From regulation to reality – challenges in translation of gene therapy and cell-based medicinal products

Gene therapy case study: ADA-SCID

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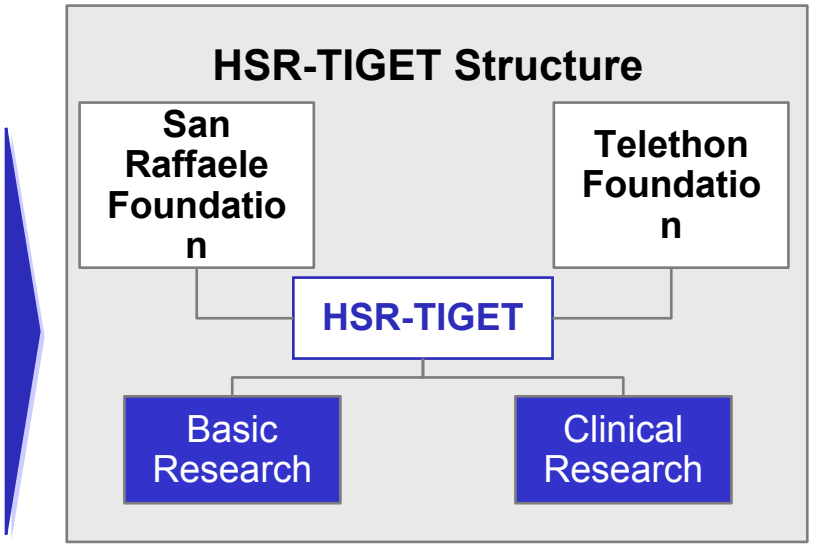
Rare Diseases

HSR-TIGET is focused on the implementation of basic and clinical research for genetic diseases

Overview

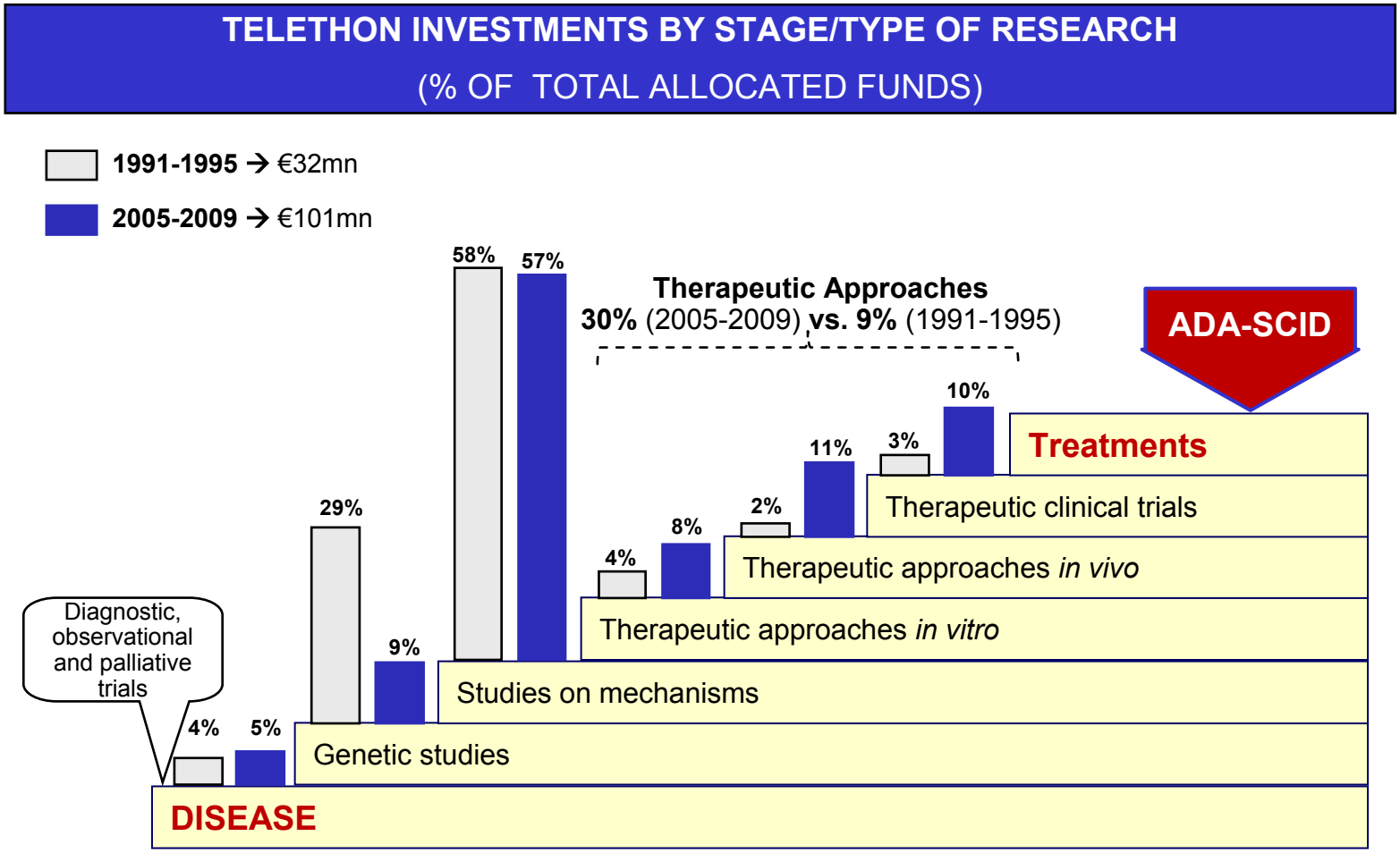
- **HSR-TIGET** is a **joint venture** between Telethon and **San Raffaele Hospital** (**HSR**)
- HSR-TIGET has a **Research staff of 93 people**, including 4 heads of unit, 10 group-leaders/project leaders, 59 junior researchers, and 20 technicians
- HSR-TIGET has also established a **Pediatric Clinical Research Unit** that focuses on the diagnosis, treatment and follow up of patients, including those enrolled in the gene therapy trials



