ASGCT and FDA Liaison Meeting

February 23, 2024
1:30-3:30 PM ET

American Society of Gene + Cell Therapy

Class Considerations for Determining Safety and Efficacy Outcomes for AAV Gene Therapies

Presenters:

Nimi Chhina, PhD, JD

James Nickas, PharmD

Terence Flotte, MD

Snehal Naik, PhD

American Society of Gene + Cell Therapy

Introduction and Presentation Goals

Nimi Chhina, PhD, JD
BioMarin Pharmaceutical

American Society of Gene + Cell Therapy

AAV Class-wide Issues

Deep Dive discussion on two topics in today's meeting:

- Integration and theoretical oncogenicity risk
- Immunogenicity

Other topics for future discussion:

- How should sponsors determine which shedding studies, if any, are necessary?
- Biodistribution
- How sponsors should approach immunosuppression regimens
- Contraception, alcohol abstinence, etc.

American Society of Gene + Cell Therapy

ASGCT Recommendations for Knowledge Sharing

- ASGCT suggests co-hosting a public virtual workshop with FDA post-Liaison Meeting to provide a more in-depth examination of AAV class considerations.
- After gathering scientific input from stakeholders, ASGCT recommends that FDA share information about considerations specific to the class of AAV vector-based gene therapies, including the topics on the prior slide as well as others as appropriate.
    - Public workshops and town halls
    - New formal guidance documents
    - Inclusion in planned PDUFA VII Q&A guidance(s)
    - Other avenues to share FDA's learnings with the sponsor community

American Society of Gene + Cell Therapy

AAV Integration

James Nickas, PharmD
BioMarin Pharmaceutical

American Society of Gene + Cell Therapy

State of Knowledge for AAV Integration

- AAV-mediated tumorigenesis has occurred in murine studies via integration into the Rian gene locus found only in rodents.
    - From integration site studies in NHPs and humans, no evidence has been provided that AAV integration in the mammalian ortholog of the Rian locus imposes a safety concern for patients.
- Hepatic clonal expansion has been observed in canine model of hemophilia B with integration of AAV vector DNA into genes associated with cell growth or transformation; no liver nodules or oncogenesis.
- Relevance and translatability of animal model findings to human risk is unclear.
- No genotoxicity has been confirmed in AAV clinical trials; however, long-term follow-up time in humans is still limited compared to the latency period for cancer development.
- A small number of different malignancy cases have been reported in persons treated with AAV GTs.
- Where robust analyses of collected tumor tissue were performed, AAV integration was ruled out as the likely cause.
    - More long-term, aggregated safety data are needed to further contextualize and understand cancer risk, if any, with AAV GTs.

Currently, there is no conclusive evidence that AAV vectors cause cancer.

Sabatino DE, et al (2022). Evaluating the state of the science for adeno-associated virus integration: an integrated perspective. Mol. Ther. 30(8), 2446-2663.

American Society of Gene + Cell Therapy

The Risk of AAV-mediated Oncogenesis in Humans is Theoretical

- AAV is used as a vector to deliver therapeutic genes into patient cells to treat a variety of monogenic diseases.
- AAV vector, itself, is not carcinogenic in humans.
- **Theoretical concern** is that integration of AAV vector DNA into human genome could disrupt/activate genes that promote cancer.
- AAV vector DNA remains mostly episomal but can integrate into host genomic DNA.
    - Vector construct, dose, and route of administration are factors that may influence extent of integration.
    - Estimates of integration frequencies remain variable, illustrating need for better assays to quantitate and characterize integration events.
- FDA's guidance finalized in January 2020 cites that AAV vectors have low propensity to integrate inferring a lower genotoxicity risk; guidance should keep pace with accumulating data.

Table 1. Propensity of Commonly Used Gene Therapy Products/Vectors to Modify the Host Genome

Product/Vector Type	Propensity to Modify Genome[1]	Long Term Follow-up Observations[2]
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno-associated virus[3]	No	Product specific
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT)[4]	No, but may persist and undergo reactivation	Product specific
Genome editing products	Yes; permanent changes to the host genome	Yes

[1] Based on product design (i.e., lack of any known mechanism to facilitate integration or genome editing), as well as cumulative preclinical and clinical evidence suggesting that a GT product does not integrate into or edit the genome or integrates in/modifies the genome at very low frequencies.
[2] Specific circumstances that indicate persistent expression of the transgene, in the absence of integration or genome editing, may be the basis for a conclusion that LTFU observations are recommended to mitigate long term risks to subjects receiving these vectors. This would depend on additional criteria, such as the transgene expressed or clinical indication, as described in this section.
[3] Replication-negative vectors only.
[4] For additional guidance we refer you to "Recommendations for Microbial Vectors used for Gene Therapy; Guidance for Industry" dated September 2016.

