Clinical Development of Gene Therapy Products

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Clinical Investigator Training Course
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Office of Tissues and Advanced Therapies
FDA/CBER

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FDA draft Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2018)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FDA draft Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2018)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

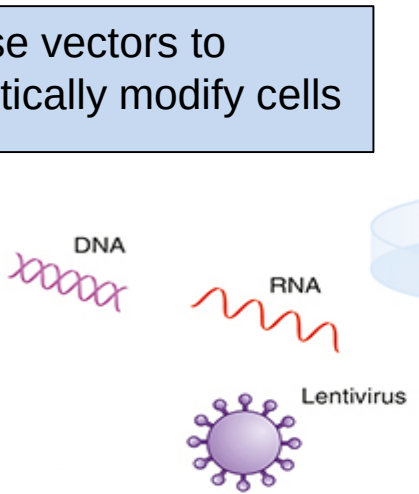
Gene Therapy
Ex vivo and In vivo Administration

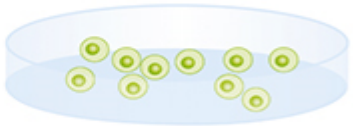
ex vivo

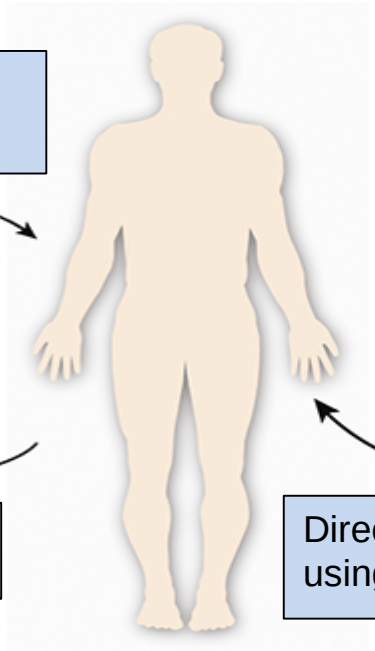
in vivo

