Learning Objectives

• General understanding of gene therapy (GT) and GT products

• Grasping important principles on efficient clinical development of GT products
Outline

• Overview of GT and GT Products
• Efficient Clinical Development of GT Products
• Regulatory requirements and Flexibility
Human Gene Therapy (GT)

Seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use

**FDA draft Guidance:** Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2018)
Gene Therapy Product

All products that mediate their effects by
  • transcription or translation of transferred genetic material or
  • specifically altering host (human) genetic sequences.

*FDA draft Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2018)*
Examples of GT Product

• Plasmids
• Genetically modified microorganisms (e.g., viruses, bacteria)
• Products incorporating genome editing
• *Ex vivo* genetically modified human cells
Gene Therapy
Ex vivo and In vivo Administration

1. Extract cells (BM, PBMCs)

2. Use vectors to genetically modify cells

3. Introduce modified cells back to patient

**ex vivo**

**in vivo**

Direct delivery to patient using viral or non-viral vector

- DNA
- RNA
- Lentivirus
- AAV
- Lipid nanoparticle
First Gene Therapy Trial in US: 1990
- Retroviral-mediated transfer of ADA gene into autologous T cells
- Two girls with ADA-deficient SCID received ~10 treatments for two years
- 10 years later: % of T cells carrying and expressing retroviral gene
  - 1st patient: 20%
  - 2nd patient: <0.1%

Setback: Death of Mr. Gelsinger: 1999
- 18 years old with OTC deficiency
- Using a virus to deliver the correct gene
- Died 4 days later
- FDA investigation:
  - Should not have been treated due to high ammonia level
  - Did not disclose the death of a monkey in informed consent

ADA: adenosine deaminase
SCID: severe combined immune deficiency
OTC: ornithine transcarbamylase
All IND Submissions with GT Products (CY 1990-2018)

IND: Investigational New Drug application
Gene Therapies

IND Applications

~70%

Rare

Common

www.fda.gov
FDA-Approved GT Products

• Tisagenlecleucel (Kymriah): 2017
  – 1st cell-based gene therapy approved in the US
  – Autologous human T cells genetically modified with a lentiviral vector encoding a chimeric antigen receptor (CAR) targeting human CD19
  – Refractory childhood lymphoblastic B cell leukemia*

• Axicabtagene ciloleucel (Yescarta): 2017
  – Autologous human T cells transduced with a retroviral vector encoding a CAR targeting human CD19.
  – Refractory adult patients with relapsed or refractory large B cell lymphoma

* Approved for treatment of large B cell lymphoma in 2018
FDA-Approved GT Products (cont.)

• Voretigene neparvovec-rzyl (Luxturna)
  – 1st FDA-approved directly administered gene therapy targeting a genetic disease due to single gene mutation
  – AAV2-based GT expressing the RPE65 gene, encoding human retinal pigment epithelium 65 kDa protein
  – Bi-allelic RPE65 mutation-associated retinal dystrophy

• Onasemnogene abeparvovec-xioi (Zolgensma)
  – 1st FDA-approved systemically administered gene therapy
  – AAV9-based GT expressing the gene encoding the survival motor neuron (SMN) protein
  – Spinal muscular atrophy with bi-allelic mutations in the SMN1 gene (< 2 years of age)
CLINICAL DEVELOPMENT OF GENE THERAPY PRODUCTS
Development of GT Products

Cellular and gene therapy Guidance documents

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
Clinical Development for GT Products

• Similar fundamental considerations for clinical development programs: GT products and other biological products

• Clinical development programs for different diseases may vary substantially

• We recommend sponsors discuss their clinical development plans with FDA early in their product development
Early-Phase Trials: Objectives

• Safety

• Activity and preliminary clinical efficacy

• Try to hit a home run!
  o Design first-in-human (FIH) clinical trial to provide evidence of effectiveness
  o Resolve manufacturing issues, as much as possible, before FIH clinical trial

*FDA Guidance: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)*
Early-Phase Trials: Design

• **Randomized** controlled trials, even in FIH studies

• **Concurrent control** with appropriate blinding, whenever feasible
Early-Phase Trials: Study Population

