

California Institute for Regenerative Medicine
601 Gateway Blvd #400
South San Francisco, CA 94080

August 27, 2024

Subject: Reconsidering DISC4 Application 16283 for funding

Dear CIRM ARS Board,

We are writing this letter to request reconsideration of our DISC4-16283 application for funding. In our project, we proposed to identify cellular and molecular effects of **maternal marijuana use on the prenatal brain**, and to elucidate the causal consequences leading to a wide range of neurodevelopmental disorders. Our proposed study will comprehensively examine the effects of marijuana derivatives on specific cell types in the developing human brain, providing mechanistic evidence for long-term health consequences that will **shape health policy**.

We note that four of the five recommended projects concern autism spectrum disorders. This condition accounts for only 5-10% of all neuropsychiatric conditions, so more than 90% of patients suffering from neuropsychiatric conditions in California would not receive potential benefits from the REMIND-L projects.

We also note that organoid models reflect fetal stages of brain development. While psychiatric diseases like autism may begin at these early stages, it is unlikely that insights will lead to therapeutic approaches since patients cannot be diagnosed or treated in utero, and can only be identified later in life when the brain is very different.

California is experiencing an epidemic of drug use. In California, the relaxation of our public health policy on cannabis consumption has exposed more unborn babies to cannabis. Over **19% of women in California actively use marijuana during pregnancy** even though population studies have repeatedly shown that marijuana use during pregnancy is strongly associated with neuropsychiatric outcomes for the developing fetus in later life. However, the public perception is that marijuana use during pregnancy is safe, and the existing population association data are considered weak, anecdotal, and non-causal, and thus are not trusted. Current evidence is not strong enough to move the needle, and it has not changed public opinion or behavior.

Therefore, as noted by the reviewers, it is extremely important to provide molecular and cellular evidence of the causal effects of marijuana use on fetal brain development. Our preliminary single-cell gene expression data suggests that in-utero exposure to marijuana strongly affects neuron proliferation and axon growth. The affected genes are strongly related to autism, schizophrenia, and attention-deficit/hyperactivity disorder. **Finding and defining the cellular and molecular consequences of cannabis exposure to the developing human brain can importantly lead to direct actionable interventional solutions that will have a direct impact on public health policies.** We are deeply committed to our Community Outreach initiatives, and several community organizations have committed to joining the community engagement program in this project, including California Preterm Birth Initiative, San Francisco Department of Public Health, and the local American Indian community (the Lakota tribe).

The major critique of our proposal concerned “a lack of innovation” in our approach, and the reviewers commented that we proposed to use commercially available reagents and that our single-cell approaches are not new. We feel we have been unfairly criticized and feel strongly that the technologies in our proposal, which include single-cell transcriptomics, single-cell proteomics, spatial transcriptomics and spatial metabolomics, are cutting-edge and have not been applied to this problem before. We are glad that the reviewers all considered our project to be extremely feasible and our team to be highly competent.

We feel there is urgency in determining the effects of marijuana use on the fetal brain. Moreover, **this is an area where the application of stem cell technology can have an immediate health care benefit.** We are happy to address the reviewer's concerns and hope that the board will reconsider our project.

Thank you,

On behalf of all members of the research teams,



Arnold Kriegstein, MD, PhD
Founding Director, Eli and Edythe Broad Center for Regeneration Medicine and Stem Cell Research
Professor, Department of Neurology
UCSF Regeneration Medicine & Stem Cell Research



Jingjing Li, PhD
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March 28, 2024

California Institute for Regenerative Medicine (CIRM)

601 Gateway Blvd #400

South San Francisco, CA 94080

To Whom It May Concern:

I am writing this letter in support of the CIRM proposed project "Prenatal Marijuana Exposure and Neuropsychiatric Predisposition: A Single Cell Perspective". The UCSF and Stanford study team will address a critical public health challenge from both scientific and community aspects and the California Preterm Birth Initiative (PTBi) is looking forward to partnering with the study team for this project. This letter is meant to demonstrate the strength of the relationships PTBi has with local and state health departments as well as clinical and social service providers in the San Francisco Bay Area. These long-term partnerships will be critical to the development of this project's community engagement program as part of Aim 4.

PTBi conducts and funds transdisciplinary research across the reproductive life course to probe risk and resilience factors and to identify promising interventions to improve maternal and infant health, especially for communities of color. We strive to address questions that have been prioritized by women with lived experience of birth disparities and that have been vetted by our community advisory board. By conducting research in partnership with the communities most affected by these disparities we are better positioned to develop programs and drive policies that can improve health outcome and that best fits the community's wants and needs. Over the years, PTBi has evolved from an initiative aimed at raising awareness of racial inequities in preterm birth outcomes to an organization that sustains strong partnerships, comprehensive strategies, and the ability to drive systemic change. At the core of our work is our ability to amplify the voices and perspectives of Black and brown mothers. With your support, we can reach the audiences that need to hear our message the most. From city leaders to decisionmakers at the state level, PTBi has consistently advocated for birth justice, with demonstrated success.

Of note, we have an ongoing partnership with the San Francisco Department of Public Health (SFDPH) and their division for Maternal, Child, and Adolescent Health and have accomplished significant milestones. In 2021, PTBi led the SFDPH hospital quality improvement project, spearheaded by Dr. Karen Scott and funded by CDPH's Perinatal Equity Initiative. As part of this project, a racial equity assessment was conducted, and we supported the development of a hospital quality improvement plan to improve health outcomes for Black birthing people in select San Francisco hospitals. In 2023, we partnered with SFDPH to produce a landscape analysis produced to outline the strengths, resources, and needs of the community regarding human milk feeding in the City and County of San Francisco. We were also responsible for the rebirth of the San Francisco Breastfeeding Coalition, which is meant to operationalize insights and recommendations provided by our analysis.



