

San Raffaele  
Telethon Institute for  
**Gene Therapy**





We perform cutting edge research on  
**gene and cell therapy**  
and translate its results  
into therapeutic advances  
with a focus on **genetic diseases**

# SR-Tiget at a Glance

The San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) is **located within the Ospedale San Raffaele in Milan**, one of Europe's major science parks, which includes a hospital, a biomedical research center, a university and also hosts several biotech companies.

SR-Tiget is **directed by Luigi Naldini since 2008**. The Institute comprises **2000 m<sup>2</sup>** of laboratory, clinical and office spaces. The personnel consists of about **200 people** coming from more than 10 different countries.

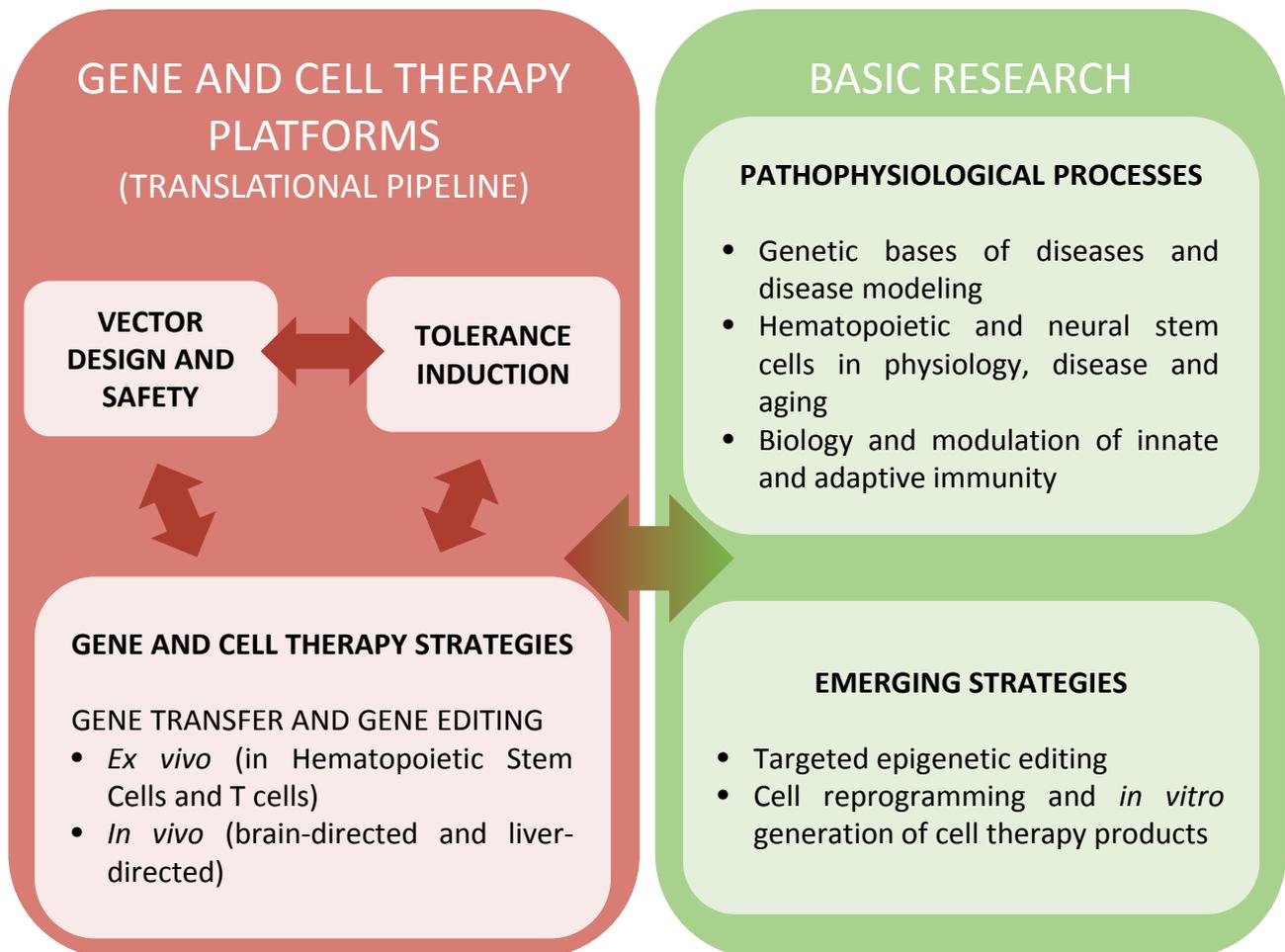


# The Mission

- Cutting edge research in **gene and cell therapy**
- Focus on **genetic diseases**
- Development of **new therapeutic strategies** and evaluation of their efficacy and safety in relevant **preclinical models**
- Priority to **clinical translation**
- Application of cell and gene therapy platforms to the **treatment of cancer**