2. Use vectors to genetically modify cells

3. Introduce modified cells back to patient



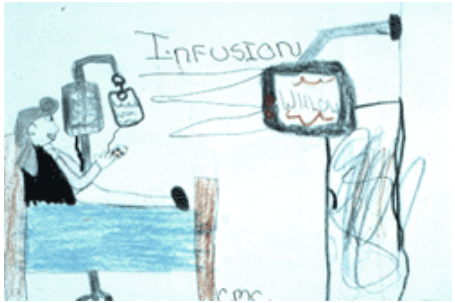




1. Extract cells (BM, PBMCs)

Direct delivery to patient using viral or non-viral vector

Milestones & Setbacks



First Gene Therapy Trial in US: 1990

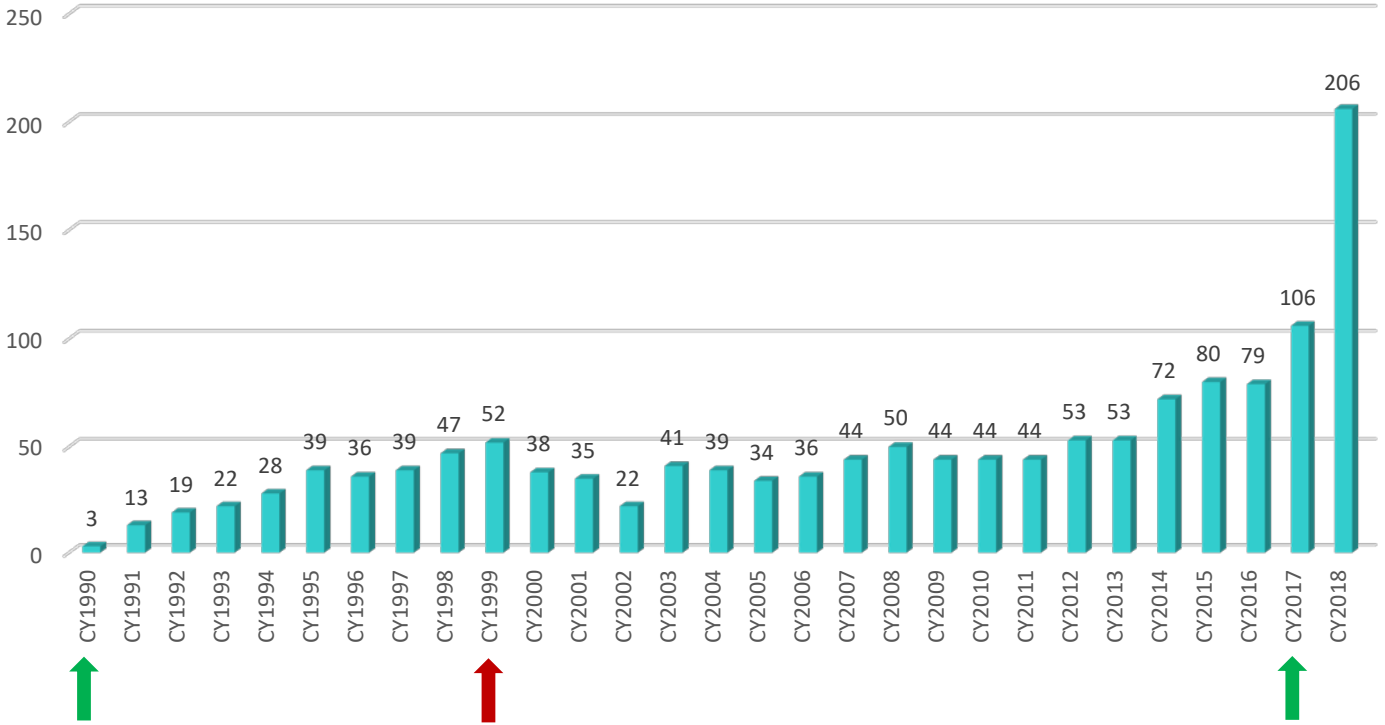
- Retroviral-mediated transfer of ADA gene into autologous T cells
- Two girls with ADA-deficient SCID received ~10 treatments for two years
- 10 years later: % of T cells carrying and expressing retroviral gene
  - 1st patient: 20%
  - 2nd patient: <0.1%

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

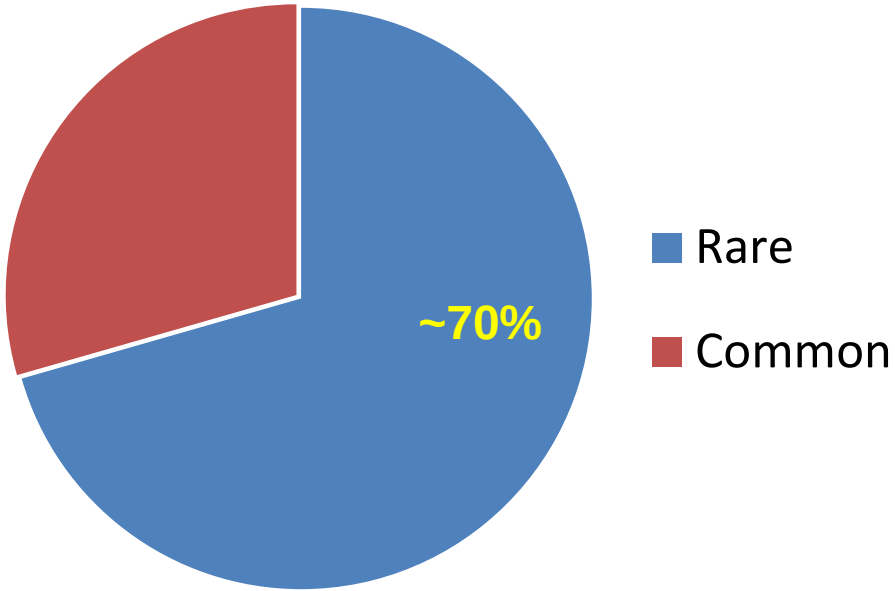
All IND Submissions with GT Products
(CY 1990-2018)



