REPROGRAMMING THE SPATIAL TRANSCRIPTOME FOR PRECISION NEURODEGENERATIVE THERAPIES

A First-in-Class Spatial Biology Initiative for Curing ALS: Bridging Engineering and Clinical Care at Stanford and UCSD

TO: Members of the CIRM Application Review Subcommittee

FROM: The DISC4-19196 Investigational Team

DATE: March 20, 2026

RE: Response to Application Review Summary – DISC4-19196

Dear Members of the Application Review Subcommittee,

We write to underscore the profound urgency of this project and why this project will bring exceptional benefit to California. We want to provide the Subcommittee with critical context regarding the **causal evidence** of our approach, why funding this specific team represents a unique, non-redundant opportunity for CIRM to lead the world in ALS therapeutics, and propose a strategic path forward that ensures California benefits from the full breadth of ALS innovation. We are honored that the Grants Working Group (GWG) identified our proposal as a high-priority project for California. We acknowledge that our application is currently "tied" with other proposals with the same score for the final funding slot within the current $84 million allocation.

ALS is a devastating, fatal neurodegenerative disease with no cure and limited treatment options. It begins by stealing a person's ability to walk, then their ability to speak or swallow, and finally, their ability to breathe. Perhaps most cruelly, it often leaves the mind perfectly intact, while forcing patients to be clear-eyed witnesses to their own physical vanishing. The recent tragic passing of California native, actor Eric Dane following his courageous struggle with ALS reminded us all that this is a crisis that strikes at the heart of our community.

California must lead the effort to find solutions to this devastating disease. California is home to the largest and most diverse population of patients and families affected by ALS and related disorders, but also one of the strongest stem cell, genomics, computational biology, cell therapy, and clinical care programs ecosystems (throughout the entire state) working together on the planet. Because of this, there is hope: new discoveries have emerged and are leading to the development of innovative new therapies to help slow down and hopefully stop ALS.

The primary concern raised by the reviewers and cited by CIRM staff as the main reason not to fund our proposal was whether RNA mis-localization is a "cause" or a "consequence" of ALS. **Of utmost importance, this concern has been addressed. We have moved beyond observation to definitive proof of causality.** In our recent work (Zeng *et al.*, Nature Neuroscience, 2025), we demonstrated that the major pathological hallmark of ALS (loss of the RNA-binding protein TDP-43 from the nucleus), results in early and profound alterations in alternative polyadenylation to disease-relevant RNAs, including the loss of *STMN2* from the distal axon, which is a primary driver of neuronal failure. Crucially, we have shown that using our "spatial reprogramming" platform to relocalize *STMN2* RNA back to the axon was sufficient to promote neurite outgrowth by 50% in ALS-challenged neurons (Han *et al.,* Nature, 2025). This is not just a "correlation"; it is a functional rescue that proves spatial intervention can reverse neurodegeneration. With the main concern addressed, we suspect that more reviewers would have increased their scores and recommended the study for funding. Our DISC4 proposal is designed to apply this proven "observation-intervention" capability to a wide range of pathological targets.

Our platform provides a fundamentally unique therapeutic framework that doesn't currently exist in the CIRM portfolio. For thirty years, the global search for an ALS cure has focused largely on a single strategy: lowering the total amount of toxic material in a cell. But despite billions in investment, ALS remains a fatal, "uncured" diagnosis. **The field has been searching for the right answer in the wrong place.** The reason is simple: the problem in ALS isn't just a "factory" problem (too much or too little gene products); it's a "logistics" problem (where the gene products are transported). Our project is designed to create something California can uniquely deliver: a new therapeutic framework for neurodegeneration based on spatial biology, correcting where RNAs go inside cells, not just how much of them are made. This work will establish a new class of "Spatial Medicines", generate accessible datasets and stem cells, and create a platform that can be extended beyond ALS to other neurodegenerative diseases. This is the missing piece of the puzzle that will change the face of ALS treatment within the next four years. In doing so, it will strengthen California's leadership in regenerative medicine, RNA therapeutics, and translational neuroscience.

We recognize that another excellent ALS-focused proposal (DISC4-19391) received the same score as our proposal but had other slightly higher metrics and was recommended for funding. While California is fortunate to have multiple high-priority teams from the ecosystem, our proposals represent the two essential, non-redundant pillars of a modern ALS solution: whereas other teams focus on traditional genetic drivers, our project targets the spatial regulation of the transcriptome. Funding both ensures CIRM is funding a complete solution. We understand the budget for this DISC4 mechanism is set at $84 million and funding our project in its entirety would exceed this number. **To ensure that California can benefit from the high-priority research of both tied ALS teams, we are eager to move the science forward through one of the following flexible options:**

- **Option A: Balanced portfolio impact.** CIRM staff or the GWG could assess if the maximum patient impact would be achieved by moving both ALS proposals forward, each with a reduced scope and budget to fit within the current $84 million allocation. By funding both, CIRM ensures that California is attacking ALS from every possible angle to achieve a cure.
- **Option B: Scope adjustment.** CIRM could evaluate whether our project, even at a strongly reduced scope and budget, remains a worthwhile and transformative investment for California. Our approach is highly modular, and we are committed to maintaining an impactful project that delivers on CIRM's mission even under reduced fiscal parameters.

