City of Hope

BECKMAN RESEARCH INSTITUTE

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December 8, 2025

Application Review Subcommittee (ARS)
Independent Citizen's Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

Re: Application #: PDEV-19139
PI Name: Yanhong Shi
Project Title: Develop a human iPSC-based cell therapy for Canavan disease

Dear Members of the Application Review Subcommittee:

I am writing to ask you to consider our PDEV proposal titled "Develop a human iPSC-based cell therapy for Canavan disease" for funding. We thank the Grants Working Group (GWG) for recognizing the novelty, feasibility, and clinical potential of our proposed autologous cell therapy using patient iPSC-derived neural progenitor cells (NPCs) that are transduced with a functional aspartoacylase (ASPA) gene to treat Canavan disease. We appreciate GWG's thoughtful review, recognition of our team's combined expertise, and their recommendation for funding (score of 85). This project is a continuation of a prior CIRM TRAN1 award, which allowed us to develop a GMP-compatible manufacturing process for human iPSC derivation and differentiation. This GMP-compatible manufacturing process will be qualified and used to generate human iPSC-based therapeutic product for Canavan disease for safety and proof-of-principle efficacy assessment in the proposed PDEV project.

Our project will meet a **critical unmet need** for developing therapy for Canavan disease, a rare, progressive and **fatal neurological disorder** that has neither a standard treatment nor approved therapy. Children with Canavan disease often die within the first decade of their life, although advances in supportive care now allow more to live into their teens. However, patients remain confined to a wheelchair starting in childhood, with the inability to speak and to feed themselves starting early in life. By using lentivirally transduced autologous iNPCs that express a functional ASPA gene, our approach has the potential to provide a long-term means of overcoming patients' deficiency in ASPA enzymatic activity and **significantly improving outcomes**. As noted by the GWG, "This treatment, if successful, would provide a meaningful and substantial improvement in clinical outcomes."

As indicated in the CIRM Team Recommendations: PDEV memo, the current CIRM portfolio contains no active PDEV or CLIN2 awards that address Canavan disease. Thus, our project will **bring novelty to the CIRM portfolio**, while continuing a productive project that has advanced from previous CIRM funding. In

addition, only a direct gene therapy approach is currently being clinically evaluated for Canavan disease — adeno-associated virus (AAV)-based gene therapy. Although there are two ongoing clinical trials testing AAV-based gene therapy for Canavan disease and interim results suggest tolerability and early effects, the long-term efficacy and safety profile of this approach remain to be evaluated over time. Moreover, a recent report for one of the trials in *Nature Medicine* indicated that no significant improvement in gross motor function was detected. Given it is unlikely that a single approach will prove effective for all patients, developing additional therapeutic strategies is essential if we are to find a cure for this fatal disease and give options to patients and their families to select the approach that fits them the best. **Thus, our project furthers CIRM's mission, expands its portfolio for neurological conditions, and has the potential for substantially broadening the scope of potential therapies for Canavan disease.**

The CIRM Team Recommendations memo noted additional factors that went into their recommendation that we have addressed below:

1. **Competitive landscape:** *"Assessment of the external competitive landscape (based on Globaldata) indicates there are 2 late-stage clinical programs but no approved US treatments addressing Canavan disease. An intracerebroventricularly delivered AAV gene therapy being developed by Myrtelle has published interim clinical results (Nature Medicine), and is part of the FDA START pilot. The second late-stage clinical program, an intravenously delivered AAV gene therapy being developed by BridgeBio has also released interim clinical results. The two late-stage AAV gene therapies and the proposed candidate in this PDEV application are all designed to deliver a functional ASPA gene. In contrast to the off-the-shelf in vivo gene therapy landscape programs, the proposed candidate in PDEV-19139 is an autologous lentiviral gene-modified iPSC-derived neural progenitor cell therapy that requires neurosurgical delivery to multiple brain regions."*