IND: Investigational New Drug application

Gene Therapies

IND Applications



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*

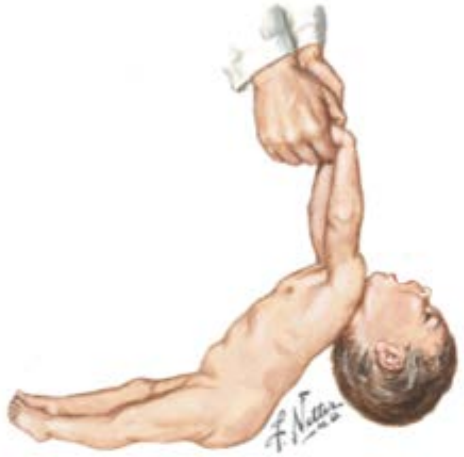
- Axicabtagene ciloleucel (Yescarta): 2017
  - Autologous human T cells transduced with a retroviral vector encoding a CAR targeting human CD19.
  - Refractory adult patients with relapsed or refractory large B cell lymphoma

*** 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

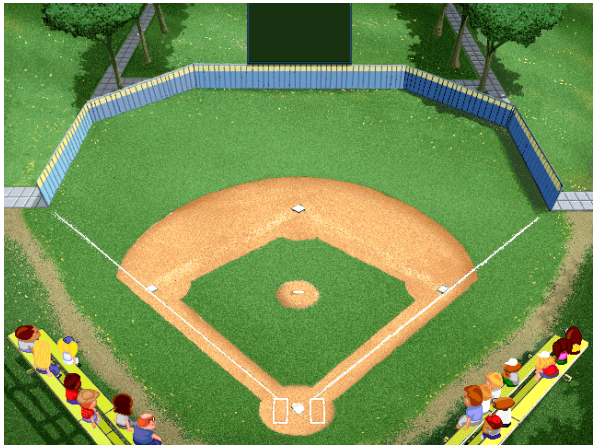
Cellular and gene therapy Guidance documents
https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

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!
  - Design first-in-human (FIH) clinical trial to provide **evidence of effectiveness**
  - 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