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

American Society of Gene + Cell Therapy

Conveying Risks of AAV Vector Integration & Tumorigenicity to Providers and Patients

- ASGCT acknowledges that while AAV-related tumorigenicity has been observed only in mice, vector integration has been observed and measured in large animals and humans making AAV a potential mutagen.
- ASGCT supports FDA's current practice of including proportionate and relevant information concerning AAV vector integration.
- Does accumulating knowledge warrant and support any AAV class-wide labeling concerning vector integration and theoretical risk of tumorigenicity? Considerations could include:
    - Information concerning vector integration that is considered applicable to the AAV vector-based gene therapy class;
    - Product-specific pre-clinical and/or clinical findings concerning vector integration and outcomes;
    - Guidance for applicable risk-adapted monitoring.

Specific AAV vector-based gene therapy guidance may facilitate consistent labeling that better educates physicians and patients to inform benefit-risk treatment decisions.

American Society of Gene + Cell Therapy

Questions and Topics to Consider at a Co-hosted ASGCT + FDA Workshop and in Subsequent AAV Vector-based Gene Therapy Guidance(s)

- Translatability concerns to human gene therapy are warranted.
  - In rodents the mechanistic establishment of AAV integration-induced cancer is evident; however, no documented cases of cancer attributed to AAV integration in gene therapy patients.
  - No evidence for an elevated risk for AAV-induced carcinogenesis found in comprehensive AAV integration studies in non-rodent preclinical models (NHP or Dog).
  - While animal models are imperfect as predictors of human cancer risk, there is currently no better alternative.

- Prolonged observation periods of gene therapy patients are likely to increase the reporting rate of malignancies.

- What is the appropriate regulatory response if clinical malignancies do occur?
  - What analyses or findings would suggest a likely causal/contributory relationship between AAV GT and the malignancy?
  - Considering benefit-risk, what level of evidence is reasonable to halt a trial vs continuing it while analyses are ongoing?
  - What findings would/should rise to class labeling?

- What approach should be taken for evidence-based updates to labeling statements?
  - How will the agency engage with sponsors, providers, and patients to explain theoretical risks?
  - What are the standards informing removal of statements on theoretical risk based on emerging data?

Specific AAV vector-based gene therapy guidance should describe how to assess the potential role of AAV integrations in observed malignancies.

