ReMIND AWARDS

1/30/25

$16,583,897 GWG RECOMMENDED

$4,091,900 REMAINING

$20,675,797 AMOUNT AVAILABLE

					Number of GWG Votes		
APP #	TITLE	BUDGET REQ	FUND?	SCORE	1	2	3
DISC4-16337	Defining Neurovascular Metabolism in Neurodevelopmental and Neuropsychiatric Disorders	**$10,330,000**	**Y**	**1**	15	0	0
DISC4-16345	Multi-gene modulation to rescue CNS-associated microdeletion syndromes	**$6,253,897**	**Y**	**1**	14	0	0
DISC4-16400	High throughput, multi-modal analyses of neuropsychiatric disorder risk genes in a diverse cohort	**$14,247,869**	**N**	**1**	8	7	0
DISC4-16360	Patient-derived organoids for early diagnosis and personalized prognosis of intellectual disability (ID)	**$10,328,056**	**N**	**2**	2	12	0
DISC4-16507	From genes to circuits: leveraging neural assembloids to decipher multi-level mechanisms in neurodevelopmental disorders	**$15,215,281**	**N**	**2**	1	10	2
DISC4-16283	Prenatal Marijuana Exposure and Neuropsychiatric Predispositions: from Single Cells to Neuronal Circuitry	**$10,330,051**	**N**	**2**	0	12	2
DISC4-16336	Human neural organoid models for opioid, cocaine and alcohol substance use disorder to identify pathomechanisms in addiction	**$12,608,943**	**N**	**2**	0	8	5
DISC4-16378	Mechanistic understanding of neuronal maturational timing	**$8,568,852**	**N**	**3**	0	6	9

Application #	DISC4-16337 #2
Title (as written by the applicant)	Defining Neurovascular Metabolism in Neurodevelopmental and Neuropsychiatric Disorders
Research Objective (as written by the applicant)	Neuropsychiatric disorders correlate to impaired metabolism, but are understudied. We will describe how metabolism impacts disorders etiology and identify new, tractable therapeutic strategies.
Impact (as written by the applicant)	We will uncover metabolic drivers of neuropsychiatric disorders, resulting in new therapeutic targets including rigorously investigated dietary interventions and novel metabolic drug targets.
Statement of Benefit to California (as written by the applicant)	Strong data suggests metabolism is involved in the emergence of neuropsychiatric disorders, impacting a large fraction of Californians. Metabolism as studied in this project opens an entirely new horizon for drug development; members of our team have already brought metabolism targeting drugs to clinic for other indications and these data may also suggest ways in which diet can be therapeutically leveraged. These new strategies will positively impact patient and family well being.
Funds Requested	$10,330,000
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 1

