Exon Skipping Gene Therapy

Astellas Gene Therapies' investigational treatment approach for Duchenne muscular dystrophy (DMD)

Who is Astellas Gene Therapies?

- Astellas Gene Therapies (formerly Audentes Therapeutics) is an Astellas Center of Excellence developing genetic medicines with the potential to deliver transformative value for patients.

- We are leveraging Astellas' global resources and deep scientific expertise to expand our reach and develop new genetic medicines for patients around the world.

- We depend on courageous patients and their families to advance our investigational therapies. Our patient communities are important partners and collaborators, informing our clinical trial programs and drug development process.

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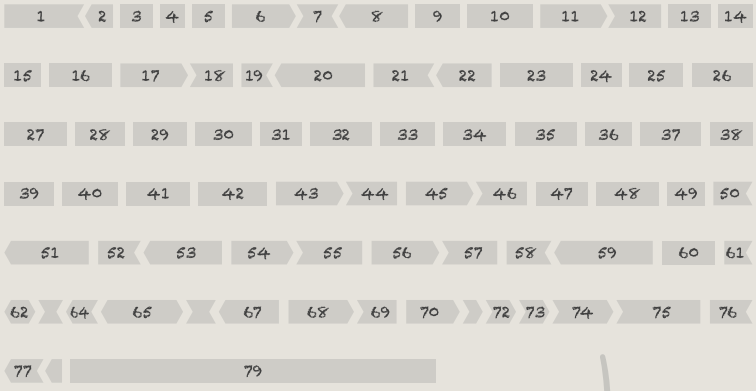
Duchenne Muscular Dystrophy

Duchenne muscular dystrophy, also referred to as DMD or Duchenne, is the most common type of muscular dystrophy in children, affecting approximately 1 in 3,500 to 5,000 male births with more than 300,000 patients living with the disease worldwide.[1]

Duchenne is caused by a genetic mutation in the DMD gene, which is responsible for producing dystrophin, a type of muscle protein.

Without dystrophin, cells become damaged and are unable to repair themselves. This results in loss of muscle strength and function, and ultimately affects the heart and breathing.

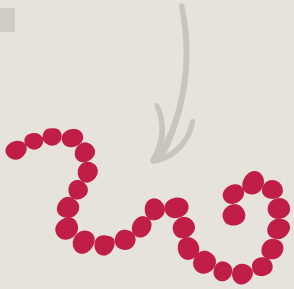
The DMD gene is the largest known human gene with 79 exons



When exons are deleted or missing, the instructions do not make sense and the body cannot make a working copy of dystrophin.

Without dystrophin, muscles do not function properly and weaken over time.

These 79 exons are linked together to form the instructions for making a protein called dystrophin



References:

1. Mendell JR, *et al*. Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Ann Neurol* 2012; 71:304-313.

While there is no cure for DMD, there are a number of approaches (both investigational and approved) that aim to slow or stop the progression of Duchenne.

One approach is exon skipping

- Exon skipping leverages small pieces of DNA called antisense oligonucleotides (ASOs) to "patch" or "mask" the exons that you want to skip (based on the specific mutation) so that the exons fit together and can be read to produce a shortened but functional dystrophin protein.

- However, ASO delivery to the muscle is limited and repeat administration is needed every week.

Another investigational approach is gene transfer therapy using AAV vectors

- AAV, or adeno-associated virus, is used as a vector, or a delivery vehicle, because it can potentially carry a new gene or genetic sequence into the appropriate cells in the body.

- However, AAV's limited DNA cargo capacity prevents large genes such as DMD from being inserted into the recombinant AAV, and therefore investigational clinical trials are underway to study significantly shorter microdystrophin genes.[2]

References:

2. Nance ME, Duan D. Perspective on Adeno-Associated Virus Capsid Modification for Duchenne Muscular Dystrophy Gene Therapy. *Hum Gene Ther.* 2015;26(12):786-800.