American Society of Gene + Cell Therapy

AAV Immunogenicity

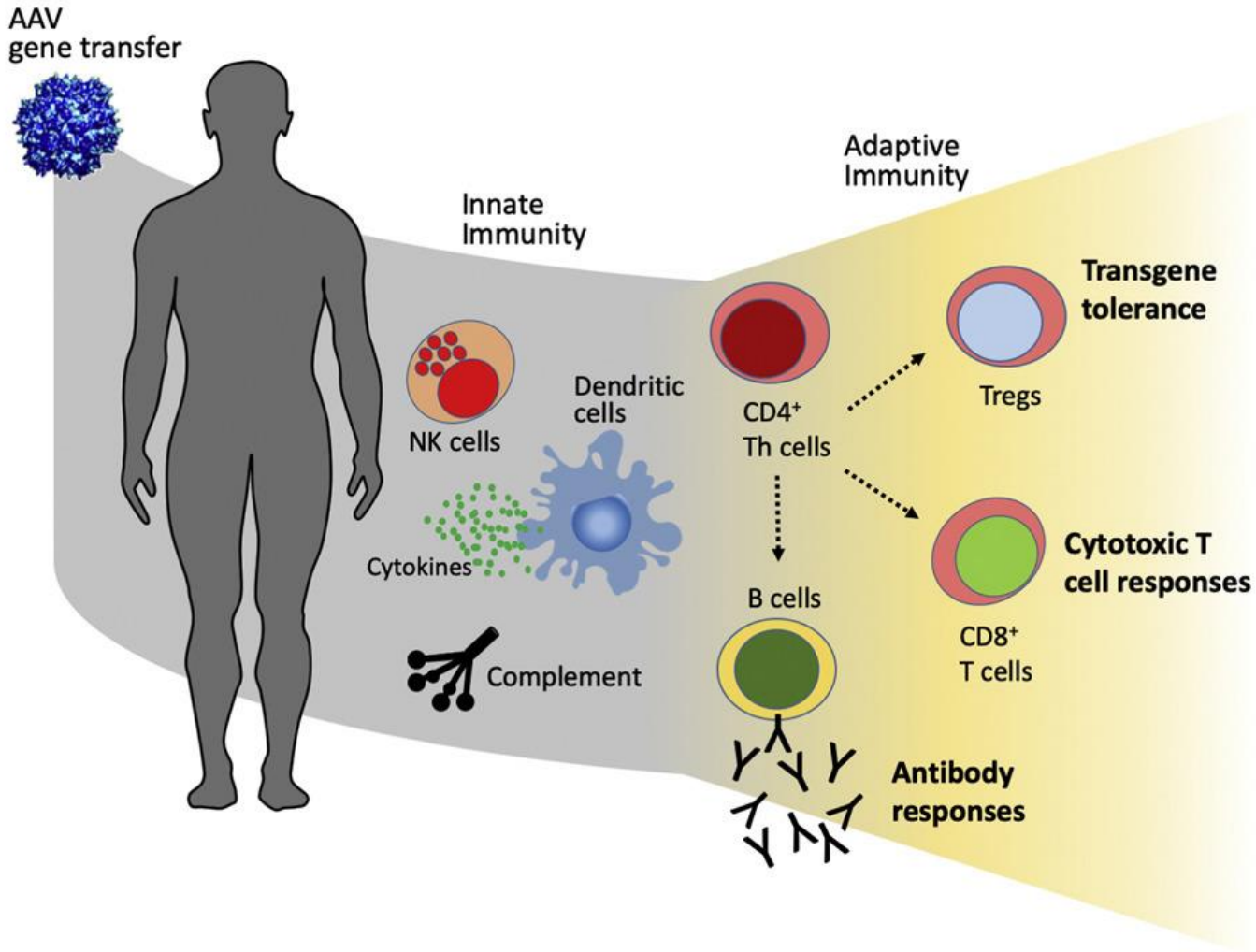
Terence Flotte, MD
University of Massachusetts Chan Medical School

Introduction

There are class-specific considerations for AAVs, but there are also patient- and product-specific considerations. Are there attributes of immunologic assays/tests we should consider across serotypes?

Factors that Affect Immune Responses to AAV

- Route of Delivery
- Dose of Vector
- AAV capsid
- Transgene
- Disease/Specific mutation
- HLA type/ immune variations
- Immunosuppressive regimen



Verdera, Kuranda, Mingozzi, Molecular Therapy 2020

Outline

A. Guidelines for Immunologic Assays Used in Patient Selection

- Assays for Pre-existing anti-AAV antibodies for selection/indication (i.e., Criteria for Exclusion of Seropositive individuals)

B. Guidelines for timing of clinical laboratory monitoring

- Early time points for thrombocytopenia
- Duration of monitoring liver enzymes

C. Future possibilities:

- T cell assays to augment liver enzymes in guiding management
- Generation of systematic clinical evidence in support of immune suppression approaches
- Standard language in informed consent and subsequently on label around immune response risks

A. Guidelines for Immunologic Assays

1. Antibody Assays: Comparison of Two Approaches to pre-existing antibody

- **Etranacogene dezaparvovec-drlb (Hemgenix)**: Neutralizing antibody assay is discussed as a possible hindrance to efficacy
- **Valoctogene roxaparvovec-rvox (Roctavian)**: Total binding antibody by companion diagnostic is part of label indication

2. Other products in various stages of clinical development: Use of antibody assays for patient selection.

American Society of Gene + Cell Therapy

Rationale Convergence on "AAV seropositivity" Across Different Products/Manufacturers

- Current state: The field has not yet created FDA-approved standard assays for Pre-existing Neutralizing antibody (NAB) and total antibody (TAB), leading to variation among clinical development programs and individual trials.
    - Cutoff values for pre-existing NAB and TAB vary with the assay.
- The current state can **impede access** of genetic disease patients to gene therapy.
    - Clinical development of gene therapies meeting other unmet medical needs could be facilitated if standardized serotype-specific assays could be developed and made available to all.
- Expanding access to gene therapy for all patients is a strategic priority of ASGCT and is in the public interest.
- **Based on this, ASGCT recommends FDA-guided data sharing and standard guidelines to harmonize tests of serologic status used in indications and contraindications.**

