The Development of Gene & Cell Therapies in Rare Diseases

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Gene Therapy,
GSK
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• Currently, GSK 2696273 has received EMA approval and is marketed under the name “Strimvelis” for the treatment of ADA SCID in Europe only. **GSK 2696273 is not approved in the United States, or in any jurisdiction outside of Europe.**

• **GSK transferred its portfolio of gene therapies for rare diseases to Orchard Therapeutics in April 2018**
  • Orchard Therapeutics is a clinical-stage gene therapy company based in the United Kingdom and United States, dedicated to transforming the lives of patients with rare diseases through innovative gene therapies.

• Peter Mooney is currently a paid employee of GlaxoSmithKline working in the GSK Gene Therapy Division.
April 2018: GSK transfers rare disease gene therapy programs to Orchard Therapeutics

Programs acquired by Orchard

- Strimvelis: first approved autologous ex vivo gene therapy (ADA-SCID)
- 2 late-stage clinical programmes in ongoing registrational studies for MLD and WAS
- 1 clinical programme for beta thalassaemia
- Rights to exclusively license 3 preclinical programmes in MPS-I, X-CGD and GLD

ADA-SCID: adenosine deaminase severe combined immunodeficiency  X-CGD: X-linked chronic granulomatous disease  GLD: globoid leukodystrophy
MPS-III: Mucopolysaccharidosis type IIIA  MLD: metachromatic leukodystrophy  WAS: Wiskott-Aldrich Syndrome  MPS-I: Mucopolysaccharidosis type I
### Orchard Therapeutics at a glance

<table>
<thead>
<tr>
<th>Overview</th>
<th>• Global, fully integrated commercial and clinical-stage company</th>
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<tbody>
<tr>
<td>Mission</td>
<td>• Transform the lives of patients with rare diseases through innovative gene therapies</td>
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<tr>
<td>Technology</td>
<td>• Autologous <em>ex vivo</em> gene therapy</td>
</tr>
<tr>
<td>Pipeline</td>
<td>• 1 marketed product (Strimvelis) + 6 clinical programs + preclinical programs</td>
</tr>
</tbody>
</table>
| Academic partners | • Partnered with leading institutions in gene therapy:  
  • University College London, Great Ormond Street Hospital  
  • The University of Manchester and Central Manchester University Hospitals  
  • The University of California Los Angeles  
  • Boston Children’s Hospital  
  • Telethon Institute of Gene Therapy/Ospedale San Raffaele |
| Offices | • Offices in the UK and the US, including London, San Francisco and Boston |
Gene Therapy and Rare Diseases. Background to the Science.
Why focus on rare diseases?

- **High Unmet Medical Need**
  - While rare diseases occur in small numbers of patients, collectively the number of patients affected is large and the impact to the patient and caregivers is immense

- **Scientific Understanding**
  - Greater understanding of rare diseases leads to opportunities for more targeted therapies
  - Greater understanding of common diseases (pathways, mechanisms, biomarkers) may lead to subtypes that are classified as “rare”

- **Innovation**
  - New technologies (Gene & Cell Therapy, Oligonucleotides) offer promising approach to multiple rare diseases
  - New technologies may also have potential application in common diseases

- **New Direction**
  - Existing small molecule or biologics medicines generally used for common diseases may have application for rare diseases
The power of cell & gene therapy to treat diseases
Two broad types of gene therapy

Cell Therapy + Gene Therapy → New ways to treat disease

Using viral vectors to change gene expression
Gene Therapy – the highs and lows . . .

1990
French Anderson and colleagues at the NIH perform the first approved gene therapy trial in patients. Retroviral-mediated transfer of the gene encoding ADA into the T cells of two children with SCID

Nature Biotechnology 29, 121-128 (2011)

1996
Development of Lentivirus vectors

In Vivo Gene Delivery and Stable Transduction of Nondividing Cells by a Lentiviral Vector


A retroviral vector system based on the human immunodeficiency virus (HIV) was developed that, in contrast to the murine leukemia virus-based counterpart, transduced transgenetic sequences into host cells and maintained expression in the cell cycle, as well as into human primary mononuclear cells. Additionally, the HIV vector could mediate stable in vivo gene transfer into terminally differentiated neurons. The ability of HIV-based viral vectors to deliver genes in vivo into nondividing cells could increase the versatility of retroviral vectors in human gene therapy.

