Clinical Development of Gene Therapy Products

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Clinical Investigator Training Course (CITC)
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Learning Objectives

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

- Understand regulatory requirements and flexibility for marketing approval

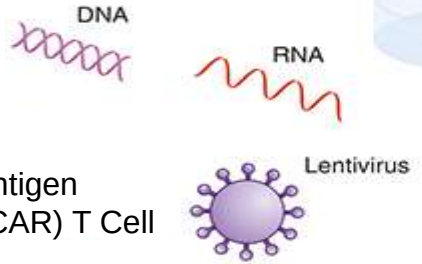
- Understand toxicities associated with adeno associated viral (AAV)-based GT products

Ex vivo and *In vivo* Gene Therapy

ex 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)

in vivo

Direct delivery to patient using viral or non-viral vector

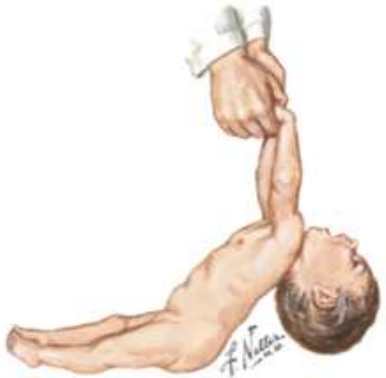
Common Vector Types:

- Gammaretrovirus
- Lentivirus

- Genetically-modified microorganisms
- Plasmids

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 survival motor neuron (SMN)
  - Spinal muscular atrophy with bi-allelic mutations in the *SMN1* gene (< 2 y/c
- Hemgenix (etranacogene dezaparvovec), 2022
  - AAV5-based GT expressing the gene encoding human Factor IX
  - Hemophilia B adults who
    - currently use Factor IX prophylaxis therapy, or
    - have current/historical life-threatening hemorrhage, or
    - repeated, serious spontaneous bleeding episodes



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

- 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, 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
- All subjects receive SOC, then be randomized to the added GT product or control (e.g., 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

Later PhaseTrials 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

- 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** (21 CFR 314.126).
- 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

Substantial Evidence of Effectiveness

- General requirement of more than one adequate and well-controlled (AWC) clinical trials to provide the substantial evidence of effectiveness necessary to support a future marketing application.
- Consistency of results across two AWC trials greatly reduces the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a product is effective.

- 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

Substantial Evidence of Effectiveness

- Under certain circumstances, FDA can conclude that one AWC clinical investigation plus confirmatory evidence is sufficient to establish effectiveness.
- FDA will consider a number of factors, including
  - The persuasiveness of the single trial
  - The robustness of the confirmatory evidence
  - The seriousness of the disease
  - The size of the patient population
  - Whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation

FDA draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019), https://www.fda.gov/media/133660/download

Luxturna (Voretigene Neparvovec)

- First-in-class AAV vector-based gene therapy via subretinal injection
- Indication: Confirmed 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

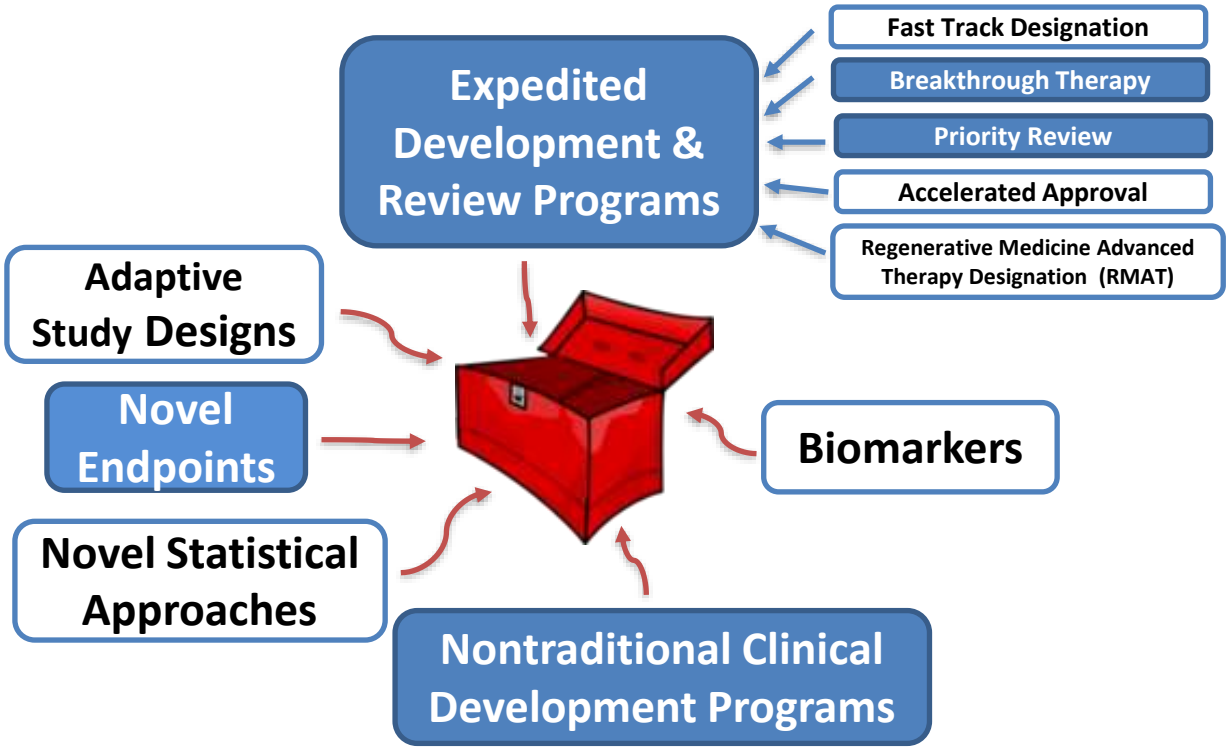
Light Levels	Examples
1 lux	Indoor nightlight; Moonless summer night
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train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

