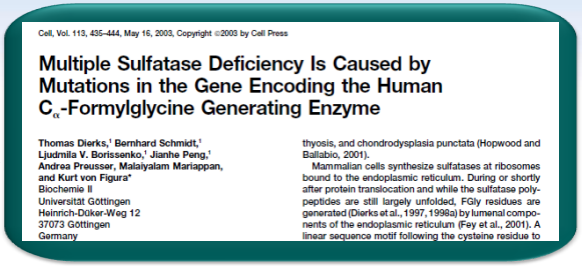
# A Track Record of Partnership: Research Collaboration to Identify and Clone the Multiple Sulfatase Deficiency Disease Gene

**Biochemical Approach**

Kurt von Figura

GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN

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



Cell, Vol. 113, 435–444, May 16, 2003, Copyright ©2003 by Cell Press

**Multiple Sulfatase Deficiency Is Caused by Mutations in the Gene Encoding the Human $C_\alpha$-Formylglycine Generating Enzyme**

Thomas Dierks,[1] Bernhard Schmidt,[1] Ljudmila V. Borissenko,[1] Jianhe Peng,[1] Andrea Preusser, Malaiyalam Mariappan, and Kurt von Figura*
Biochemie II
Universität Göttingen
Heinrich-Düker-Weg 12
37073 Göttingen
Germany

thyosis, and chondrodysplasia punctata (Hopwood and Ballabio, 2001).

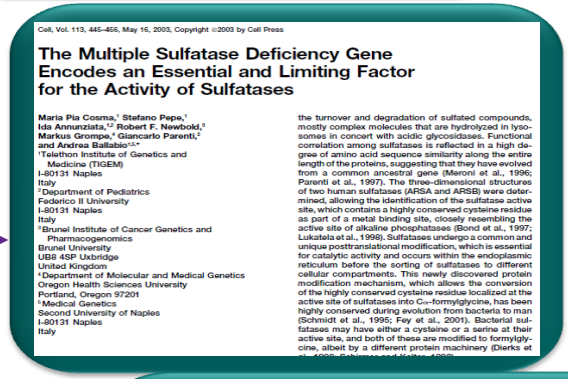
Mammalian cells synthesize sulfatases at ribosomes bound to the endoplasmic reticulum. During or shortly after protein translocation and while the sulfatase polypeptides are still largely unfolded, FGly residues are generated (Dierks et al., 1997, 1998a) by lumenal components of the endoplasmic reticulum (Fey et al., 2001). A linear sequence motif following the cysteine residue to

**Genetic Approach**

Andrea Ballabio

TELETHON INSTITUTE OF GENETICS AND MEDICINE

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



Cell, Vol. 113, 445–456, May 16, 2003, Copyright ©2003 by Cell Press

**The Multiple Sulfatase Deficiency Gene Encodes an Essential and Limiting Factor for the Activity of Sulfatases**

Maria Pia Cosma,[1] Stefano Pepe,[1] Ida Annunziata,[1,2] Robert F. Newbold,[3] Markus Grompe,[4] Giancarlo Parenti,[2] and Andrea Ballabio[1,5,*]
[1]Telethon Institute of Genetics and Medicine (TIGEM)
I-80131 Naples
Italy
[2]Department of Pediatrics
Federico II University
I-80131 Naples
Italy
[3]Brunel Institute of Cancer Genetics and Pharmacogenomics
Brunel University
UB8 4SP Uxbridge
United Kingdom
[4]Department of Molecular and Medical Genetics
Oregon Health Sciences University
Portland, Oregon 97201
[5]Medical Genetics
Second University of Naples
I-80131 Naples
Italy

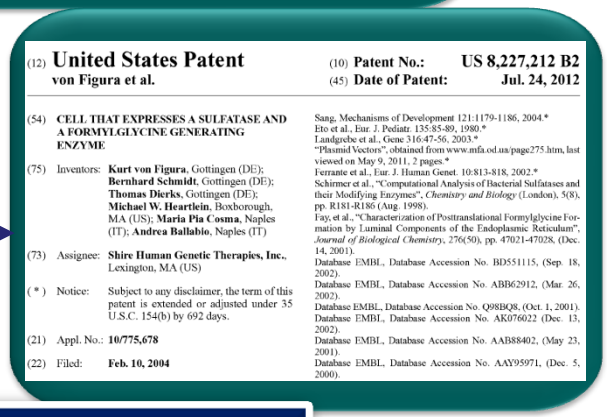
the turnover and degradation of sulfated compounds, mostly complex molecules that are hydrolyzed in lysosomes in concert with acidic glycosidases. Functional correlation among sulfatases is reflected in a high degree of amino acid sequence similarity along the entire length of the proteins, suggesting that they have evolved from a common ancestral gene (Meroni et al., 1996; Parenti et al., 1997). The three-dimensional structures of two human sulfatases (ARSA and ARSB) were determined, allowing the identification of the sulfatase active site, which contains a highly conserved cysteine residue as part of a metal binding site, closely resembling the active site of alkaline phosphatases (Bond et al., 1997; Lukatela et al., 1998). Sulfatases undergo a common and unique posttranslational modification, which is essential for catalytic activity and occurs within the endoplasmic reticulum before the sorting of sulfatases to different cellular compartments. This newly discovered protein modification mechanism, which allows the conversion of the highly conserved cysteine residue localized at the active site of sulfatases into $C_\alpha$-formylglycine, has been highly conserved during evolution from bacteria to man (Schmidt et al., 1995; Fey et al., 2001). Bacterial sulfatases may have either a cysteine or a serine at their active site, and both of these are modified to formylglycine, albeit by a different protein machinery (Dierks et

