MyoGene Bio

907 Westwood Blvd
#376
Los Angeles, CA 90024
303-506-1681

November 12, 2021

Re: Application Review Subcommittee meeting for CIRM TRAN1-12920

Dear Independent Citizens Oversight Committee,

We thank CIRM and the Grants Working Group for their favorable reviews and recommendation for funding of our proposal, TRAN1-12920, *Development of MyoDys$^{45\text{-}55}$, a gene editing therapy for Duchenne muscular dystrophy*. Our goal at MyoGene Bio is to develop a highly effective gene editing therapy that is applicable to a large proportion of Duchenne muscular dystrophy patients. **The reviewers were extremely positive, noting *"The rationale is ingenious and novel and overcomes many limitations of previous strategies."* Importantly, there is currently no cure and only limited treatment options for Duchenne. Thus, there is still an unmet medical need, and our approach *"…would be a much needed treatment for a significant number of Duchenne muscular dystrophy (DMD) patients."***

Duchenne Muscular Dystrophy Prevalence in Underserved Communities:

We are also grateful for the reviewer's acknowledgement that *"The company itself is headed by a diverse team, and the applicants plan to collaborate with organizations already active in underserved communities for future recruitment"* However, we respectfully disagree with the reviewer's comment that "…*DMD is a disease where the vast majority of patients are boys or young men, and with white or caucasian families being more significantly affected."* **In fact, the CDC-funded MD STARnet estimates that Duchenne is not more common in white and Caucasian families**. The data show that the prevalence of Duchenne is highest in Hispanics (2.24-4.02 per 10,000 males) compared to non-Hispanic whites (1.78-2.26 per 10,000), non-Hispanic blacks (0.74-1.26 per 10,000) and non-Hispanic American Indian, Alaska Native and Asian or Native Hawaiian or Pacific Islander (0.61-1.83 per 10,000) (Zhang et al. *Neuroepidemiology* 2021; 55:47-55). **Thus, the prevalence of Duchenne does not significantly impact white or Caucasian families more than others and in fact, it impacts Hispanic populations the most.** Secondly, it has been demonstrated that good quality of care can extend walking time and the lifespan of patients with Duchenne. Because there is disparity in the access to and quality of health care for those who have a lower socioeconomic status (SES), their disease burden is disproportionately and negatively higher. For example, corticosteroid use in Hispanic and non-Hispanic black males is less than in non-Hispanic white males (Fox et al. *J Child Neurol.* 2015; 30(1):21-26). Since corticosteroids significantly impact disease progression (Kim et al. *J Child Neurol.* 2015; 30(10):1275-80), delay development of heart disease (Barber et al. *J Pediatr.* 2013; 163(4):1080-4.e1) and improve lung function, the reduced steroid use means that patients with lower SES are even more disproportionately affected by the Duchenne disease course and have a greater need for disease modifying therapies. Third, there is a great economic burden on Duchenne patients and their families because of the time and equipment needed to care for patients that lose the ability to walk and breathe. Often, one family member will become the full-time caregiver, and thus, this individual loses income due to the inability to hold an outside job, so the financial burden on those in a lower SES is significantly more than for families with greater means who can afford to pay for a caregiver. **Therefore, the impact of Duchenne disease is higher on patients who are not Caucasian and/or who are in a lower SES class.** Thus, there is a significant need in these communities for a therapy like ours, where **our gene editing approach is expected to significantly improve the disease and increase lifespan since our therapy acts on the underlying cause of Duchenne.** As described in our 'Addressing the Needs of Underserved Communities' section on page 13, we have efforts ongoing to ensure our approach will work for all ethnic and racial backgrounds and we have collaborators who are actively involved in recruiting patients from all backgrounds. MyoGene Bio is committed to fostering diversity and treating all underserved communities.

MyoGene Bio

Scientific Review - Safety and Toxicity:

We would also like to address some of the reviewers' comments with respect to concerns around toxicity and safety considerations because of the high doses of AAV-MyoDys$^{45\text{-}55}$ being used for delivery of our therapy. Through the aims in this proposal, we will bolster these data by testing different doses with and without immune suppression while also carefully assessing toxicity in two animal species (Grant Proposal Section C. Pilot Safety). Importantly, we expect the use of immune suppression (as described in our proposal) will be beneficial in three regards related to toxicity: 1) it will potentially allow for **redosing** (Figure 7) to improve efficacy; 2) it will help **dampen the immune response** to overcome some adverse events that have been observed in human gene therapy trials; and 3) redosing may allow for repeated administration of **lower doses**, which mitigate some of these safety concerns. With regards to point #2, use of immune suppression at time of dosing may prevent complement activation as well as the downstream immune responses to the viral carrier from developing. For example, it was shown that SMA patients given a B cell blocker, rituximab, prior to AAV dosing had reduced complement activation (public presentation, MDA meeting 2021), which is important since complement activation appears to significantly contribute to adverse events. Together, these effects have the benefit of improving both the safety profile and providing an opportunity to redose AAV if necessary. Lastly, we would like to note that we did show lack of gross liver toxicity in Figure 6D, as requested by the reviewer.