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Votes for Tier 3	0

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KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13 **No:** 0	• Vascular development influences brain development, including developmental neuropathology. This interaction has not been well studied in human stem cells. • Multiple innovative experiments are proposed that could inform the study of many additional neurodevelopment disorders (NDDs). • The project will create both data and experimental protocols for the field. • This is a well designed and well revised project. The project is highly relevant and feasible. • The focus on autism spectrum disorder (ASD) will increase the potential impact of the project. • The proposal describes very significant and potentially impactful studies. • The authors revised the application to focus on ASD, and this will likely lead to more stringent and impactful outcomes. • The project demonstrates a high level of significance and potential for impact, particularly due to its innovative and multidisciplinary approach. • The proposal will provide a substantial advance in understanding how maternal metabolism can drive cell fate specification in the CNS, in particular, in the developing neocortex. • The proposal addresses a key non-neuronal contribution (vascular component) to brain development and its relationship with metabolic dysfunctions. • The project will decipher how neurovascular coupling develops and how, when dysregulated, it contributes to the etiology of NDDs. Narrowing the focus to ASD will enhance the clarity and impact of the outcomes. • The proposal will provide innovative technology in the field, such as combined LCMS-based metabolomics, and single cell-capture and transcriptomic analysis leading to the generation of metabolic tracer studies that could be extended to the study of other NDDs in the future. • By addressing the role of metabolism and vasculature in ASD this proposal will result in new knowledge (data quantity, quality, availability) and research venues and provide novel therapeutic approaches. • A project focusing on ASD will establish a strong foundation for advancing the understanding and treatment of NDD • The multidisciplinary approach will accelerate science and, hopefully, drive the development of new metabolic and non-invasive interventions (systemic treatments through diet) in NDDs. • The proposal will generate novel datasets of high quality and accessibility, which will be deposited in repositories and integrated with existing published data from human stem cells, animal models, and postmortem studies. • Identification of metabolic pathways controlling cell fate specification in the developing neocortex. • Characterization of the link between metabolism and specific genetic models underlying ASD (16p11.2 deletion syndrome). • Data deposition of five major data types in proper repositories, generation of foundational knowledge. Integration of the generated data with existing published data. • Sharing of novel datasets and resources with the research community and, in general, with clinicians and the neuropsychiatric community. For instance, the single-cell data generated—spanning neural and neurovascular organoids from patient and control lines, as well as xenografted organoids—will serve as an important resource for the field. • The revised proposal incorporates rescue experiments to establish a direct causal link between genes, pathways, and cellular phenotypes, enhancing its translational potential. It also will provide updated Developmental and brain ASD atlases, foundational references for primary brain biology. • The project incorporates a patient focus group, adding a novel dimension of inclusivity and real-world applicability.
GWG Votes	**Is the proposal innovative?**
Yes: 13	• This is a highly innovative proposal on multiple levels combining vascularized organoids with xenotransplantation and metabolomics. • Yes, in multiple ways.

No: 0	• This is not exactly new. Neurovascular and metabolic influences on brain development have been studied for many years. • The proposed system for studying neurovascular components of neurodevelopment is innovative. • Yes. Innovative technologies are proposed to evaluate the hypothesis that altered metabolism can impact the target diseases. The project combines in-depth studies of the latest in vitro organoid/assembloids, in vitro technologies, in vivo maturation, and state-of-the-art omics. Each is not novel on its own, but the combined use in context of diet and metabolism makes the project highly interesting. • Study of neurovascular effects is important and innovative. • Yes, the study includes cutting-edge methodologies, to name a few: (i) two-photon imaging neuronal structure of human organoids in vivo, (ii) development of neurovascular unit organoid models, (iii) neurovascular coupling functional studies in neurovascular assembloids, and (iv) a xenograft system during critical developmental periods. • The project comprises application of advanced technologies such as LCMS-based metabolomics, single-cell capture, and transcriptomic analysis, machine learning tools, cell chat. • Yes. This multidisciplinary approach assures complementary visions and engages different disciplines. • The team has proven records and expertise (metabolism, cell fate specification with single-cell transcriptomic, in vitro physiology, etc.) that will expand our understanding of metabolism's impact on human brain development and neuropsychiatric disorders onset at key developmental stages leading to the identification of metabolic pathways controlling cell fate specification in the developing cortex. • The project comprises integration of developmental biology, neuroscience, metabolomics, and electrophysiology to produce fundamental knowledge. • Yes, the project investigates how altered metabolism, potentially modifiable through dietary interventions, impacts neurodevelopment in ASD. The team has the potential to offer new perspectives in the treatment and prevention of ASD. • By combining metabolism, vascular, and neurobiology the team proposes to study a new disease mechanism that could explain how ASD brain abnormalities emerge during development. The team will innovate by learning how metabolism drives key developmental transitions, focusing on the neurovascular crosstalk, that, when perturbed, results in NDD. • With a robust data sharing plan the results could potentially be extended to other, broader studies in NDD.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The rationale behind the proposed project is grounded in evidence from genetic, postmortem, and neuroimaging studies suggesting that metabolic and microvascular abnormalities may contribute to NDDs such as ASD and schizophrenia. While the hypothesis that neurovascular coupling is relevant to these conditions is compelling, the justification based on existing literature and preliminary data requires refinement, particularly with regard to metabolism. • The revised focus on ASD - in the16p11.2 deletion syndrome model system - has a strong literature rationale (new publications were added). The main hypothesis is reinforced by well-presented preliminary results that substantiate the rationale. • The preliminary results are promising and compelling for the proposed research. • The research team has shown that vascular cells of the prenatal human brain express neurotransmitter receptors and transporters, providing evidence of the maturation of neurovascular coupling. • The research team has generated a metabolic atlas of the developing human brain. • Metabolism has been measured in organoids, and metabolomics in organoids as compared to primary fetal tissue shows similarity, validating the organoid model system. • The proposal includes recent data showing how maternal hyperglycemia leads to altered fetal metabolism and lower levels of metabolite-derived neurotransmitters. • Absolutely. Schizophrenia and ASD have no cure and pharmacological treatments are only partially effective. The cellular and molecular mechanisms that trigger and predict