American Society of Gene + Cell Therapy

N Engl J Med 2023;388:706-18.
DOI: 10.1056/NEJMoa2211644

HEMGENIX® (etranacogene dezaparvovec-drlb) suspension, for intravenous infusion
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------

HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

5.3 Immune-mediated neutralization of the AAV5 vector capsid

In AAV-vector based gene therapies, preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with HEMGENIX all subjects developed neutralizing anti-AAV antibodies. Currently, there is no validated neutralizing anti-AAV5 antibody assay.

American Society of Gene + Cell Therapy

Valoctogene roxaparvovec-rvox

----------INDICATIONS AND USAGE----------

ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. (1)

ARUP LABORATORIES

News Careers Contact Us | Connect Sign In

Testing Services Education Center About

ARUP Home › Lab Test Directory › AAV5 Detect CDxTM -AAV5 Total Antibody Assay for ROCTAVIAN (valoctocogene roxaparvovec-rvox) Eligibility in Hemophilia A

Search by name, keyword, or number

Browse Tests A-Z

3000959

AAV5 Detect CDxTM -AAV5 Total Antibody Assay for ROCTAVIAN (valoctocogene roxaparvovec-rvox) Eligibility in Hemophilia A

AAV5 TAB

B. Timing of Clinical Laboratory Monitoring

- Comparison of SAEs in high-dose intravenous AAV trials has revealed a paucity of data on early time points (3 to 14 day range) in some patients developing Thrombotic Microangiopathy (TMA), thrombocytopenia and cardiac toxicity.
- Comparisons of published data and labels on timing of AAV hepatotoxicity have varied in the duration of monitoring for transaminase elevations.
- Lack of complete data sets on clinical laboratory monitoring makes it difficult to use published data to optimally manage gene therapy patients.
- Recognizing that current FDA practice does not require standards, we recommend a standard approach to early and late timing of clinical monitoring and sharing of data within the vector class until sufficient evidence is generated to better guide labeling information.