Our approach is Exon Skipping Gene Therapy for DMD

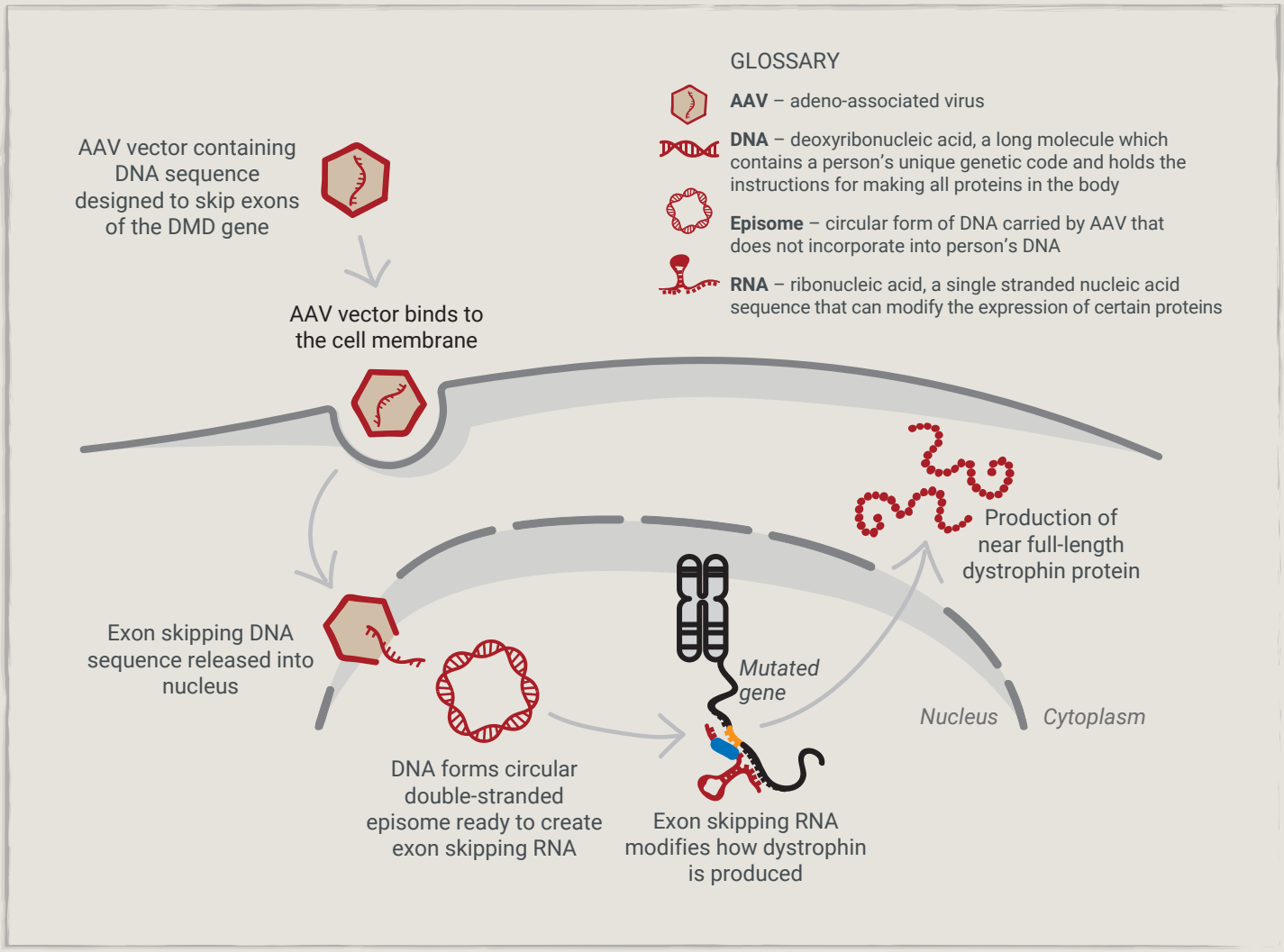


Image adapted from Wang D *et al*. 2019[3]

- Exon skipping gene therapy leverages two technologies - **single administration** of an AAV (adeno-associated virus) gene transfer therapy and exon skipping.
- AAV functions as a delivery vehicle which is being investigated to introduce a DNA sequence designed to skip sections (or exons) of the DMD gene.
- Exon skipping gene therapy is intended to be a **mutation-specific** treatment.
- The goal of this approach is a one-time treatment to potentially enable **ongoing production of a near full-length functional dystrophin protein***

* The dystrophin length will be determined by the specific mutation it is targeting.