Despite our team's deep commitment to California's biotechnology ecosystem and our track record of launching clinical-stage ventures (e.g., Epicrispr, Maze, Trace, Lyterian), **this team has never received CIRM funding.** Funding DISC4-19196 enables CIRM to diversify its portfolio through a pioneering framework distinct from other strategies that have dominated the ALS field for 30 years.

We re-emphasize that our spatial reprogramming platform is a fundamentally new and potentially transformative concept providing a therapeutic framework that doesn't currently exist in the CIRM portfolio. While we start with ALS, this is a universal platform. Failure of spatial biology is now recognized as a hidden driver in Alzheimer's and Parkinson's. By funding this work, CIRM is investing in a strategic infrastructure, "Spatial Therapeutics," that can be deployed across the entire spectrum of neurodegeneration, potentially benefiting millions of Californians.

California is the epicenter of the ALS crisis, but also it is the epicenter of its solution. By leveraging the unique patient cohorts at Stanford and UCSD, we are intervening ALS in the context of California's immense genomic diversity. This ensures that the targets we identify are effective across all populations, fulfilling CIRM's mission of health equity and accessible regenerative medicine.

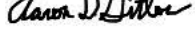
We respectfully ask the Subcommittee to recognize the "high-risk, high-reward" nature of our score. **The GWG's 8-6 vote highlights the 'high-risk, high-reward' innovation CIRM was mandated to fund.** We invite CIRM to partner with us in making ALS a thing of the past. We are ready to translate these breakthroughs into clinical realities and respectfully urge the Committee to consider funding both high-priority teams, even if it requires a strategic adjustment of project budgets.

Thank you for your consideration.

Sincerely,

Electronically signed by: Stanley Qi
Reason: I have reviewed and am approving this document.
Date: Mar 22, 2026 09:40:08 PDT

Lei S. (Stanley) Qi, PhD
Associate Professor of Bioengineering
Stanford University
Founder, Epicrispr Biotechnologies



Electronically signed by: Aaron Gitler
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Date: Mar 23, 2026 02:21:10 GMT +8

Aaron D. Gitler, PhD
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Electronically signed by: Marius Wernig
Reason: I have reviewed and am approving this document.
Date: Mar 22, 2026 15:16:23 PDT

Marius Wernig, PhD
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Electronically signed by: John Ravits
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Date: Mar 22, 2026 09:42:30 PDT

John Ravits, MD
Professor of Clinical Neuroscience
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Electronically signed by: Alice Ting
Reason: I have reviewed and am approving this document.
Date: Mar 22, 2026 09:43:59 PDT

Alice Ting, PhD
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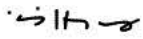

Electronically signed by: Wing Hung Wong
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Wing H. Wong, PhD
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Electronically signed by: Xiaojie Qiu
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Xiaojie Qiu, PhD
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Electronically signed by: Rongxin Fang
Reason: I have reviewed and am approving this document.
Date: Mar 22, 2026 10:56:44 PDT

Rongxin Fang, PhD
Assistant Professor of Neurosurgery and, by courtesy, of Genetics
Stanford University

March 16, 2026
California Institute for Regenerative Medicine
RE: Letter of Support for DISC4-19196, "Reprogramming the Spatial Transcriptome for Precision Neurodegenerative Therapies"

Dear Members of the CIRM Application Review Subcommittee,

My father died of ALS on August 24, 2024, fourteen months after his first symptoms appeared. I carry the same C9orf72 mutation that killed him, a hexanucleotide repeat expansion that gives me an estimated 95% lifetime risk of developing ALS or frontotemporal dementia. I am a physician-scientist in training at the University of Pennsylvania, where I completed my PhD in Cellular and Molecular Biology and am now finishing my MD. I am writing in support of Dr. Gitler and application DISC4-19196 because I can speak to what it looks like when a scientist of his caliber decides to invest in a person, and what that investment can become.

In the months after my father's death, I made the decision to redirect my career toward C9orf72 ALS and FTD research. I was a mitochondrial biologist with no connections in the ALS field, no collaborators, and no clear path forward. I reached out to Dr. Gitler, and he agreed to meet with me that same day. He did not have to do that. He listened, asked questions, and then did something I have come to understand is characteristic of him: he opened doors. He introduced me to his colleagues and championed my attendance at the Packard Center ALS Research Symposium, one of the most competitive closed meetings in ALS research. He did this not because I had proven anything yet, but because he recognized what I was trying to build and believed it mattered.

