Open Letter to the Application Review Subcommittee

Re: *PDEV-19751 – Autologous ABCD1 ex vivo gene-modified iPSC-derived microglia cell therapy for cerebral adrenoleukodystrophy (CALD). (Xiaokui Zhang, P.I.)*

Dear Members of the Application Review Subcommittee,

We thank the Grants Working Group for their thoughtful and rigorous evaluation of our application and appreciate the recognition of the program's strength, including its high clinical impact, strong scientific rationale, compelling value proposition, and experienced translational team.

We respectfully submit this letter to clarify several aspects of the review that we believe may have been misunderstood and materially impacted scoring.
Most importantly, we wish to underscore the profound unmet medical need in cerebral adrenoleukodystrophy (CALD), a devastating pediatric neurodegenerative disease for which many patients lack viable treatment options.

Approximately 70% of CALD patients lack a suitable donor for stem cell transplantation, and currently available interventions carry substantial risks and access limitations. We believe our program offers a highly differentiated regenerative medicine approach with the potential to fundamentally expand treatment access and improve outcomes particularly in ethnically diverse geographies, such as in California.

Key Scientific Clarifications

- **Engraftment and CNS Repopulation:** The review referenced a benchmark of <8% engraftment and concluded this threshold was not achieved. We respectfully believe this reflects an interpretation of an intentionally early dataset included to demonstrate initial CNS entry after intrathecal administration at four weeks. Since submission, we now demonstrate **complete brain and spinal cord microglial repopulation within three months following intrathecal delivery,** and **near-complete CNS repopulation within one month using intracisterna magna administration.** These findings substantially exceed the benchmark referenced during review and support robust therapeutic feasibility.
- **GLP Toxicology Study:** Reviewers noted concerns regarding GLP toxicity alignment. Our application outlines an **FDA INTERACT-informed translational strategy**, combining disease-relevant safety assessment in the FIRE mouse model with formal GLP toxicology studies

10835 Road to the Cure, Ste. 100, San Diego, CA 92121 858.263.1222 AspenNeuroscience.com

through a CRO. This staged approach was intentionally designed to support scientific rigor while aligning with supportive regulatory feedback.

- **CMC/GMP Compliance:** Reviewers noted incomplete CMC detail. As an Early PDEV application operating under strict page limitations, the submission intentionally prioritized key translational elements while not fully elaborating the breadth of the manufacturing readiness. Importantly, Aspen Neuroscience has already established a **clinically validated autologous iPSC manufacturing and analytical framework** supporting an active Phase 1/2a Parkinson's disease clinical program. This includes GMP manufacturing infrastructure, patient-specific chain-of-identity controls, release and characterization assays, and experience supporting IND-enabling and clinical stage operations. From the CALD program specifically, we have completed a **comprehensive GMP gap assessment**, and required CMC materials and manufacturing plans are available to support translational advancement. We believe this substantially reduces execution risk and represents an important strength of the program. Notably, reviewers recognized the value of our automated autologous manufacturing and analytical framework, strong characterization for patient identity and off-target effects, and an existing CA-licensed CMC facility supporting a clinical-stage Parkinson's disease program.
- **Conditioning Regimen:** The review noted the conditioning regimen was not fully addressed. As an Early PDEV application, we intentionally preserved flexibility while pilot studies mature rather than prematurely committing to a single conditioning paradigm. Our leading strategy focuses on **PLX-mediated microglia niche depletion**, designed to minimize toxicity while supporting engraftment as extensively documented in the literature.

Why CIRM Support Matters

CALD remains an ultra-rare pediatric disease with limited commercial development pathways despite devastating consequences for affected children and families.

Aspen Neuroscience has made significant investments in advancing autologous iPSC-based regenerative medicine into the clinic. However, rare pediatric CNS disorders such as CALD face substantial translation and financing barriers that conventional funding mechanisms rarely support.

CIRM funding represents a critical opportunity to advance this highly innovative program through key translational milestones. Without such support, further development of this program may not be feasible, potentially delaying or preventing a promising therapeutic option for children with limited alternatives.

We believe this application reflects the type of **high-risk, high-impact regenerative medicine innovation** that CIRM was established to enable.

In summary, we respectfully believe our application aligns strongly with CIRM's PDEV priorities through:

- **a first-in-class gene-edited, pluripotent stem cell-derived therapy,**
- a program addressing a **devastating pediatric CNS disease with profound unmet need**,
- an **FDA-informed translational strategy**, and
- a platform with broader implications for microglial replacement in neurological disease.

We are grateful for your consideration and respectfully ask for your support in enabling this potentially transformative therapy to move forward for children and families affected by CALD.

Sincerely,
Xiaokui Zhang, PhD
Principal Investigator
Aspen Neuroscience, Inc.

May 29, 2026

CIRM Grants Working Group / Application Review Subcommittee,

On behalf of ALD Connect, we are pleased to provide this strong letter of support for Application PDEV-19751, "Autologous *ABCD1* ex vivo gene-modified iPSC-derived microglia cell therapy for cerebral adrenoleukodystrophy (CALD)."

ALD Connect is a patient-driven organization dedicated to improving outcomes for individuals and families affected by adrenoleukodystrophy (ALD). Through our engagement with patients, caregivers, and clinicians, we understand the urgent need for safer, faster, and more accessible treatment options for CALD. Although ALD is rare, cerebral ALD develops in an estimated 35–40% of boys with an *ABCD1* mutation and can lead to irreversible neurologic decline, severe disability, and death within a few years if untreated.

We have engaged with Aspen Neuroscience for more than three years through ALD Connect conferences and regular Industry Advisory Council meetings, giving us confidence in both the scientific rationale for this program and Aspen's commitment to the ALD community.