**SR-Tiget is a joint venture between  
Telethon Foundation and Ospedale  
San Raffaele  
(since 1995)**

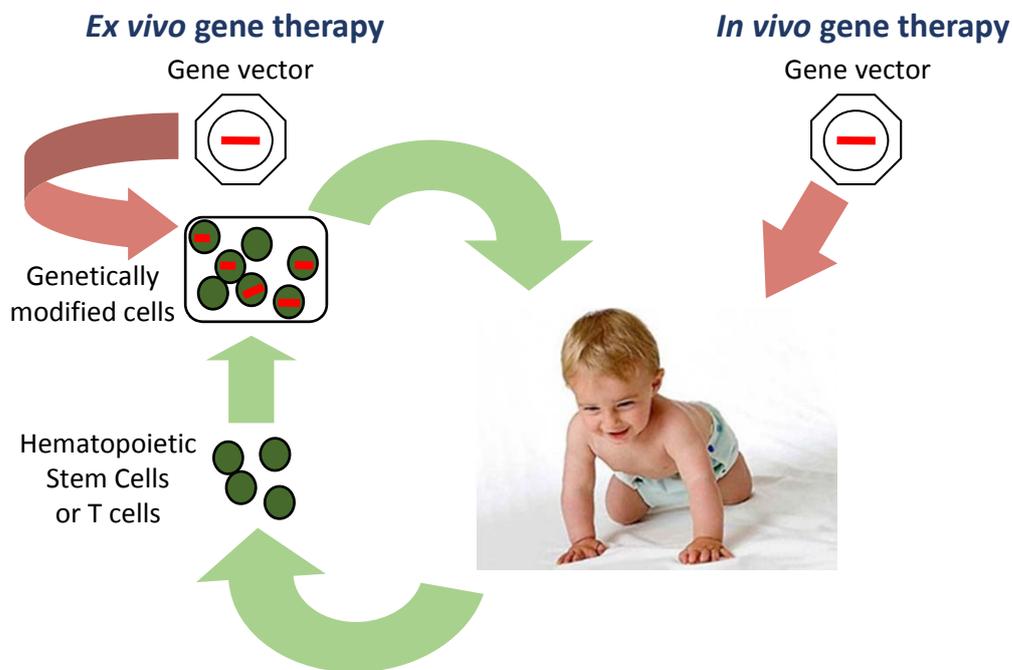
# Research interests



SR-Tiget is internationally renowned for its substantial contribution to the field of gene and cell therapy. The Institute's **translational pipeline** is devoted to the development of new gene and cell therapy strategies up to the clinics. This involves a continuous effort to ameliorate the technologies used for these applications and to develop approaches to induce immunological tolerance to gene and cell products. SR-Tiget also strongly invests in **basic research**, which fuels the translational pipeline and gets in turn nourished by it. Specifically, basic research efforts are aimed to gain a better understanding of the diseases and cell types under investigation and to develop technological advances for their improved isolation, manipulation and transplantation.

