From bench to bedside through industry collaborations: the Telethon’s Model

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Technology Transfer Office
R&D Division, Fondazione Telethon
EVERY MINUTE OF EVERY DAY, TEN CHILDREN AROUND THE WORLD ARE BORN WITH A RARE GENETIC DISEASE. TOMMASO IS ONE OF THEM.
Who we are: Mission & Vision

- **Fondazione Telethon** is a major Italian biomedical charity focused on genetic diseases
- **Founded in 1990** at the behest of a group of patients
- Supported through **fundraising**

**OUR MISSION**

*Advance biomedical research towards the cure of genetic diseases*

- **498 M€** research investment
- **2,629** research grants
- **10,615** papers published
- **1,611** PIs awarded
- **571** genetic diseases studied

**OUR VISION**

*Convert the results of excellent, selected and sustained research into available therapies*

- **9** active clinical trials
- **79** patients treated
- **1 Therapy on the market**
Telethon supports its own institutes in Italy as well as the Italian research system.

3 Telethon Institutes + 187 laboratories in Research Institutes, Clinical Centers and Academias.

**INTRAMURAL research**
- Focus
- Critical Mass
- Peer Reviewed
- IP Ownership

**EXTRAMURAL research**
- Flexibility
- Opportunities
- Peer Reviewed
Enabling factors for transformative research

- Excellent fundamental and pre-clinical research
  - Stringent selection system (funding to max. top 20% proposals)
  - Adequate funding

Evaluation of projects by independent reviewers, on the basis of the American NIH model. The process is managed by internal Research Program Managers.

- Identifying projects with translational potential
  - Monitoring research progression and results
  - Intellectual property protection and technology transfer

- Effective translational research
  - Management of clinical trials
  - Management of regulatory affairs
  - Competences in drug development
Enabling factors for transformative research

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  - Monitoring research progression and results
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- Effective translational research
  - Management of clinical trials
  - Management of regulatory affairs
  - Competences in drug development

A dedicated team manages activities relevant for clinical trial and postmarketing drug use as well as established industrial alliances that are moving toward clinic.
Enabling factors for transformative research

- Excellent fundamental and pre-clinical research
  - Stringent selection system (funding to max. top 20% proposals)
  - Adequate funding

- Identifying projects with translational potential
  - Monitoring research progression and results
  - Intellectual property protection and technology transfer

Research progresses are monitored by internal Research Program Managers. Support for IP protection and industrial partnerships from the internal TTO.

- Effective translational research
  - Management of clinical trials
  - Management of regulatory affairs
  - Competences in drug development
The research development pipeline: Telethon’s collaborative model

**Research**
- Basic research
- Pre-clinical studies

**Development**
- Pre-clinical development
- Clinical trials

**Delivery to patients**
- Marketing authorization

**Telethon**
- Selection of excellent research
- Patent protection
- GLP laboratories
- GMP production investment
- Clinical Trial Unit GCP certified
- Regulatory competencies
- Clinical Operation
- Alliance management
- ODD filing

**Pharma & Biotech & Investors**
WHY DO WE NEED BIOPHARMA?

Cooperation based on the recognition of specific capacities and competences
Telethon industrial partnerships: different models

2010
Telethon-GSK
14 ADA SCID pts treated, MLD & WAS trials to begin. 2 patents

- GSK: no experience on gene therapy or on the specific diseases, but great experience to define the path to registration
- Development up to clinical PoC under Telethon control; upon option exercise registration strategy under GSK control

by Lucia Faccio – Telethon Convention 2015
The alliance with GSK

15 October 2010 – Telethon-HSR entered into a **research collaboration and license agreement** with GlaxoSmithKline to develop gene therapies for seven genetic diseases.

