Gene and cell therapies

Tim Mustill
Principal Consultant

MedComms Networking Brunch Club
Oct 4, 2017
Agenda

• Gene and cell therapy primer
• Development pitfalls and therapeutic promise
• Challenges and opportunities for growth
• How can medcomms help?
Key questions

• Why is this such an exciting and dynamic field?
• What’s taking so long?
• Why are advanced therapies so different?
• (How) can medcomms help?
What Happens When Underperforming Big Ideas in Research Become Entrenched?

A new wave of gene therapies ready to hit US shores
On a more positive note
Why is it interesting and exciting?

Figure 1. North America CAR T Cell Therapy Market Size and Forecast, US$ Million and Y-o-Y Growth (%)
Simple concept!

Genetically determined or mediated dysfunction

- Cell with non-functioning gene

- Functioning gene

- Cell functioning normally

Cured or QOL improvement
Breaking out the 3 step process

1. Identify the gene defect
2. Find vector or delivery method
3. Insert to target cell
   - Create a replacement sequence
4. Express gene
   - Transfect/insert to genome
5. Insert to body
6. Cured or QOL improvement

Genetically determined or mediated dysfunction
Main strategies

A. Gene replacement
- mutant gene
- functional gene
- replacement
- disease
- correction

B. Gene addition
- genetic factors and/or environmental factors
- therapeutic gene
- addition
- disease
- alleviation

C. Gene knockdown
- mutant gene
- gene silencer
- knockdown
- disease
- correction

D. Gene editing
- mutant gene
- gene corrector
- editing
- disease
- correction
Gene expression cassette

Not just a few base pairs!
Insert to body step

**In vivo**

1. Direct Delivery
   - Therapeutic transgene
   - The therapeutic transgene is packaged into a delivery vehicle such as a virus
   - ... and injected into the patient
   - Target organ (e.g., liver)

**Ex vivo**

1. Cell-based Delivery
   - Therapeutic transgene
   - The therapeutic transgene is introduced into a delivery cell such as a stem cell that is often derived from the patient
   - ... and readministered to the patient
   - Genetically modified cells (e.g., stem cells) are multiplied in the laboratory
Even seven steps is a simplification

Each step has many options and creates many challenges.
Advanced therapies really need new paradigm – especially when it comes to commercialisation models.
Agenda

• Gene and cell therapy primer
• Development pitfalls and therapeutic promise
• Challenges and opportunities for growth
• How can medcomms help?
Pitfalls and setbacks

1999

The Biotech Death of Jesse Gelsinger

by SHERRI GAY STOLBERG NOV. 28, 1999

2006

Letter

Published online: 12 February 2006 | doi:10.1038/nm1358

There is a Corrigendum (May 2006) associated with this Letter.

Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response

2008

Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1

2017

Unique withdraws €1m drug Glybera from market
But…

Bluebird Bio’s gene therapy for blood disorders yields some impressive results — but also raises questions

First gene therapy could hit the market in January
Indications Addressed by Gene Therapy Clinical Trials

- Cancer diseases 64.6% (n=1590)
- Monogenic diseases 10.5% (n=259)
- Infectious diseases 7.4% (n=182)
- Cardiovascular diseases 7.4% (n=178)
- Neurological diseases 1.8% (n=45)
- Ocular diseases 1.4% (n=34)
- Inflammatory diseases 0.6% (n=14)
- Other diseases 2.3% (n=56)
- Gene marking 2% (n=50)
- Healthy volunteers 2.2% (n=54)

The Journal of Gene Medicine, © 2017 John Wiley and Sons Ltd

www.wiley.co.uk/genmed/clinical
Number of GT drugs by TA

Source: Pharmaprojects, 2016
Agenda

• Gene and cell therapy primer
• Development pitfalls and therapeutic promise
• Challenges and opportunities for growth
• How can medcomms help?
## Challenges

<table>
<thead>
<tr>
<th>Technical</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity of vectors</td>
<td>Manufacturing scalability and supply chain</td>
</tr>
<tr>
<td>Off-target effects</td>
<td>Regulatory needs, outcomes and measures</td>
</tr>
<tr>
<td>Non-vector delivery methods</td>
<td>Evidence generation</td>
</tr>
<tr>
<td>Base pairing restrictions (for editing)</td>
<td>Ethical dilemmas</td>
</tr>
<tr>
<td>Sequence size restrictions (i.e. 5Kb in AAV)</td>
<td>Value assessment and pricing modelling</td>
</tr>
<tr>
<td>Scale up and scale out</td>
<td>Affordability and equity</td>
</tr>
<tr>
<td></td>
<td>Supply chain</td>
</tr>
</tbody>
</table>
Lentiviral vector manufacture

Biggest challenge – paying for it!