In the year since, I have built eleven collaborative C9orf72 research projects spanning seventeen laboratories and eleven organizations across eight countries. I founded the CureC9 program within EverythingALS and built its Scientific Advisory Board, have secured $150k of funding for my collaborator and raised another $40k for research, recruited families into research, and connected investigators who had never worked together before. None of it would have happened the way it did without Dr. Gitler's early and decisive support. He gave me access to a community that I now work within every day, and he did when most people of in his position wished me well and moved on.

This is also why I believe so deeply in the work proposed in DISC4-19196. Dr. Gitler has always understood that the ALS field needs new perspectives and new approaches, and he has spent his career in California acting on that conviction, whether by bringing together scientists from different disciplines, translating his own discoveries toward the clinic, or mentoring people like me who come to the field from unexpected directions. His DISC4 team embodies this same principle: investigators who have pioneered technologies in spatial transcriptomics, CRISPR-based RNA engineering, and stem cell biology, now turning those tools toward the fundamental question of why and where RNA goes wrong in neurodegeneration, and leverage this integrated technology into a novel treatment approach for ALS. This is exactly the kind of bold, cross-disciplinary science that California's research ecosystem is built to support, and that ALS patients and carriers like me are counting on.

A year ago, Dr. Gitler believed in me before I had given him any reason to. Having now spent a year in this field, having seen the breadth of his contributions and the depth of his commitment to patients, families, and the next generation of ALS researchers, I am here to say that I believe in him. I urge the committee to fund this proposal, for the tens of thousands of ALS patients and presymptomatic carriers in California and beyond who are waiting for science like this to reach them.

Respectfully,

Yentli Soto Albrecht, PhD
MD-PhD Candidate, Class of 2027
Perelman School of Medicine at the University of Pennsylvania

ALS Network
Formerly ALS Golden West

March 18, 2026

CIRM Application Review Subcommittee (ARS)
Re: Application # DISC4-19196

"Reprogramming the Spatial Transcriptome for Precision Neurodegenerative Therapies"

Dear Members of the CIRM Application Review Subcommittee,

On behalf of the ALS Network, I am pleased to offer our strong support for the proposal titled "Reprogramming the Spatial Transcriptome for Precision Neurodegenerative Therapies." The ALS Network is one of the nation's largest organizations dedicated to advancing care, research, and advocacy for people living with amyotrophic lateral sclerosis (ALS). Across California and Hawai'i, we serve individuals and families affected by ALS while working to accelerate the scientific breakthroughs needed to end this devastating disease.

ALS remains one of the most urgent challenges in neurodegenerative medicine. While meaningful advances have been made in understanding the genetic and molecular drivers of the disease, ALS remains fatal and therapeutic options are extremely limited. Continued progress will depend on bold approaches that challenge long-standing assumptions and open entirely new therapeutic pathways.

This proposal represents exactly that kind of forward-looking science. By investigating how RNA localization within neurons and glial cells contributes to disease - and by developing technologies capable of experimentally repositioning RNA within cells - the project aims to transform our understanding of ALS biology and establish a new framework for therapeutic development. The concept of addressing disease through the spatial organization of RNA is scientifically compelling and may represent an important shift in how neurodegenerative diseases are understood and treated.

Importantly, the significance of this work extends well beyond ALS. Increasing evidence suggests that disruptions in RNA regulation and intracellular organization represent a fundamental cellular mechanism across multiple neurodegenerative diseases, including frontotemporal dementia, Alzheimer's disease, and Parkinson's disease. Research that clarifies how RNA localization contributes to neuronal vulnerability therefore has the potential to illuminate shared biological pathways that drive neurodegeneration more broadly.

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The ALS Network is particularly confident in this project because of the exceptional investigative team leading the work. Dr. Aaron Gitler and Dr. John Ravits, both members of ALS Network's Scientific Advisory Committee, are internationally recognized leaders in ALS research and clinical care. Their longstanding commitment to scientific rigor and to the ALS community is evident not only through their groundbreaking work, but through their dedication to collaboration and to advancing research that can meaningfully impact patients.

This proposal also reflects the unique strength of California's biomedical ecosystem. By bringing together expertise in stem cell biology, RNA biology, spatial transcriptomics, computational biology, and clinical neuroscience from leading institutions including Stanford University and the University of California, San Diego, the project leverages the capabilities that have made California a global leader in regenerative medicine and translational neuroscience.

From the perspective of the ALS community, the importance of innovative research like this cannot be overstated. People living with ALS and their families urgently need new ideas that can move the field beyond incremental progress toward transformative therapies. Research that deepens our mechanistic understanding of disease while building platforms for therapeutic development is essential to achieving that goal.

The ALS Network is proud to support scientific efforts that combine bold innovation, collaborative leadership, and a clear commitment to improving the lives of people affected by ALS and related neurodegenerative diseases. We believe this proposal represents an important step toward that future.

Thank you for your consideration of this important work and for CIRM's continued leadership in supporting ambitious research aimed at addressing some of the most devastating diseases affecting Californians.

Sincerely,

Sheri Strahl, MPH, MBA
President & CEO
ALS Network