Clinical Development of Gene Therapy Products

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Clinical Investigator Training Course (CITC)
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Learning Objectives

- Grasp important principles on efficient clinical development of investigational gene therapy (GT) products

- Understand regulatory requirements and flexibility for marketing approval

Outline

- Overview of GT
- Efficient Clinical Development of GT Products
- Regulatory Requirements and Flexibility
- Example of GT Development Program

Human Gene Therapy

- Human Gene therapy products mediate their effects by
  - transcription or translation of transferred genetic material, or
  - specifically altering host (human) genetic sequences
- Common gene therapy products:
  - Plasmids
  - Viral vectors (e.g., adeno-associated virus [AAV])
  - Bacterial vectors
  - *Ex vivo* genetically modified cells
  - Products incorporating genome editing

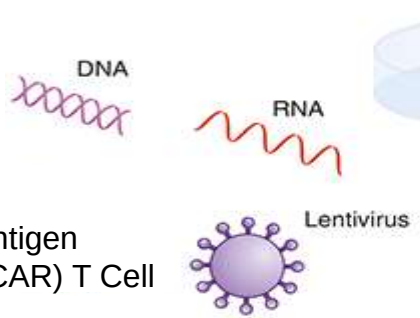
Ex vivo and *In vivo* Gene Therapy

ex vivo

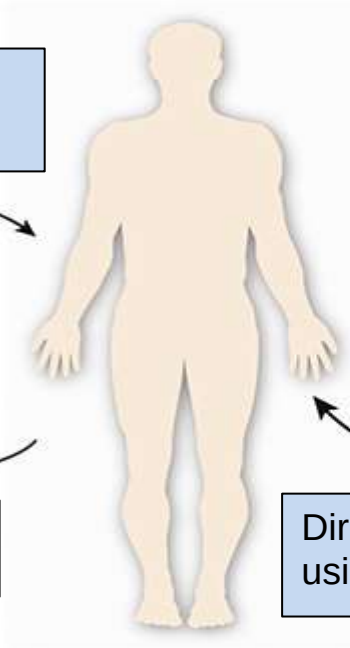
in vivo

2. Use vectors to genetically modify cells

3. Introduce modified cells back to patient



Chimeric Antigen Receptor (CAR) T Cell



1. Extract cells (BM, PBMCs)

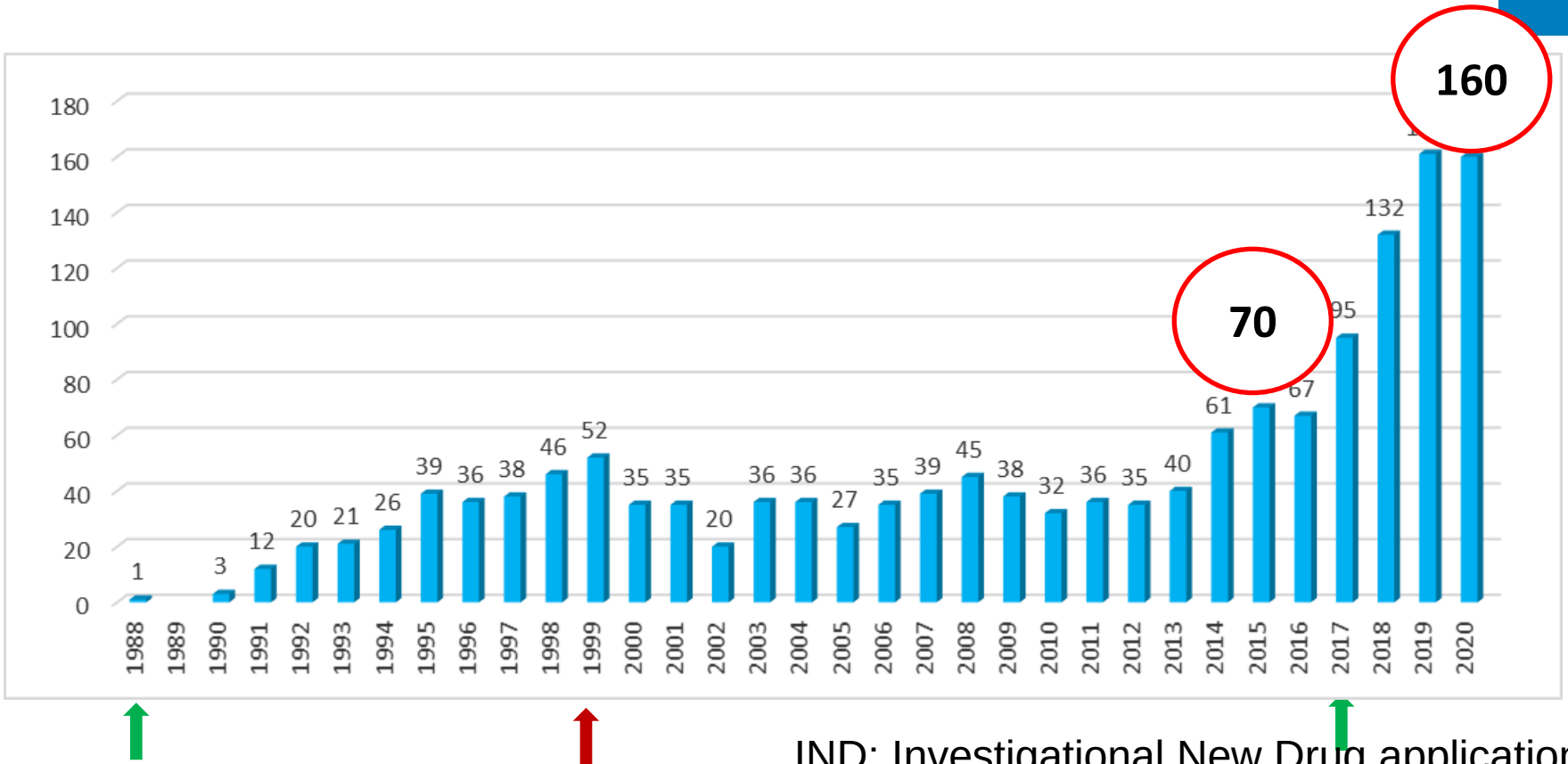
Direct delivery to patient using viral or non-viral vector