Science 272: 263, 1996

2002
Clinical benefit of hematopoietic stem cell retrovirus-mediated gene therapy for X-SCID


2009
Clinical benefit of hematopoietic stem cell retrovirus gene therapy for ADA SCID

DOI 10.1007/s12026-009-8107-8

2016
European Commission approves Strimvelis for ADA SCID, the first ex vivo gene therapy product worldwide

European Commission approves Glybera, the first approved gene therapy in Europe

2012
FDA and EMA refuse to accept application of two gene therapy products due to incompleteness of the file submission and due to insufficient efficacy respectively

Nature Biotechnology 29, 121-128 (2011)

2000
Patient dies in a gene therapy trial using an adenovirus vector

New York Times, Sept 29, 1999

2002
Five of Twenty children develop leukemia, one of whom died, after the activation of proto-oncogenes in the X-SCID study

Nature Biotechnology 29, 121-128 (2011)

2008
FDA approves Luxturna for rare Inherited Vision Loss. First directly administered gene therapy approved in the U.S
## Vector design

<table>
<thead>
<tr>
<th></th>
<th>Integrating Vectors</th>
<th>Non-Integrating Vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retrovirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td>Genome</td>
<td>ssDNA</td>
<td>ssDNA</td>
</tr>
<tr>
<td>Infection/Tropism</td>
<td>Dividing cells</td>
<td>Dividing cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dividing and nondividing cells</td>
</tr>
<tr>
<td>Genome integration</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Transgene expression</td>
<td>Long lasting</td>
<td>Long lasting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential long lasting</td>
</tr>
<tr>
<td>Packaging capacity</td>
<td>8 kb</td>
<td>8 kb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 kb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 kb</td>
</tr>
</tbody>
</table>

*ss* = single stranded; *ds* = double-stranded; *kb* = kilobases

Dramatic increase in the number of gene therapy clinical trials in recent years

899
Clinical trials underway worldwide by mid-year 2017

Ph. I: 284
Ph. II: 539
Ph. III: 76

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q2 2017

<table>
<thead>
<tr>
<th>Gene Therapy &amp; Gene-Modified Cell Therapy</th>
<th>Cell Therapy</th>
<th>Tissue Engineering</th>
</tr>
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<tbody>
<tr>
<td>Total: 504</td>
<td>Total: 586</td>
<td>Total: 24</td>
</tr>
<tr>
<td>Ph. I: 184</td>
<td>Ph. I: 174</td>
<td>Ph. I: 6</td>
</tr>
<tr>
<td>Ph. II: 286</td>
<td>Ph. II: 365</td>
<td>Ph. II: 14</td>
</tr>
<tr>
<td>Ph. III: 34</td>
<td>Ph. III: 47</td>
<td>Ph. III: 4</td>
</tr>
</tbody>
</table>
Potential benefits of gene therapy

• **Successful gene therapy offers the potential for**
  – Long-term, stable correction of the enzyme or protein defect
  – Leading to durable clinical benefits with a single, one-time administration\(^1,2\)

• **Ex vivo gene therapy:**
  – Because gene therapy is autologous, it does not rely on the availability of a suitable donor\(^3\)
  – Use of autologous cells avoids the risk of graft rejection and Graft vs Host Disease\(^3\)
  – Immunosuppressive prophylaxis or high-dose conditioning regimens usually not required: \(^3\)
    • In many cases only a non-myeloablative conditioning regimen is needed
  – Autologous treatment minimizes the risk of development of neutralizing antibodies against the enzyme\(^2,4\)

• **In vivo gene therapy:**
  – Ability to target specific organs or tissues
  – No conditioning regimen is necessary
  – In some cases, gene therapy may be delivered via standard i.v. infusion

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Potential risks of gene therapy

• **Insertion site:** Insertion at the wrong location within the DNA, may result in oncogenic or mutagenic events.
  – No mutagenic event observed in >200 patients treated with lentiviral vectors

• **Uptake by reproductive cells:** Unintentional viral uptake by the patient’s reproductive cells and the possibility of changes that may be passed on if a patient has children after treatment.

• **Overexpression of the target protein:** Over production of the missing/target protein could be harmful.

• **Immune reaction:** The viral vector could cause an immune reaction.

• **Viral transmission:** The virus could be transmitted from the patient to other individuals or into the environment.

