UC San Diego

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Jerome Mertens, PhD
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Alex Chaim, PhD
Assistant Professor
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Professor in Residence
Dept. of Neurosciences

Sanford Burnham Prebys

Anne Bang, PhD
Associate Professor
Center for Therapeutics Discovery

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Rusty Gage, PhD
Professor
Laboratory of Genetics

March 23, 2026

Letter in support of the proposal DISC4-19291: "Reversing age-dependent neurodegeneration by elimination of RNA pollution"

Dear Members of the ICOC and Application Review Subcommittee,

We are grateful to the GWG and for the thoughtful and highly supportive evaluation of our proposal, reflected in an overall score of 87. We note that the GWG reviewers unanimously recommended the project for funding. We are encouraged by the panel's recognition of both the conceptual innovation and the strong translational trajectory of this work, and we appreciate the opportunity to clarify several points raised.

1. A key concern raised by reviewers is the **breadth of the proposal**, particularly the risk that studying RNA dysfunction across multiple diseases and biological layers could dilute focus. We would like to clarify that the project is structured around a prioritization framework that enforces focus at each stage: Aim 1-2 (Discovery) define RNA pollution signatures and their drivers using standardized, cross-disease metrics. Aim 3 (Functional prioritization) serves as the critical narrowing step, identifying a small number of high-confidence regulatory nodes. Aim 4 (Translation) is explicitly restricted to top-ranked targets and pathways, ensuring depth rather than breadth at the therapeutic stage. Thus, while the datasets are broad by design, decision-making is highly selective, with clear criteria for advancing only the most robust and therapeutically actionable candidates. This staged funnel directly mitigates the risk of loss of focus.

2. The reviewers noted potential challenges related to **integration of large, multi-modal datasets**. We agree that this is a central challenge, one that our team is uniquely positioned to address. We have extensive experience integrating multi-omic RNA datasets (eCLIP, long-read RNA-seq, Ribo-STAMP, proteomics, metabolomics) at scale. The proposal leverages established computational pipelines and also prior datasets, rather than building this infrastructure de novo. These factors substantially reduce execution risk and support feasibility within the proposed timeline.

3. The inclusion of **multiple neurodegenerative diseases** was viewed as both a strength and a potential limitation. We agree that depth is critical; however, the cross-disease design is intentional and mechanistically motivated. RNA dysregulation, particularly involving RNA-binding proteins such as TDP-43, is already a shared feature across ALS and a substantial fraction of Alzheimer's disease and related dementias, supporting the hypothesis that RNA vulnerability is a convergent axis of aging-related neurodegeneration. By identifying shared versus disease-specific features, this work enables generalizable therapeutic targets and disease-specific refinements where needed.

4. Reviewers raised questions regarding **heterogeneity across diverse donor populations**. Rather than a limitation, we view this as a core strength of the study design. Our analytical framework will explicitly model age, sex, ancestry, and metabolic state as covariates**.** This approach enables identification of robust, population-relevant therapeutic targets, aligning directly with CIRM's priorities in equity and broad clinical applicability.

Letters of support and translational relevance: The strength and relevance of this proposal are further underscored by external support from leading foundations, industry partners, patients and caregivers, and philanthropic stakeholders:

The BrightFocus Foundation, supporting innovative research in Alzheimer's disease and related dementias

The Michael J. Fox Foundation, a global leader in Parkinson's disease research and therapeutic translation;

Target ALS Foundation, a major driver of open-science, large-scale ALS research infrastructure and therapeutic development;

Denali Therapeutics, a Bay Area based biotechnology company pioneering CNS-targeted delivery of ASOs and biologic therapeutics;

Over 70 study participants (patients and caregivers) of the **UCSD Alzheimer's Disease Research Center (ADRC)**;

Philanthropist **Dan Epstein**, a patient advocate who has funded high-impact Alzheimer's research in California.

In summary, we are grateful for the GWG's strong endorsement of this proposal's significance, innovation, and translational potential. The concerns raised, primarily regarding scope, data integration, and heterogeneity, are valid but are explicitly addressed through the project's staged design, prioritization strategy, and experienced team. We believe this project is well-positioned to deliver high-impact, insights and therapeutic entry points for age-associated neurodegenerative diseases, fully aligned with CIRM's mission.

Sincerely,

Gene Yeo, PhD, MBA
Professor
Dept. of Cellular and Molecular Medicine
UC San Diego

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Dept. of Neurosciences
UC San Diego

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BrightFocus™ Foundation
Cure in Mind. Cure in Sight.