## Focus on: what is gene therapy?

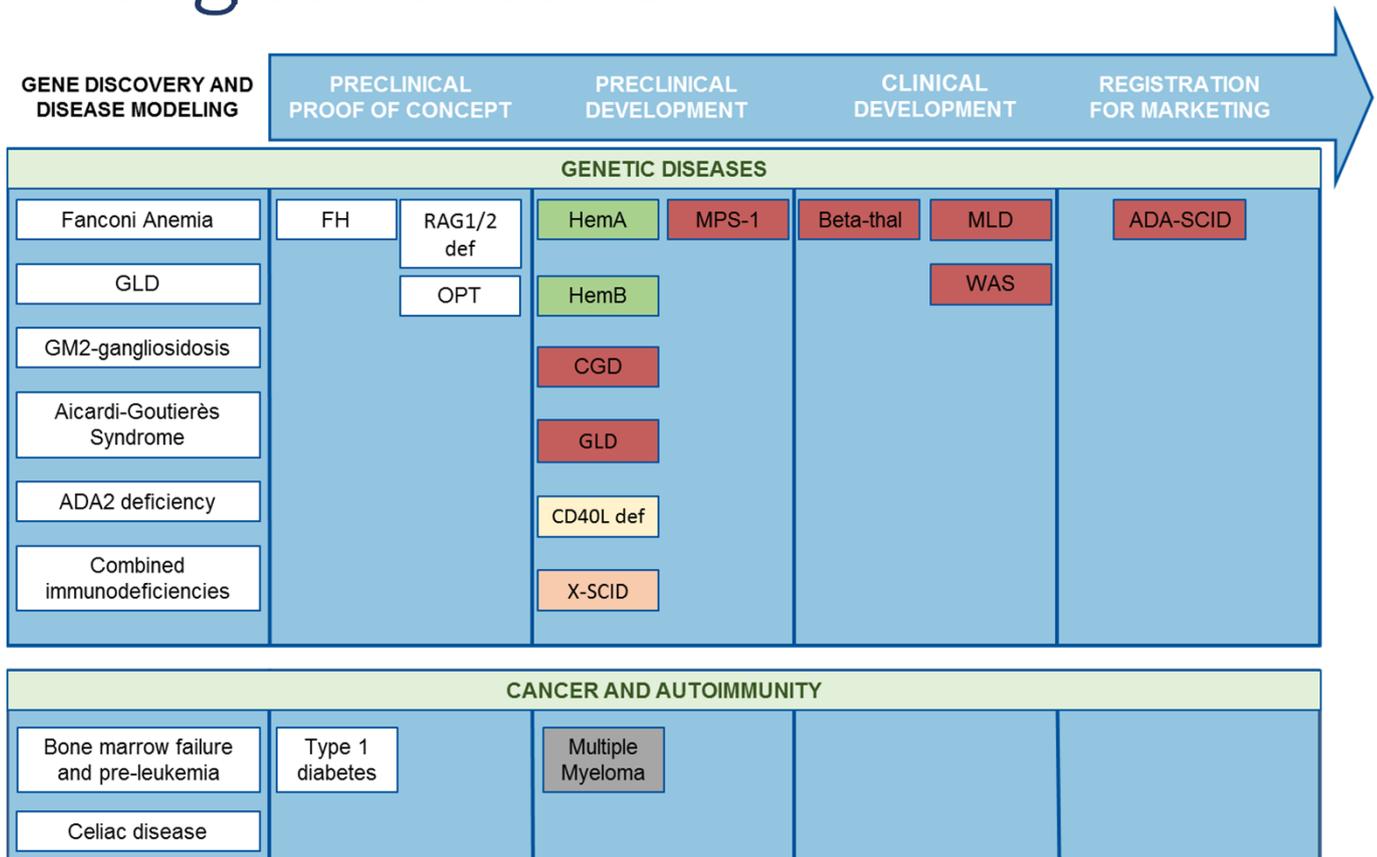
**Gene therapy** holds the potential to treat a disease at its genetic roots, by replacing, repairing or counteracting a malfunctioning gene within the cells affected by the condition. It bears the promise of a long-term clinical benefit with a single administration of the treatment.



In the **ex vivo approach**, the target cells (e.g. Hematopoietic Stem Cells, T cells) are harvested from a patient, genetically modified *ex vivo* to correct the inherited defect and infused back into the patient.

In the **in vivo approach**, the therapeutic gene is directly delivered or restored into the target cells of a particular tissue in the patient's body (e.g. liver, brain).

# Target diseases



## LEGEND:

Alliance with GSK
Alliance with Bioerativ
Alliance with Editas
Research agreement with Sangamo
Spin-off Genenta Science

