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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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)

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<tbody>
<tr>
<td>Genetic studies</td>
<td>4%</td>
<td>5%</td>
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<td>Studies on mechanisms</td>
<td>9%</td>
<td>58%</td>
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<tr>
<td>Therapeutic approaches in vitro</td>
<td>2%</td>
<td>8%</td>
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<tr>
<td>Therapeutic approaches in vivo</td>
<td>4%</td>
<td>11%</td>
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<tr>
<td>Therapeutic clinical trials</td>
<td>3%</td>
<td>10%</td>
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<tr>
<td>Treatments</td>
<td>30% (2005-2009) vs. 9% (1991-1995)</td>
<td>29%</td>
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ADA-SCID
ADA-SCID

Immunodeficiency
Infections
Autoimmunity

Adenosine deaminase

HSC → PSC → CLP
NK cell → T cell → B cell

Organ alterations

dAdo, Ado, dAXP

Autosomal recessive
1:375,000
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
Day -4: Purification of BM CD34+ cells

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)

Day 0: Infusion

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

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

BM Harvest

ADA
Neo
MLV LTR
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

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Improved T-cell counts

N=14 Aiuti et al. NEJM 2009 and unpublished data
Development of gene therapy for ADA-SCID

- **Pilot Studies**
- **Phase I/II study**
- **Long-term FU**
- **Orphan drug designation**
- **Protocol assistance**
- **CMC and preclinical activities**
- **Telethon**
- **GSK**

Timeline:
- 2000
- 2002
- 2005
- 2008
- 2009
- 2010
- 2011
- 2012

Key Events:
- GSK
- EMA
- FDA
- GSK/MolMEd
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