Flexible and Feasible Approaches



Courtesy of Julienne Vaillancourt, PharmD

TOXICITIES ASSOCIATED WITH AAV-BASED GT PRODUCTS

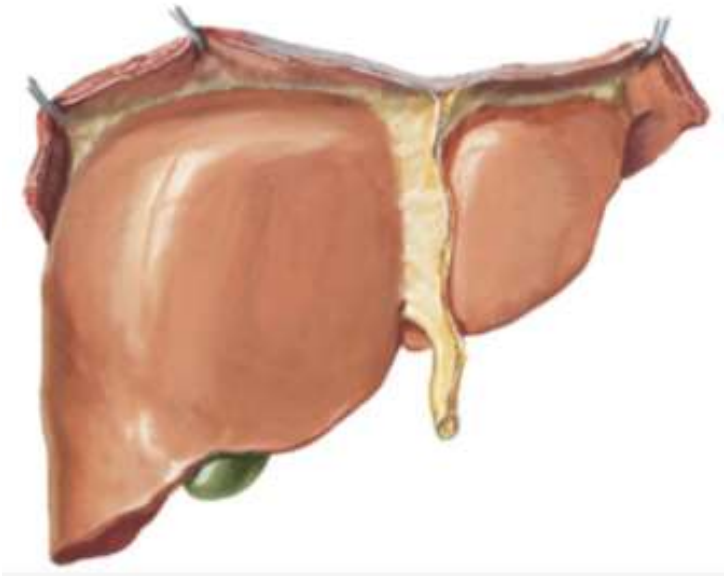
Severe Adverse Events in AAV-Based GT Clinical Trials

Toxicity	Serious Adverse Event	Vector Serotype	Indication	Route of Administration
Hepatotoxicity	Elevated liver enzymes, serious liver injury, liver failure, death	AAV9	SMA	Intravenous
	Elevated liver enzymes	AAV5	Hemophilia	Intravenous
	Liver failure	AAV8	XLMTM	Intravenous
Thrombotic Microangiopathy (TMA)	Microvascular thrombosis: Thrombocytopenia, hemolytic anemia, acute kidney injury	AAV9	SMA, DMD	Intravenous
Neurotoxicity (Dorsal root ganglia [DRG] Histopathology)	DRG neuronal loss	AAV9	GAN	Intrathecal
Neurotoxicity (DRG Histopathology)	DRG neuronal loss	AAVrh10	ALS due to mutation in *SOD1*	Intrathecal
Neurotoxicity (Brain MRI)	Abnormal T2 hyperintensities	AAVrh10	Late infantile Batten disease	Intraparenchymal

TMA, thrombotic microangiopathy; DRG, dorsal root ganglion; SMA, spinal muscular atrophy; XLMTM, X-linked myotubular myopathy; DMD, Duchenne muscular dystrophy; GAN, giant axonal neuropathy; ALS, amyotrophic lateral sclerosis; *SOD1*, superoxide dismutase 1 gene