Research

- **State-of-the-art research** in gene transfer technologies and gene and cell therapy strategies
- **Genetic diseases** currently under investigation include:
  - Primary immunodeficiencies
  - Thalassemia
  - Autoimmune diseases
  - Leukodystrophies
  - Other lysosomal storage disorders

As research progresses, funds to therapeutic approaches are increasing (approx. 30% of Telethon funds)

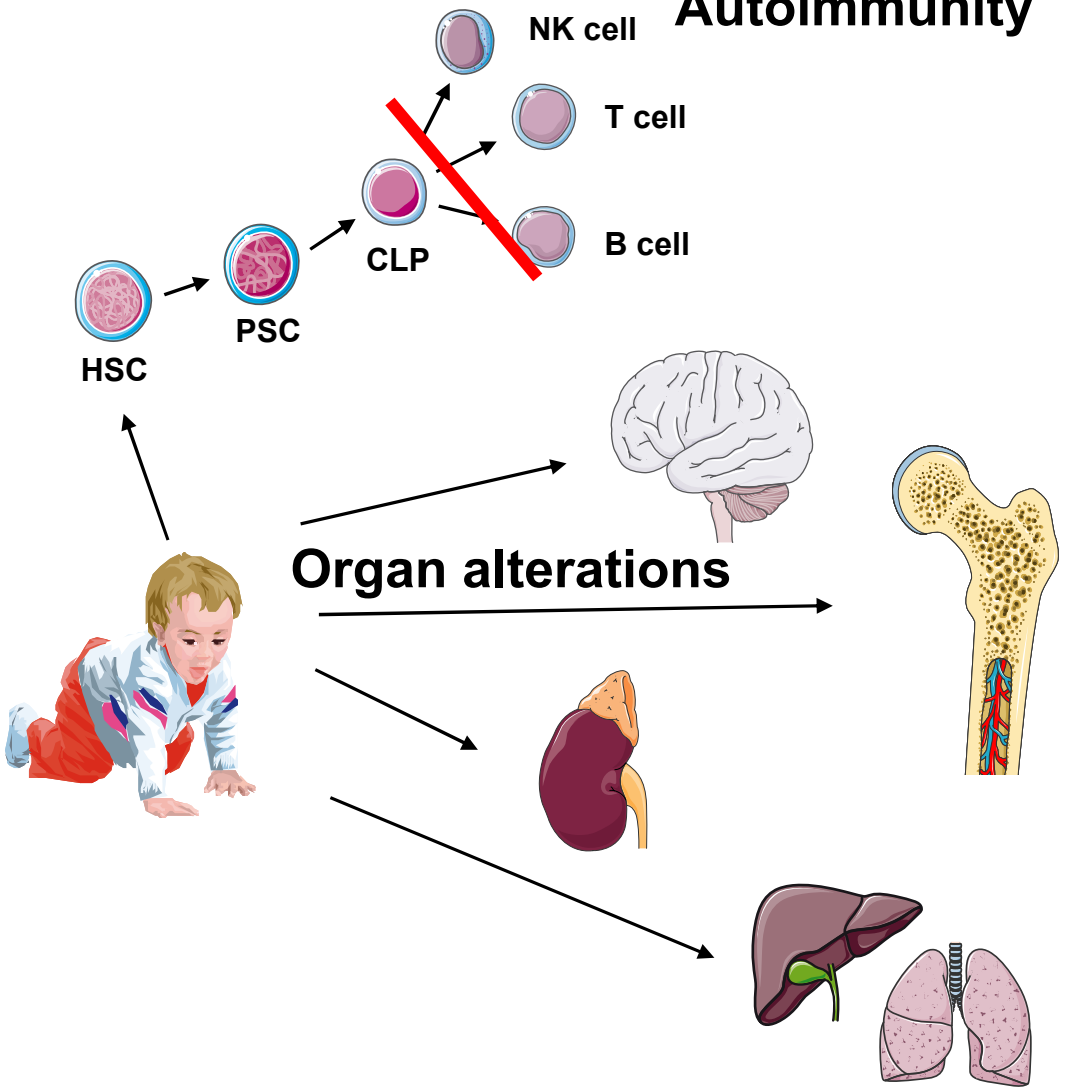


ADA-SCID

Immunodeficiency
Infections
Autoimmunity

~~Adenosine deaminase~~

↑ **dAdo, Ado**
dAXP



Autosomal recessive
1:375,000

RATIONALE FOR GENE THERAPY

Scientific rationale

- The ADA gene is constitutively and ubiquitously expressed
- Correction of HSC could correct the defect in all blood cells
- Gene-corrected lymphocytes have an advantage over ADA-deficient cells.
- 10% of normal ADA expression may be sufficient

Unmet medical need

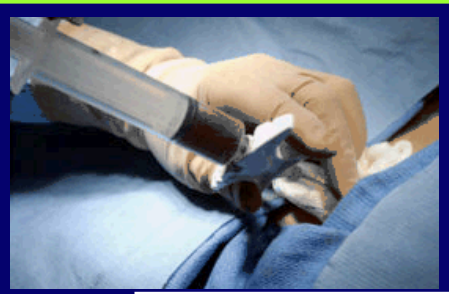
- 90% of children lack an histocompatible donor in the family
- High risk of bone marrow transplant from alternative donors
- Treatment with bovine enzyme (PEG-ADA) requires weekly administration, not always effective and very expensive

Gene transfer protocol into autologous bone marrow CD34+ cells

Medicinal Product:
Autologous transduced cells

No PEG-ADA

Busulfan
2 mg/Kg/day x 2
(days -3, -2)



BM Harvest

Day 0: Infusion

Day -4: Purification of BM CD34+ cells

Days -3 to -1:
3 cycles of transduction on retronectin + cytokines

Day-4: Prestimulation (TPO, FLT3-ligand, SCF, IL-3)

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Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

