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Members of the Application Review Subcommittee (ARS)
California Institute for Regenerative Medicine
1230 Market Street, San Francisco, CA 94102

Dear members of the ARS , June 15, 2026

I am writing in strong support of Siren Biotechnology's PDEV-19728 application, "AAV Gene Therapy for Brain Metastases." I am a neurosurgeon at the UCSF Brain Tumor Center, where my clinical practice includes the surgical management of adult patients with primary and metastatic brain tumors. I see firsthand the limitations of our current treatment paradigm for patients with brain metastases, particularly those with recurrent, progressive, or surgically challenging intracranial disease after standard local therapy.

From a neurosurgical perspective, I believe SRN-101 addresses a clinically important and underserved problem. Surgery and radiosurgery are essential tools, but they are not curative systemic strategies, and they do not eliminate the need for better local biologic control. Many patients cycle through surgery, stereotactic radiosurgery, whole-brain radiation, systemic therapy, and observation, yet still recur intracranially. These patients are not theoretical. They are in our clinics every week.

One concern raised in the review was whether the initial clinical population is too narrow or insufficiently justified. In my view, an initial focus on patients with a single accessible intracranial lesion is not a weakness; it is the appropriate and responsible way to begin clinical development of an intracranially delivered gene therapy. A single-lesion, surgically accessible population allows careful evaluation of safety, delivery feasibility, dose distribution, imaging response, and tissue-level effects in a setting where local treatment is clinically meaningful. That is exactly the kind of controlled first-in-human setting that should precede broader clinical expansion.

I also believe the proposed delivery strategy is operationally feasible. MRI-guided convection-enhanced delivery and image-guided catheter-based approaches are well aligned with the capabilities of specialized brain tumor centers. For an early-phase study, this is not a general community oncology intervention; it is a procedure-based therapy that should be developed first at experienced academic centers with neurosurgical, neuro-oncology, radiation oncology, imaging, and clinical trial infrastructure. In that context, the proposed approach is realistic.

The review also noted that the team would benefit from additional clinical and neurosurgical input specific to brain metastases. I agree that this expertise is important, and I am willing to advise Siren as the program advances. My input would focus on patient selection, surgical feasibility, lesion accessibility, procedural workflow, imaging considerations, and clinical trial practicality for adults with brain metastases.

Importantly, this program fills a gap that is not addressed by existing treatment modalities or by most current drug development efforts. Brain metastases remain a major cause of neurologic morbidity and mortality across common cancers, yet patients with active or recurrent intracranial disease are often underserved by systemic oncology development. A locally delivered immuno-gene therapy designed to act directly within the intracranial tumor microenvironment is a highly differentiated approach and one that is well suited to California's leadership in both neurosurgery and gene therapy.

I recognize that this is an ambitious program. However, ambition is appropriate when it is matched to a serious unmet clinical need, a rational mechanism, an experienced development team, and a feasible first clinical population. In my opinion, PDEV-19728 meets that standard. I urge the ARS to support this application and allow this program to advance.

Sincerely,

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