Common Vector Types:

- Gammaretrovirus
- Lentivirus

- Genetically-modified microorganisms
- Plasmids

Research INDs with GT Products

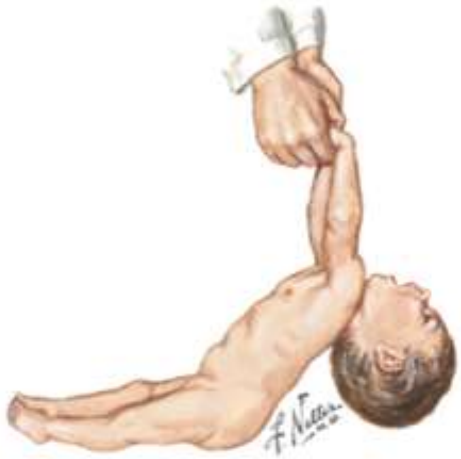


IND: Investigational New Drug application

FDA-Approved AAV-Based GT Products

- Luxturna (Voretigene neparvovec), 2017
  - **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

- Zolgensma (Onasemnogene abeparvovec), 2019
  - **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)



FDA-Approved Cell-Based GT Products

CD19-directed genetically modified autologous T cell immunotherapies

- Kymriah (Tisagenlecleucel), 2017
  - Relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) (≤25 y/o) and large B cell lymphoma (adult)
- Yescart (Axicabtagene ciloleucel), 2017
  - R/R large B cell lymphoma and follicular lymphoma (adult) (2017)
- Tecartus (Brexucabtagene autoleucel), 2020
  - R/R mantle cell lymphoma, and B cell ALL (adult)
- Breyanzi (Lisocabtagene maraleucel), 2021
  - Relapsed/refractory large B cell lymphoma (adult)

FDA-Approved Cell-Based GT Products (con't)

B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy

- Abecma (lidecabtagene vicleucel), 2021
  - Relapsed / refractory Multiple Myeloma (adult)

CLINICAL DEVELOPMENT OF GENE THERAPY PRODUCTS

Guidance for Industry

Cell and Gene Therapy Guidances access: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), 2020.
- Potency Tests for Cellular and Gene Therapy Products, 2011
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products, 2013
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry, 2015
- Long Term Follow-up After Administration of Human Gene Therapy Products, 2020

Clinical Development for GT Products

- Similar fundamental considerations: GT products and other biological products
- Clinical development programs for different diseases may vary substantially
- Discuss with FDA early in 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), https://www.fda.gov/media/106369/download

Study Design

- Randomized, concurrent-controlled clinical trials
  - May be the most efficient means of obtaining persuasive evidence of effectiveness
- Many diseases
  - Have poorly understood etiology and/or pathophysiology
  - Are poorly characterized or have highly variable natural history
- Consider randomized, concurrent-controlled (e.g., placebo, sham-procedure), double-blind clinical trials, even for FIH studies
  - Facilitate data interpretation
  - Especially important for rare diseases
    - Maximize the use of valuable resources
    - May provide sufficient evidence of effectiveness to support a marketing application.