Response: As discussed above, although there are two ongoing clinical trials testing AAV-based gene therapy for Canavan disease, interim outcomes are mixed, and long-term efficacy and safety remain to be determined. Therefore, further studies and therapeutic approaches are needed. Our combined cell and gene therapy approach offers several advantages over the AAV-based gene therapies. Compared to direct gene therapy, our combined approach will allow for extensive *in vitro* characterization of genetically modified cells before in vivo administration, thus reducing risks that may arise from potentially faulty cells. Furthermore, the lentivirus-introduced *ASPA* transgene will likely be more stable because it will be integrated into the cells, therefore allowing sustained, long-term ASPA activity in the host brains. This is an advantage over AAV-mediated transgene delivery, which is non-integrative and thus allows only transient expression, meaning patients will likely need repeated dosing for continued benefit. Our autologous cellular products could also avoid potential immunogenicity, eliminating the need for long-term immunosuppressive drugs and avoiding reduced efficacy due to immune response. In contrast, AAV immunogenicity, including immune responses against the AAV capsid and transgene, remains an unmet challenge that can adversely impact clinical success. Finally, because stem cells naturally replicate and regenerate, our approach has the added benefit that the cells are expected to have a sustained, long-term presence in patients, eliminating the need for repeat dosing throughout the patient's lifetime.

2. **Manufacturing and administration:** *"The proposed autologous genetically-modified cell therapy requires a time and resource intensive manufacturing process as well as a complex invasive neurosurgical procedure for delivery to patients."*

Response: In terms of the manufacturing process, combined cell and gene therapy manufacturing is well-established for cellular products such as CAR T cells. Furthermore, **the GWG agrees "The manufacturing has been well developed with good feedback from the FDA pre-IND meeting."**

Reassuringly, we successfully conducted manufacturing development activities under a previous CIRM TRAN1 award, and have recently finished a full round of qualification run for the manufacturing process. The resulting cell product **met all release criteria**, supporting the feasibility of our manufacturing process. Regarding surgical complexity, **the planned surgical procedure for delivery is a routine surgical procedure** that our neurosurgeon is highly experienced with, as are many other neurosurgeons. A similar procedure has been used to deliver dopaminergic progenitors to Parkinson's disease patient brains at other institutions and the results were recently published in two *Nature* papers; the surgical procedure was well tolerated and showed no adverse effect in both studies (Sawamoto et al. 2025 Nature, PMID: 40240591; Tabar et al. 2025 Nature, PMID: 40240592). Furthermore, our proposed approach is expected to have a sustained therapeutic effect; therefore, there will be no need for repeated dosing, unlike for AAV-mediated therapy. We believe the potential for only a single dose of our cell therapy product outweighs the concerns raised about administration for this incurable disease, and increases accessibility over the long-term compared to other options in development. This is especially pertinent considering that care of Canavan disease patients is extremely expensive, on the order of $1 million per patient per year. The development of our therapeutic approach will not only improve the quality and save the lives of children with Canavan disease, but also reduce the healthcare costs for these patients substantially.

3. **Progress to IND:** *"The inability to achieve IND clearance with existing NIH U01 funding raises concerns about timely execution of project activities and efficient use of the CIRM requested funds toward achievement of the expected outcome of the PDEV award."*

Response: While working to achieve IND clearance, we communicated regularly with Canavan disease patient families and patient advocates. To **increase the accessibility** of our product, an advocate recommended we switch the starting material for iPSC manufacturing from skin biopsies to blood samples. The advocate advised us that this change would increase the likelihood that families would participate in the trial, and also make the final therapy more accessible should it go to market, due to the ease of blood sample acquisition compared to skin biopsy acquisition, which requires anesthesia that can be challenging to Canavan children. To make this change, we spent extra time developing an IRB-approved protocol to recruit CD patients for blood samples to serve as the starting material for qualifying our revised manufacturing process, instead of using skin fibroblasts from deceased CD patients as the starting materials as we had initially proposed in the NIH U01 grant. We had to recruit patients for blood sample acquisition because no fresh blood samples from CD patients are available from any repositories that we could use directly as the starting material for our manufacturing process qualification. Although this increased our timeline to IND application, it has improved our research and its relevance to Canavan patients and their families, and will benefit the conduct of the future clinical trial. Through patient recruitment for blood sample acquisition, we have established connections with the Canavan disease community and relevant, patient-focused logistics for blood sample acquisition, which will greatly facilitate patient recruitment and processes for the proposed clinical trial.

