

ARTICLE DISCUSSION:

***SEVERE TOXICITY IN NONHUMAN
PRIMATES AND PIGLETS FOLLOWING HIGH-
DOSE INTRAVENOUS ADMINISTRATION OF
AN ADENO-ASSOCIATED VIRUS VECTOR
EXPRESSING HUMAN SMN***

MARCH 2018 IRB MEMBER TRAINING

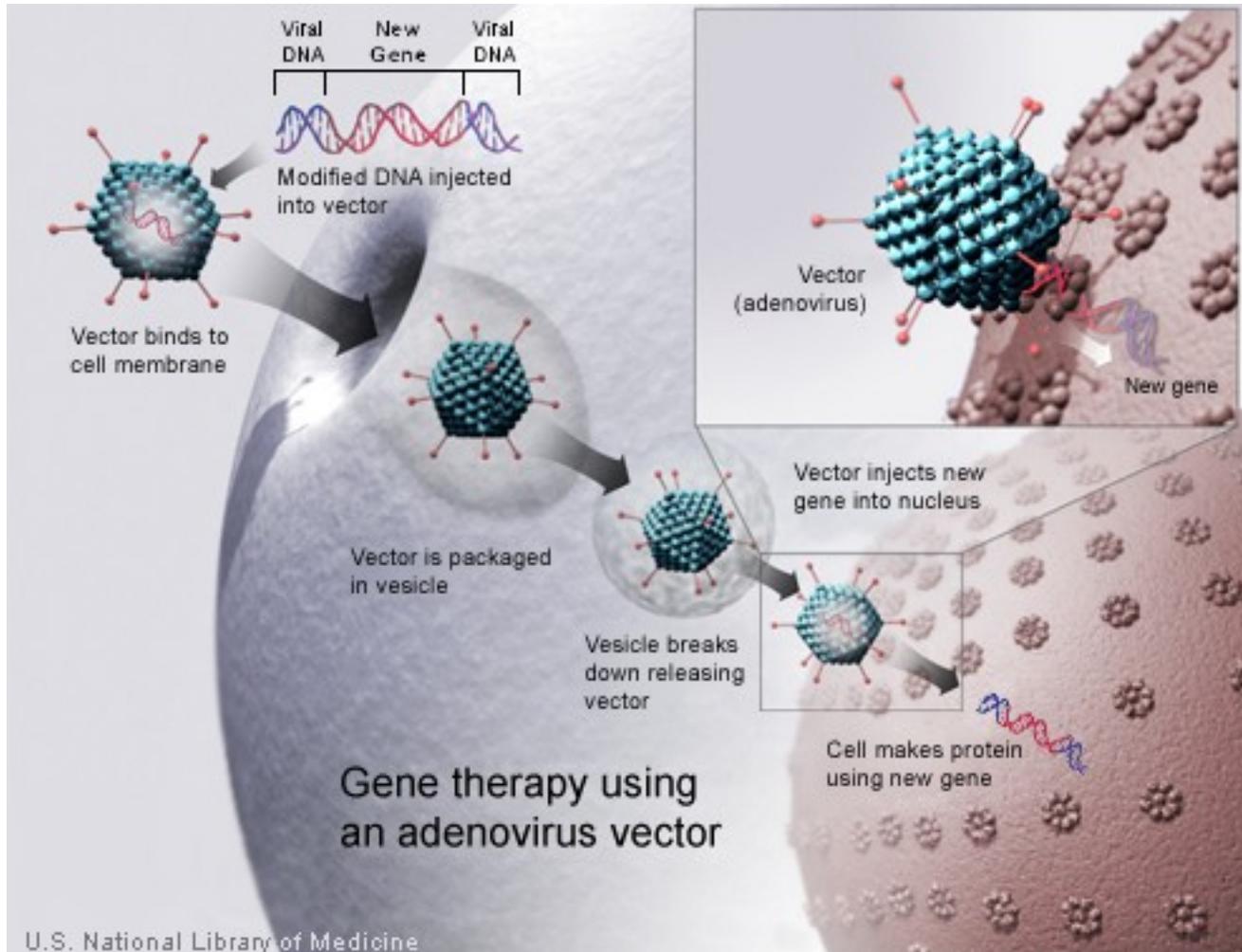
INTRODUCTION

- ▶ Penn researcher Dr. James Wilson and colleagues raised alarm in a paper recently published in the journal Human Gene Therapy.
- ▶ The article reported nerve and liver damage which occurred in two separate animal tests of a potential gene therapy for **spinal muscular atrophy (SMA)**.
- ▶ The findings raise some important questions about ongoing and planned human experimental gene therapies trials.

GENE THERAPY

- ▶ Transfer of genetic material (DNA or RNA) into a subject with the goal of improving health.
- ▶ While it was first conceptualized in the early 1970s, these approaches are still in very early stages of development.
- ▶ May be transferred alone (i.e. “naked”), or within a vector organism (e.g. a virus). The transfer of transgenic materials can be supplemented with gene editing technologies (e.g. CRISPR/Cas9).
- ▶ Many potential applications, such as:
 - Compensation for **defective genes** (e.g. hemophilia)
 - Immune system activation to **fight infectious disease** (e.g. HIV/AIDS)
 - Treatment of conditions of more **complex etiology** (e.g. cancer and cardiovascular illness).
- ▶ In addition to IRB approval, gene therapy studies require approval from the **Institutional Biosafety Committee (IBC)**, and the **NIH Recombinant DNA Advisory Committee (RAC)** to ensure that research using transgenic materials is conducted in a way that protects the study staff, human research subjects, the public, and the environment.

A new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.