Study Design

- Standard of care (SOC) for all subjects
- No subject should be denied effective therapies in order to be randomized to a placebo-only arm
- Add-on designs: All subjects receive SOC, then be randomized to the added GT product or placebo

External / Historical Controls

- External, historical controls may be appropriate if all criteria are met:
  - An unmet medical need
  - A concurrent control: not practical or ethical
  - Disease course: well-documented, highly predictable
  - Study population and historical controls: suitably comparable
  - Expected effect: large, self-evident, and temporal to the intervention
- Historical controls may be inadequate
- Generally, use of external, historical controls in place of a concurrent comparator group is not encouraged

Dose Selection and Product Delivery

- Early Phase studies: dose ranging
  - Initial dose
    - Supported by preclinical studies and/or available clinical information
    - Reasonably safe and have therapeutic potential
- Substantial dose exploration throughout clinical development
- Invasive surgical procedure
    - Staged approach
      - Unilateral first, then bilateral
    - Detailed description of delivery procedure and devices used

Safety Considerations

- Monitor risks associated with GT product and the administration procedure:
  - Standard safety monitoring
  - Immune response: immunoassays measuring cellular and humoral immune responses to both the vector and the transgene-encoded protein
  - Potential insertional mutagenesis

Safety Monitoring Duration

- Duration of monitoring
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products
- Long term follow-up required for certain GT products
  - e.g., 15 years of follow-up for integrating viral vector-based products
  - Clinical development can continue while long term follow-up of early phase trial subjects is ongoing

FDA Guidance: Long Term Follow-Up After Administration of Human Gene Therapy Products (2020), https://www.fda.gov/media/113768/download

Study Endpoints: Early Phase Studies

- Safety as the primary endpoint
- Encouraged to explore a wide spectrum of endpoints
  - Clinical endpoints – assess potential clinical benefit
  - Biomarkers - may indicate activity of the GT product
  - Guide further clinical development

Endpoints in Trials Supporting the BLA

- Primary efficacy endpoints
  - Clinically meaningful endpoints - directly measure how patients feel, function or survive, or
  - Surrogate endpoints - reasonably likely to predict a clinical benefit

- FDA Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998), https://www.fda.gov/files/drugs/published/Providing-Clinical-Evidence-of-Effectiveness-for-Human-Drug-and-Biological-Products..pdf
- FDA draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019), https://www.fda.gov/media/133660/download

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 patient population that would be treated after marketing approval
  - the concern for potential of harm from the treatment

Luxturna (Voretigene Neparvovec)

- First-in-class AAV vector-based gene therapy via subretinal injection
- Approved by OTAT/CBER in December 2017
- Indication: 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:
  - 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 Levels

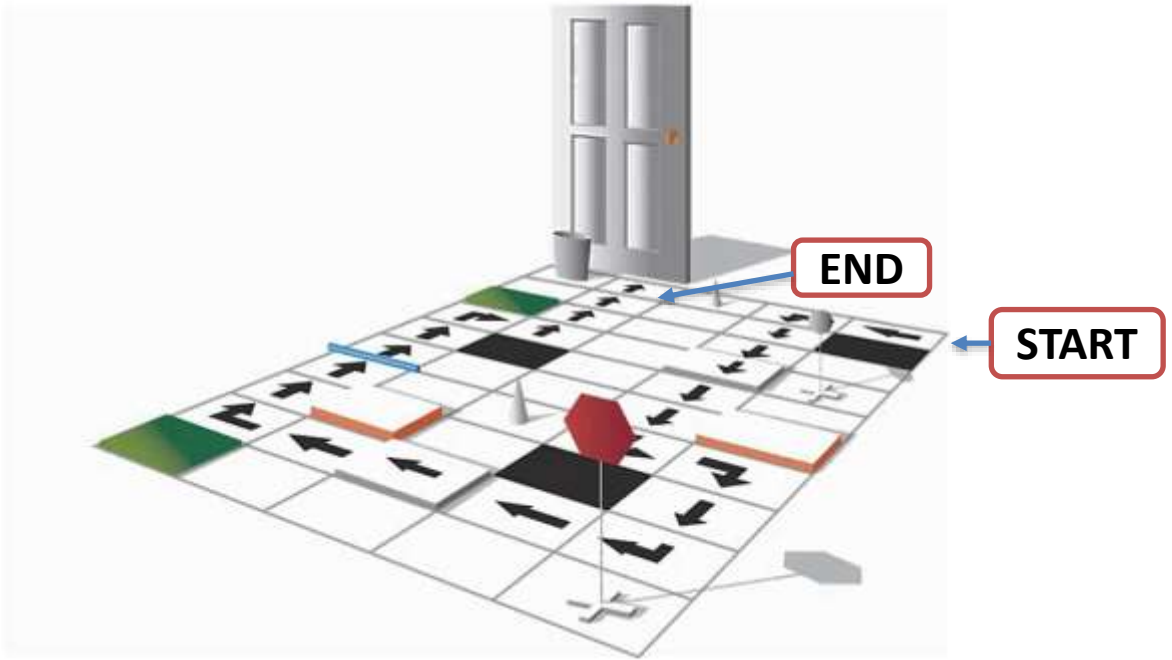
Light Levels	Examples
1 lux	Indoor nightlight; Moonless summer night
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / 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