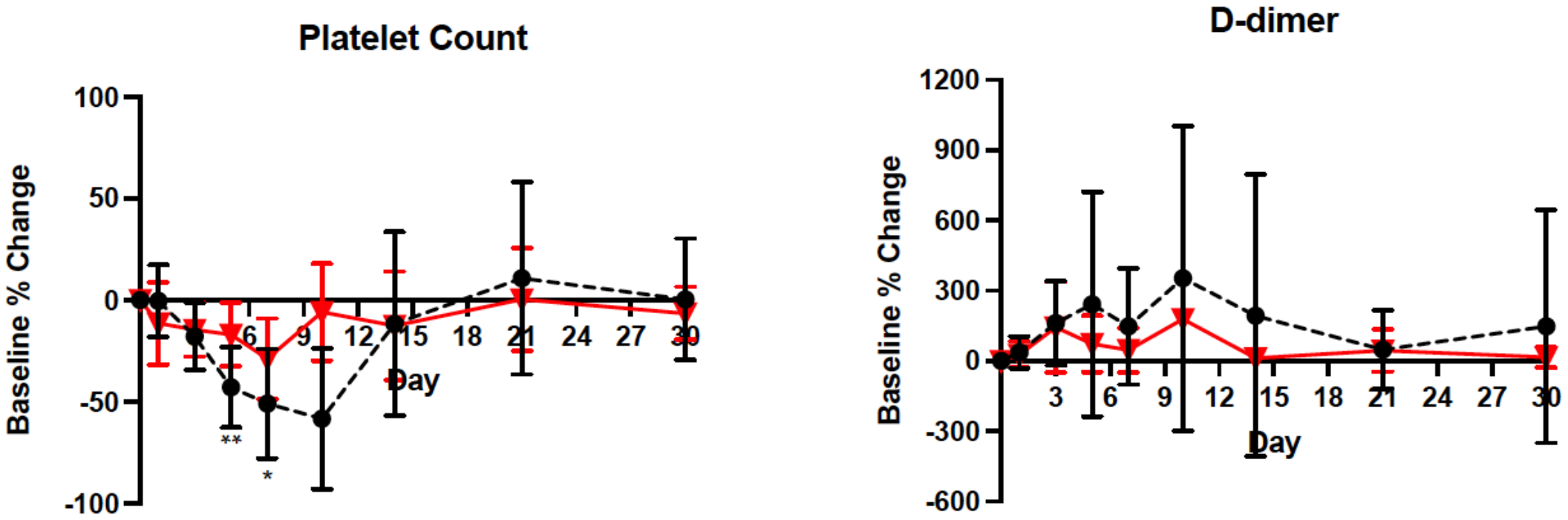


Figure 2. Hematology. Figure shows the percent change from baseline for platelet count and D-dimer for Group 1 (dashed black lines, full circles) and 2 (full red lines, full triangles). Data suggest that IMR as an adjunctive therapy to AAV used in Group 2 limits the depletion of platelets and the increase of D-dimer after AAV infusion. Data shown as mean ± SEM of Group 1 and Group 2 baseline % change for hematology; *p>0.05 (non-significant), p≤0.05(*), p≤0.01 (**).*

Salabarria, Corti,… Byrne et al.

J Clin Invest. 2023. https://doi.org/10.1172/JCI173510.

American Society of Gene + Cell Therapy

C. Possible Future Guidelines for Immunologic Assays

T cell response assays (gIFN-ELISPOTS, Fluorospots, intracellular cytokine staining)

- Are these assays important in assessing anti-transgene responses in a manner that could affect a genotype specific indication (see example)?
- Do these assays have value in determining the relatedness of AEs to anti-vector responses?
- If so, are there common desirable aspects across products and serotypes?