Alzheimer's Disease Research
Macular Degeneration Research
National Glaucoma Research

Gene Yeo, PhD, MBA
Professor
Cellular and Molecular Medicine
Sanford Consortium for Regenerative Medicine
University of California San Diego

Jerome Mertens, PhD
Associate Professor
Department of Neurosciences
Sanford Consortium for Regenerative Medicine
University of California San Diego

Dear Jerome and Gene,

I am writing to strongly recommend your CIRM DISC4-19291 proposal, "Reversing age-dependent neurodegeneration by elimination of RNA pollution." The project aligns closely with BrightFocus Foundation's mission to catalyze bold, innovative science that can transform our understanding and treatment of Alzheimer's disease and related dementias.

Through our Alzheimer's Disease Research program, BrightFocus has invested nearly $200 million in Alzheimer's research and currently supports more than one hundred active projects worldwide. A central focus of our portfolio is identifying and supporting early, high-risk ideas that have the potential to open entirely new therapeutic directions.

As appreciation grows for the role of RNA dysregulation, including TDP-43 and tau pathology, in brain aging and Alzheimer's disease, these mechanisms are emerging as important contributors that remain difficult to study using conventional systems. BrightFocus was among the earliest funders to recognize the potential of directly induced neuronal (iN) models for studying age-related disease mechanisms in sporadic Alzheimer's disease, and we have supported foundational work from your lab demonstrating the value of age-equivalent iN models for studying disease biology. Your work has helped establish a platform that now makes it possible to examine aging-dependent RNA dysregulation and its downstream consequences in a human neuronal context that preserves key features of biological aging.

Your CIRM DISC4 proposal builds directly on this foundation by investigating the causal relationships between metabolic changes, mitochondrial dysfunction, nuclear stress, and RNA dysregulation. This line of inquiry is especially relevant for Alzheimer's disease, where metabolic alterations are a consistent feature but their mechanistic links to upstream molecular changes and downstream pathology remain poorly understood. In our view, this project fills an important gap in Alzheimer's research by leveraging the iN platform to address these questions in a mechanistically rigorous and highly translational way. We strongly support this proposal for funding by CIRM.

Sincerely,

Sharyn Rossi, PhD
Senior Director of Neuroscience Programs

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Date: March 22, 2026

Dr. Gene Yeo
Cellular and Molecular Medicine
Sanford Consortium for Regenerative Medicine
University of California San Diego

Dr. Jerome Mertens
Department of Neurosciences
Sanford Consortium for Regenerative Medicine
University of California San Diego

Dear Gene and Jerome,

I write on behalf of The Michael J. Fox Foundation for Parkinson's Research (MJFF) to share our perspective and strong support on the relevance of the research area addressed in your DISC4-19291 proposal to CIRM, entitled "Reversing age-dependent neurodegeneration by elimination of RNA pollution." MJFF's mission is to accelerate transformative research and therapeutic development for PD. The Michael J. Fox Foundation has invested more than $2 billion in PD research and remains the world's largest nonprofit funder of PD science, supporting a broad portfolio spanning fundamental biology through translational science.

A growing body of evidence points to RNA dysregulation, including TDP-43 pathology and RNA-binding protein mislocalization, as key contributors to dopaminergic neuronal vulnerability in aging and PD. However, the field still lacks adequate human model systems that faithfully recapitulate this aging-dependent dimension of the disease pathogenesis. Human neuronal models that better preserve aging-related features may offer unique opportunities to study age-dependent mechanisms relevant to PD. Research efforts that examine the intersection of metabolic changes, mitochondrial dysfunction, and RNA dysregulation in aging neurons address important biological questions that remain poorly understood in PD.

Approaches that leverage patient-derived materials and human-relevant systems can help complement insights from iPSC-based and animal models. From MJFF's perspective, advancing experimentally tractable, human-relevant models that better capture age-associated biology represents an important direction for the PD research community.

This letter reflects MJFF's perspective on the relevance of the research area to Parkinson's disease. MJFF has no financial interest in CIRM's funding decision and is not a sponsor of this application.

Best regards, Shalini P

Shalini Padmanabhan, PhD
Senior Vice President, Head of Translational Research
The Michael J Fox Foundation for Parkinson's Research

Dear Gene,

I am writing on behalf of Target ALS to strongly support your proposed CIRM project as it comes before the Independent Citizens' Oversight Committee for funding consideration.

As you know, Target ALS is a public nonprofit foundation focused on accelerating ALS therapeutic development through open, collaborative research across academia and industry. We have funded 750+ research projects (including two of yours) and invested over $80 million, with over half of our industry-led consortia advancing into drug discovery programs and multiple efforts progressing to clinical trials. We have also built critical shared infrastructure, including six research cores that provide open access to datasets, biofluids, reagents, stem cell models, and postmortem tissue from over 500 patients, now supporting over 1,800 projects worldwide.