**Therapeutic Applications**

Mike Heartlein

Shire Human Genetic Therapies

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



(12) **United States Patent**
**von Figura et al.**

(10) **Patent No.: US 8,227,212 B2**
(45) **Date of Patent: Jul. 24, 2012**

(54) **CELL THAT EXPRESSES A SULFATASE AND A FORMYLGLYCINE GENERATING ENZYME**

(75) Inventors: **Kurt von Figura**, Gottingen (DE); **Bernhard Schmidt**, Gottingen (DE); **Thomas Dierks**, Gottingen (DE); **Michael W. Heartlein**, Boxborough, MA (US); **Maria Pia Cosma**, Naples (IT); **Andrea Ballabio**, Naples (IT)

(73) Assignee: **Shire Human Genetic Therapies, Inc.**, Lexington, MA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 692 days.

(21) Appl. No.: **10/775,678**

(22) Filed: **Feb. 10, 2004**

Sang, Mechanisms of Development 121:1179-1186, 2004.*
Ito et al., Eur. J. Pediatr. 135:85-89, 1980.*
Landgrebe et al., Gene 316:47-56, 2003.*
"Plasmid Vectors", obtained from www.mfa.od.ua/page275.htm, last viewed on May 9, 2011, 2 pages.*
Ferrante et al., Eur. J. Human Genet. 10:813-818, 2002.*
Schirmer et al., "Computational Analysis of Bacterial Sulfatases and their Modifying Enzymes", *Chemistry and Biology* (London), 5(8), pp. R181-R186 (Aug. 1998).
Fey, et al., "Characterization of Posttranslational Formylglycine Formation by Luminal Components of the Endoplasmic Reticulum", *Journal of Biological Chemistry*, 276(50), pp. 47021-47028, (Dec. 14, 2001).
Database EMBL, Database Accession No. BD551115, (Sep. 18, 2002).
Database EMBL, Database Accession No. ABB62912, (Mar. 26, 2002).
Database EMBL, Database Accession No. Q9BQ8, (Oct. 1, 2001).
Database EMBL, Database Accession No. AK076022 (Dec. 13, 2002).
Database EMBL, Database Accession No. AAB88402, (May 23, 2001).
Database EMBL, Database Accession No. AAY95971, (Dec. 5, 2000).

**FGE cloned within 10 months of establishing collaboration**

# 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

GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN

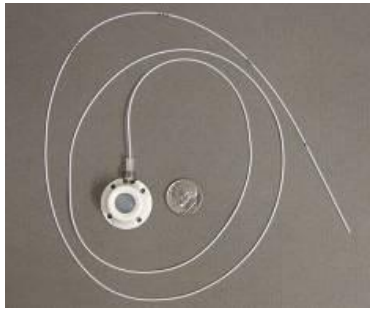
Tigem
TELETHON INSTITUTE OF GENETICS AND MEDICINE

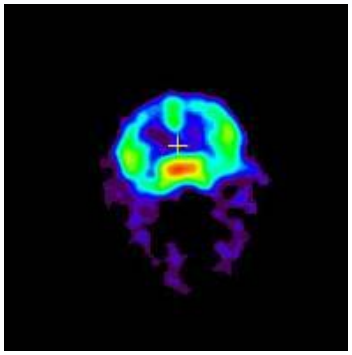
- **Identified the enzyme and clarified the mechanism of a unique posttranslational modification**
- **Established the role of a single gene in knocking-down multiple enzyme activities in a genetic disease**

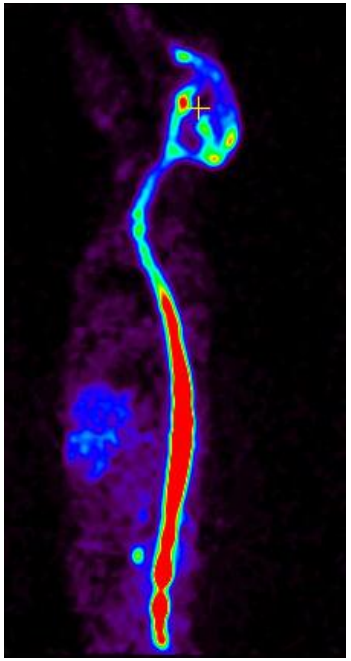
- **Enabled sulfatase manufacturing**
- **Opened a pipeline of sulfatase therapeutics**
- **Generated Intellectual Property**
- **Translated excellent science into therapeutics**

Shire
Human Genetic Therapies

# 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

# 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**
*VP, Head Research and Early Development*

**Mike Heartlein**
*VP, External Science & Technology*

**Albert Seymour**
*VP, Head of Discovery Research*

**Susan Kalled**
*Senior Director, External Alliances Discovery Research*

**Gary Clements**
*Senior Director, Business Development*