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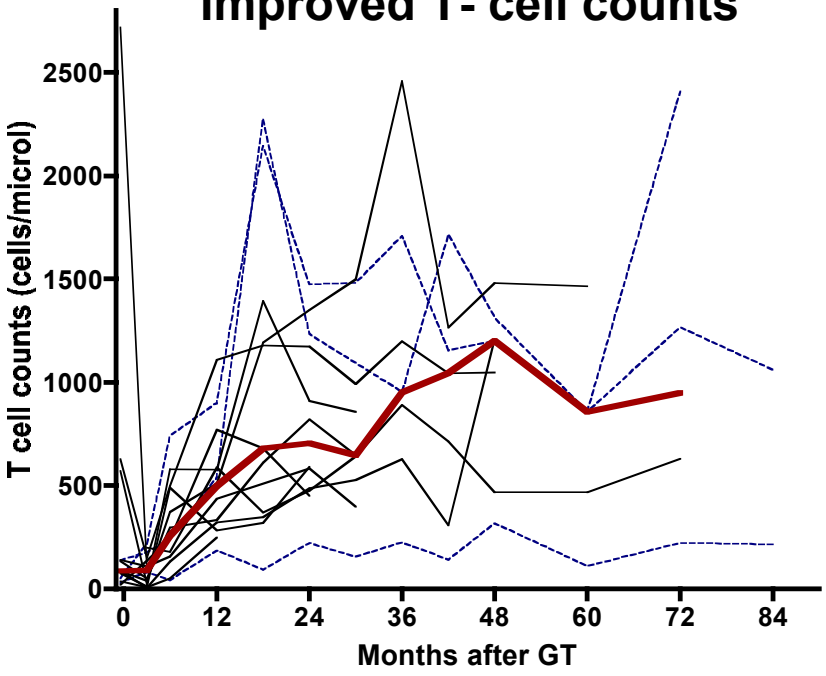
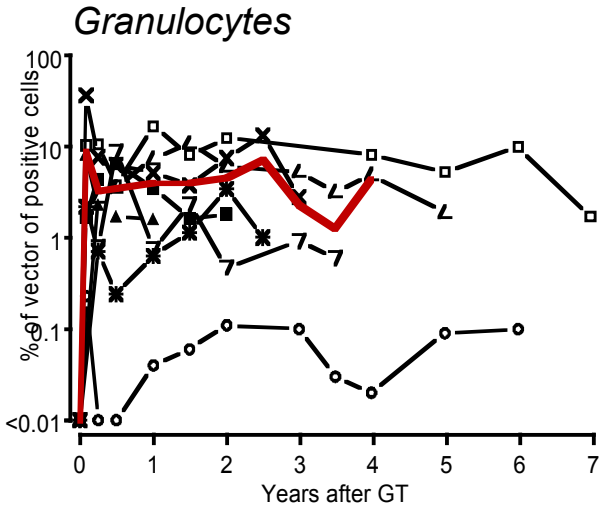
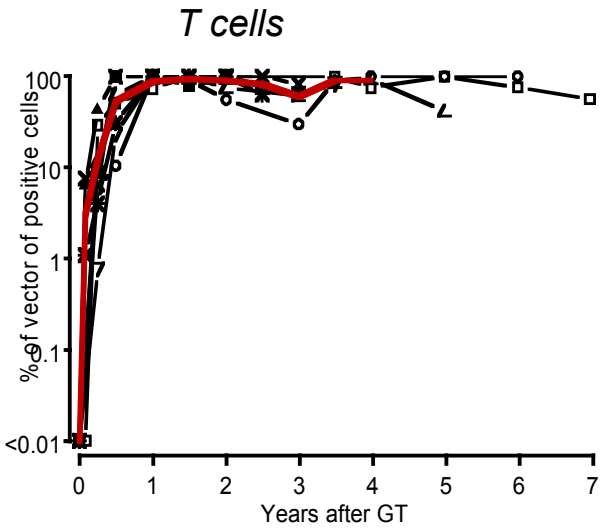
Improved T- cell counts