## ABBREVIATIONS LIST:

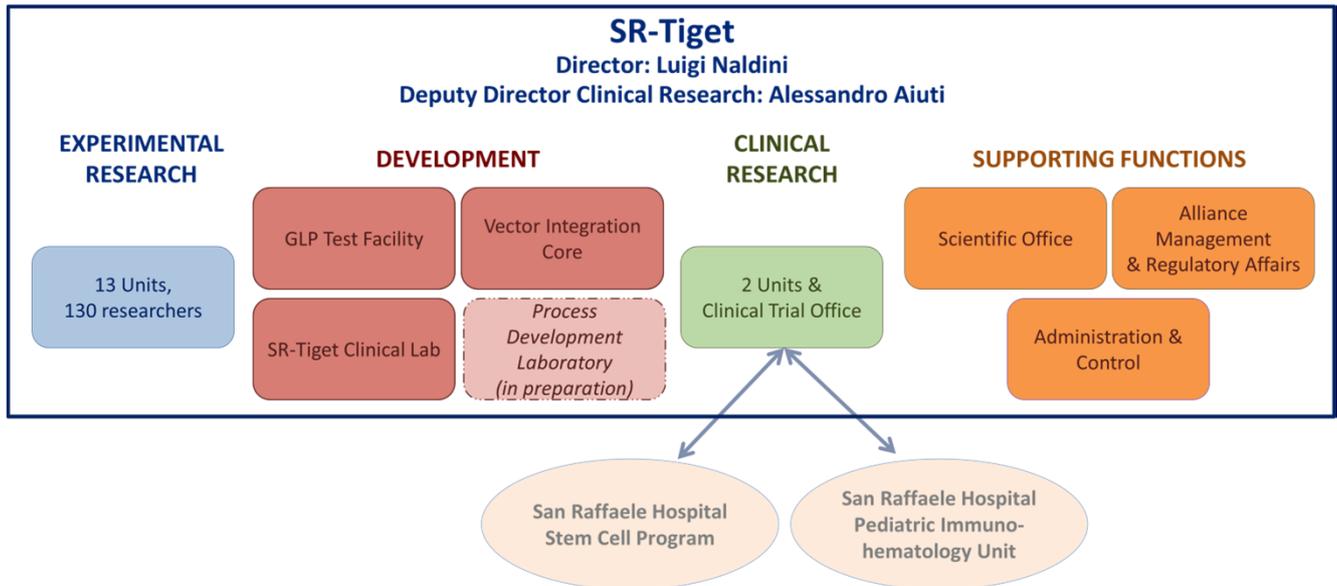
**ADA-SCID:** Adenosine Deaminase Severe Combined Immunodeficiency; **MLD:** Metachromatic Leukodystrophy; **WAS:** Wiskott-Aldrich Syndrome; **Beta-thal:** Beta-thalassemia; **MPS-1:** Mucopolysaccharidosis type 1; **HemA** and **HemB:** Hemophilia A and B; **CGD:** Chronic Granulomatous Disease; **GLD:** Globoid Cell Leukodystrophy; **CD40L def:** CD40 ligand deficiency; **X-SCID:** X-linked Severe Combined Immunodeficiency; **RAG1/2 def:** RAG1/2 deficiency; **OPT:** Osteopetrosis; **FH:** Familial Hypercholesterolemia caused by mutations in the PCSK9 gene

**SR-Tiget target diseases** are represented along an imaginary translational pipeline, showing how the Institute's portfolio of gene and cell therapies embraces the full spectrum of drug development.

The most advanced steps in this roadmap are undertaken in the context of strategic alliances with industrial partners, which are crucial to secure the resources and the multi-disciplinary expertise required to attain the ultimate goal of delivering the therapies to patients worldwide.



# The Institute structure



## EXPERIMENTAL RESEARCH

Pathogenesis and therapy of primary immunodeficiencies | Alessandro Aiuti

Senescence in stem cell aging, differentiation and cancer | Raffaella Di Micco

Human hematopoietic development and disease modeling | Andrea Ditadi

Gene transfer into stem cells | Giuliana Ferrari

Translational stem cell and leukemia research | Bernhard Gentner

Mechanisms of peripheral tolerance | Silvia Gregori

Gene/neural stem cell therapy for lysosomal storage diseases | Angela Gritti

Retrovirus-host interactions and innate immunity | Anna Kajaste-Rudnitski

Epigenetic regulation and targeted genome editing | Angelo Lombardo

Safety of gene therapy and insertional mutagenesis research | Eugenio Montini

Gene transfer technologies and new gene therapy strategies | Luigi Naldini

Genomics of the innate immune system | Renato Ostuni

Pathogenesis and treatment of immune and bone diseases | Anna Villa

## DEVELOPMENT

### GLP (GOOD LABORATORY PRACTICES) TEST FACILITY | Patrizia Cristofori

First academic GLP center for performing biodistribution, toxicology/tumorigenicity and validation studies on gene and cell therapy products.

Certified by the Italian Ministry of Health in March 2014, renewed in April 2016.

### VECTOR INTEGRATION CORE | Eugenio Montini

Performs tracking of vector integration sites as readout of cell growth at clonal level, in basic research studies and technology development, in preclinical safety studies and in gene therapy treated patients.

