Written Testimony of Pat Furlong
Founding President & CEO, Parent Project Muscular Dystrophy

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"Time is really the only capital that any human being has, and the only thing he can't afford to lose." -- Thomas Edison

In 1986, the *DMD* gene was cloned. The "hunt" for the gene spanned the United States, Canada, and Europe and finally, Louis Kunkel/Harvard was credited with this discovery. A young post-doc in his lab, Eric Hoffman, identified the protein product, dystrophin.

My sons, Chris and Patrick, were diagnosed in 1984. When the gene was discovered the press at that time suggested "gene therapy will cure Duchenne, soon". *Soon*, it turns out, takes at least 40 years.

Once the basic science was known, the quest expanded. Touring the country to learn about the federal investment in Duchenne muscular dystrophy (Duchenne), I met with NIH Director Dr. Bernadine Healy and FDA Commissioner Dr. David Kessler. Both suggested the identification of the gene and protein product were major steps forward, but insufficient for near term development of a treatment.

Dr. Kessler suggested **"come back when you know more"**. I thought we had enough information to move ahead with a gene and protein product, but Dr. Kessler compared it to looking at the globe, from a 60-thousand-foot view, and thus insufficient. We needed to understand the natural history of Duchenne and the role of the dystrophin protein to create treatments. Dr. Kessler suggested that we had only a single basic step toward understanding the complexity of Duchenne.

Over the next 30 years, many of those complexities were characterized. Individuals with mutations in their *DMD* gene leading to mild dystrophinopathy would be identified. Stories of active adults experiencing leg cramping and pain, when blood tests revealed elevated CK and found mutations in their *DMD* gene. Through early gene sequencing studies, researchers discovered there were several individuals with functional stability, despite mutations in the *DMD* gene, largely due to the production of a smaller version of the dystrophin protein that remained functional. Over time, and with the identification and sequencing of these individuals, researchers were able to identify specific exons within the *DMD* gene that would be critical for the development of a dramatically shortened version of the dystrophin protein that could "fit" into an adeno-associated virus (AAV) and be delivered as gene therapy.

By the early 2000s, genetic testing was readily available and was used widely for definitive diagnosis. Thousands of variants in the *DMD* gene were identified.[1] As these data were analyzed, the "in-frame, out-of-frame" rule evolved. *"Out-of-frame"* mutations indicated Duchenne – the absence of dystrophin, and the *"in-frame"* mutations referred to as Becker muscular dystrophy – based on the expression of a truncated, but functional, dystrophin. With the advent of this more common sequencing, individuals with large deletions were identified and studied, which increased

[1] Aartsma-Rus, A., Van Deutekom, J.C.T., Fokkema, I.F., Van Ommen, G.-J.B. and Den Dunnen, J.T. (2006), Entries in the Leiden Duchenne muscular dystrophy mutation database: An overview of mutation types and paradoxical cases that confirm the reading-frame rule. Muscle Nerve, 34: 135-144. https://doi.org/10.1002/mus.20586

understanding of the relationship of specific genetic mutations and dystrophin protein production, providing insight into the development of a dystrophin protein that could be delivered via an AAV.

These dramatically shortened versions of the protein, now labeled “micro-dystrophin,” have been developed over time by several researchers and have been tested in numerous and varied animal models. In these models, micro-dystrophin proteins have been found to be both stable and efficient, and in large animal models, resulted in improved function and lifespan.

The Duchenne community has invested, researched, and committed to what Dr. Kessler recommended as **“come back when you know more,” and now we have four decades of discoveries upon which to build.** The natural history of Duchenne is well-documented and the disease is well-characterized. Mutations in the *DMD* gene and their relationship with phenotype are better understood today and the role of dystrophin is well known. The micro-dystrophin construct, while not found in human nature, has been deliberately developed based on sequencing the variants from individuals with functional dystrophin in an effort to fully exploit critical domains of the dystrophin protein. Sarepta’s micro-dystrophin construct via AAVrh74, developed over 30 years and based on functional variants, is reasonably likely to provide benefit in our view.

We know more today, **and we are back. Patients and their families are waiting for the tipping point of “we know enough” to move forward with dramatic and life-changing interventions, such as gene therapy for those with unmet need and who live with relentless decline from Duchenne.** We ask that you thoughtfully weigh and factor in the voice and needs of the patient, and of our families, when making your decision.

Disclosure

Parent Project Muscular Dystrophy (PPMD) was an early funder of Dr. Jerry Mendell's research at Nationwide Children’s Hospital leading to SRP-9001. We have recovered some of that investment from Sarepta Therapeutics, and will receive an additional payment from the company if SRP-9001 is approved. We also have received milestone-based payments from Nationwide Children’s Hospital based on its licensing of the therapy; and expect additional payments if the therapy is approved. Any returns will be reinvested in programs supporting PPMD’s mission. PPMD has a comprehensive approach to identify opportunities to accelerate development of all therapies in Duchenne, including regulatory, research, and patient-recruitment counsel to help expedite the progress of SRP-9001.

1012 14TH STREET, NW, SUITE 500
WASHINGTON, DC 20005
ENDDUCHENNE.ORG