	the evolution of these diseases remain largely unknown. The proposal addresses critical gaps in understanding neurovascular and metabolic contributions to ASD (16p11.2 deletion syndrome models). ● The results of this proposal will be a step towards the identification of new biomarkers and the development of new treatments for ASD. ● Yes, overall, BUT despite high enthusiasm for the proposal there are many examples where the literature seems mis-cited and results over-interpreted based on extrapolations from correlations of single cell RNA data into causal inferences. As an example, the proposal states that human brain endothelial cells "switch" from oxidative phosphorylation to glycolysis during the second trimester (citing reference 30). That paper (ref 30) did not provide direct evidence for such a switch - that would require oximetry studies - but interpreted gene expression and some EM data as consistent with increased neurovascular reliance on OXPHOS in the first trimester and glycolysis in the second. Importantly, that paper (ref 30) also mis-cites a review in Cell Metabolism as supporting this general contention, when the CM review does not address brain neurovasculature. Brain vasculature barrier integrity appears highly dependent on OXPHOS in multiple studies. ● The proposal fails to define whether they are studying influences of nascent, extending neurovasculature versus blood brain barrier-like properties that would likely also be affected in 16p11.2 and influence neuronal activity in the proposed model system. ● This project is strongly grounded in previous data. ● With the revised focus on ASD, the rationale is sound. ● The applicants have significant preliminary data that sufficiently support the proposal, though the applicant should be careful about drawing too wide conclusions from others' and their own data.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	● There is high enthusiasm for most of the proposed experiments, which are truly ground-breaking. The proposal has been well revised by focusing on one mutation (16p11) and one clinical phenotype (ASD) rather than the previous mix of multiple mutations and both ASD and schizophrenia phenotypes, such that impactful and reproducible findings are more likely to be made. The 16p11.2 model mice have been published to have a neurovascular phenotype, which strengthens the proposal. ● The table on page 18 refers to 17.5mM glucose. This is at least 8x higher than brain concentration, and many studies have demonstrated that glycolysis can be artifactually favored over OXPHOS in vitro under high glucose concentrations. It is however admirable that in Fig. 15 they show evidence that glucose concentration affects organoid development - but then it would be reassuring to know whether glucose concentration in metabolic studies will be considered in interpreting that data. ● Aim 2a indicates that synapses will be studied on NGN2 neurons after one week of differentiation. There will be no synapses after just one week of differentiation, and at any rate synaptophysin puncta in neurites would not be a reliable way to count synapses. The more standard approach (as per Aim 4) of counting psd95 puncta on a map2+ dendrite and apposed by a presynaptic marker (vGlut, synaptophysin, others) should be used for older cultures. ● There is tremendous enthusiasm for the "mix and match" neurovascular/organoid design in Aim 3. ● Interpretation of effects of diet on xenografts will be complicated by the mix of autonomous and non-autonomous effects. For example, a given diet could enhance mouse vascularization of the transplant, generating an artifactual finding not related to neurovascular coupling. However, the results of Aim 4 might help with this interpretation. ● The experimental platform is well designed, and the team was responsive to feedback from the prior GWG review. ● Yes. With the revised description of limitations and clarifications, the project plan is clear and well designed. ● This is a well developed proposal. All aspects are well supported by preliminary data. There is a high likelihood of success. ● The research team defines 4 aims, each with several activities and milestones, to be accomplished in parallel throughout the project, to study their main hypothesis - that