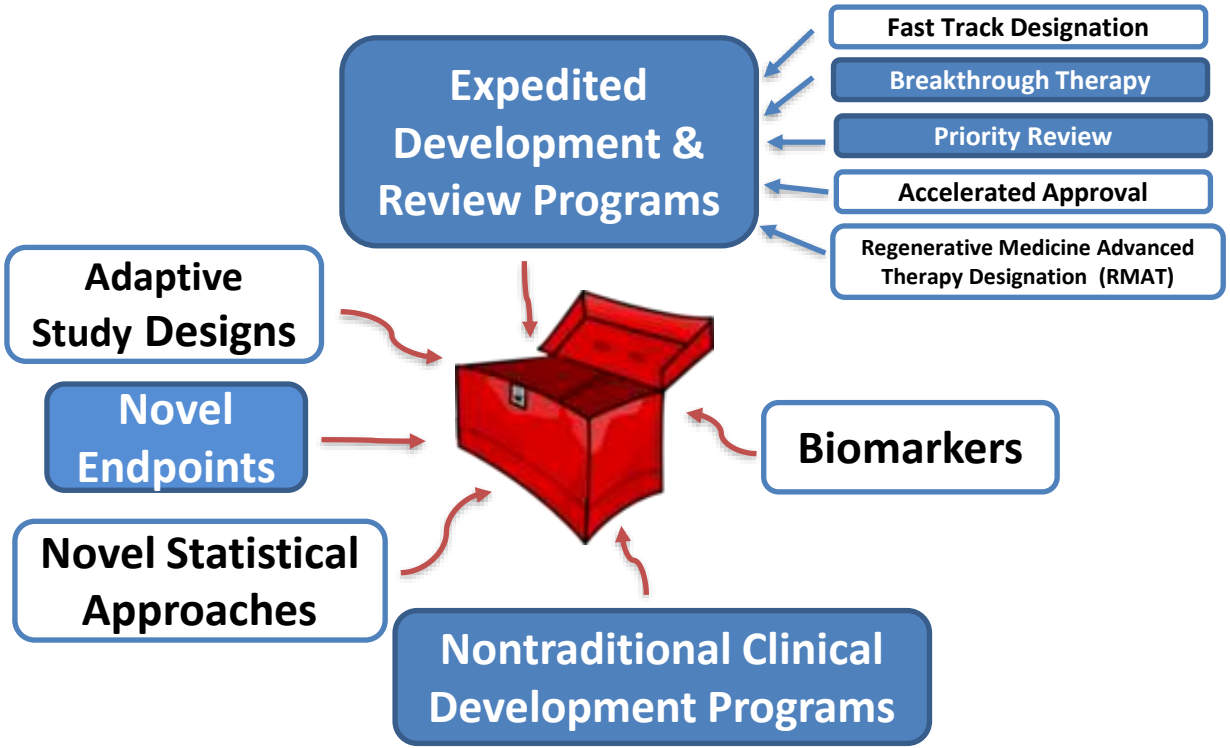
Proportion of MLMT Score Change: Using Single Eyes at 1 Year

Score Change	First-treated Eye (N=21)	Control (N=10)	Second-treated Eye (N=21)	Control (N=10)
-1	0	1 (10%)	0	2 (20%)
0	4 (19%)	6 (60%)	2 (10%)	5 (50%)
1	2 (10%)	3 (30%)	4 (19%)	3 (30%)
2	8 (38%)	0	8 (38%)	0
3	6 (28%)	0	5 (23%)	0
4	1 (5%)	0	1 (5%)	0
5	0	0	1 (5%)	0

MLMT Score Change of 2 or more:

- 15/21 (71%): treatment group
- 0/10: control group

Flexible and Feasible Approaches



Courtesy of Julienne Vaillancourt, PharmD

Summary

- 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

Challenge Question #1

A concurrently controlled, randomized First-in-human early phase study is not necessary or recommended because the objective of such a study is to assess safety.

A. True

B. False

Challenge Question #2

Which of the following can be used as a gene therapy vector?

A. Plasmids
B. lentivirus
C. Adeno associated virus vector
D. All of the above

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- **OTAT Learn Webinar Series:**

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

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

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