### SR-TIGET CLINICAL LAB | Luigi Naldini

To ensure data integrity and reliability in analyses of samples from clinical trials. Such analyses are performed according to GCLP (Good Clinical Laboratory Practices).

In 2017 completed auto-certification pursuant to DETERMINA AIFA n. 809/2015.

### PROCESS DEVELOPMENT LABORATORY - IN PREPARATION -

To develop new protocols for vector production, gene editing and *ex vivo* cell manipulation in a context of GSP (Good Scientific Practices) and Quality by Design.

## CLINICAL RESEARCH

Translation of novel gene and cell therapies developed at SR-Tiget into treatments available to patients.

- 2 UNITS:
  - Clinical pediatric research unit | Alessandro Aiuti
  - Clinical hematology research unit | Fabio Ciceri
- SR-Tiget clinical trial office | Stefano Zancan



SR-TIGET PEOPLE

# Research results and their valorization

## SCIENTIFIC PUBLICATIONS

- ~50 publications per year of which ~75% original research articles
- 9 average Impact Factor per publication

## INTELLECTUAL PROPERTY

- 22 active patent families
- 150 active patents and/or patent applications, of which 128 included in industrial agreements

## INDUSTRIAL AGREEMENTS

- 3 strategic alliances with pharma and biotech companies
- 20 sponsored research agreements
- 20 license agreements

## REGULATORY AFFAIRS

- 6 Orphan Drug Designations for 4 products (4 at EMA, 2 at FDA)
- 4 Pediatric Investigational Plan at EMA (3 by GSK)
- Scientific Advice at EMA for 4 programs

In order to effectively develop new therapies and deliver them to patients, excellent academic research - as shown by the Institute's output of **scientific publications** - is a necessary, but not sufficient condition.

The process of valorization of research results starts by protecting **Intellectual Property**. Patentable inventions are identified taking into account their content, the prior art and the existence of a potential market. Once a patent application is filed, different kinds of agreements for the development of the protected invention are negotiated with **industrial partners**, depending on the technology readiness level and the broadness of the scope of the partnership.

It is also crucial to define the **clinical testing strategy** very early, to inform the whole development program, take advantage of interactions with regulatory agencies and the incentives they offer, and ensure the implementation of relevant laws and guidelines.



# Industrial Alliances

The establishment of strategic alliances with industrial partners is of paramount importance to make therapies available to patients. Indeed, the path from bench to bedside also requires competences and processes which are more typical of **pharmaceutical companies** than of academia.

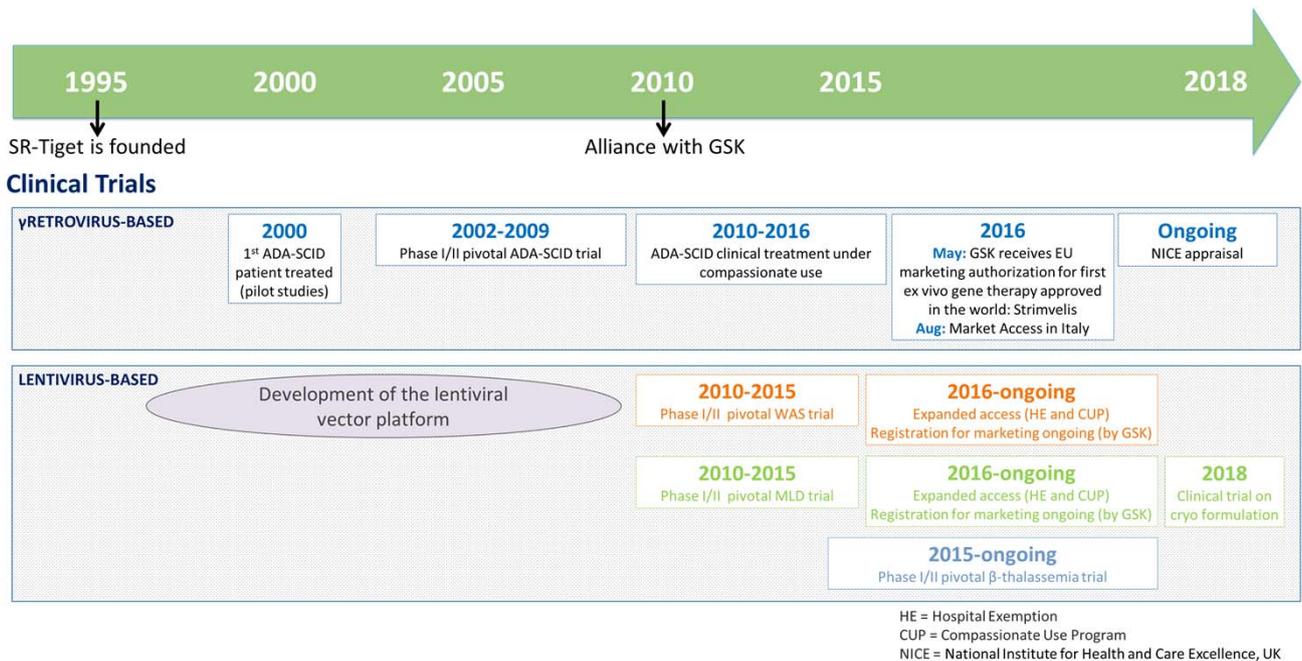
This scheme illustrates the alliances SR-Tiget is currently engaged in:

Partner	Start	Scope
GlaxoSmith Kline (GSK)	2010	<p><math>\gamma</math>Retrovirus-based <i>ex vivo</i> gene therapy for <b>ADA-SCID</b></p> <p>Lentivirus-based <i>ex vivo</i> gene therapy for <b>WAS, MLD, Beta-thal, MPS-I, GLD, CGD</b></p> <p><b>Licensed programs ; Optioned programs</b></p>
Bioverativ	2014	<p>Lentivirus-based <i>in vivo</i> gene therapy for <b>hemophilia A and B</b></p> <p><b>Optioned programs</b></p>
Editas	2016	<p>Genome editing of Hematopoietic Stem Cells and T cells for the treatment of CD40 ligand deficiency</p>

SR-Tiget is responsible for the programs until clinical Proof of Concept. The partner has the option to exercise exclusive worldwide development and commercialization rights on each program. After option exercise, SR-Tiget collaborates to further clinical development and marketing.

If the partner drops any program of the alliance, the Institute gets back all rights on results and shall be free to pursue development with other partners.

# Clinical Trials



SR-Tiget pioneered the **gene therapy of ADA-SCID**, a severe form of immunodeficiency, developing a Hematopoietic Stem Cell (HSC)-based gene therapy employing  $\gamma$ Retroviral vectors. With more than 15 years of follow-up of the first treated patients, this seminal work provided evidence of substantial clinical benefit without treatment-related adverse events and resulted in the EU marketing authorization for this therapy, under the name of Strimvelis.

The successful results obtained with ADA-SCID provided a rationale for extending the HSC gene therapy approach to other diseases, employing the more advanced lentiviral vectors. In particular, two clinical trials for **Wiskott-Aldrich Syndrome (WAS)** and **Metachromatic Leukodystrophy (MLD)** started in 2010 and have shown persistent therapeutic benefit in the absence of treatment-related adverse events. A third trial, for **beta-thalassemia**, started in 2015 and is showing promising preliminary results. In addition, a trial for **Mucopolysaccharidosis type I (MPS-I)** is planned to start in 2018.