Source: Gene Therapy. Viewed on 10th Oct, 17
Developing a Gene Therapy from early phase through to Market Authorisation. Using our experience as a case study.
Collaboration between GSK / Telethon / OSR

Pre-clinical

Telethon Institute for Gene Therapy (SR-TIGET) responsible for advancing all programs to Proof of Concept

clinical

Hospital San Raffaele runs clinical studies with GSK design and operational support

File and Launch

Hospital San Raffaele treats patients after EMA approval

Commercial Product

After licensing, GSK is responsible for global Regulatory, Manufacture and Commercial activity

ZINC RD/SVE/0005/18  25th April 2018
Gene Therapy for ADA SCID: Challenges - Clinical evidence

- Life Threatening Disease
- Irreversible Effects
- Gene Therapy for ADA SCID for the first time
- Rarity of ADA SCID
- No dose range study
- Safety Risks associated with integrating vectors

- No placebo
- No active-controlled studies
- Restricted to patients who had exhausted other options
- Comparison with natural history data
- Marked inter-patient variability provided data to support dose recommendations
- No cases of malignancy
- Retroviral insertion site analysis
Regulatory Challenges: Scientific advice and non-clinical assessments – No prior precedents

- Limited Prior Examples
- Lack of extensive non-clinical history
- Most non-clinical studies not feasible
- Non-clinical test items differed

- Required extensive discussions with regulators
- Non-clinical test items (e.g. cell type, cell source) differed to the clinical study and/or to the commercial product
- No predictive animal models
- Non clinical risk assessment was based on clinical study results or literature review
Challenges for Developing Cell & Gene Therapies

- Small Patient numbers
- Individualised treatments
- High development costs
- High Cost of Production
- New Regulatory Pathways
- Uncertain reimbursement pathways
- Challenging Health outcomes
- No proven long-term efficacy
- No clear Surrogate outcomes

ZINC RD/SVE/0005/18  25th April 2018
Regulatory disharmony is more evident with CGT than other platforms

Congress passes 21st Century Cures Act with billions for new research, treatments

Mixed in with:

- Variability of starting material vs standardization
- Consistency/presence of standards
- Control of manufacturing process
- Clinical qualifications to treat patients

How well is ICH really working?

Regulatory Approval ≠ Reimbursement

ICH: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ATMP regulatory pathway and challenges

• Many issues considered for the first time for Strimvelis
  – Principles of the active ingredient
  – How to define the dose and strength
  – Quality system and quality assurance
  – Environmental Risk Assessment for a GMO
  – Product release criteria
  – Comparability
  – Retroviral site insertion analysis
  – ATMP RMP

• Long term follow up – 50 patients for at least 15 years

• Constructive dialogue throughout

• Early and frequent regulatory engagement encouraged

GMO: Genetically Modified Organism; ATMP: Advanced Therapy Medicinal Product; RMP: Risk Minimisation Programme
Other Challenges and Considerations post MA
Beyond the science, key challenges remain . . .

Manufacturing and Supply Chain

Regulatory Pathways

Focus on the Patient

Patient Identification (e.g. Newborn screening)

New Pathways for Reimbursement
Reimbursement of innovative gene therapies for rare disorders: positive drivers

• Single interventions with sustained benefits

• Potential for significant clinical benefits:
  – Survival benefits
  – Significant morbidity benefits
  – Safety benefits, e.g. lack of risk of graft rejection or graft-versus-host disease
  – No requirement for immunosuppressive regimen to manage alloreactive complications associated with allogeneic hematopoietic stem cell transplants

• Potential for cost-offsets:
  – Saving of chronic ERT costs
  – Savings related to reduced morbidity vs. allogeneic HSCTs

• Manageable budget impact for Payors

• ERT: Enzyme Replacement Therapy; HSCT: Haemopoetic Stem Cell Transplantation
Post MA Challenges

• RMP commitments
  – Healthcare Professional Materials
  – Patient and Family Materials
  – Informed Consent
  – Long term Follow Up Registry

• RIS analysis

• Moving the delivery paradigm
  – from single centre to multi centre without making it too complex

• Health Technology Appraisals

• Finding the patient!
  – Many diseases have no validated new-born screening or diagnostic test
  – Even if there is a validated test many countries still have not adopted them
When the patient and parent or caregiver arrive at San Raffaele Hospital:

- A specialised nurse, plus a translator if need be, will be available to offer guidance and emotional support
- Assistance will also be provided with the logistical and practical aspects of treatment
Providing an ex-vivo cryopreserved gene therapy requires co-ordination of logistics, chain of custody and clear responsibilities and accountabilities between all parties.
Infrastructure for access and reimbursement significantly lags payer willingness to fund innovation.

