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December 3, 2025

Subject: PDEV-19165: Solving Key Barriers in DMD Therapy

Dear Members of the Application Review Subcommittee,

We respectfully request that the ARS review the programmatic value of application **PDEV-19165** and consider elevating it for funding. The Grants Working Group (GWG) assigned this application a strong score with minor comments and coupled with the urgent unmet need in Duchenne Muscular Dystrophy (DMD) we feel this proposal warrants immediate action.

PDEV-19165 overcomes the primary failure points of current DMD therapies: hepatotoxicity and poor muscle targeting, by using a novel AAV capsid that achieves unprecedented liver detargeting and superior muscle delivery. To safely treat DMD, we use our novel capsid to deliver an optimized RNA payload via a single all-in-one vector which causes 'skipping' of the problematic exons resulting in restoration of full-length dystrophin production.

To bring this to patients, we have assembled a **strong scientific, clinical, and commercial team** uniquely capable of execution, combining genetic medicine leaders at UCSD (Mali and Engler Labs), NHP toxicology expertise at UC Davis (Dr. Alice Tarantal), and gene therapy vector engineering/manufacturing specialists at Pi Bio and Charles River Labs. Clinically supported by the UCSD Altman Clinical and Translational Research Institute (ACTRI) and commercially by an advisory board of seasoned biotech founders (former Founders/CEOs of Shape Tx, Carmot, OriBiotech), our team possesses the full spectrum of expertise required to drive this therapy to the clinic.

We ask you to consider three critical factors that argue against delaying funding of this therapy:
1. We Enable Safer DMD Therapy Delivery: Our proposal demonstrates **best-in-class muscle targeting** (highly superior to FDA-approved AAV9) across mice, rhesus macaques, and human cells. Crucially, our capsid achieves **up to ~100X liver detargeting**, offering a safety profile far superior to current clinical options. We have confirmed manufacturing yields comparable to AAV9 and identified the conserved receptor mediating muscle delivery. Thus, we are ready to transfer to our CDMO and conduct GMP/GLP studies.
2. We Enable Safer DMD Therapy Payloads: Unlike riskier gene-editing alternatives, our platform uses AAV delivered therapeutic RNA for exon skipping. This enables facile packaging in a **single AAV vector**, **no immunogenicity** as no foreign prokaryotic proteins are delivered, and avoids the permanent risks of DNA editing while achieving clinically relevant dystrophin levels. Our approach also naturally avoids off-target dystrophin expression and produces a larger dystrophin protein compared to microdystrophin based approaches.
3. Benefits to California & Urgency: Recent FDA restrictions on Sarepta's *Elevidys* due to liver toxicity (the exact issue our technology solves) have caused private capital to retreat from the DMD space. Without CIRM

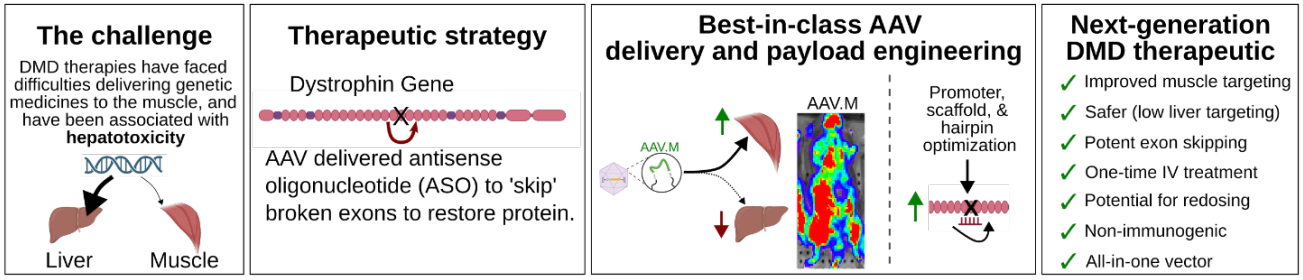
intervention, progress on this superior asset will likely halt, leaving California patients with few options. PDEV-19165 fills a critical gap in the CIRM portfolio, which has only ever funded one other late-stage translational DMD project (in 2021). Looking to the future, we have developed multiple novel muscle-tropic capsids to enable immune 'stealth' for potential redosing, providing a path to follow on medicines for the DMD community and highlighting the long-term value of this proposal.

Thank you for your consideration of this grant proposal. We have included a visual summary of our relevant data below.

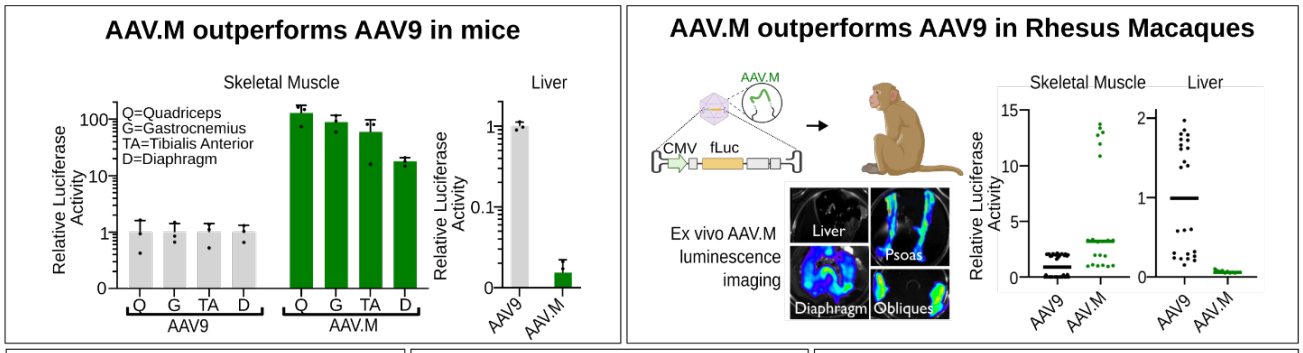
Sincerely,

Prashant Mali, Ph.D.

Optimized technologies solve the key problems facing DMD therapy development



AAV.M is well validated and ready for GMP manufacturing scale up



AAV.M.DMD: Potent exon skipping for DMD via a one-time genetic treatment