In addition, extra time was spent to develop the method for generating iPSCs from blood samples and differentiating PBMC-derived iPSCs into NPCs, which we have successfully done now. Moreover, we took extra time to compare the attributes of NPCs derived from PBMC-iPSCs and NPCs derived from fibroblast-iPSCs and showed that they are comparable. We presented these results to the FDA for approval to change our starting material from skin biopsies to blood samples for GMP manufacturing. The response from the FDA was delayed, which further delayed overall progress of the project.

Reassuringly, we have now obtained FDA approval to change the starting material for the manufacturing from skin to blood and have established revised SOPs for the manufacturing process starting from blood. Our PDEV application package included both the data we sent to the FDA (2023 0626

request_for_feedback_qualrun_preclin_PS005387, page 3-6) and the FDA approval (2023 1006 FDA Corres_Response_CMC_FU_PTS_PS005387). The FDA approval of this change supports feasibility of manufacturing our product from PBMCs, addressing the GWG concern regarding pilot data supporting this approach. Indeed, **GWG reviewers noted that "The risks to achieving objectives for this grant have been mitigated by the extensive meetings and correspondence with the FDA."** Moreover, we have finished a full qualification run starting with blood samples and shown that the product generated from our established manufacturing process meets all release criteria. With the FDA approval and established manufacturing process in hand now, we are confident that we will be able to execute the project activities in a timely manner and use the requested CIRM funds efficiently to advance the product to IND and achieve the expected outcome of the PDEV award.

We would also like to assure the committee that there is no overlap between the activities of the PDEV application and our U01 grant. Because we propose to develop an autologous cell therapy, the CIRM PDEV funds will be used to conduct preclinical efficacy studies for two qualification run products that were not proposed in the U01 grant, enabling three total qualification run products to be tested to demonstrate robust and consistent efficacy. CIRM PDEV funds will also be used to build a comprehensive access and affordability plan and support clinical trial startup activities that were not included in the U01 grant. The activities supported by the CIRM PDEV funds will make our program more robust and better aligned with regulatory requirements, enhance the accessibility and affordability of our therapeutic product, and accelerate the IND clearance for moving this product to the first-in-human clinical trial.

Again, I am very grateful for CIRM's previous support of this work, the positive review and a score within the fundable range from GWG reviewers. I ask for your kind consideration to fund this application at the December 11 meeting of the ICOC and Application Review subcommittee. I will be attending the meeting via Zoom and will be happy to answer any questions regarding this application.

Sincerely,

Yanhong Shi

Yanhong Shi, Ph.D.
Herbert Horvitz Endowed Professor of Neurosciences
Professor and Chair, Department of Neurodegenerative Diseases
Director, Division of Stem Cell Biology Research
Beckman Research Institute of City of Hope

Kianna McBride
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December 5, 2025

Application Review Subcommittee
Independent Citizen's Oversight Committee
California Institute for Regenerative Medicine
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

Re: Application #: PDEV-19139
PI Name: Yanhong Shi
Project Title: Develop a human iPSC-based cell therapy for Canavan disease

Dear Members of the Application Review Subcommittee,

I am Kianna, the mother of Dallas, a young boy with Canavan disease. On behalf of Canavan disease patients and families, I would like to offer our most enthusiastic support to Dr. Yanhong Shi's grant application titled "Develop a human iPSC-based cell therapy for Canavan disease" (PDEV-19139). I kindly request that you approve Dr. Shi's application, which received a score indicating it has exceptional merit and warrants funding.