Lack of Infrastructure + One-time Treatments + Small populations ≠ Clear routes for reimbursement
Health Technology Appraisals

- No clear unified approach by Health Technology Agencies for these new and innovative but potentially high cost therapies

- Strimvelis was the first gene therapy to receive a positive recommendation by NICE (Feb 2018)\(^1\)
  - Assessed as part of NICE’s Highly Specialised Technologies programme that looks at treatments for very rare diseases that are commissioned nationally by NHS England.
  - “The cost of Strimvelis is high and there are some uncertainties in the evidence. However, Strimvelis is likely to provide important benefits for people with ADA–SCID, at a cost that provides value for money in the context of a highly specialised service.”\(^1\)

- A positive NICE decision should help with gaining reimbursement in other countries.
  - Many countries now share HTAs as a way of reducing duplication and effort.

1. [www.nice.org.uk/guidance/hst7](http://www.nice.org.uk/guidance/hst7)
Is Gene Therapy starting to deliver on its promise?
ADA – SCID.
**Strimvelis Clinical Results**

**Increased T cell count**

**Reduced Severe Infections**

Severe infections were defined as those leading to hospitalization or prolonging hospitalization.

Strimvelis is a collaboration with Telethon and Ospedale San Raffaele

Cicalesse et al. 2016 Blood 7, 45-53
GSK2696273 safety profile

- All identified adverse events, apart from those potentially related to busulfan, are considered to be related to immune reconstitution because of their nature and timing\(^1\)
- Autoimmune reactions, positive antinuclear antibody, and antithyroid antibody tests are thought to be related to immune reconstitution:\(^1\)
  - These occurred mostly during the 3-month to 3-year follow-up period and resolved, with the exception of hypothyroidism and positive antinuclear antibody tests
- Allergy-related adverse reactions and positive blood IgE and eosinophilia tests were also reported mostly during the 3-month to 3-year follow-up\(^1\)
- The most common adverse event was pyrexia,\(^1\) and no event led to patient withdrawal\(^1,2\)
- Because gene therapy is autologous, it is considered unlikely to provoke an immunogenic response:\(^1\)
  - No immunogenicity testing has been carried out with GSK2696273

Overall, the GSK2696273 safety profile was in line with that expected in a paediatric population who had received busulfan conditioning and were undergoing immune reconstitution following autologous gene therapy\(^1\)

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1. Strimvelis Summary of Product Characteristics. 2017
2. https://www.gsk-clinicalstudyregister.com/study/115611#ps
The long-term effects of Strimvelis are unknown and patients should be carefully monitored.

**Strimvelis Registry:** 50 patients will be monitored long term with annual visits (minimum) for the first 11 years and then at 13- and 15-years post-treatment with Strimvelis\(^1\). Registry will close when the 50\(^{th}\) patient reaches 15 year Follow Up.

To date, no cases of leukaemic transformation or myelodysplasia have been reported following treatment with Strimvelis\(^1\)

Patients treated with Strimvelis should not donate blood, organs, tissues, and cells for transplantation at any time in the future\(^1\)

To date there is a 100% Overall and 83% Event Free Survival for Strimvelis treated Patients

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Gene Therapy: Ongoing Rare Disease Programmes also showing encouraging signs of delivering on the promise\(^1\)

- Not a comprehensive list!
- **AAVs**
  - Haemophilia A & B: Spark, Sangamo, Biomarin
  - Mucopolysaccharidosis type II: Sangamo
  - Inherited retinal dystrophy: Spark, MeiraGTx, Uni of Florida
- **Ex-Vivo GT**
  - ADA SCID: TIGET/GSK, Orchard Therapeutics
  - WAS: TIGET/GSK, Orchard Therapeutics
  - MLD: TIGET/GSK, Orchard Therapeutics
  - X-CGD: UCLA/NIH/BCH/GOSH, Orchard Therapeutics
  - Adrenoleukodystrophy: Bluebird Bio, St. Vincent de Paul, Paris
  - B-Thalassaemia: Bluebird Bio, TIGET/GSK, Orchard Therapeutics
  - Sickle cell anaemia: Bluebird Bio, UCLA/California Institute of Regenerative Medicine

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1. Dunbar et al., Science 2018, 359, eaan4672
Conclusions

• Development of Gene Therapies has had its highs and lows

• Being the first has meant also trailblazing the Regulatory Pathways
  – Challenges do not stop at approval
  – RMP, Registries etc

• Managing the delivery and supply chain will be critical to the success of GT
  – Local treatment centres giving easier patient access
  – Long shelf life products

• We are now seeing sustained durable clinical effects in a number of rare diseases

• Gene Therapy may at long last be starting to deliver on its promise for patients and their families
Thank You