Hepatotoxicity

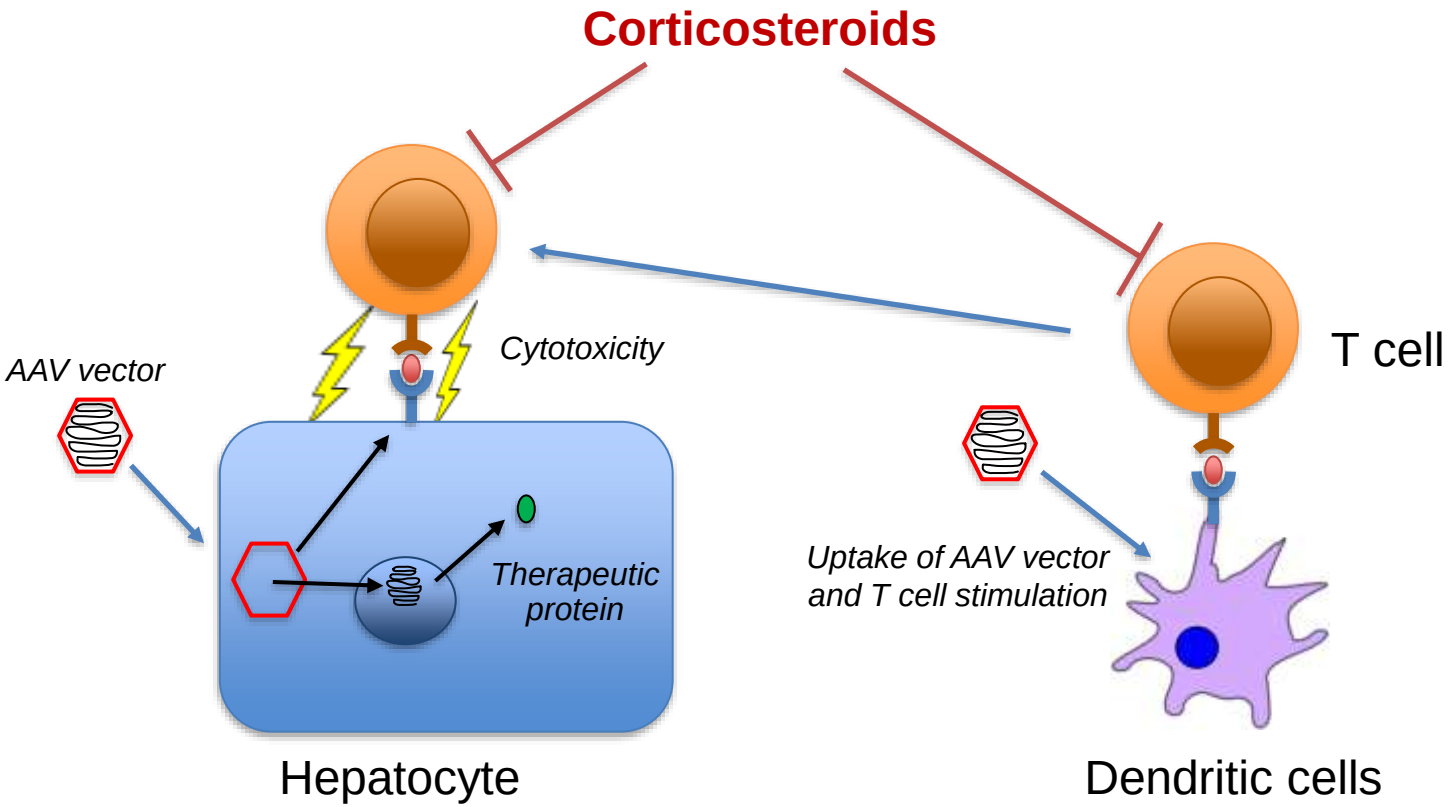
- Most common adverse event associated with intravenous (systemic) administration of AAV-based gene therapy products
- Prophylactic use of corticosteroids
- Presentations of hepatoxicity
  - Elevated liver enzymes (ALT, AST)
  - Drug-induced liver injury*
  - Hepatic failure
  - Death



[Image modified from *Netter Atlas of Human Anatomy, 6th edition*]

**As defined by Hy's Law*

Anti-AAV T Cells Can Mediate Hepatotoxicity

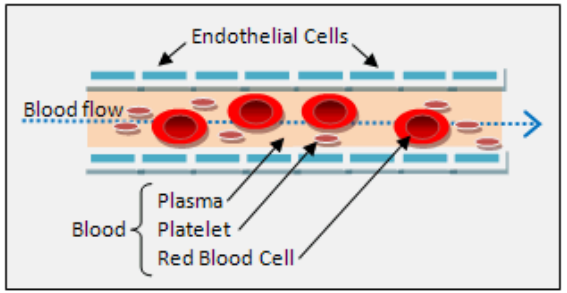


Clinical Experience

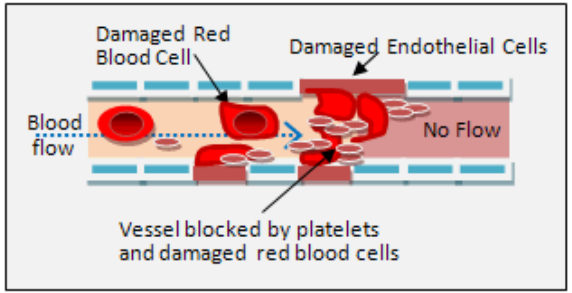
- ~1/3 of SMA clinical trial participants had at least one adverse event of hepatotoxicity
- Elevated aminotransferases > 20x ULN, treated with corticosteroids
- One case of acute serious liver injury / liver failure
  - Baseline aminotransferases ↑, unknown etiology
  - Jaundice, total bilirubin ↑, prothrombin time ↑ about 7 weeks after treatment
  - Biopsy: Massive hepatocytes degeneration and inflammatory infiltrates
  - Recovered with prednisolone
- Risk mitigation in the US Prescribing Information (PI)
  - Boxed warning
  - Systemic corticosteroids
- Additional post-marketing cases

