June 22, 2026

California Institute for Regenerative Medicine / Application Review Subcommittee

RE: CIRM PDEV-19728 "AAV Gene Therapy for Brain Metastases"

Deer esteemed members of the CIRM ARS,

I am writing as the Founder and CEO of Siren Biotechnology to ask the ARS to do something highly unusual, but deeply aligned with CIRM's mission: to fund PDEV-19728 despite the majority GWG and CIRM team's recommendation not to fund.

I make that request with the utmost respect for the thoughtful review process. We are not appealing the review. We are not claiming the reviewers were biased or conflicted. The review was rigorous, and many of the concerns raised are real. SRN-101 in brain metastases *is* ambitious. The efficacy package in animals is not yet complete. The eventual clinical population and basket design need refinement. The program will require careful gating, clinical input, and close collaboration with CIRM. I acknowledge all of that directly. But I am asking you to consider whether this is precisely why ARS discretion exists.

PDEV-19728 received a score of 84, one point below automatic funding consideration. Six scientific reviewers voted to fund it. The minority report recognized the same core truth that drives our work every day at Siren: metastatic brain cancer is a devastating, under-addressed disease, and SRN-101 is a highly translatable, potentially high-impact approach that could generate meaningful clinical learning for patients who have no time to wait for a resubmission.

The majority reviewers saw risk. The minority reviewers saw possibility. I am asking the ARS to look carefully at both. The question before you is not whether this program is risk-free. It is not. The question is whether the risk is worth taking now, in a disease where waiting carries its own ethical cost.

Brain metastases are common, life-limiting, and profoundly underserved. These patients are routinely excluded from systemic oncology trials, passed between treatment paradigms, and treated with repeated interventions like radiation that can preserve time but often at the cost of neurologic function and quality of life. There are no approved gene therapies or locally delivered biologics for brain metastases. For patients whose intracranial disease progresses after surgery or radiation, the treatment landscape remains shockingly thin. This is exactly the kind of gap CIRM was created to address.

SRN-101 is not an incremental systemic oncology drug being repurposed for the brain. It is a locally delivered AAV immuno-gene therapy designed specifically to treat intracranial tumor tissue by inducing sustained local expression of an immunomodulatory cytokine at the site of disease. The proposed brain metastases program builds from an active adult CNS oncology IND for the same construct, capsid, formulation, and delivery approach. We are not asking CIRM to fund an idea disconnected from prior development. We are asking CIRM to help us extend an existing CNS gene therapy platform into a patient population that has been woefully left behind by conventional oncology development.

Several reviewers questioned whether our tumor-agnostic strategy is too broad. I understand that concern. To be clear, we are not proposing to treat "every brain metastasis patient" as though all tumors are biologically identical. We are proposing a staged, disciplined, mechanism-based preclinical development path in which SRN-101 is evaluated across histologies because the shared therapeutic challenge is the intracranial site of disease, local delivery constraints, immune microenvironment, and lack of durable local control. We fully expect the PDEV work to refine the initial clinical population, define cohort structure, and identify where SRN-101 is most likely to have impact.

That is not a flaw in the PDEV plan. That is the purpose of the PDEV plan.

Other letters submitted in support of this application address the clinical, neurosurgical, regulatory, patient, and advocacy perspectives. Those letters are important because they show that the concerns raised in review are not being dismissed; they are being actively addressed, now. Brain metastasis clinicians are helping to refine patient selection and trial feasibility. Neurosurgical experts are advising on lesion accessibility and delivery practicality. Regulatory experts have explained why a basket strategy is ideal and with strong clinical precedent. Patients and advocacy leaders have made clear that the unmet need is not abstract. As CEO, I want to address a very different point: timing.

The easiest decision would be to tell us to wait. Wait for the adult recurrent HGG clinical program to mature. Wait for additional brain metastasis data in animals. Wait for a resubmission. Wait for the next cycle to get one more point. Wait until the risk is lower. But for this patient population, “wait” is not neutral. Waiting likely means years before our other clinical program has sufficient data readouts we could share with PDEV reviewers. Patients with brain metastases do not have years.

I am not asking the ARS to fund this application blindly. If the concern is scope, we are prepared to work with CIRM to streamline. If the concern is sequencing and leveraging the adult rHGG program first, we are prepared to tie Late PDEV activities to specific clinical, regulatory, or nonclinical milestones. We would gladly accept a disciplined, CIRM-guided award structure. We will accept gates with hard milestones. We will accept a development path that forces the decisive questions to be answered before the program expands. We will accept a change in budget.

What I am asking you not to do is let a one-point threshold become the reason this program loses years. CIRM’s own materials recognize that this application is an entirely unique modality in the CIRM portfolio for this indication. They also recognize that there are no approved cell or gene therapies addressing metastatic brain tumors. That matters. This is not a crowded field. This is not a redundant program. This is not another version of something patients can already access. This is an opportunity for California to lead in a space where the most vulnerable patients have been consistently underserved.

I understand why the majority did not recommend funding. I also understand why six reviewers believed the program should be funded anyway. I am asking the ARS to consider the minority report not as a footnote, but as a signal. A signal that our project is risky but potentially transformative. A signal that the unmet need is large enough to justify action now. A signal that this may be one of those rare cases where portfolio value, patient need, and CIRM’s mission warrant a decision beyond rank order.

Please give this program the opportunity to answer the questions reviewers raised with you. Please give patients with brain metastases a chance to benefit from the same urgency CIRM has brought to other devastating diseases. Please consider funding PDEV-19728 now, with appropriate strict gates and oversight, rather than asking this patient community to wait years for a resubmission.

We are ready to do the work arm-in-arm with you. We are ready to be held accountable. We are ready to partner closely with CIRM as we have in the past with our highly successful TRAN1 that brought us to this moment. On behalf of patients with brain metastases, we are asking you not to wait.

Respectfully and as a cancer patient myself,

Nicole K. Paulk, PhD
CEO, Founder, President
Siren Biotechnology