Advancing Manufacturing for Advanced Therapies

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Center For Biologics Evaluation and Research, FDA
CASSS Cell & Gene Therapy Symposium
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Overview

Cell and gene therapy products hold the promise of transforming the treatment of many diseases

• Where have we come?
• Where are we going?
• How will we get there?
Relative Product Complexity

One subunit of a protein

- L-tryptophan
- Small Molecule Drug
- $10^2$ Atoms

Protein composed of about 1100 subunits

- IgG antibody molecule
- Protein Biologic
- $10^5$ Atoms

Cell composed of about $3.6 \times 10^6$ proteins

- Mesenchymal stem cell
- Cellular Biologic
- $10^{14}$ Atoms
Examples of Cell and Gene Therapies

- Bioengineered skin
- Bioengineered blood vessel
- Bioengineered bladder
- Chimeric antigen receptor-T cell (in red) attacking a cancer cell (in yellow)
Using molecular genetics, novel protein receptors can be created that combine features of different proteins into one.

This allows one to both target and activate T cells to eliminate a cancerous or undesirable cell type.
Overview of CAR-T Cell Therapy

Patient may receive pre-conditioning chemotherapy prior to infusion. Sometimes cytokine support (IL-2) post-infusion.

Apheresis

Product

T cell activation and transduction with gene transfer vector

Expand in culture CD3/CD28 beads + IL-2 / IL-15

Dose formulation

Product testing

Gene modified T cell Infusion
Potential Advantages to Use of Genetically-Modified Cellular Therapies

• Appropriate methods can be used to address the issue of location of genomic integration
  – Ability to select appropriately transduced cells for administration to recipients
  – Use of newer technologies such as CRISPR possible
  – Control of effector function is possible, if necessary, through use of various approaches

• Possibility to provide therapeutic benefit with an extended duration of effect
Potential Challenges to Use of Genetically-Modified Cellular Therapies

• Process must be developed to consistently manufacture and characterize cells
• Logistics of manufacturing for autologous cells can be challenging
  – Though an allogeneic cell line (one product) may be preferable, there are developmental challenges
• Administration of therapies may be associated with various short and longer term side effects
Two Cell-Based Gene Therapies Approved in 2017

• **Tisagenlecleucel (KYMRIAH):** indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

• **Axicabtagene ciloleucel (YESCARTA):** indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
One Directly-Administered Gene Therapy Approved in 2017

- **Voretigene neparvovec-rzyl (LUXTURNA):** indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the attending physician(s).
  - Novel endpoint used for approval developed by sponsor with input from FDA
Multi-Luminance Mobility Test

Negotiating a path with obstacles at different light levels

Scoring based on time and accuracy

<table>
<thead>
<tr>
<th>Illuminance (lux)</th>
<th>Luminance (cd/m²)</th>
<th>Corresponding environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.32 mesopic vision</td>
<td>Moonless summer night; or indoor nightlight</td>
</tr>
<tr>
<td>4</td>
<td>1.3 mesopic vision</td>
<td>Cloudless summer night with half moon; or outdoor parking lot at night</td>
</tr>
<tr>
<td>10</td>
<td>3.2 mesopic vision</td>
<td>60 min after sunset in a city setting; or a bus stop at night</td>
</tr>
<tr>
<td>50</td>
<td>15.9 photopic vision</td>
<td>Outdoor train station at night; or inside of illuminated office building stairwell</td>
</tr>
<tr>
<td>125†</td>
<td>39.8 photopic vision</td>
<td>30 min before cloudless sunrise; or interior of shopping mall, train or bus at night</td>
</tr>
<tr>
<td>250‡</td>
<td>79.6 photopic vision</td>
<td>Interior of elevator, library or office hallway</td>
</tr>
<tr>
<td>400</td>
<td>127.3 photopic vision</td>
<td>Office environment; or food court</td>
</tr>
</tbody>
</table>

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Yearly submissions to the Center for Biologics Evaluation and Research
Regenerative Medicine Advanced Therapy Designation (RMAT)

• To expedite the development and review of regenerative medicine advanced therapies
  – Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
  – Genetically modified cell therapies and gene therapies producing durable effects included
Regenerative Medicine Advanced Therapy Designation (RMAT)

- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval
- Expanded range of options for fulfilling post approval requirements of accelerated approval
RMAT Designations Granted

- 24 products granted designation
- 15/24 products have Orphan Product designation
- Most are cellular therapy products or cell-based gene therapy products

Data as of June 30, 2018
Issues in the Manufacture of Cell and Gene Therapies

• Challenges of developing and validating manufacturing processes for autologous cell therapies

• Need for standards for the reproducible production of regenerative medicine products such as cellular therapies
Issues in the Manufacture of Cell and Gene Therapies

• Lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors is limiting clinical development
• Process of production in current cell lines is still not able to meet demand despite some improvement over past few years
Solutions on the Horizon for Cell and Gene Therapy Manufacturing

- Partially automated closed manufacturing systems
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Solutions on the Horizon for Cell and Gene Therapy Manufacturing

- Modular manufacturing facilities
  - Scalable pre-built biotechnology

- Continuous manufacturing applied to biologics
Improving the Manufacture of Cell and Gene Therapies

- CBER is working with NIH and National Institute of Standards and Technology (NIST) and others to facilitate the development of standards for use in regenerative medicine
- Plans for CBER laboratory research programs and collaborations with academic and public private partners to advance field
  - Improved cell lines for vector production
- FDA guidance suite to be issued in FY2018
Simplifying Agency Interactions for Gene Therapy Products

• Gene therapy protocol sponsors interact with both the Recombinant DNA Advisory Committee (RAC) at NIH and the FDA for approval and reporting of adverse events

• Given recent advances in gene therapy, FDA and NIH reviewed the utility of the existing framework

• FDA and NIH are collaborating on a proposal to reduce regulatory burden while enhancing the value added provided by the RAC
INTERACT Program

INitial Targeted Engagement for Regulatory Advice on CBER producTs

• To further encourage interaction with sponsors and replace the pre-pre-IND meeting process across the Center
• Anticipate ultimately having an external-facing web page describing the program in detail
The Path Toward Progress

- Keep pace with advancing technology
- Refine regulatory framework as necessary
- Overcome limitations in manufacturing
- Facilitate optimal product development