<table>
<thead>
<tr>
<th>Genetic Disease</th>
<th>Oct 2010</th>
<th>May 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA-SCID</td>
<td>Phase I/II clinical trial (n=14)</td>
<td>Clinical treatment under compassionate use</td>
</tr>
<tr>
<td></td>
<td>Preclinical studies</td>
<td>Post approval surveillance</td>
</tr>
<tr>
<td>Syndrome di Wiskott Aldrich</td>
<td>Preclinical studies</td>
<td>Phase I/II clinical trial (n=8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-Term FU Hospital Exempt (n=3)/NPP</td>
</tr>
<tr>
<td>Leucodistrofia Metacromatica</td>
<td>Preclinical studies</td>
<td>Phase I/II clinical trial (n=20)(CUP (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-Term FU Hospital Exempt (n=3)/NPP</td>
</tr>
<tr>
<td>Beta Talassemia</td>
<td>Preclinical studies</td>
<td>Phase I/II clinical trial (n=10)</td>
</tr>
<tr>
<td>Mucopolisaccaridosis I-Hurler</td>
<td>Preclinical studies</td>
<td>Phase I/II clinical trial</td>
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**Clinical trials and studies**

- **ADA-SCID**
  - Clinical treatment under compassionate use
  - Post approval surveillance

- **Syndrome di Wiskott Aldrich**
  - Preclinical studies
  - Phase I/II clinical trial (n=8)
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  - Phase I/II clinical trial (n=20)(CUP (n=1)
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  - Preclinical studies
  - Phase I/II clinical trial
15 October 2010 – Telethon-HSR entered into a research collaboration and license agreement with GlaxoSmithKline to develop gene therapies for seven genetic diseases.

**Exclusive license to GSK**
- GSK is granted exclusive license to complete development of the ADA-SCID therapy production and to commercialize it.

**LV based gene therapy for 6 genetic diseases**

**Exclusive Option to license**
- Telethon-HSR is responsible for research on the six diseases of the LVV platform up to clinical Proof of Concept.
- GSK is granted exclusive option for the license of each of the six programs for the development and commercialization of the therapies.
- HSR-TIGET and GSK collaborate on lentiviral platform and vector manufacturing improvements necessary or useful for the collaboration programs.

10 M€ downpayment

Milestone payments upon completion of development milestones on a program by program basis.
Telethon industrial partnerships: different models

**2010**
Telethon-GSK
14 ADA SCID pts treated, MLD & WAS trials to begin.
2 patents

**2011**
Telethon-Biomarin
HTS screening for modulators of TFEB, a validated target.
2 patents

**2012**
Telethon-Shire
Validated targets for LSD and neurodegenerative disorders via gene therapy & small molecules screening

- **Biomarin:** strong experience in the rare disease field through ERT and small molecules
  - Research up to assay validation and lead validation under Telethon control; BMR exclusive option on leads
  - 2 patents

- **Shire:** strong experience in the rare disease field through ERT and small molecules
  - Research up to clinical development under Telethon control; upon opt-in clinical studies under Shire control.
  - 7 patents

- **GSK:** no experience on gene therapy or on the specific diseases, but great experience to define the path to registration
  - Development up to clinical PoC under Telethon control; upon option exercise registration strategy under GSK control

- **Telethon industrial partnerships:**
  - **Basic research**
  - **Pre-clinical studies**
  - **Pre-clinical development**
  - **Clinical trials**
  - **Commercialization & post marketing surveillance**
The alliance with SHIRE

1 October 2012 – Telethon entered into a 5-year research collaboration and license agreement with Shire to identify new treatments for lysosomal storage disorders (LSDs) and neurodegenerative diseases.