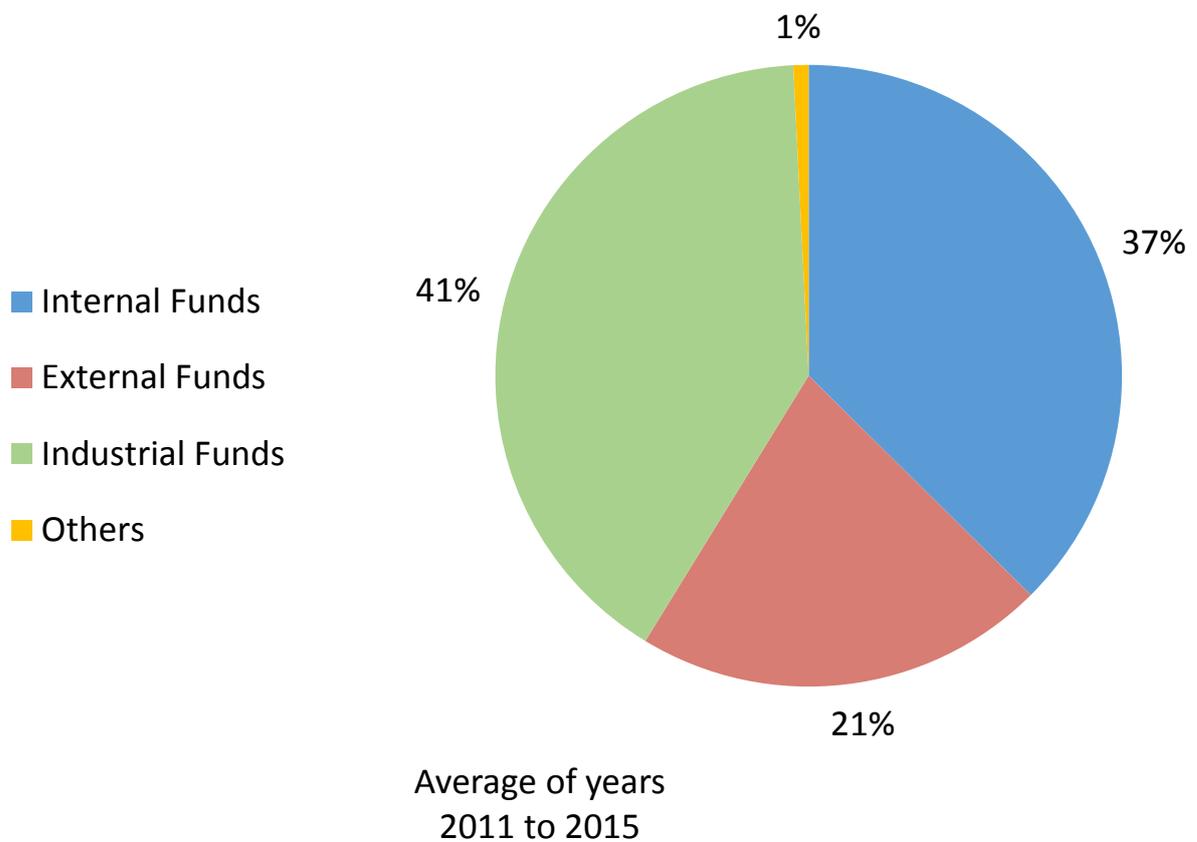
# On the market

**27<sup>th</sup> May 2016**  
EU marketing  
authorization for  
**Strimvelis**

**Strimvelis** is the first *ex vivo* gene therapy worldwide, for the treatment of **ADA-SCID** (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency). It consists of autologous CD34+ cells transduced to express the enzyme Adenosine Deaminase.

**Developed at SR-Tiget and brought to the market under the alliance among Fondazione Telethon, Ospedale San Raffaele and GlaxoSmithKline.**

# Funding sources



**Internal funds:** from Fondazione Telethon (“Core Grant”, every 5 years, subject to a peer review process with initial and interim site visits) and Ospedale San Raffaele

**External funds:** international (ERC, EU FP7 and H2020, charities) and national (Ministries of Health and of Scientific Research, AIRC, Cariplo Foundation) grants awarded on a competitive basis