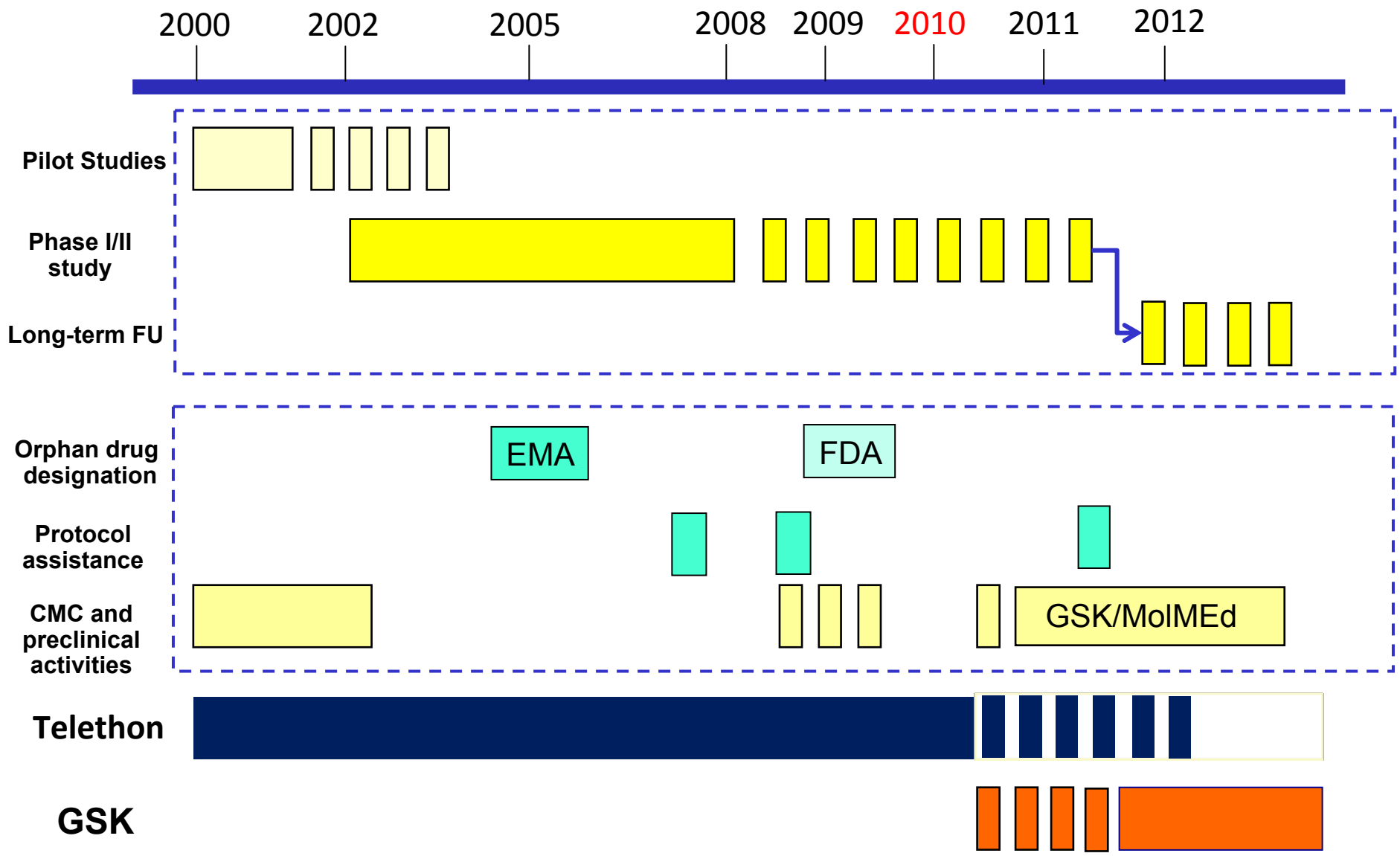
Multilineage stable engraftment





N=14 Aiuti et al. NEJM 2009 and unpublished data

Development of gene therapy for ADA-SCID



Academia and industry joining forces for developing ATMP

- Basic studies on disease mechanism
- State of the art research in gene transfer technology
- Expertise in non clinical models for safety and efficacy of ATMP
- Pediatric clinical trial center with experience in ATMP
- Knowledge of specific regulatory aspects in this field

- Manufacturing to industrial scale
- Development of commercial Quality Systems
- Patient Access
- Pharmacovigilance

Practical Challenges

- **Rare Populations**
- **Local vs Global regulations**
- **Duration of follow up**
  - **EU and FDA guidance**
  - **Pharmacovigilance and risk assessment / mitigation plans**
- **Safety Assessment**
  - **Bespoke complex studies with limited background information**
- **Manufacturing**
  - **Industry Leading Standards**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