MyoGene Bio

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December 4, 2025

Re: PDEV-19136 Discussion

Dear Members of the Application Review Subcommittee,

We thank CIRM and the GWS for their positive comments on our application, PDEV-19136, "IND-enabling activities for a gene editing therapy for Duchenne muscular dystrophy". They highlighted our key strength of a "novel approach" that would "offer significant value" for a disease with an "urgent unmet medical need" and commented the "Project plan and design is excellent" and "Project team and resources are excellent". This application aims to develop a novel gene editing therapy for Duchenne, a fatal muscle wasting disease with no cure. I re-focused my research career towards Duchenne after my cousin was diagnosed, and I have remained committed to developing a therapy for this disease ever since. He is now approaching his 20s, which underscores the urgent need to advance promising therapies for this devastating disease as quickly as possible. As CIRM has no other advanced translational projects for Duchenne in their current portfolio, we urge the Subcommittee to consider recommending PDEV-19136 for funding. The application was just below the funding line, and we are well-positioned to address the key concerns.

1. **Concerns around dual vector strategy**. As mentioned in the application, a key advantage of the dual vector system is the ability to include Cas9 inactivation, which greatly enhances the safety of the platform. Instead, if combined in a single vector, Cas9 could self-cleave during manufacture, making it impossible to obtain purified intact cargo. Furthermore, we tested the platform with and without Cas9 inactivation *in vivo* and did not observe any significant difference in dystrophin levels, so inclusion of Cas9 inactivation does not adversely affect the efficiency of on-target editing. Additionally, during discovery we compared the efficacy of dual and single vector designs and observed superior efficacy with the dual vector strategy. Thus this approach does not appear to limit efficacy and including Cas9 inactivation is an important safety feature.

2. **Concerns around high vector doses**. Reviewers commented on potential safety concerns and manufacturing costs associated with high doses of AAV9. We will mitigate these risks with an enhanced immune suppression regimen targeting B and T cell responses to AAV and Cas9. Because most adverse events have an immune basis, this approach is expected to substantially reduce AAV-related toxicities. The selected drugs directly address the key safety risks associated with high dose AAV, as highlighted in the table below.

Intervention/ Target	Prednisone	Sirolimus	Rituximab	Intended safety effect	Intended efficacy effect
B cells		-	- -	Lower antibodies to reduce complement activation and TMA	Increase transduction
Cytotoxic T Cells	- -	- -	-	Reduce liver and cardiac injury	Prevent loss of transduced muscle
Tregs	+	+	+	Decrease T cell activation	Increase tolerance to capsid and transgene

- = inhibition, + = promoting

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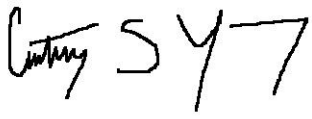
In preclinical and clinical studies (see Salabarria et al. *JCI* 2023, Patel et al. *Molecular Therapy* 2023, Corti et al. *Mol Ther Methods Clin Dev* 2014, Mueller et al. *NEJM* 2020, Neumann et al. *Pediatr Neurol* 2025) this regimen has been demonstrated to reduce antibody formation, prevent complement activation, prevent or reduce T cell activation responses, and could be used to prevent or revert liver enzyme elevation, including at doses of 1E14vg/kg. Additionally, we and others (Saha et al. *Hum Gene Ther* 2025) have observed in murine studies that this regimen significantly increases AAV transduction and transgene expression. During our pre-IND meeting, FDA supported the use of this immune suppression regimen and confirmed it should be used in our IND-enabling BD toxicity study in NHPs. This study, proposed in our application, would determine the impact of the immune suppression regimen on safety outcomes, transduction and cargo expression. It would allow us to select a dose that is expected to be safe when combined with enhanced immune suppression. Since this regimen has shown promising benefit in other preclinical and clinical studies, it is important to evaluate it in the context of our vector and doses. Regarding manufacturing costs, in the application we included process development activities to optimize the yield of AAV. Additionally, our CDMO partner has also recently introduced improved plasmids that have improved yields by up to 14x. This would decrease manufacturing costs.

3. **Meaningfulness of low DNA cutting levels**. Duchenne is caused by loss of dystrophin protein, thus our primary outcome is restoration of dystrophin, not raw DNA editing frequency. Relatively few edited genomes can yield disproportionately high levels of dystrophin. We have shown after *in vivo* delivery, up to 60-80% dystrophin positive fibers and 20-25% total dystrophin protein levels, which are well within the range associated with functional benefit. Each edited muscle nucleus supports translation of a more stable dystrophin transcript and protein that could supply dystrophin to the entire fiber. For these reasons, dystrophin protein restoration is a more meaningful outcome than editing.

Of note, no major concerns were identified with the projects proposed in our application. Our proposed studies would evaluate manufacturability and safety, so ultimately the reviewers' questions would be answered by the work. Duchenne remains a disease where muscle degeneration increases over time and is fatal in the 20-30s, so innovative translational work is urgently needed. We appreciate CIRM's prior support through our TRAN grant and are eager to continue development as quickly as possible. Thus, we urge the Subcommittee to consider recommending PDEV-19136 for funding so a next generation approach for Duchenne can be advanced to patients as quickly as possible.

Sincerely,



Courtney Young, PhD

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