Achieving a vision of birth equity at the population level requires cross-sector partnerships and system-level changes. PTBi aims to turn the curve on birth disparities by harnessing the potential of collective impact and collaboration. Through this work we have solidified valuable partnerships with neighborhood associations, public health departments and government, academia, health and social service organizations, faith-based groups, and the media, not only within our three focus geographies, but across the state of California as well. Our positionality at UCSF allows us to establish important relationships with groups like Team Lily for instance, a Zuckerberg San Francisco General Hospital-based multidisciplinary care team providing person-centered, trauma-informed, wrap-around services to pregnant and postpartum people, who we can turn to for direct engagement with this project.

The California Preterm Birth Initiative has the infrastructure and partnerships in place to advance the most promising approaches to improve infant and maternal health outcomes, especially for underserved communities. Leveraging our expertise, relationships with key stakeholders and experienced staff, we will ensure the strength and success of the community engagement arm of this project. We express our full support of this project and are excited to engage a broader community in substance use research and look forward to building trusted sources of information for our communities that support their health and wellbeing.

Sincerely,

A handwritten signature in black ink that reads "Solaire Spellman". The script is fluid and cursive, with a mix of uppercase and lowercase letters.

Solaire Spellman, MPH

Interim Executive Director | California Preterm Birth Initiative
Co-Founder | CA Coalition for Black Birth Justice



D. Andrew Tompkins, MD MHS

Professor and Director, Division of Substance Abuse and Addiction Medicine
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March 7, 2024

Re: Letter of Support for the CIRM DISC4 Team Grant Application

Dear Dr. Li,

With great enthusiasm, we are writing this letter to support your research on the effects of prenatal marijuana exposure on the developing human brain. As clinician-scientists specializing in the treatment of persons with substance use disorders, we have witnessed an increase in substance use in our communities in California; specifically, the prevalence of using cannabis products has increased over the past decades, even among pregnant women. The recent legalization of cannabis for personal use in California as well as in many other states has contributed to an increase in the public perception that cannabis is relatively safe to use; however, several large-scale population studies have associated fetal developmental consequences with maternal marijuana consumption during pregnancies. We are excited to see that you will leverage single cell technologies to rigorously examine the responses of every single cell to marijuana exposure in the developing human brain. Identifying the potential underlying mechanisms of the consequences of cannabis use on fetal development will provide scientific evidence to aid in public policy decisions around cannabis regulation and provide information to expectant mothers and their OB/GYN clinicians to improve pregnancy outcomes.

As you are aware, the Division of Substance Abuse & Addiction Medicine (DSAAM) at Zuckerberg San Francisco General Hospital provides substance use disorder treatment, research, and education in service to our community. We treat over 1500 patients yearly in our various outpatient programs, are actively engaged in clinical research, and have partnered with our OB/GYN colleagues in the Team Lily Program to study and treat pregnant women with substance use disorders. Led by Dr. Caravella McCuistian, the Director of Special Projects at DSAAM, we have built our own research community advisory board to engage patients and diverse community stakeholders in the planning, conduct and dissemination of research findings. We believe the use of a community advisory board for your project is a unique strength of the application.

As investigators in the field of substance use disorders collectively for over 30 years, we see the importance of cell biology studies to elucidate the mechanisms of disease progression, which will foster future development of novel prevention and treatment strategies. Good luck with this submission! We are excited to see the results.

Sincerely,

A handwritten signature in black ink, appearing to read "D. Tompkins".

D. Andrew Tompkins, MD, MHS
Professor and Director,
Division of Substance Abuse & Addiction Medicine
Department of Psychiatry and Behavioral Sciences
UCSF School of Medicine

A handwritten signature in black ink, appearing to read "C. McCuistian".

Caravella McCuistian, Ph.D.
Assistant Professor and
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March 28, 2024

RE: Letter of Support for the CIRM Project “Prenatal Marijuana Exposure and Neuropsychiatric Predisposition: A Single Cell Perspective”

To Whom It May Concern:

I am writing in strong support of the CIRM proposed project “Prenatal Marijuana Exposure and Neuropsychiatric Predisposition: A Single Cell Perspective”. Considering the prevalence of marijuana use in California, the UCSF and Stanford study team will address a critical public health challenge from both scientific and community aspects. The study team’s goal is to identify cell types and developmental window that are likely affected by prenatal marijuana exposure, followed by determination of their association with neuropsychiatric predispositions, all with a strong community engagement component. This is especially important considering researchers have called for increasing education and treatment – not stigmatization and penalties - as vital regarding cannabis use in pregnancy.

The UCSF Bixby Center for Global Reproductive Health integrates research, training, clinical care, and advocacy to advance reproductive autonomy, equitable and compassionate care, and reproductive and sexual health worldwide. Advancing compassionate and equitable care for pregnant people who use substances is a priority in our advocacy efforts to advance person-centered and evidence-based policy, practice, clinical training and public discourse. We have convened experts from around the country to create resources for communicating about pregnancy and substance use with compassion and accuracy.

We express our full support of this project and are excited to engage in conversations about marijuana use in pregnancy and building on our work to communicate about these issues in ways that support health, wellbeing, dignity and autonomy.

Sincerely,

Rebecca Griffin
Communications Manager
UCSF Bixby Center for Global Reproductive Health