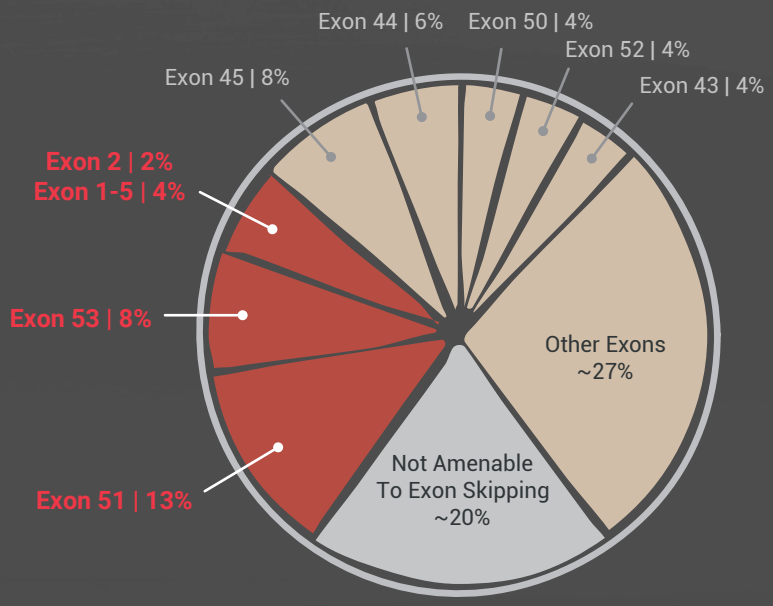
References:

3. Wang D *et al. Nature Reviews Drug Discovery* 2019; 18:358.

Leveraging a Platform Approach to Address Multiple Mutations

- It is possible that more than half of the prevalent DMD patient population could potentially benefit from eight exon-skipping products.[4,5,6]

- A "platform approach" may enable an accelerated pathway to clinical development for each exon skipping gene therapy.



Astellas Gene Therapies' initial DMD programs include*:

- AT702: Duplications of exon 2, mutations in exons 1-5
- AT751: Genotypes amenable to exon 51 skipping
- AT753: Genotypes amenable to exon 53 skipping

* All of these programs are still in a preclinical stage, meaning they are not yet being investigated in humans.

References:

4. Aartsma-Rus A. *et al., Hum. Mutation* 30:293, 2009.
5. Aartsma-Rus A. *et al., Muscle Nerve* 34:135, 2006.
6. Flanigan K. *et al., Human Mutation* 30:1657, 2009.

Hello

We are the Patient Advocacy & Engagement Team at **Astellas Gene Therapies**

WHO are we?

We are a team dedicated to you, the patient community.

WHAT do we do?

We engage with and listen to you, the patient community. We then bring those important messages back to Astellas Gene Therapies so we can plan our work on clinical trials, regulatory activities, and commercialization in a way that is most meaningful to you. Your experience as a person or family member living with a rare condition inspires our work.

Our priority is to weave your perspective into the fabric of our work and the daily activities at Astellas Gene Therapies

We are here to advocate for YOU with our colleagues at Astellas Gene Therapies

The definition of "advocate" is "to support a cause or proposal." However, we believe that truly advocating for patients and families requires much more than "support". It requires commitment, dedication, and passion to ensure we are continually doing what is right for patients.

Our Commitment to the Duchenne Community

Your input makes all the difference. We are committed to developing potential therapies that can have a meaningful impact on the lives of people and their families who are living with Duchenne.

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