	metabolism can play a role in the etiology of NDDs, and diets can modify these disease phenotypes. ● The proposal has been revised to focus on 16p11.2 deletion syndrome, a form of ASD, to limit genetic alterations. The study will use cell lines from a diverse cohort, and male and female lines will be used. ● Through the use of neurovascular organoids the research team is recapitulating the complex interactions between cells and tissues during brain development. ● The work plan is clear, and explanatory, and includes expected results and pitfalls. ● The Gantt chart presents activities by objectives, in detail, incorporating milestones. ● Yes, pitfalls are identified and alternative experiments are presented. ● The team is building upon existing collaborations, has high-impact shared publications, and presents complementary approaches to tackle the different aims. ● An integrative multi-approach will speed up the development of non-invasive cures for ASD and expedite the testing of new drugs. ● State-of-the-art infrastructure and core facilities are available at the main hosting institution, and all the necessary logistics and expertise have been recruited or are included in the proposal revealing excellent collaborations with other center members (e.g., assuring access to patient cell lines and databases, electrophysiology).
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	● The increased focus has reduced the diffuseness of the previous scope, which increases feasibility. ● Yes; the applicants outlined a feasible plan. ● The research team possesses proven expertise in relevant fields, including metabolism, single-cell transcriptomics, and human neurodevelopment, ensuring rigorous exploration of metabolic pathways influencing cortical cell fate. ● Researchers with different academic backgrounds and expertise, at different stages of their careers (senior investigators and young investigators), balance between developmental neuroscientists and clinical experts, and adequate formation of human resources (graduate students and postdocs). ● The revised version includes additional personnel dedicated to the electrophysiology component, and fewer IPS lines will be analyzed, ensuring the team's capacity and the project's feasibility. The main contribution is the linkage between modalities: metabolomics, single-cell transcriptomics, and in vitro physiology (focusing on neurons) assuming converging phenotypes in ASD. ● Yes, coordinated efforts assure interdisciplinary collaboration: adequate distribution of workload among institutions, Key Personnel assigned for each aim led by one of the core research team members, variety of experimental approaches covered by several Investigators (multiple labs can generate cortical organoids, metabolomics). ● The collaboration manual is a good initiative. ● Yes. There is coherence between what is requested in resources and what is available. ● The investigative team has all the necessary resources, is very active and well-funded, has a strong record of interaction, and has a broad collaboration network. ● Yes. The budget is well-organized. By reducing the scope of the project focusing on one disorder (ASD) and including and adequate number of patient-derived lines and mouse models the budget is well justified.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13 **No:** 0	● Yes, the DEI plan is sufficient given the nature of the disease. ● The team describes activities related to DEI - involvement in community college and other educational activities. ● Yes. The research team plans to use cell lines that reflect gender diversity and a range of racial backgrounds. The revised version includes a detailed table outlining the proposed lines for the ASD 16p11.2 deletion syndrome. ● The project incorporates use of sex and racially matched control lines in all the experiments, and these lines are already available. Lines derived from underrepresented minorities are included. ● The research team states that DEI is central to the accomplishment of their mission. Currently, investigators are engaged in stem cell and neuroscience education programs for community college and high school students, and creating opportunities (e.g.,

	training sessions and laboratory mentorships) for students from underrepresented backgrounds and ethnicities. • Educational development in STEM is another initiative to be developed within the research plan. This aspect is headed by a team member with extensive experience in this regard.

Application #	DISC4-16345 #2
Title (as written by the applicant)	Multi-gene modulation to rescue CNS-associated microdeletion syndromes
Research Objective (as written by the applicant)	Chromosomal microdeletion syndromes result in severe neuropsychiatric syndromes and lack therapy. This proposal will define critical genomic regions needed to generate new tools for functional rescue.
Impact (as written by the applicant)	This work offers a new approach to restore gene function in 16p and 22q deletion syndromes. Success will create a model for treatment of >200 microdeletion syndromes with neuropsychiatric symptoms.
Statement of Benefit to California (as written by the applicant)	Microdeletion syndromes have neuropsychiatric manifestations and few therapeutic options. Given the cognitive deficits and need for lifelong care, these conditions affect the resources and well-being of patient caregivers and providers. Our studies will generate novel therapeutic approaches using 16p and 22q deletion syndromes as exemplars. We will also use clinical outreach and advocacy panels to understand the patient experience and ensure patient-driven goals are part of the research process.
Funds Requested	$6,253,897
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