Credit: U.S. National Library of Medicine

James M. Wilson and the OTD Clinical Trial

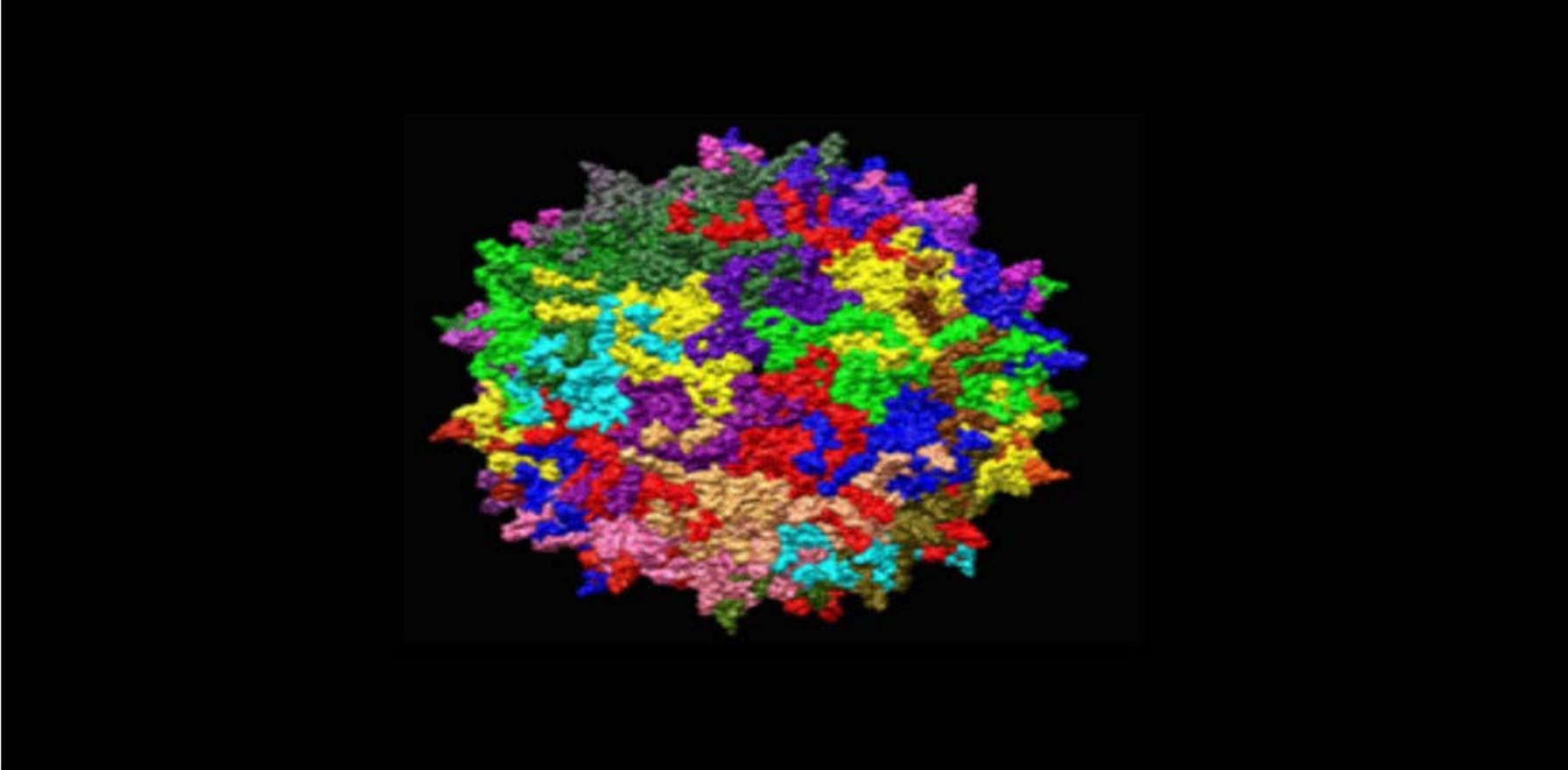
- ▶ Dr. James Wilson is a medical geneticist at Penn.
- ▶ In 1997, Dr. Wilson and his colleagues initiated a trial at Penn using gene therapy to treat **ornithine transcarbamylase deficiency (OTD)**.
- ▶ In 1999, Jesse Gelsinger, a subject in this trial, died after receiving the experimental gene therapy.



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- ▶ Regulatory investigation revealed that:
 - Jesse should never have been enrolled as his blood ammonia levels exceeded the maximum allowed per the eligibility criteria
 - The consent form failed to disclose information regarding the deaths of monkeys given a similar treatment.
 - Dr. Wilson had significant financial stakes in the research which had not been appropriately managed.
 - ▶ Penn settled a lawsuit with the subject's family and Wilson agreed to a five-year ban on participating in clinical trial research. This case put a damper on gene therapy research in general.
 - ▶ Since then, Dr. Wilson has become the Director of the University of Pennsylvania Gene Therapy Program and Orphan Disease Center.

Adeno-Associated Viruses (AAV)

- ▶ Dr. Wilson's current work focuses on development of safer and more effective gene therapy delivery mechanisms, namely, Adeno-Associated Viruses (AAV).
- ▶ AAV is a class of a small viruses which infect humans and some other primate species. AAV are not currently known to cause disease.
- ▶ In addition to its relative lack of pathogenicity, AAVs' ability to infect both non-dividing and dividing cells make it an attractive gene therapy vector.
- ▶ AAV is currently used in the approved blindness gene therapy, Luxturna (Spark Therapeutics) and under investigation for a number of other applications.
- ▶ In most cases, AAV-delivered gene therapy involves *direct* injection into targeted tissues (e.g. the retina, the liver).
- ▶ Recent trials are investigating intravenous (IV) administration for *systemic* distribution to tissues which the vector may not otherwise penetrate (e.g. hemophilia, skeletal muscle for the treatment of Duchenne muscular dystrophy).



