29th November 2025

Subject: Letter of support regarding application PDEV-19165

Dear Members of the Application Review Subcommittee,

I am writing to offer my unequivocable support for application **PDEV-19165** ("*Novel muscle-tropic AAV and RNA targeting strategy for safe and efficacious gene therapy for Duchenne Muscular Dystrophy*") and to respectfully request that the ARS select this project for funding. I wish to address the reservations regarding preclinical readiness and highlight why this technology represents a specific, critical evolution for the field of Duchenne Muscular Dystrophy (DMD) therapy.

Please can I first provide some background information. I am an internationally recognized leader in cell and gene therapy, with over 30 years of experience spanning R&D, clinical medicine, bioprocessing (CMC) and commercialization. I am a full Professor of Cell and Gene Therapy in the Department of Biochemical Engineering at University College London, UK. I moved to the US in 2015 (US citizen) to found AVROBIO (Cambridge, MA) and was the company's Chief Scientific Officer (CSO) until 2022. I am the Founder and Board Member of OriBiotech (London, UK and Philadelphia, PA), a company focused on next-generation fully-automated cell therapy bioprocessing. I am also Founder and CEO of a gene therapy company, Sun Vectors, based in San Diego, CA. I am on the Board of Krystal Biotech (Pittsburgh, PA), a NASDAQ-listed biotech company, and Papillon Therapeutics (San Diego, CA), and a Board Member of the Foundation for mRNA Medicines in Washington DC. I am the Senior Editor of the journals Cell and Gene Therapy Insights and Regenerative Medicine. In 2019, I was elected as a Fellow of The Academy of Medical Sciences. I therefore believe that I am highly qualified to make expert comments on this application.

My support for PDEV-19165 is motivated by the robust muscle targeting capabilities of the proposed team, and I am especially excited about work they have done to develop **redoseable muscle targeting AAVs.**

The greatest barriers to systemic gene therapy is hepatotoxicity and the liver acting as a giant sink for vectors, therefore requiring bigger doses and further increasing the risk of hepatotoxicity whilst driving up the cost of goods. This proposal utilizes the novel AAV.M capsid, which demonstrates an unprecedented **reduction in liver targeting** and **increase in muscle targeting** compared to AAV9. This massive

detargeting provides the safety margin necessary to unlock DMD treatments, and the proposing team has developed additional muscle targeting capsids that are sufficiently divergent from AAV.M to avoid immune cross reactions. This technological advancement **enables <u>redosing regimens, which would be a major clinical breakthrough.</u>**

The current clinical reality for DMD (exemplified by the limitations of products like Sarepta's *Elevidys*) is that existing gene therapy approaches are limited by life threatening hepatotoxicity. Hepatotoxicity creates profound dose limitations, critically limiting treatments for a degenerative disease where expression must persist over a patient's lifetime. PDEV-19165 offers a distinct departure from this constraint. PDEV-19165 presents a novel liver detargeted AAV capsid and therapeutic approach, which on its own would be worthy of investment and pre-clinical development. But the capability to develop novel AAV capsids for re-administered therapies would fundamentally alter the management of DMD and gives this proposal unprecedented long-term commercial potential and potential to develop an entire franchise of DMD drugs.

Regarding the specific concerns over capsid readiness, the data provided is robust and reassuring. The team has validated AAV.M across mice, rhesus macaques, and human cardiomyocytes, demonstrating best-in-class muscle targeting in every model. While more pre-clinical development work is yet to be done, this is a de-risked asset and technology ready to revolutionize DMD treatment.

Finally, the timing for CIRM support is critical. Following recent regulatory setbacks for existing DMD treatments, private investment in this space is non-existent. Without CIRM funding, this project and its potential to solve the durability and safety issues currently stalling the field with be paused and potentially lost.

<u>I mostly strongly urge the committee to look past the minor hesitation regarding readiness and focus on the transformative potential of a safe, redoseable therapy for DMD patients who currently have very few options.</u>

Yours sincerely,

Christopher Mason MD, PhD, FRCS, FRSB, FMedSci
Professor of Cell & Gene Therapy
Advanced Centre for Biochemical Engineering
University College London
Gower St, London WC1E 6BT, UK
chris.mason@ucl.ac.uk