**Basic Research**

Early stage research programs selected from the existing independent research at TIGEM

**Clinical development**

- 5 year funding of the research programs with go/no go decision points
- Right to license the most interesting results
- Development and delivery of effective therapies to patients
- Drug development due diligence
Telethon industrial partnerships: different models

- **Biomarin**: strong experience in the rare disease field through ERT and small molecules
  - Research up to assay validation and lead validation under Telethon control; BMR exclusive option on leads
  - 2011 Telethon-Biomarin
    - HTS screening for modulators of TFEB, a validated target.
    - 2 patents

- **Shire**: strong experience in the rare disease field through ERT and small molecules
  - Research up to clinical development under Telethon control; upon opt-in clinical studies under Shire control.
  - 2012 Telethon-Shire
    - Validated targets for LSD and neurodegenerative disorders via gene therapy & small molecules screening
    - 7 patents

- **Biogen**: 2 products on the market for hemophilia, no experience on gene therapy
  - Development up to clinical PoC under Telethon’s control. Multicenter trials and registration under Bi control
  - 2014 Telethon-Biogen
    - 2 patents

- **GSK**: no experience on gene therapy or on the specific diseases, but great experience to define the path to registration
  - Development up to clinical PoC under Telethon control; upon option exercise registration strategy under GSK control
  - 2010 Telethon-GSK
    - 14 ADA SCID pts treated, MLD & WAS trials to begin.
    - 2 patents
Telethon’s intramural research is significantly supported by industrial alliances.

Funds allocated*, M€

* Research costs excluding unallocable costs such as intramural fixed costs, open access fees, etc.

- **TIGEM + TIGET (Industrial partnerships)**
- **TIGEM + TIGET (Telethon and non-profit funds)**
- **Extramural + DTI**

<table>
<thead>
<tr>
<th>Research Type</th>
<th>2005-2010</th>
<th>2011-2016</th>
</tr>
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<tbody>
<tr>
<td>Basic research</td>
<td>68,9</td>
<td>40,1</td>
</tr>
<tr>
<td>Preclinical research</td>
<td>10,7</td>
<td>7,2</td>
</tr>
<tr>
<td>Clinical research</td>
<td>7,2</td>
<td>11,9</td>
</tr>
<tr>
<td>Extramural + DTI</td>
<td>18,7</td>
<td>27,5</td>
</tr>
<tr>
<td>TIGEM + TIGET</td>
<td>11,9</td>
<td>6,3</td>
</tr>
<tr>
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<td>7,9</td>
<td>6,7</td>
</tr>
<tr>
<td>Industrial partnerships</td>
<td>11,3</td>
<td>30,3</td>
</tr>
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Source: Telethon TRic database, January 2017
Telethon’s intramural research is significantly supported by industrial alliances.

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- TIGEM + TIGET (Industrial partnerships)
- TIGEM + TIGET (Telethon and non-profit funds)
- Extramural + DTI

All agreements between Telethon and industrial Partners

- Safeguard research independence of Telethon investigators
- Retain intellectual property rights
- Require mandate commitment in developing therapies
- Imply return of any IP and results co-developed, in case the Partner does not pursue therapy development
- Provide funding in support of the research in the collaboration programs and
- Supply additional funding through milestones/royalties, in support of further research activities

Source: Telethon TRic database, January 2017
Why academia should partner?
Why Telethon partners with industry?

- Donors
- Patients
- Biotech/pharma
- Telethon
- Selected research projects

Money flow and know-how exchange among entities.
Why academia should partner with industry?

- To access new funds dedicated to research
- To access know-how and new expertise
- To play a proper role in the socio-economic development
The academia-industry alliance: building on complementary competencies to reach patients

- Access to treatment between end of trial enrollment and availability on the market
- Share knowledge acquired on the disease and on the therapeutic approach
- Strategy to MAA
- Long term Follow-up of treated patients
- Production process optimization and scale-up
- Preclinical studies in GLP
- Set-up of an internal facility
- Change of sponsorship for the trial
- Transfer of clinical data
Am I an inventor? and other key questions

- What is the technical problem to be solved?
- How does your invention work?
- What solutions are in the prior art?
- How differs your invention from prior art?
- What improvements and advantages favour your invention?
- Industrial applications (disease indications, research tools)?
- Alternative form of the invention?
- Development stage now and in one year?
- Next steps and priorities of the research plan?
- Any disclosure (abstracts, oral presentations, thesis, posters, papers)?
- Any contribution (inventive contributions, materials, money) from colleagues and third parties?
The "social contract" implicit in the patent system

- A patent is an **exclusive right** granted by a government to the owner of the patent
  - to **exclude others** from making, using, importing, selling or offering for sale the patented invention
  - for a set **period of time**
  - in the **territory**
  - in exchange for **detailed public disclosure** of the invention.

