Challenges of developing Cell and Gene Therapy products in Europe

Dr Sven Kili
VP & Head of Cell & Gene Therapy Development, Rare Disease Unit, GSK
The unmet need is overwhelming

Thirty percent of children with a rare disease will die before reaching their fifth birthday

“With some conditions that are common and maybe better understood, people can tell you what you are supposed to do, or set out 2 or 3 options, but basically it is not going to be too different – but with ADA SCID we found that every place seems to recommend something different… it leaves you feeling confused”
ADA SCID Carer

I can't have her suffer any more. I would need something that is 100%...and proven beyond reasonable doubt
MLD Carer

“It was not so much a case of isolating him within our house, it was a case of isolating our house from everyone else.... no-one was allowed into our house if they were unwell”
ADA SCID Carer

“She cannot do a whole lot, she cannot sit up, so we hold her – she loves to be held, so we hold her a lot. She has a little recliner we put her in, she lies on the couch by the window. In summer we take her outside a lot, we go for walks, we get in the pool”
MLD, Carer

“We did not know what was wrong and I was begging, but they kept switching us between doctors… I remember praying and begging doctors not to send us home. I knew something was wrong...my heart just knew. I think I felt gratitude when we got the diagnosis. Of course there is fear of not knowing about the condition, and we had no idea what was ahead of us.”
ADA SCID Carer
The opportunity to help people is great
Delivery of autologous gene therapy to the patient

Critical interface between clinician and manufacturer defines operating model more than logistics

Challenge of ‘Hub and Spoke’

Collection of hematopoietic stem cells (HSCs)

Stem cells isolation / purification

Gene-corrected cells administered to patient

QA release

Conditioning

Transduction

Vector
Virus modified to implant a functional transgene into the patient’s cells

Patient-facing activities
(perform by the clinician)

Non-patient-facing activities
(perform by the sponsor)
The strategic alliance with the Fondazione Telethon and Ospedale San Raffaele, acting through their joint Telethon Institute for Gene Therapy (TIGET) was established to research and develop autologous ex vivo gene therapy for rare genetic disorders.

GSK gene therapy program overview

<table>
<thead>
<tr>
<th>Indication</th>
<th>Stage</th>
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<tr>
<td>ADA deficiency (ADA-SCID)*</td>
<td>Approved</td>
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<tr>
<td>Metachromatic leukodystrophy (MLD)*</td>
<td>Ongoing trial in patients</td>
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<td>Wiskott-Aldrich Syndrome (WAS)*</td>
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<tr>
<td>Beta-thalassemia</td>
<td>Ongoing trial in patients</td>
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<td>Mucopolysaccharidosis type I (MPS type I)</td>
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<tr>
<td>Globoid-cell leukodystrophy (GLD)</td>
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</tr>
<tr>
<td>Chronic granulomatous disorder (CGD)</td>
<td>Pre-clinical</td>
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* Exclusively licensed to GSK
ADA SCID
Molecular and cellular pathology of ADA-SCID

- Absence of ADA leads to accumulation of deoxyadenosine triphosphate (dATP) and deoxyadenosine (dAdo)

  - dATP inhibits
    - ribonucleotide reductase (DNA repair)
    - terminal deoxynucleotidyl transferase (VDJ recombination)

  - dAdo inhibits
    - S-adenosylhomocysteine hydrolase (prevents lymphocyte activation)

- Profound lymphopenia
  - T cells
    - CD4 Helper, CD8, cytotoxic T cells
  - CD19 B-cells
  - CD16 NK-cells

ADA-SCID, adenosine deaminase severe combined immune deficiency; DNA, deoxyribonucleic acid
Autologous retroviral gene therapy for ADA-SCID: Clinical data overview

- 18 patient reported in MAA submission Q2 2014\(^1\):
  - All patients alive after a median follow-up of > 7 years (100% survival)
  - Soc (matched unrelated SCT) <70% survival.

- Immune reconstitution:
  - 15/18 patients free from the need for long-term enzyme replacement or rescue Stem Cell Therapy
  - Gradual and sustained improvement in T-cell counts

- Reduced rate of severe infections\(^2\):
  - Reduction from 1.1 event per person-year of observation before GT to 0.43 events per person-year of observation after GT (0-3 year data; n=12 pivotal study)

- Overall favourable safety and AE profile:
  - No deaths to date
  - No leukaemia
  - SAEs & AE’s consistent with the disease and HSCT intervention

\(^1\) including 12 patients treated in the pivotal study
\(^2\) severe infection = infection requiring hospitalization or prolonging hospitalization

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency (NEJM, 2009)
Paradigm shift is needed to establish cost effective and patient friendly long-term follow up

Traditional Long-Term Follow up has high per patient costs and is complex

Need new solutions that:

- Hold patient interest and engagement
- Maintain safety monitoring
- Drive down per patient costs
- Reduce clinical site overhead
- Improve patient retention
- Cater to changing needs of patients (e.g. moving countries, increased mobility)
- Increase capability to combine disease registries and product registries
- Meet Regulatory needs

How to engage patient families over 15+ year period?

How to motivate physicians to enter high amount of data for such small patient numbers?
Must advance opportunities to decrease cost of goods so to increase access to patients

Optimise Development
- Comparability - Academia → Industry
- Scale up – Manual → Auto
- Assay Development
- Manufacture location- global vs hub vs in hospital
- Logistics and transport – cross border
- Autologous vs Allo / ex-vivo vs in-vivo

Commercial Viability
- CoGs reduction – Global availability
- Cell Types
- Early Manufacturing development
- Biomarkers to support or predict efficacy
- Reproducibility & process
- Automation
- Manufacturing by design
Market Access Challenges
Challenges for Gene Therapies

- Cheaper, less efficient therapies?
- Small Patient numbers
- Individualised treatments
- High Cost of Production
- New Regulatory Pathways
- Uncertain re-imbursement pathways
- Challenging Health outcomes
- No proven long-term efficacy
- No clear Surrogate outcomes
- Very high development costs
- Uncertain reimbursement pathways
- Challenging health outcomes
- Very high development costs
- High cost of production
Value should always be defined around the customer, and in a well-functioning health care system, the creation of value for patients should determine the rewards for all other actors in the system.

Michael E. Porter, Ph.D.
Stakeholders often have conflicting Goals

Various goals: Healthcare stakeholders

- Patient centeredness
- Access to service
- Profitability
- High quality
- Cost containment
- Safety and convenience
- Satisfaction

Achieving high value for the patients must become the overarching goal, leading to improved performance and accountability of all stakeholders including payers, providers, patients and suppliers

Source: Personal communication Nazanin Mehin
Cell & Gene Therapies carry with them the potential promise of “intervention free survival”

How do we price these treatments? + How do we pay for these treatments? = To deliver valued medicines to patients
Significant challenges exist to find a balance

- Take medicines from the lab and bring access to patients the world over
- Ensure access to as many patients who may need it
- Ensure focused innovation so that science can continue to grow and achieve new frontiers
- Economic value for health systems
- Affordability of healthcare for patients and for the healthcare ecosystem
- Appropriate payments that match efficacy and safety
Infrastructure for access and reimbursement significantly lags payer and producer intent.
So why continue to focus on rare and ultra-rare diseases?
"IF SOMETHING IS IMPORTANT ENOUGH, EVEN IF THE ODDS ARE AGAINST YOU, YOU SHOULD STILL DO IT."

—ELON MUSK
Thank you