

June 18, 2026

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

Dear Members of the CIRM ARS,

I write to you today with my strong support of the PDEV-19728 application, “**AAV Gene Therapy for Brain Metastases**” from Siren Biotechnology. I am a neuro-oncologist at NYU Langone Health, where my clinical and research work focuses on patients with primary and metastatic brain tumors. I also serve as the NYU Site PI for Siren’s upcoming Phase 1/2 clinical trial of SRN-101 in adults with recurrent high-grade glioma. In addition, I participate in the KI-NYU Metastasis Alliance, a newly formed collaboration between NYU Langone Health and Sweden’s Karolinska Institute focused on accelerating translational research for metastatic cancer.

Brain metastases remain one of the most clinically important and under-addressed problems in all of oncology. Compared to primary brain tumors, metastatic brain tumors are 8 times as prevalent. Further, CNS “escape” disease, where systemic disease is controlled and progression is only in the CNS, is increasing in incidence. Despite the increase in CNS metastatic disease, brain metastases are often treated as an afterthought in drug development. Many systemic trials exclude patients with active or unstable intracranial disease, and even when systemic therapies show extracranial benefit, durable control in the brain remains a major challenge. For patients with recurrent or progressive brain metastases after local therapy, the need for new approaches is dire.

The grant reviewers correctly recognized the magnitude of the unmet need, but also questioned whether SRN-101’s eventual proposed clinical role was too broad. I believe the most compelling near-term opportunity is not to replace surgery or radiation, but to develop SRN-101 as a rational local biologic therapy for patients with recurrent or progressive intracranial disease where existing options are limited, repetitive, or associated with cumulative toxicity. That is a clinically meaningful population and one in which a single-administration, locally delivered therapy could have substantial impact.

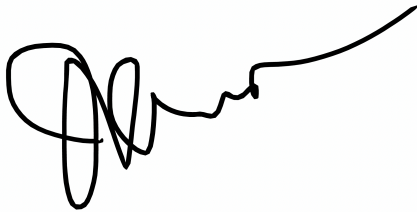
I also believe the tumor-agnostic positioning is scientifically and clinically reasonable for this program. SRN-101 is not a targeted small molecule dependent on a tumor-specific oncogenic driver. It is a locally delivered AAV immuno-gene therapy designed to induce sustained intratumoral expression of an immunomodulatory cytokine directly within the brain tumor microenvironment. For brain metastases, the shared therapeutic problem is not only the primary tumor histology, but the intracranial site of disease, the limitations of systemic drug penetration, and the need for better local control. The goal of a tumor-agnostic basket trial follows from the mechanism and the clinical problem.

The reviewers also raised concerns about whether the clinical development plan has sufficient brain metastasis-specific input. Siren has already established a deep clinical and regulatory foundation for SRN-101 in adult neuro-oncology. The proposed preclinical PDEV award is precisely the mechanism by which the team can build the additional brain metastasis-specific clinical, operational, and translational infrastructure needed for a responsible basket trial. I am willing to continue advising the team as this program develops, particularly on clinical

positioning, eligibility criteria, neuro-oncology workflow, response assessment, and practical trial execution for adults with brain metastases.

This program is highly aligned with CIRM's mission. It brings together California-based innovation in gene therapy, a serious unmet clinical need, and a potential therapeutic strategy that is not represented by existing standards of care or other programs in your grant portfolio. I recognize that PDEV-19728 is ambitious. However, it is imperative to invest more research effort to address the unmet need of treatments for brain metastases. I urge the ARS to support funding of PDEV-19728.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Schulte', with a long horizontal flourish extending to the right.

Jessica D. Schulte, MD, PhD

Associate Professor of Neurology, Medicine, and Pediatrics
Director, Adolescent and Young Adult Neuro-Oncology
NYU Langone Health
Member, KI-NYU Metastasis Alliance