Canavan disease is a devastating neurological disorder with no cure. Not only is there no cure, there are not even approved therapies. Current treatments only help to manage symptoms and provide supportive care. My son and other patients are unable to speak or feed themselves and became confined to a wheelchair starting in early childhood.

Although there are two ongoing clinical trials evaluating gene therapy for Canavan disease and early results have shown promise in some patients, other patients have had limited improvements. Moreover, the interim results of the Myrtelle trial reported recently showed no significant improvement in gross motor function. These mixed outcomes are worrisome to me, and the long-term efficacy and safety of these gene therapy trials remain to be determined. It seems only reasonable for other approaches for treating Canavan disease to be developed to increase the chances that an effective therapy may be discovered. For these reasons, I strongly request your support of Dr. Shi's research to develop an alternative therapeutic strategy for treating Canavan disease, so that Canavan patients and families will have more options and a greater chance for cure.

Importantly to Dallas and me, both ongoing trials are designed specifically for younger children. The inclusion age for the BridgeBio trial is only up to 30 months and is between 3 months and 5 years of age for the Myrtelle trial. Dallas just celebrated his 5th birthday and isn't eligible for either of these trials. Dr. Shi's planned trial will allow children from age 3 to 16 years to participate, and therefore, will give opportunity to patients like Dallas who are not eligible for the two ongoing gene therapy trials.

Dr. Shi's research is my only hope, and the only hope for many other parents like me.

I also have more faith and hope in Dr. Shi's research because it combines the advantages of cell and gene therapy. It will not only introduce a functional gene but also have regenerative potential from cell therapy. The regenerative potential is so important. Gene therapy alone has not shown the success I was hoping to see. It cannot repair the damage that this disease has already done in Canavan children. And for Dallas, because he is 5 years old, the risks of gene therapy outweigh the benefits. I am not interested in prolonging Dallas' suffering. I want to improve his quality of life, which is something gene therapy alone cannot do but combined cell and gene therapy has the potential to do.

Without cell-based therapy for this disease, like what Dr. Shi is developing, I feel like I am just waiting for my son to die. But I will not accept that. My son was not born with this disease just to die. His life has meaning, his life has purpose, and his participation in this research is what GIVES him purpose. He has the ability to make a difference in the world and in the life of others. Please don't take that away. The approach in Dr. Shi's proposal could be applied to numerous genetic neurodegenerative diseases! We will never know how many children we could save if we don't try.

I understand there are concerns about the affordability of cell therapy approach, but costs for Dr. Shi's proposed therapy would pale in comparison to the already astronomical medical costs for Dallas' care. From December 2024 – December 2025, Dallas' healthcare spending was over $1 million, and these costs are only going to increase as his disease progresses. A successful therapy, such as could come from Dr. Shi's research, would pay for itself by saving tremendous amounts through reduced healthcare spending by Dallas and other Canavan disease children.

Once again, I urge you to fund Dr. Shi's research. It means Dallas' life could make difference in the world, and for other children with this terrible disease. On behalf of Canavan disease patients and families, we greatly appreciate your support of Dr. Shi's research to save the lives of Dallas and many more Canavan children.

Sincerely

Kianna McBride
Mother of Dallas

December 5, 2025

Meagan Rockwell
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Application Review Subcommittee (ARS)
Independent Citizen's Oversight Committee (ICOC)
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Re: Application #: PDEV-19139
PI Name: Yanhong Shi
Project Title: Develop a human iPSC-based cell therapy for Canavan disease

Dear Members of the Application Review Subcommittee,

I am Meagan, the mother of Adley and Tobin, two young girls with Canavan disease. I wake up every day hoping for a viable treatment option for this devastating neurological disease. I am excited by Dr. Yanhong Shi's combined cell and gene therapy approach that differs from other approaches being evaluated and ask that you please approve her grant application titled "Develop a human iPSC-based cell therapy for Canavan disease" (PDEV-19139).