While current treatment approaches, including hematopoietic stem cell transplantation and gene-modified cell therapy, represent important advances, they remain associated with significant limitations. These options often require intensive conditioning regimens that carry substantial risk, particularly for pediatric patients, and access remains inequitable for families facing barriers to timely care or suitable donor availability. Patients from racially and ethnically diverse backgrounds may face even greater difficulty finding suitably matched donors. We also hear directly from families who are scared of the oncogenic risks associated with the currently approved gene-modified cell therapy and are urgently seeking safer treatment options.

Families in our community consistently express the need for therapies that reduce treatment burden, improve safety, and expand access. As ALD Connect has emphasized in calls with our community, "Time is Brain" for children with CALD, and a safer, more rapidly delivered alternative would represent a meaningful advancement for patients and caregivers.

The approach proposed in this application, a gene-corrected autologous microglial replacement therapy, leverages a cutting-edge therapeutic technology to address the underlying biology of CALD while potentially improving safety, speed, access, and patient outcomes. An autologous approach will reduce dependence on donor matching, support more timely treatment, and broaden access to stem cell-based genetic therapy across patient populations, including those less likely to find a suitably matched donor through current approaches.

We strongly support investment in this program and believe it is well aligned with CIRM's mission to advance transformative regenerative medicine approaches for Californians with serious unmet medical needs, including strategies that improve patient access to stem cell-based and genetic therapies. By leveraging a cutting-edge therapeutic technology, this program has the potential to deliver transformative improvements in outcomes for patients and families affected by CALD, including those in California, where newborn screening has already identified boys with ALD.

Thank you for your consideration.

Sincerely,

Kelly Miettunen

Kelly Miettunen, MHA
ALD Connect
Executive Director

University of Minnesota

Twin Cities Campus ***Pediatric Blood and Marrow Transplantation & Cellular Therapy***
Medical School

Mail Code Mayo 366
420 Delaware Street S.E.
Minneapolis, MN 55455
Phone: 612-281-7825
Fax: 612-626-4074

May 26th, 2026

PDEV CIRM Grants Working Group / Application Review Subcommittee,

I am writing in strong and unequivocal support of Application PDEV-19751, "Autologous ABCD1 ex vivo gene-modified iPSC-derived microglia cell therapy for cerebral adrenoleukodystrophy (CALD)." As a clinician caring for boys with CALD, including approximately 20 patients in California currently, I can attest firsthand that the current standard of care (SOC) inadequately addresses patients' needs and creates a profound urgency to develop safer, more effective, and more accessible therapeutic options.

This proposal strongly aligns with CIRM's mission and directly addresses key priorities. First, it has clear potential to deliver transformative improvements in patient outcomes by leveraging cutting-edge therapeutic technologies. The use of autologous, gene-corrected iPSC-derived microglial precursors represents a highly innovative strategy aimed at correcting the underlying disease biology. iPSC-derived microglia have emerged as a promising platform capable of supporting neuronal health and enabling CNS-targeted therapeutic approaches. In contrast to hematopoietic stem cell transplantation (HSCT) and lentiviral gene therapy, which require intensive conditioning and carry significant risks, including therapy-related malignancy (related to lentiviral gene therapy), this approach offers a fundamentally novel mechanism with the potential for both improved safety and durability.

Second, the application advances strategies to improve patient access to stem cell-based and genetic therapies. Donor availability for allogeneic HSCT remains limited, particularly for non-Caucasian patients due to HLA diversity and underrepresentation in donor registries. In addition, safety concerns continue to impact treatment decisions; for example, lentiviral gene therapy for CALD has been associated with an increased risk of hematologic malignancy, with multiple cases of myelodysplastic syndrome or acute myelogenous leukemia reported in clinical studies. The proposed autologous approach eliminates donor dependence and may reduce reliance on toxic conditioning, thereby broadening access across diverse patient populations in California. This is well aligned with CIRM's mission to deliver regenerative medicine therapies equitably across the state.

Third, while focused on CALD, this work has broader implications that address both rare and more prevalent diseases affecting Californians. Microglial biology is increasingly implicated in a wide spectrum of neurological and neurodegenerative disorders, and iPSC-derived microglia platforms are being explored as scalable therapeutic systems beyond rare monogenic diseases.

In my clinical practice, families no longer desire the risk associated with the currently approved gene therapy, Skysona, as the best option due to safety concerns. Families are often forced to weigh rapid neurodegeneration against substantial treatment-related risks and long-term uncertainty. The Aspen approach, direct microglial replacement with autologous, *ABCD1*-corrected precursors, has the potential to address the root cause of disease while reducing risks of graft-versus-host disease and eliminating donor dependency. If successful, this program would directly benefit California families by expanding access to a potentially safer and more equitable therapeutic option.

University of Minnesota

Twin Cities Campus ***Pediatric Blood and Marrow Transplantation & Cellular Therapy***
Medical School

Mail Code Mayo 366
420 Delaware Street S.E.
Minneapolis, MN 55455
Phone: 612-281-7825
Fax: 612-626-4074

In summary, Application PDEV-19751 is highly responsive to CIRM priorities and represents a compelling, innovative, and impactful approach to addressing a critical unmet medical need.

Thank you for your thoughtful consideration.

Sincerely,

Troy Lund MSMS PhD MD FAAP
Professor
Associate Director Metabolic Program
Pediatric Medical Director Fairview Home Infusion
University of Minnesota, A NORD Rare Disease Center of Excellence
Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy
Leukodystrophy Center of Excellence
Stem Cell Institute
Global Pediatrics
Minneapolis, MN 55455