AAV2 capsid, shown as a ribbon diagram, with the back half hidden for clarity. One fivefold symmetry axis is shown center.

The Article: *Severe Toxicity in Nonhuman Primates and Piglets Following High-Dose Intravenous Administration of an Adeno-Associated Virus Vector Expressing Human SMN*

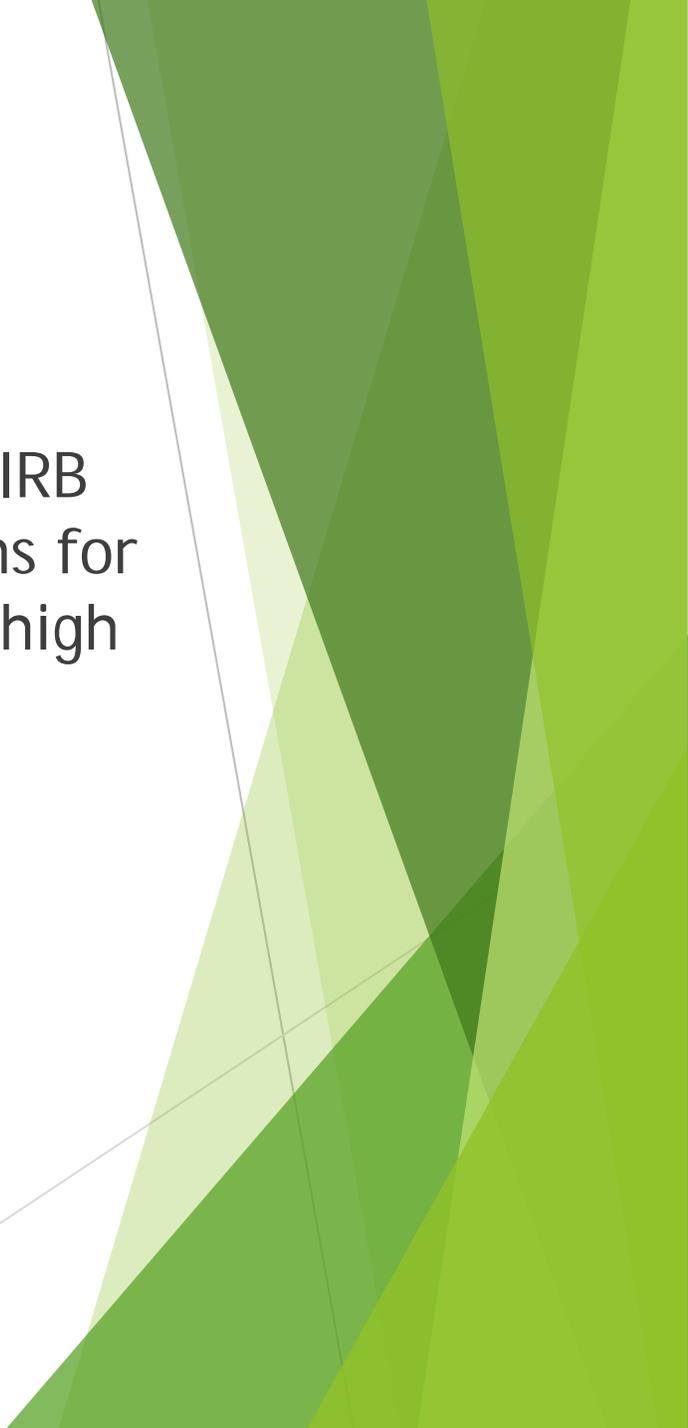
- ▶ Dr. Wilson and his colleagues initiated animal studies to determine whether IV AAV administered gene therapy could correct a genetic deficiency linked to neuromuscular diseases.
- ▶ The research involved IV administration of high doses of AAV-packaged human **survival of motor neuron** (SMN) transgene in 3 rhesus macaques and 3 piglets.
- ▶ The results of the research, which were recently published in journal, *Human Gene Therapy*, reported the following:
 - 4 days following administration, one of the macaques suffered severe liver damage and shock necessitating euthanasia. The two other monkeys survived, but also experienced toxicity.
 - All 3 piglets experienced toxicity necessitating euthanasia.