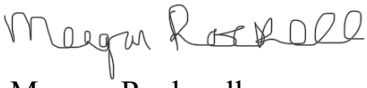
I am familiar with the two current phase 1/2 clinical trials studying gene therapy for Canavan disease and am intimately aware that the outcomes from these studies are mixed. In fact, my younger daughter, Adley, participated in the Myrtelle study in April 2023, but, unfortunately, it has not been a cure. She is still symptomatic, and she and our family face many daily challenges. Our experience makes it very clear that one treatment approach is not enough for this disease, continued research is essential, and approaches like Dr. Shi's that go beyond gene therapy alone are urgently needed.

Moreover, my older daughter, Tobin, is eight years old and has no treatment options at all. She is considered too old for the current gene therapy trials, even though she is still fighting every day and could benefit from new approaches. This is why Dr. Shi's research matters so much. Families like mine are running out of time and we urgently need alternative approaches so that our children will have better outcomes. The Canavan disease community especially needs approaches that can help older children and those who were not able to receive early intervention. Dr. Shi's approach combining stem cells with gene therapy will both introduce a functional gene and offer regenerative capacity from stem cell therapy, thus, giving families like ours hope that someone is working toward solutions that may be able to include every child, not only the youngest ones.

Speaking from the perspective of a parent who has already walked through gene therapy with one child and has another child who has been left without options, I want to emphasize

how difficult it is to live in this gap and how critical it is that Dr. Shi's research can be continued with support from CIRM. Therefore, I request that you approve Dr. Shi's research for funding, both because the scientific review committee has deemed her research to be of exceptional merit and because the Canavan disease community desperately needs her approach to save the lives of our children. Thank you for your consideration.

Sincerely,



Meagan Rockwell
Mother of Adley and Tobin

Ilyce Randell
President, Canavan Research Illinois

December 5, 2025

Application Review Subcommittee
Independent Citizen's Oversight Committee
California Institute for Regenerative Medicine
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

Re: Application #: PDEV-19139

Dear Members of the Application Review Subcommittee,

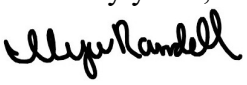
I am writing in strong support of Dr. Yanhong Shi's CIRM PDEV application (PDEV-19139) titled "Develop a human iPSC-based cell therapy for Canavan disease," which received a median score of 85 indicating that it warrants funding. I am excited by this positive review, and believe that the stem cell-based cell therapy approach Dr. Shi proposes for children with Canavan disease is a promising strategy for the treatment of this devastating disease that has no cure. Please consider Dr. Shi's application for funding.

I am the President of Canavan Research Illinois, a patient advocacy group with the mission to direct funding towards research aimed at developing therapies to treat and cure Canavan disease while networking families to form an engaged community poised to support efforts to bring effective therapies to the clinic. In addition to my role in Canavan Research Illinois, I am the mother of a Canavan disease patient. My son participated in two gene therapy trials, yet he still passed away in 2020. By supporting him in these clinical trials, I have a great understanding of the needs of Canavan disease patients and families and the challenges they face when entering a clinical trial.

Although the Canavan disease community is encouraged by the two ongoing phase 1/2 clinical trials studying gene therapy for Canavan disease, and their interim results showing tolerability and early effects, we know this is still early stages and long-term efficacy and safety remain to be evaluated in follow-up studies. Moreover, in the Myrtelle trial reported in a recent paper, no significant improvement in gross motor function was detected. Therefore, it is essential that the research community continues developing therapeutic strategies for treating Canavan disease. We cannot place all our hope on only one approach, which may not pan out or may not be appropriate for all patients. Importantly, considering Canavan patients may now live into their teens, both ongoing trials are designed specifically for younger children. The BridgeBio trial only accepts children up to 30 months of age, while the Myrtelle study only allows participants between 3 months and 5 years. Dr. Shi's intended trial, with an inclusion age range of 3 to 16 years (due to the advantages of the regenerative capacity of cell therapy) will give patients who are not eligible for the two ongoing gene therapy trials an opportunity to access a novel approach. The regenerative