Only with collaborative efforts can the opportunities presented by GT be realised while addressing the significant challenges related to:
- Evidence generation
- Value assessment
- Affordability

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

GENE THERAPY:
Understanding the Science, Assessing the Evidence, and Paying for Value
A Report from the 2016 ICER Membership Policy Summit
March 2017
## Developer payer conversation

<table>
<thead>
<tr>
<th>Agree</th>
<th>patient centred outcomes and drivers of value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborate</td>
<td>on robustness of registration studies (often not RCT)</td>
</tr>
<tr>
<td>Partner</td>
<td>on post-approval studies, PVG, RWE generation etc.</td>
</tr>
<tr>
<td>Match</td>
<td>trial eligibility criteria to payment coverage measures</td>
</tr>
<tr>
<td>Agree</td>
<td>criteria for designation of COE (therapy delivery centres)</td>
</tr>
<tr>
<td>Explore</td>
<td>potential patient population size</td>
</tr>
<tr>
<td>Determine</td>
<td>place for the new therapy in the care pathway</td>
</tr>
</tbody>
</table>

Opportunities – across sector

• Pre-competitive collaboration (e.g. scalability issues, vector agnostic development)
• Focused technical support to tackle specific technical issues
• Brokerage of the payer and developer dialogue
• Raise awareness of broader societal questions and issues with the specialist developers
• Leverage multi-therapy area patient groups like Genetic Alliance and other rare disease advocates
• Improved patient engagement across the sector
Agenda

• Gene and cell therapy primer
• Development pitfalls and therapeutic promise
• Challenges and opportunities for growth

• (How) can medcomms help?
Opportunities for medcomms

- Pre-competitive collaboration awareness and support (novel client partnerships)
- Be sympathetic to the new value chain complexities
- Help to brokerage the payer and developer dialogue – with creative ideas
- Encourage multi-disciplinary advisory boards
- Publications will be wider and potentially more varied
- Learn from rare diseases but understand larger scale TA’s will be much more challenging
- Support post-approval data generation and communication
Embrace wide collaboration

Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access

DAVIN DRISCOLL, STEPHANIE FARHIA, PANOS KEFALAS, RICHARD T. MAZARZ

Key Words: Acute myelogenous leukaemia • Autologous stem cell transplantation • Hematopoietic stem cell transplantation • Cellular therapy

ABSTRACT

Cellular therapies and other regenerative medicines are emerging as potentially transformative additions to modern medicine, but likely at a staggering financial cost. Public health care systems’ budgets are already strained by growing and aging populations, and many private insured’s budgets are equally stretched. The current systems that most payers employ to manage their cash flow are not structured to absorb a sudden onslaught of very expensive prescriptions for a large portion of their covered population. Despite this, developers of new regenerative medicines tend to focus on the demands of regulators, not payers, in order to be compliant throughout the clinical trials phases, and to develop a product that ultimately will be approvable. It is not advisable to assume that an approved product will automatically become a reimbursed product, as examples from current practice in hematopoietic stem cell transplantation in the U.S. demonstrate; similarly, in Europe numerous Advanced-therapy Medicinal Products achieved market authorisation but failed to secure reimbursement (e.g., Glybera, Provenge, ChondroCelact, MACI). There are however stra-
Ideas for novel payment

How to cover Novartis’ $475K CAR-T drug Kymriah? A ‘new payment model’ is the only way, Express Scripts says

by Arlene Weintraub | Sep 22, 2017 11:30am
ICER Gene therapy report – Dec 2016

Progresses towards safe and efficient gene therapy vectors

Gene Therapy: progress and predictions
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707739/

Cell and Gene therapy Catapult papers
https://ct.catapult.org.uk/resources/publications/scientific-publications/all

Gene Therapies for Cancer: Strategies, Challenges and Successes
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4363073/

STATE-OF-THE-ART HUMAN GENE THERAPY: PART II. GENE THERAPY STRATEGIES AND APPLICATIONS
Thank you

Tim.Mustill@astrocyte.co.uk