- ▶ The investigators attributed these effects to **innate immune response** to the viral vector.
- ▶ Dr. Wilson resigned as Chair of the biotechnology company Solid's scientific advisory board a few days in advance of the publication of these findings citing "emerging concerns about the possible risks" of the Duchenne gene therapy the company is developing.
 - ▶ In a separate filing, Solid disclosed that the FDA had partially suspended testing of the therapy in November.
 - ▶ Solid has not been able to administer a high dose to patients but is allowed to continue testing a lower dose.

WHAT'S NEXT?

- ▶ The results of this research were unexpected and raised alarm given the relatively favorable safety profile of AAV demonstrated in prior and ongoing gene therapy trials.
- ▶ While this has impacted the biotechnology sector and has prompted some researchers to question whether current/planned AAV gene therapy human trials should continue, many researchers have tempered the interpretation of the Wilson team's findings, pointing to the small size of the Penn studies and other variables (e.g. possible vector contamination) which could have impacted the results.

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- ▶ General consensus in the field is that while the results of the Penn studies do not merit discontinuation of clinical trials, that researchers should nonetheless heed the Wilson team's recommendations that:
 - Close monitoring of subjects in such trials is warranted
 - The research community should be highly transparent in terms of sharing of pre-clinical data
 - Decisions about future applications should be based on careful reconciliation of the potential risks against the unmet needs of patients and the likelihood of benefit
 - ▶ Suggestions for mitigating the potential risks associated with systemic administration of AAV gene therapy have been proposed, most notably, the concurrent administration of immune modulating drugs.

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- ▶ In light of the Penn research findings, how do you, as IRB members feel about the Penn team's recommendations for moving forward with human gene therapy trials using high dose AAV?
 - ▶ Should this research continue before additional pre-clinical data is accrued?
 - ▶ What kind of information (e.g. bench, animal, prior human) should be provided in support of dose?

RESOURCES

- ▶ Hinderer C, Katz N, Buza EL, et al.
Severe toxicity in nonhuman primates and piglets following high-dose intravenous administration of an adeno- associated virus vector expressing human SMN
Hum Gene Ther 2018; 29
- ▶ T.R. Flotte and H. Buning
COMMENTARY: Severe Toxicity in Nonhuman Primates and Piglets with Systemic High-Dose Administration of Adeno-Associated Virus Serotype 9-Like Vectors: Putting Patients First
Hum Gene Ther 2018; 29
- ▶ Forbes Article: Why A Gene Therapy Pioneer Is Raising Concerns About Treatments He Championed (M. Herper; 2.7.18)
<https://www.forbes.com/sites/matthewherper/2018/02/07/why-a-gene-therapy-pioneer-is-raising-concerns-about-treatments-he-championed/#7e5a494a4123>
- ▶ XConomy Article: After Paper Shakes Sector, Gene Therapy Leader Jim Wilson Talks Safety (B. Fidler; 1.29.18)
<https://www.xconomy.com/national/2018/01/30/after-paper-shakes-sector-gene-therapy-leader-jim-wilson-talks-safety/>

- ▶ **University of Pennsylvania Institutional Biosafety Committee (IBC)**
<http://www.ehrs.upenn.edu/programs/bio/ibc/>
- ▶ **The NIH Review Process for Human Gene Transfer Trials**
<https://osp.od.nih.gov/biotechnology/faq-onthe-nih-review-process-for-human-gene-transfer-trials/>
- ▶ **How does gene therapy work? NIH U.S. National Library of Medicine Genetics Home Reference**
<https://ghr.nlm.nih.gov/primer/therapy/procedures>