Thrombotic Microangiopathy (TMA)

- Hematologic emergency
- Damage to arterioles and capillaries; microvascular thrombosis
- Syndrome of hemolytic anemia, thrombocytopenia, and acute kidney injury
- Two primary forms:
  - Thrombotic thrombocytopenic purpura
  - Hemolytic uremic syndrome (HUS)



Normal capillary



Capillary damaged by TMA

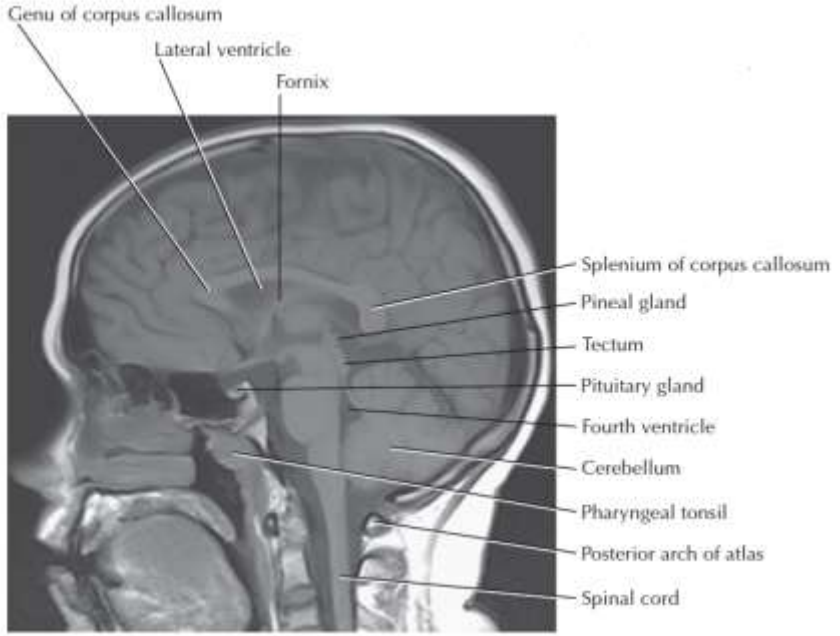
[Image modified from unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/thrombotic-microangiopathy-tma/

Clinical Experience

- Several cases of TMA reported, about 1 week after receiving onasemnogene abeparvovec
- All received recommended dose of prednisolone
- Role of concomitant triggering events?
- Laboratory evidence of complement activation
- Outcomes:
  - Recovery from TMA within 2-4 weeks in some
  - One patient: persistent hypertension
  - One patient: hypertension and nephrotic syndrome; resolved 3 months later

Neurotoxicity: Brain MRI Finding

- Direct intraparenchymal delivery of AAV vectors to specific parts of brain may:
  - Improve targeting efficiency: Avoid administering high systemic doses of AAV vectors to cross blood-brain barrier
  - Decrease risk of systemic toxicity of intravenous delivery



[Image modified from Netter Atlas of Human Anatomy, 6th edition]

Clinical Experience: Late Infantile Batten Disease

- Brain MRI T2 hyperintensities associated with intraparenchymal administration of AAVrh10 vector
  - Seen in all 13 participants 48 hours after vector administration
  - Localized to the sites of administration
  - Persistent in 7 participants on MRI after 18 months; resolved in 2 participants
  - Serious adverse events in 6 participants during acute period
  - Difficult to determine cause: AAV vector, delivery procedure, delivery devices

Summary

- An early phase trial of a GT product for a rare disorder may provide evidence of effectiveness and safety
- FDA encourages randomized, concurrent controlled early phase trial
- FDA encourages the sponsors to resolve the product's manufacturing issues, as much as possible, before initiating the FIH clinical trial
- Approval of gene therapy products must be based on substantial evidence of effectiveness and sufficient evidence of safety.
- Evidence of effectiveness should be obtained from adequate and well-controlled clinical trials.
- Serious and life-threating toxicities have been reported as more patients receive AAV-based gene therapy products.

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 is the most common toxicity of the AAV-based gene therapy products?

A. Oncogenicity
B. Hepatoxicity
C. Thrombotic microangiopathy
D. Neurotoxicity

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- **OTAT Learn Webinar Series:**

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

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