Scientific Review - Efficacy:

In terms of efficacy, it was noted *"There is evidence that some level of dystrophin production can be restored by the gene correction strategy. This is a complex gene correction though and likely to be comparatively inefficient with large amounts of cells that do not receive all the edits which would be needed for functional outcome."* We would like to point out that **we have already achieved dystrophin levels up to 85% in the heart and observed functional improvements in mice (Rodent Efficacy #1-4; Figures 5, 6, 8)** and that there is no evidence that our platform is significantly less efficient than other approaches. It is known that dystrophin levels as low as 1% can restore some function in Duchenne, and that levels of 15-30% can improve muscle function similar to that in healthy controls (Godfrey et al. *Hum Mol Genet.* 2015; 24:4225-37; Neri et al. *Neuromuscul Disord.* 2007; 17:913-8). **Thus, we are already achieving levels of dystrophin that are known to modify the disease course. The benefits of using a gene editing strategy to generate a dystrophin protein that has been associated with a mild disease course in humans makes our platform highly advantageous and superior to other approaches designed to skip single exons**. Furthermore, our ability to target **a large percentage of the patient population** in combination with our redosing approach implies that our single therapy will be highly effective across a large population of patients.

Scientific Review - Durability:

We appreciate and are addressing the concerns around the question *"Is there evidence that the vectors will work in children (the target population) in their growing tissues with dividing cells?"*. We should point out that muscle cells do not divide (page 16 of the grant proposal), however we acknowledge that as young boys grow and exercise there is a chance the levels of dystrophin may become diluted. This fact is the reason we are implementing measures to **redose** the platform if necessary. In our mouse studies, young mice treated at 3 days after birth show dystrophin levels up to 45% eight weeks after dosing, but in order to develop a long-lasting therapy, we anticipate that redosing will be needed at some point after the initial dose. We envision that the use of immune suppression will prevent an immune response from occurring to the viral carrier which could then allow redosing later after the patient has grown if there is a decrease in the amount of dystrophin over time. This aspect of our approach sets us apart from any others, since using a redosing strategy will lead to improve safety, better efficacy and the ability to redose patients as needed when they grow.

Scientific Review – Mouse and Dog Functional Testing:

We also appreciate the comments around the need for showing heart (cardiac) and breathing (respiratory) function as these are the leading causes of death in Duchenne. We would like to point out that **we did show an improvement in pulmonary (breathing) function in Figure 6C and we have ongoing cardiac assessments in mice.** In terms of the large animal model, we stated that we have **planned long-term and functional studies in the canine model**

MyoGene Bio

with additional funding (see page 25 of the grant proposal). The long-term and functional experiments in the dog are only justified if we first observe short-term efficacy. Thus, we plan to complete functional assessments, including heart function, in the canine model; however, these studies will be done with separate funding. Testing our therapy in a second animal species is critical to determine its ability to restore dystrophin in a larger animal model and to assess safety assessments as required by the FDA. The canine model is commonly used in the muscular dystrophy field (McGreevy et al. *Dis Model Mech.* 2015; 8(3)195-213) and our studies are in line with others that have moved into phase I trials.

Scientific Review – Comparison to Existing Treatments:

With respect to a comparison to existing treatments, such as exon skipping, our gene editing approach has significant advantages. We highlighted some of the problems with exon skipping in the Rationale on page 14, including that they are not permanent, only work for small subsets of patients (13% or less), and have only shown low levels of protein restoration and modest functional benefit. **In contrast, our gene editing approach permanently removes mutations in the patient's own DNA. Additionally, we target 50% of patients with a single therapy so will have a significantly larger target market. Lastly, we restore a dystrophin protein that has been associated with a very mild disease course in humans.** Thus, our approach is expected to be effective and longer lasting for more patients.

Scientific Review – Off-Target Studies Based on FDA Recommendations:

Additionally, we would like to address the reviewer's comment that "*More detailed quantification on the spectrum of genetic outcomes is needed*." **We sincerely agree that careful assessment of on and off-target changes is required.** We proposed detailed studies in Section C. Pilot Safety (pages 26-28) to look at off-target changes in human cells including specific targets as well as unbiased assessment across multiple methods. **These studies were designed based on feedback from the FDA in our INTERACT meeting** so we feel this approach should be sufficient. Additionally, we proposed to assess any changes at the on-target site in the animal studies since assessing off-target changes in a mouse or canine genomic background is not relevant for humans and was the recommended course from the FDA.

Fostering Diversity in Biotech:

Finally, we would like to highlight that **we are a fully women-founded startup**. According to the Harvard Business Review, women-led startups only obtained 2.3% of VC funding last year (Bittner and Lau https://hbr.org/2021/02/women-led-startups-received-just-2-3-of-vc-funding-in-2020). This CIRM grant opportunity would help us with venture funding, for example our co-funding linked to this application is partly from CureDuchenne Ventures. **As there is a significant disparity for women-founded startups, this grant will also help foster diversity within the biotech startup ecosystem and encourage further investment in our startup, which will ultimately allow us to bring this therapy to patients at a faster rate**.

In conclusion, we are sincerely appreciative of the Grants Working Group's thorough reviews and positive feedback of our proposal. We are committed to targeting diverse, underserved communities and are passionate about developing therapies to have a true impact on the disease course for this devastating muscle wasting disease. We hope the ICOC committee will agree with the points brought up in this letter and support this work to enable development of our gene editing platform to significantly improve the lives of Duchenne patients.

Sincerely,

Courtney Young, PhD
Principal Investigator
Co-founder and CEO, MyoGene Bio

April Pyle, PhD
Co-founder and advisor, MyoGene Bio

Melissa Spencer, PhD
Co-founder and advisor, MyoGene Bio