The work you describe in your proposal is built on the compelling concept that neurodegenerative diseases, including ALS, may fundamentally be disorders of RNA misregulation, driven by what your team defines as "RNA pollution": widespread RNA-binding protein dysfunction, RNA damage, and splicing errors that accumulate with aging and progressively impair neuronal resilience. Critically, rather than focusing on downstream pathology, this approach reframes neurodegeneration as a disorder of RNA homeostasis rooted in upstream, shared mechanisms across multiple diseases. While elements of this concept have been discussed in the field, I view this project as the first to systematically define and interrogate it, enabled by the directed differentiation of patient fibroblasts to neurons, developed by team members Mertens and Gage, in which you recently demonstrated baseline RBP mislocalization and RNA dysregulation without exogenous stress. The metabolic changes you've described in these neurons appear to drive this loss of resilience, making it essential to establish whether they arise from underlying RNA dysregulation. If they do, this will directly connect RNA processing defects to neuronal vulnerability and reveal upstream points of intervention, where there is still the potential for reversibility.

As a patient-focused foundation, we are particularly supportive of work like this that focuses on upstream disease processes, leverages new, disease-relevant human model

systems, and is set up to move beyond description toward targets. The study is also built on a unique and well-matched set of patient-derived samples, tissues, and biofluids that is not otherwise available, allowing the same biology to be examined across systems rather than inferred from any single model. For these reasons, I strongly support this proposal for funding by CIRM.

Sincerely,

Manish Raisinghani
President and CEO
Target ALS Foundation, Inc.
244 Madison Avenue #1025
New York, Ny 10016
Manish.raisinghani@targetals.org

Joseph W. Lewcock, Ph.D.
Chief Scientific Officer
Denali Therapeutics
161 Oyster Pt. Blvd.
South San Francisco CA 94080
Phone: (650)745-5247
Email: lewcock@dnli.com

3/22/2026

Re: DISC4-19291 grant application

Dear CIRM Application Review Subcommittee and Independent Citizens' Oversight Committee,

I am writing in strong support of this grant application, entitled "Reversing Age-Dependent Neurodegeneration by Elimination of RNA Pollution", submitted to the CIRM DISC4 program by Dr. Yeo and colleagues.

Denali Therapeutics is a biotechnology company headquartered in South San Francisco, California focused on developing disease-modifying therapies for neurodegenerative diseases by combining genetically validated targets with platforms that enable efficient delivery across the blood-brain barrier, including antibody-based transport vehicles for oligonucleotide therapeutics. A key limitation in the field has been not only delivery, but the identification of targets that are both mechanistically relevant to chronic neurodegenerative disease and amenable to therapeutic modulation in the human central nervous system.

From this perspective, the work proposed by Yeo and colleagues addresses this critical gap. By focusing on RNA dysregulation as an upstream driver of neuronal vulnerability and systematically identifying regulators of this process in the investigators' novel human cellular system that recapitulates age-dependent decline of RNA processing control, the project is positioned to generate targets that are directly compatible with RNA-directed therapeutic strategies. Their ability to define these targets in the context of comprehensive molecular and cellular readouts, including restoration of RNA homeostasis and metabolic function, across several neurodegenerative conditions, substantially increases the likelihood of translational relevance.

This is particularly important given the emergence of delivery platforms, including the ones we develop at Denali, that now make it feasible to modulate targets in the central nervous system using antisense oligonucleotides and related approaches. In this regard, the integration of systematic genetic perturbation of targets prioritized based on mechanistic insights, and comprehensive validation, including in an innovative in vivo model distinguishes this work from others that stop at association and provides a clear path toward therapeutic development.

In our view, this proposal is the kind of upstream, target-generating biology that is needed to fully leverage advances in CNS delivery technologies. We strongly support this proposal for funding by CIRM.

Sincerely,

Joseph W. Lewcock
CSO, Denali Therapeutics

3/18/2022

UC San Diego
SCHOOL OF MEDICINE
SHILEY-MARCOS ALZHEIMER'S DISEASE RESEARCH CENTER

To: Eugene Yeo, PhD, MBA
Professor, Department of Cellular and Molecular Medicine, UC San Diego

Cc: Review panel, California Institute of Regenerative Medicine

I am writing in strong support of the grant titled "*Reversing Age-Dependent Neurodegeneration by Elimination of RNA Pollution*," submitted to the DISC4 program at the California Institute for Regenerative Medicine.

Although new treatments have emerged in recent years, significant gaps remain in the treatment and prevention of Alzheimer's disease and related neurodegenerative disorders. As a community member engaged with the Shiley-Marcos Alzheimer's Disease Research Center at UC San Diego, I am pleased to express my strong support for this research team. The collaboration brings together investigators from across UC San Diego, the Salk Institute for Biological Studies, and the Sanford Burnham Prebys, reflecting the kind of multidisciplinary effort needed to advance meaningful progress in this field.

