UCSF Medical Center

Department of
Neurological Surgery

University of California
San Francisco
UCSF
Comprehensive
Cancer Center

**DIVISION OF
NEURO-ONCOLOGY**

Nicholas Butowski, M.D.

Professor, Neurological Surgery

Director, Translational Research in Neuro-Oncology

Director, UCNS Fellowship in Neuro-Oncology

Program Leader
CNS Tumors for UCSF Helen Diller Family Comprehensive Cancer Center

Chair, CNS Site Committee
UCSF Helen Diller Family
Comprehensive Cancer Center

Medical Director
Clinical Research Support Office
UCSF Helen Diller Family
Comprehensive Cancer Center

Department of Neurological Surgery
University of California, San Francisco
400 Parnassus Avenue
Room A-808
San Francisco, California
94143-0372

Tel: 415/353-2966

Fax: 415/353-2167

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California Institute for Regenerative Medicine (CIRM)
Application Review Subcommittee (ARS)
Independent Citizens Oversight Committee (ICOC)

RE: CLIN2-19526 "SRN-101 AAV Immuno-Gene Therapy for High-Grade Glioma" Grant Letter of Support

Dear Members of the CIRM ARS/ICOC,

I am writing in support of Siren Biotechnology's CIRM CLIN2-19526 application for SRN-101 and to address the clinical trial design questions raised during review. As the Trial PI and Site PI at UCSF and a physician-scientist with extensive experience conducting early-phase clinical trials in neuro-oncology, I am well-positioned to speak to the scientific soundness and clinical feasibility of this program.

I have reviewed the review comments on the clinical protocol in detail and can share that Siren and I had already independently been actively working on a revised protocol, which is currently in preparation for IRB submission. The revision directly addresses the design questions raised by reviewers, including DLT management and escalation governance, eligibility criteria, statistical analysis, tumor type stratification, interim analysis, and enrollment contingency planning. These are well-understood challenges in early-phase oncology trials, and the solutions are straightforward to implement. I am confident the revised protocol will satisfy all the reviewer's and committee's concerns.

The scientific rationale for SRN-101 is exceptionally strong. AAV-mediated local delivery of cytokines is mechanistically well-supported and represents a logical approach to engaging the immune microenvironment in a disease where systemic immunotherapies have consistently failed. The extensive preclinical dataset provides a solid foundation for first-in-human testing, and the early groundwork with the Siren team and the external CRO, the existing open IND, drug product readiness, and prior CIRM TRAN1 support, positions this program to move rapidly and efficiently into the clinic.

UCSF's Brain Tumor Center evaluates among the largest volumes of high-grade glioma patients in California. As a CIRM Alpha Clinics Network

member, UCSF is purpose-built to execute early-phase oncology trials with the rigor, patient diversity, and institutional depth this program requires. I am fully committed to the success of this trial and to working closely with the Siren team throughout its conduct.

I strongly endorse this CIRM CLIN2-19526 application and look forward to serving as Trial PI and Site PI on this extraordinary first-in-human study for our patients.

Sincerely,

Nicholas Butowski, M.D.
Professor of Clinical X | UCSF Neurological Surgery
Director, Translational Research | UCSF Neuro-Oncology Div.
Director, UCNS Fellowship | UCSF Neuro-Oncology Div.
Chair, CNS Tumors Site Committee | UCSF Helen Diller Family Comprehensive Cancer Center
Program Co-Leader, CNS Tumors Section | UCSF Helen Diller Family Comprehensive Cancer Center
Medical Director |CRSO UCSF Helen Diller Family Comprehensive Cancer Center
Department of Neurological Surgery
University of California, San Francisco
400 Parnassus Ave., Rm A808 | San Francisco, CA 94143
Ph: 415-353-2966 | Fax 415-353-2167