ICOC Application Review Subcommittee
601 Gateway Blvd, Suite 400
South San Francisco, CA 94080

August 25, 2024

Regarding: ReMind-L Proposal DISC4-16360

Dear ICOC Application Review Subcommittee,

We are writing to make a case for why our proposal to develop transformative tools for understanding intellectual disability (ID) should be urgently funded. Our project aims to identify and validate electrophysiological biomarkers for early diagnosis of ID using a revolutionary approach. We have assembled a team of world-leading experts from diverse scientific fields in the Los Angeles area, committed to tackling this challenging and debilitating neurodevelopmental disorder.

Our proposal stands out for receiving a unanimous "yes" vote from the GWG (14 in favor and 0 against) in three key categories: potential impact and significance, innovation, and diversity, equity, and inclusion. The few concerns raised in other categories can be fully addressed.

Key strengths of our proposal include:

- **Immediate Translational Potential:** Our approach to finding electrophysiological biomarkers for intellectual disability (ID) is groundbreaking and could significantly improve patients' lives. Currently, there are no objective, quantitative methods to diagnose and monitor ID. Doctors must rely on subjective assessments of a person's cognitive and behavioral symptoms. This makes it difficult to track disease progression, identify effective treatments, and provide personalized care. Especially for young children, IQ tests and other exams often fail to provide a clear picture of the severity of ID and the potential onset of co-occurring conditions such as epilepsy. By correlating electrophysiological findings from brain organoids with clinical EEG (electroencephalogram) data, we aim to discover new biomarkers that could revolutionize ID diagnosis and management. This approach does not require lengthy clinical trials and could be swiftly implemented to categorize patients and make prognosis-related decisions.
- **Attract New Talents into the Field of Neuropsychiatric Research:** We've brought together and seeded new partnerships with leading researchers from USC, Caltech, UCLA, and the Children's Hospital Los Angeles (CHLA). The majority of them are new to the field of neuropsychiatric research. This unique collaboration will enable us to develop cutting-edge tools and experimental platforms that will benefit the entire neuropsychiatric research field.
- **Development of Transformative Tools:** Beyond biomarker discovery, we're pioneering closed-loop neuromodulation paradigms for personalized, adaptive therapeutic strategies. Co-PI Dr.

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Shanechi's research involving deep brain stimulation is currently validating the efficacy of this promising approach for treating neuropsychiatric disorders, such as depression. We're also developing new methods for real-time tracking and analysis of organoids, as well as sophisticated computer models to integrate lab and clinical data.

- **Commitment to Diversity and Inclusion and Proven Track Record of Community Engagement**: We are well-connected with diverse communities in California, specifically underrepresented minority groups diagnosed with ID through our partnership with the division of neurology at CHLA. Our project aims to utilize cell lines from a diverse group of patients to further the understanding of idiopathic ID. With our institutions' connections to Federally Qualified Health Centers (FQHCs) and community organizations in Los Angeles County, we are well-positioned to reach underserved communities. We have also formed partnerships with patient advocacy groups that focus on rare disorders. Indeed, a crucial component of the project includes creating thirty cell lines from patients with pathogenic Syngap1 variants. Identification and engagement of Syngap1 patients is supported by the patient advocacy group Syngap Research Fund (SRF).

We have effectively mitigated risks associated with our primary objectives. However, due to the highly innovative nature of our work, certain aspects of our approach may deviate from the expected outcomes. Nevertheless, the project's high modularity will serve as an additional safety measure, as most proposed experiments can be conducted independently. Consequently, the potential impact of our work is immense.

Our world-class team is well-prepared to deliver revolutionary tools and insights that have the potential to positively transform the lives of individuals with ID. We firmly believe that our efforts are fully aligned with CIRM's mission to enhance the lives of all Californians and deserve your support.

We hope you'll agree that this proposal warrants CIRM's funding. **We're ready to get started.**

Sincerely,

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