**Industrial funds:** funds from industrial agreements

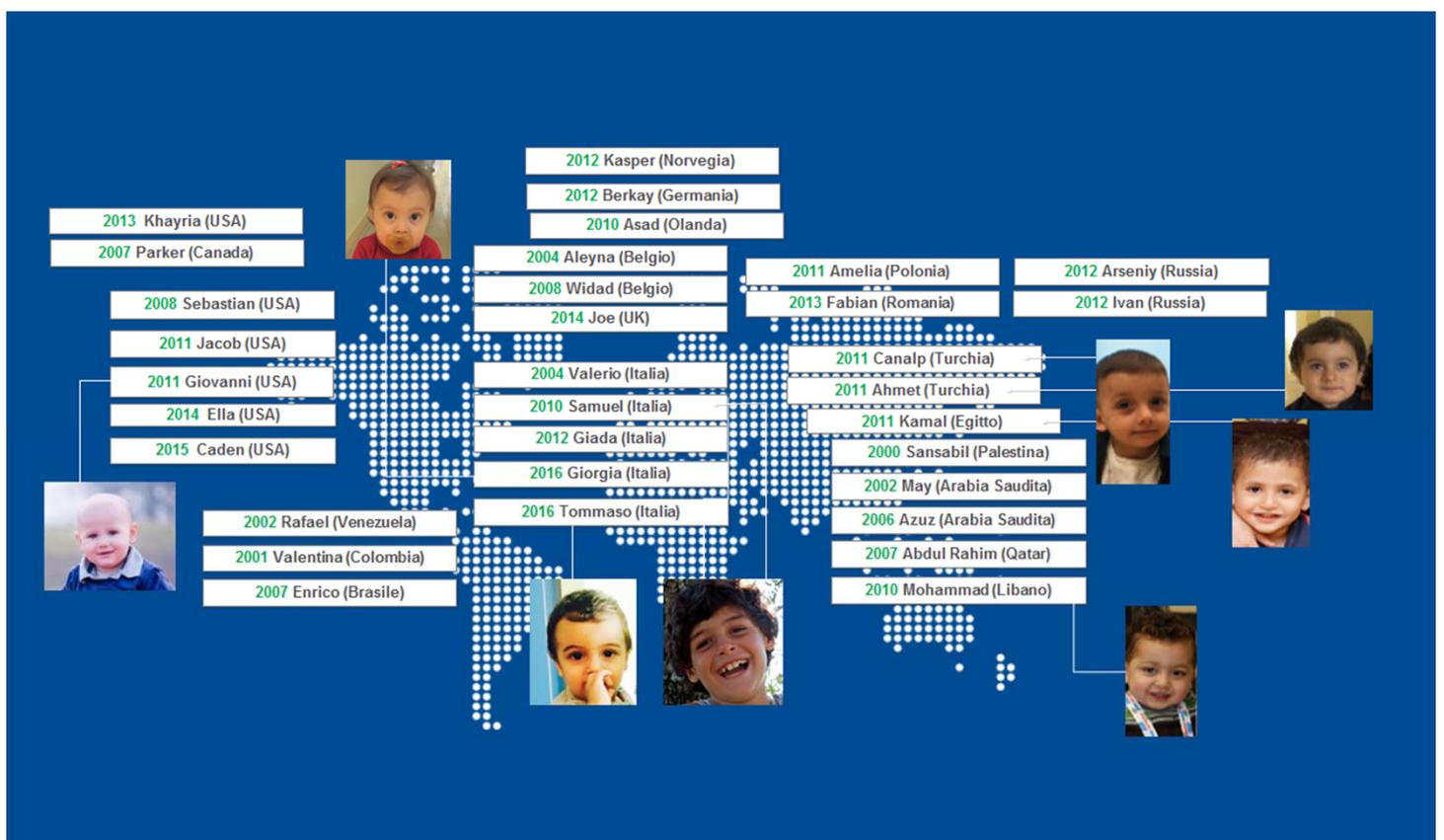
**Others:** donations

# SR-Tiget in the international context

- **Active role in scientific societies and organizations;** e.g. American Society of Gene and Cell Therapy (ASGCT), European Society of Gene and Cell Therapy (ESGCT), International Society for Stem Cell Research (ISSCR), American Society of Hematology (ASH), European Group for Blood and Marrow Transplantation (EBMT), European Hematology Association (EHA)
- **Called to take part in advisory and policy making committees;** e.g. Committee for Advanced Therapies of the European Medicines Agencies (EMA), World Health Organization, US National Academy of Sciences
- **Prizes;** e.g. ASGCT and ESGCT Outstanding Achievement Award; ASGCT Excellence in Research Award; ESGCT Young Investigator Award
- **Keynote / plenary talks and organization of international conferences**
- **Outwards and inwards mobility, attesting to mentorship capabilities and attractiveness of the Institute;** e.g. **out** to faculty position: M.G. Roncarolo (to Stanford Uni, 2014); R. Bacchetta (to Stanford Uni, 2015); A. Biffi (to Harvard Uni, 2016); L. Biasco (to Harvard Uni, 2016); M. Bosticardo (to NIH, 2017); **in** as new Group Leaders in 2016: R. Di Micco (from New York Uni), R. Ostuni (from IEO, Milan), A. Ditadi (from Toronto Un)

SR-Tiget has gained worldwide recognition as a center of excellence in the field of cell and gene therapy

# The children we treated all over the world



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**Fondazione Telethon** is a major biomedical charity in Italy whose mission is to advance biomedical research towards the cure of rare genetic diseases. Throughout its 27 years of activity, the Telethon Foundation has invested over €475 million in funding over 2,600 projects to study 540 diseases, involving more than 1,600 researchers. For further information, visit [www.telethon.it/en](http://www.telethon.it/en)



**Ospedale San Raffaele** is a clinical-research-university hospital established in 1971 to provide international-level specialized care for the most complex and difficult health conditions. Since 2012 OSR is part of Gruppo Ospedaliero San Donato, the leading hospital group in Italy. The hospital is a multi-specialty center with over 50 clinical specialties and has over 1,300 beds. Research at OSR focuses on integrating basic, translational and clinical activities to provide the most advanced care to our patients. For further information, visit [www.hsr.it](http://www.hsr.it)





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