- Healthy volunteers: Unfavorable benefit/risk profile
- Patients with more severe vs. less severe condition
- Adults vs. pediatric patients
Early-Phase Trials: Dose Exploration

- **Substantial** dose exploration to identify safe and effective dose(s)
- May be continued throughout product development
Early-Phase Trials: Treatment

• Operator training
• Staggered administration
• Limited number of study sites, particularly for FIH studies
Early Phase Trials: Safety Monitoring

• Routine general safety evaluations - standard clinical measurements
  - e.g., physical exams, routine labs.,

• Safety assessments to monitor for adverse events that can be anticipated with a GT product
  - e.g., immune responses

• Safety assessments informed by *a priori* safety concerns
Safety Monitoring Duration

- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products

- Long term follow-up may be required for certain GT products
  - e.g., 15 years of follow-up for integrating viral vector-based products
  - Clinical development can move on while long term follow-up ongoing

*FDA draft Guidance: Long Term Follow-up After Administration of Human Gene Therapy Products (2018)*
REGULATORY REQUIREMENTS AND FLEXIBILITY
Regulatory Requirements

• Approval of drugs and biologics must be based on **substantial evidence of effectiveness** and evidence of safety.

• Evidence of effectiveness should be obtained from **adequate and well-controlled studies**.

• Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide **flexibility** in applying regulatory standards (21 CFR 314.105).
Evidence of Effectiveness – Rare Disease

• No specific minimum number of patients to be studied to establish effectiveness and safety of a treatment for any rare disease.

• The number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration
  o the persuasiveness of the data (e.g., comprehensiveness and quality)
  o the nature of the benefit provided (or expected in the case of surrogate endpoints)
  o the length of treatment or exposure
  o the patient population that would be treated after marketing approval
  o the concern for potential of harm from the treatment
Flexible and Feasible Approaches

Adaptive Study Designs

Novel Endpoints

Novel Statistical Approaches

Nontraditional Clinical Development Programs

Expedited Development & Review Programs

Fast Track Designation

Breakthrough Therapy

Priority Review

Accelerated Approval

Regenerative Medicine Advanced Therapy Designation (RMAT)

Biomarkers

Source: Julienne Vaillancourt
www.fda.gov
Voretigene Neparvovec (LUXTURNA)

• First in class adeno-associated virus vector-based gene therapy via subretinal injection
• Approved by OTAT/CBER on Dec. 19, 2017
• Applicant: Spark Therapeutics Inc.
• Indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy
Biallelic RPE65 Mutation-Associated Retinal Dystrophy

• A rare disease, 1000-2000 patients in US

• Various clinical manifestations:
  - Blindness in early infancy
  - Night-blindness and progressive visual field loss
  - Complete blindness in all patients
  - Impaired activity of daily living

• No approved pharmacological treatment
MLMT: Evaluate Mobility at Different Light Level

<table>
<thead>
<tr>
<th>Light Levels</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 lux</td>
<td>Indoor nightlight; Moonless summer night</td>
</tr>
<tr>
<td>4 lux</td>
<td>Cloudless night with half moon; Parking lot at night</td>
</tr>
<tr>
<td>10 lux</td>
<td>1 hour after sunset in city; Bus stop at night</td>
</tr>
<tr>
<td>50 lux</td>
<td>Outdoor train station at night; Inside of lighted stairwell</td>
</tr>
<tr>
<td>125 lux</td>
<td>30 minutes before sunrise; Interior of train / bus at night</td>
</tr>
<tr>
<td>250 lux</td>
<td>Interior of elevator or office hallway</td>
</tr>
<tr>
<td>400 lux</td>
<td>Office environment or food court</td>
</tr>
</tbody>
</table>

Images presented for illustrative purposes only
Light meter: National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

Source: Spark Therapeutics
MLMT: 12 Different Course Layouts

MLMT: multi-luminance mobility test
Recommendations

• Collaborate: scientists, clinicians, patients, advocacy groups, industry, regulatory bodies

• Plan ahead
  – An early phase trial of rare disorders may provide evidence of effectiveness and safety

• Concurrent controlled, randomized early phase trial

• Early communications with FDA
Challenging Question

True or False:

A concurrently controlled, randomized early phase trial is not recommended because the objective of such a trial is to assess safety.
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  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm

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