American Society of Gene + Cell Therapy

C. FUTURE direction:
ELISPOT ASSAY (was used to define genotype exclusion)

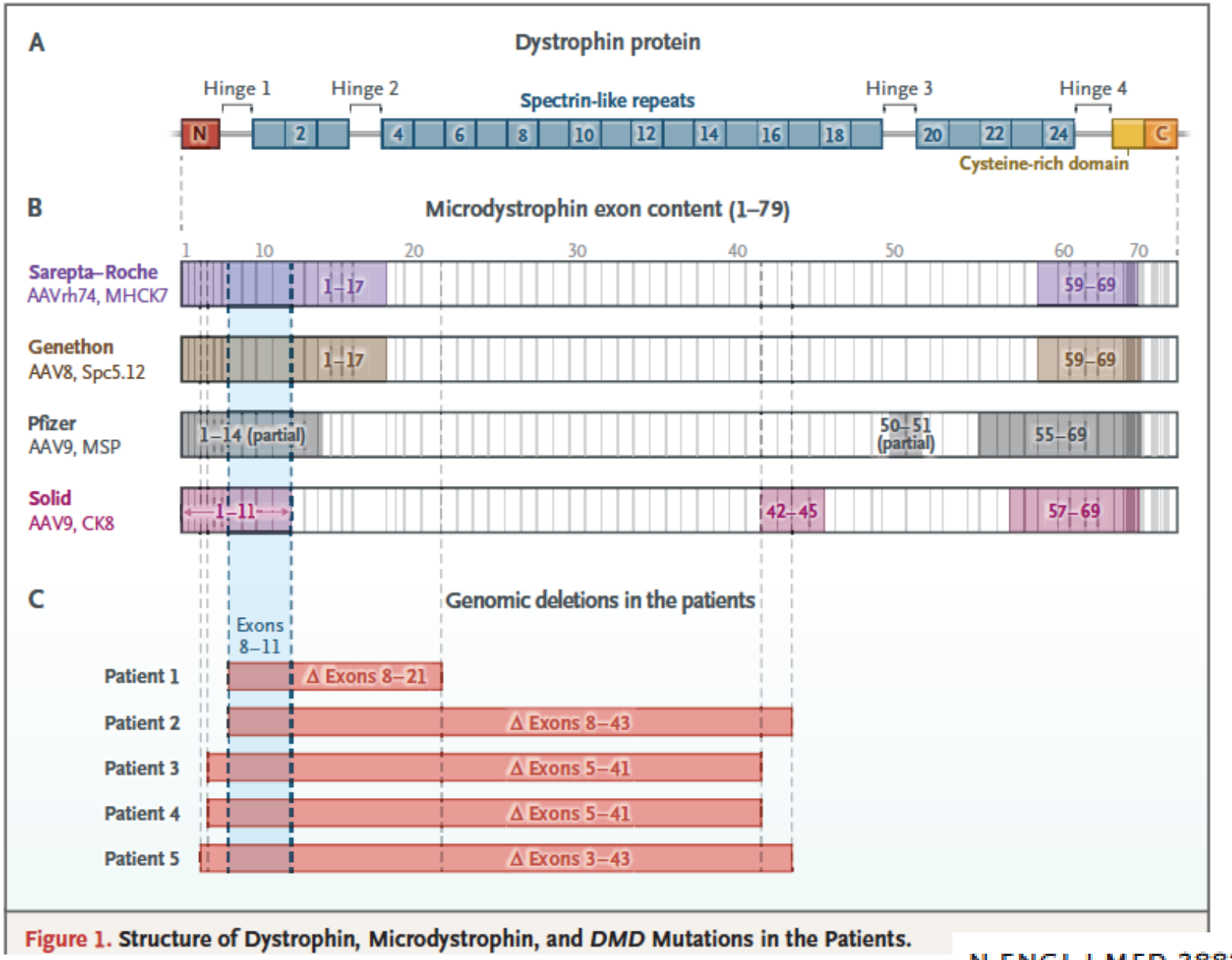


Figure 1. Structure of Dystrophin, Microdystrophin, and *DMD* Mutations in the Patients.

Carsten G. Bönnemann, M.D.
National Institute of Neurological Disorders and Stroke
Bethesda, MD
carsten.bonnemann@nih.gov

Beth A. Belluscio, M.D., Ph.D.
Pfizer
New York, NY

Serge Braun, Pharm.D., Ph.D.
Genethon
Evry, France

Carl Morris, Ph.D.
Solid Biosciences
Charlestown, MA

Teji Singh, M.D.
Sarepta Therapeutics
Cambridge, MA

Francesco Muntoni, M.D.
University College London Great Ormond Street Institute of Child Health
London, United Kingdom
f.muntoni@ucl.ac.uk

epitopes. Consistent with this constellation of findings, data from preliminary enzyme-linked immunospot testing (fully available for two of the patients) and antibody epitope mapping revealed reactivity to peptide pools contained within exons 8 through 11, which suggested the presence of an immune response to this nonself epitope (Fig. 1). These findings resemble those in one of the patients in the study by Mendell et al. (deletion of exons 3 through 17).[1]

RECOMMENDATIONS

ASGCT recommends that FDA create guidelines on:

- The attributes of immunologic assays for patient selection.
- The timing of safety assessments with considerations specific to the class of AAV-based gene therapies.

ASGCT suggests co-hosting a post-Liaison meeting:

- Building on success of 2023 workshop on "Immune Responses to AAV Vectors," the Society **suggests another public virtual workshop to enable a more in-depth examination of class considerations.**

American Society of Gene + Cell Therapy

Conclusion

Snehal Naik, PhD
Spark Therapeutics

Final Thoughts

- ASGCT thanks FDA for this opportunity to present our membership's views and identify future opportunities for collaborative information sharing

- Again, ASGCT would welcome a co-hosted workshop to delve deeper into class considerations for cell and gene therapies and help the field move toward standardization, such as in the assessment of AAV therapies where appropriate.

- ASGCT also wishes to acknowledge the November announcement on FDA's investigation of T-cell malignancies in BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies.

American Society of Gene + Cell Therapy

Acknowledgements: Presentation Work Group

- Carsten Bonnemann, MD, NIH/NINDS
- Nimi Chhina, PhD, JD, BioMarin Pharmaceuticals
- Manuela Corti, PhD, University of Florida
- Ron Crystal, MD, Cornell University
- Terence Flotte, MD, University of Massachusetts
- Soumi Gupta, PhD, BioMarin Pharmaceuticals
- Mark Kay, MD, PhD, Stanford University
- Klaudia Kuranda, PhD, Spark Therapeutics
- Eugenio Montini, PhD, San Raffaele Telethon Institute for Gene Therapy
- Snehal Naik, PhD, Spark Therapeutics
- James Nickas, PharmD, BioMarin Pharmaceuticals
- Ali Nowrouzi, PhD, Spark Therapeutics
- Kristin Van Goor, PhD, Takeda Pharmaceuticals
- Keith Wonnacott, PhD, Lexeo Therapeutics

American Society of Gene + Cell Therapy

Thank You