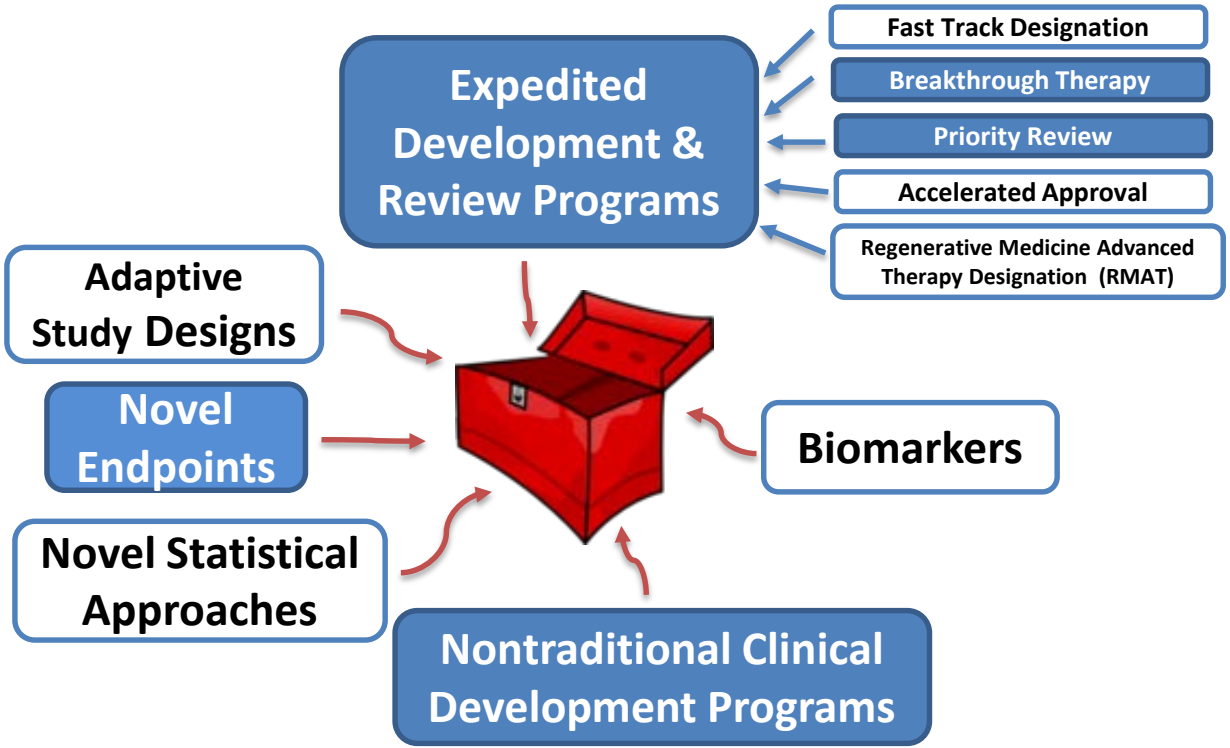
Regulatory Requirements

- 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
  - the persuasiveness of the data (e.g., comprehensiveness and quality)
  - the nature of the benefit provided (or expected in the case of surrogate endpoints)
  - the length of treatment or exposure
  - the patient population that would be treated after marketing approval
  - the concern for potential of harm from the treatment

Flexible and Feasible Approaches



Source: Julienne Vaillancourt

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

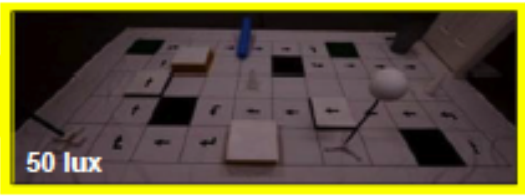
Normal Vision

Decreased Light Sensitivity

Source: Spark Therapeutics

MLMT: Evaluate Mobility at Different Light Level

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

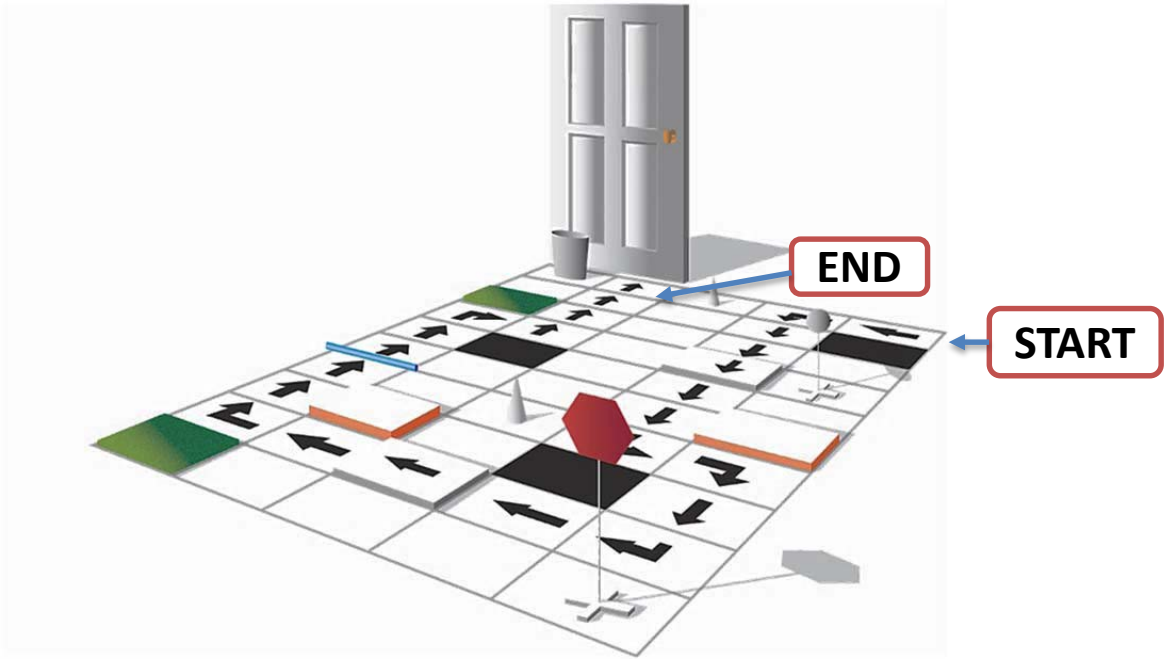


Images presented for illustrative purposes only
Light meter: National Institute of Standards and Technology-calibrated,
Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

MLMT: multi-luminance mobility test

Source: Spark Therapeutics

MLMT: 12 Different Course Layouts



MLMT: multi-luminance mobility test

Source: Spark Therapeutics

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.

Contact Information

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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