- Patent laws and rules are world-wide almost equal.

- The Venetian Patent Statute, issued by the Senate of Venice in 1474, and one of the earliest patent systems in the world.

(modified from European Patent Office)
Why do we need to patent?

Patents prohibit anyone other than the patent holder from making, selling or importing the patented invention without the permission of the patent holder. **It is a right to exclude others.**

Such right is granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for **detailed public disclosure of the invention.**

By preventing others from distributing, selling, or manufacturing your invention, you preserve your **right to earn profits from the invention.**

By licensing (not assigning) the right to develop and produce the invention and retain ownership of the IPRs behind a project, you can have such **rights back if the company abandons the project.**
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If the company abandons any program of the alliance, Telethon gets back all rights on results, including those obtained through the alliance and is free to proceed development with other partners.
Why do we need to patent

1 product on the market (cost 1.5-2 bl $)

Pharma

Biotech

University

10-30,000 potential products

Basic research

Preclinical & Clinical up to Ph II

Clinical Ph III/Registration

Licensing

0 years

13 years
Patents add value to science

By providing a business competitive advantage (the right of exclusively producing/commercializing) therefore promoting investment.

By encouraging dissemination of information therefore promoting technology transfer and encouraging technological innovation and competition.

This is a must for high cost/high risk research fields which cannot get proper revenues in the absence of exclusivity of commercial acts.
Recombinant DNA (rDNA) products provided a new technology platform for a range of industries, resulting in over US$35 billion in sales for an estimated 2,442 new products. Over the duration of the life of the patents (they expired in December 1997), the technology was licensed to 468 companies, many of them new biotech companies who used the licenses to establish their business. Over the 25 years of the licensing program, Stanford and the University of California system accrued US$255 million in licensing revenues (from 1981 to the end of 2001), much of which was subsequently invested in research and research infrastructure. The first licensed drug generated using recombinant DNA technology was human insulin, developed by Genentech.
The don’t’s before patenting

- **No publication/disclosure prior to filing**
e.g. no article, press release, conference presentation/abstract/poster/proceedings or blog entry/ students’ thesis/ laboratory web pages, reports to funding agencies etc...

- **No Material Transfer to external laboratories without the appropriate agreement in place**

- **No lecture or presentation to third parties prior to filing except under a confidentiality agreement (CDA)**

- **Seek Technology Transfer Office support and advice soon!**
- **File before others do!**

Patenting and Publication can move together!!!
A **Material transfer agreement** (MTA) is a contract that governs the transfer of tangible research materials between two organizations, when the recipient intends to use it for his or her own research purposes.

The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives, research results and publications.
A Non Disclosure Agreement is a legal contract between at least two parties that outlines confidential material, knowledge, or information that the parties wish to share with one another for certain purposes.

Each party agrees not to disclose the other party information covered by the agreement.

An NDA creates a confidential relationship between the parties to protect any type of nonpublic business information (confidential and proprietary information or trade secrets).
Do patents limit research?