potential of Dr. Shi's approach is especially exciting because it gives the potential for a lasting, potentially life-long, effect, sparing patients from repeated treatments needed for continued effect from AAV, which can be very expensive and straining to the patients, let alone the immunological complications that may arise from repeated AAV treatments. Therefore, I strongly support Dr. Shi's proposal that combines the advantages of cell and gene therapy and will bring more hope, and potentially improved treatment, to Canavan patients and families. I am confident that the development of this cell therapy will benefit Canavan children and their families substantially. I hope that you will approve Dr. Shi's proposal for funding.

Sincerely yours,



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December 8, 2025

Application Review Subcommittee (ARS)
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California Institute for Regenerative Medicine (CIRM)
210 King Street
San Francisco, CA 94107

Re: Application #: PDEV-19139
PI Name: Yanhong Shi
Project Title: Develop a human iPSC-based cell therapy for Canavan disease

Dear ARS members,

I am a Co-Investigator on PDEV-19139 and Chief of Neurosurgery at City of Hope. I am grateful to the Grants Working Group for their thoughtful review of our proposal and for recognizing both the expertise of our team and the clinical potential of our therapeutic approach. I would like to take this opportunity to address the concern regarding the complexity of the neurosurgical procedure required for delivery of our therapy.

As a clinician-scientist and neurosurgeon, I have led the design and execution of multiple clinical trials involving local delivery of cells, viral vectors, drugs, and biologics into the brain. I serve as a Co-Investigator on first-in-human trials evaluating neural stem cell–mediated therapies in patients with high-grade glioma (NCT01172964, NCT02015819, NCT02192359). In addition, I have served as Principal Investigator on trials assessing the safety of anti-IL-13Rα2 and anti-HER2 engineered CAR T-cell therapies in this patient population (NCT01082926, NCT02208362, NCT03389230, NCT04003649). Each of these studies required precise local delivery of cell-based therapies into the brain.

The surgical procedure proposed in our PDEV application is a standard neurosurgical technique routinely performed and not associated with serious adverse events. Two recent *Nature* papers describe similar approaches for delivering stem cell-derived dopaminergic cells to patients with Parkinson's disease. In the study by Sawamoto et al., cells were bilaterally transplanted into the putamen using six trajectories (via six burr holes) per brain—three per hemisphere—with 4 to 8 injections at varying depths along each trajectory. No serious adverse events were reported among the seven patients enrolled in this safety study (Sawamoto et al., *Nature*, 2025, PMID: 40240591). In a companion paper, cells were delivered into the post-commissural putamen bilaterally using nine deposits per putamen, achieved through three cannula passes (via three burr holes) per hemisphere and three depth-specific deposits per pass.

This trial met predefined safety criteria, and the surgical procedure was well tolerated (Tabar et al., *Nature*, 2025, PMID: 40240592). Comparable multi–burr hole brain surgeries have also been performed safely in pediatric patients (Kupu et al., *J Pediatr Neurosci*, 2010, PMID: 21559155; Blauwblomme et al., *Neurosurgery*, 2017, PMID: 28327981).

Based on both our surgical experience and published evidence, we are confident that the proposed procedure is widely practiced and well tolerated. I am deeply impressed by the strength of our team's preclinical data and the sound rationale underlying the clinical trial design. I firmly believe that our combined cell and gene therapy approach has the potential to deliver transformative benefits to children with Canavan disease and their families. For these reasons, I respectfully request your consideration of PDEV-19139 for funding. Thank you for your time and thoughtful review.

Sincerely,

Behnam Badie, M.D.
Professor & Chief, Division of Neurosurgery
Co-Director, Brian Tumor Program
Heritage Provider Network Professor in Gene Therapy