Joyce Camiel - support group leader 20 yrs,
[signature] - caregiver
Aya [signature] - Caregiver
Barbara Rensink
Todd Bryson - caregiver
Margaret Kemeny -
Rozanne Bryson - ADRC participant
Michael Vander Vorst - caregiver
Julio A Baez - program participant [signature]
Steve Newberg (Care Giver)
Linda Erskian (participant)
Holly Amara - Participant
Mostafa Amara - Study Partner

3/18/2026

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Joyce Slade - Support Group Leader
[illegible] Frenberg - group facilitator
Robert Rafael, MD, PhD
Allison Gutteridge
John Drummond
Daniel Dennison
Sandra Fowler
Mary Wall
Margaret Roark
Bert David Wood
Thomas Cowell
Raoul Harpin - Long Term Aging Study - ADRC UCSD
The cost savings of reducing the impact of AD on the American population will be enormous in terms of healthcare, disability, care, etc.!
[illegible] Jones - Study Partner / spouse

3/18/2026

UC San Diego
SCHOOL OF MEDICINE
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Dallas Clarke, PhD.
John A. Bair
Steve & Lucy Sandhaus
Donna Cardin
Tim Carlin
Cheryl Geyerman - This program is very important!
Judy Desleffka
Jack Leshefka
Hyatt Baker (Participant)
Rita Rogers
Jennifer K. Steber
Marilyn B. Gedeon
Janice M. Hartwig
Dalour Youman

3/18/2026

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Cynthia Knight, care partner, support group participant, poet
Jan Hawkins, support group participant, & Caregiver.
Helen Wilker, Care partner, support group participant
Clynn Wilker, Support Group participant
Ladson Wilson, support group member, CareGiver
Claudette Wilson Support Group participant
Lynne L. Joseph
Fred T. Rose - Caregivor
Rachel Yeats - Carepartner - Support Group Attendee
Anais Barthelet - volunteer at ADRC
MYRON MONROE - participant for 12 years.
Joan Natolo — participant
Joan Wagner - Volunteer @ ADRC
Alice Fisher
Jack Fisher participant
Sandra Fowler

3/18/2025

UC San Diego
SCHOOL OF MEDICINE
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Professor, Department of Cellular and Molecular Medicine, UC San Diego

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Nancy R Bell
Ganesh. Thothathri
Charlotte Ann Weber
Richard E
Richard R Espy
Betty B. Ball
Florence E Reisman
Valle I
Annette Moore
THOMAS MOORE
Susan Hiromi
DOUGLAS D. BALLIS

Harry R. Peacock
Lynn D Covarrubias

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Daniel J. Epstein
Founder

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March 23, 2026

Anne Bang, PhD
Associate Professor, Center for Therapeutics Discovery
Sanford Burnham Prebys Medical Discovery Institute

Eugene Yeo, PhD, MBA
Professor, Department of Cellular and Molecular Medicine,
UC San Diego

Cc: California Institute for Regenerative Medicine Review Panel

Dear Anne and Gene,

I write to strongly support your DISC4-19291 grant application, entitled **"Reversing Age-Dependent Neurodegeneration by Elimination of RNA Pollution."**

Alzheimer's disease has had a profound impact on my family. My identical twin brother lived with the disease for 15 years before his passing, and through that experience we saw firsthand how devastating and prolonged this condition can be. It is also clear that, despite the scale of the problem, affecting millions of Americans today and many more to come, we still lack effective treatments that meaningfully alter the course of disease.

With this in mind, my wife Phyllis and I have committed significant resources to advancing Alzheimer's research, including a $50 million gift to establish a joint research collaboration between USC and UC San Diego. A central idea behind this effort is that progress will require bringing together strong science, human-relevant systems, and a clear path toward intervention. As part of this broader collaboration, we have also been pleased to support Dr. Anne Bang's research at Sanford Burnham Prebys through the Powder for Pennies drug repurposing program for Alzheimer's disease. Through this support, we have seen firsthand the value of innovative, translational research approaches designed to accelerate the identification of new therapeutic opportunities.

This proposal reflects that same way of thinking. It focuses on mechanisms that arise early in disease, before neurodegeneration is fully established, and therefore may still be amenable to intervention. The use of human patient-derived systems and the integration of multiple data types provide a level of grounding that is often missing, while the emphasis on RNA biology and its downstream consequences opens important and increasingly tractable avenues for discovery. The effort to connect RNA dysregulation with metabolic and cellular dysfunction speaks directly to gaps that need to be addressed if we are to make meaningful progress against neurodegenerative disease.

From my perspective, this is exactly the kind of work that deserves support at this critical stage. It combines a compelling biological question with a practical strategy for identifying intervention points relevant to Alzheimer's disease and related neurodegenerative disorders. I strongly endorse this proposal and hope CIRM will give it full consideration for final funding approval.

Sincerely,

D. J. Epstein

Daniel J. Epstein