Although the precise scope of specific provisions varies in the content of national laws, generally the **Research or Experimental Use Exception** provisions allow the free use of knowledge disclosed in a patent for **non commercial** research:

- General research aiming at improving the invention
- Experimentation in the context of clinical trials
- Experimentation to satisfy regulatory requirements

From **The Agreement on Trade-Related Aspects of Intellectual Property Rights**:

“Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.”
Academia vs Industry

ACADEMIA
- Curiosity driven research
- Academic freedom
- Open source

INDUSTRY
- Profit driven research
- Business constraints
- Limited Public Disclosure

CONFLICT OF INTERESTS??
Scientists should contribute to negotiation

INDUSTRIAL PARTNERSHIP

Purpose
- purpose, field, territory, exclusivity;

What do we give
- background IP and know-how access of future results

What do we get
- consideration access to tools and competences

IP
- patent management ownership of development/joint IP license back

Drug Dev.
- development & regulatory milestones steering committee

Legalities
- confidentiality, publications use of name termination
Must have in an industrial collaboration contract

- Definition of background IP and Know how
- Definition of ownership of future results
- Definition of access by Pharma to background and future results (i.e. option, license exclusive vs non exclusive etc)
- Publication rights and evaluation of patentability
- Management of joint IP
- Contract Termination: access by the parties to non patentable material/know how developed during the collaboration
Research value: know how and patents

**KNOW HOW**
- SPONSORED RESEARCH
- SERVICE CONTRACTS

**PATENTABLE TECHNOLOGIES**
- PATENTING (composition/products, method or new medical use)
- MARKETING
- LICENSING
Nine things to remember in licensing

1. Universities should reserve the right to practice licensed inventions and to allow other non-profit and governmental organizations to do so.
2. Exclusive licenses should be structured in a manner that encourages technology development and use.
3. Strive to minimize the licensing of “future improvements”.
4. Universities should anticipate and help to manage technology transfer related conflicts of interest.
5. Ensure broad access to research tools.
6. Enforcement action should be carefully considered.
7. Be mindful of export regulations.
8. Be mindful of the implications of working with patent aggregators.
9. Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.

From www.autm.net/Nine_Points_to_Consider.htm
ADA SCID severe combined immunodeficiency ex vivo gene therapy

Treatment design

- Discontinuation of PEG-ADA
- IV BUSULFAN (4 mg/kg)
- CVL positioning and collection and freezing of back up CD34+ cells
- Low Intensity Conditioning
  - Day -3 → Day -2

START
- Day -4: BM Harvest
- Day -4: Purification of CD34+ cells
- Production of the Medicinal Product: RV-ADA transduced autologous CD34+ cells (GSK 2696273)

TARGET CD34+ cell dose: 5 – 10 x 10^6/kg
- Day 0: Intravenous Infusion
- Day -4 → -3: 22h stimulation
- Day -3 → Day -1: 3 cycles of transduction

References:
We bring therapies to market: Strimvelis
ADA-SCID a severe combined immunodeficiency

1995
SR-Tiget
Is launched in collaboration with OSR

1991
In Vivo PoC

1991
1st ADA-SCID patient treated

1995
Is launched in collaboration with OSR

2000
1st ADA-SCID patient treated

2002-2009
Phase I/II trial (12 pts)

2002
Science publication on first 2 children treated

2007
Protocol Assistance from EMA

2009
NEJM publication on first 10 children treated

2005
EMA ODD

2005
GMP

2007
EMA ODD

2009
FDA ODD

2009
GLP

2009
ODD

2010
Alliance with GlaxoSmithKline

2010-2016
Clinical treatment under compassionate use (9 pts)

2015
File MAA to EMA

2016
First ex-vivo gene therapy treatment approved in the world

May 2016
First ex-vivo gene therapy treatment approved in the world

March 2017
First reimbursed patient treated

for the treatment of patients with ADA-SCID
USHER IB retinitis pigmentosa gene therapy

Dual Vector System

Retinal Pigment Epithelium

Introduction of healthy gene

Subretinal injection

Photoreceptor
USHER IB as a non-profit collaborative approach

18 months Translation (2016-2017)

5 years Discovery (2011-2016)

5 years First-in-human (2018-2020): consortium of expertise including clinical centres, CRO and CMO
Think about therapeutic and other exploitation or your research, while keeping in mind to...

- Do Not disclose before evaluating patentability
- Contact the Technology Transfer Office
to discuss about the potential industrial application of your results
... as well as when an industrial partner approaches you
Thank you!