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Highest	1
Lowest	1
Count	14
Votes for Tier 1	14
Votes for Tier 2	0
Votes for Tier 3	0

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KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12 **No:** 0	• The applicants propose a novel method for therapeutic regulation of multiple genes that potentially can be very impactful and significant for diseases even outside the scope of the application. • The total incident of 1:100 is relatively high and the approach would provide a roadmap to all 200 known microdeletion syndromes. • This is a high risk-high reward project that has great promise. Successfully addressing haploinsufficiencies across multiple genes is potentially curative. • The approach of correcting or modulation of an entire gene set in the context of microdeletion syndromes is exciting and interesting. • Upregulating multiple genes is a strength and novel for microdeletions. • Highly relevant, well designed, ambitious but also highly rewarding. • The project, if successful, would lead to a better understanding of the cellular and circuit dysfunctions in neuropsychiatric disorders. • The project utilizes new tools for gene restoration and develops in vitro human cell-based and xenograft mouse assays that could improve the understanding of these diseases. • Potential path for utilizing iPCSs to evaluate multi-gene upregulation for disorders with genetic deletion etiology. The concern is how far investigators can get in terms of the stoichiometric aspects such as variable degrees of upregulation of different genes.
GWG Votes	**Is the proposal innovative?**
Yes: 12 **No:** 0	• There are several novel aspects of this approach of gene regulation. • The approach is highly innovative and uses cutting-edge approaches. • A proposed technology will be used to target multiple genes for microdeletion syndromes. This approach could lead to new insights into neuropsychiatric disease mechanisms that are caused by microdeletions. • Highly innovative with regard to multiple gene upregulation as well as applications of iPSC related assays to argue for application to human treatment. • The concept is not new but the approach to achieve the goal of adjusting multiple genes simultaneously is challenging. The applicant now shows in the revised version successful regulation of 5 genes at the same time. • Yes, the proposal utilizes a technology for gene activation, 2D and 3D in vitro models, and xenotransplant systems. • Yes, a multidisciplinary team of six investigators with complementary expertise.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The rationale is straightforward - restore gene function across the micro deletion. • With the new added preliminary data, the approach and rationale is sound. There is a risk of not being able to control doses, but the rationale for therapy holds. • Yes, the project has been scaled back to address only the 22q11 deletion. • The systematic analysis of alterations in cellular and circuit function using electrophysiological approaches is a strength that will identify core excitability traits disrupted in these syndromes. • The xenograft model is innovative and clever, and will allow longitudinal studies. • Given preliminary data, the goal appears possible and the data generated will be highly informative with regard to application to treatment development for certain disorders with features that might have generalizable utility of iPSC organoids as translational tools.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• With the focused and scaled-down experimental plan focusing on one microdeletion disease the project is well planned. • The proposal is focused, shows high impact, and has a high likelihood of success. • The research plan is sound and the focus on one microdeletion syndrome addresses the overambitious nature of the previous submission. • The systematic analysis of alterations in cellular and circuit function using electrophysiological approaches is a strength that will identify core excitability traits disrupted in these syndromes. • The applicant uses human iPSCs, organoids, and mouse models to test their hypothesis.

	• Multiple components to go from multiple up regulation concept to showing effects first in vitro and then in a humanized mouse brain assay are neatly aligned. • While the new data showing five genes upregulated at one time is a great addition, the question about stoichiometry is still out there. Can they get the genes to the right levels by just swapping out promoters?
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• New preliminary data address a previous core concern of the ability to simultaneously regulate multiple genes. Using Angleman Syndrome as an example, the approach resulted in successful upregulation of five genes simultaneously in neurons. • New preliminary data and a more narrow focus highly increase feasibility. • Yes, there is a reduction in budget because of the focus on one deletion. • The strength of the participating researchers and the preliminary data supports the feasibility of the project. • Well defined plan. • Convincing preliminary data on the potential of each component to deliver. As noted, the big question is whether it is feasible to control the degree of upregulation across multiple genes. • Stoichiometry may be an issue.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12 **No:** 0	• Yes, the team is being intentional about selecting lines from diverse donors. Aim 4 focuses on patient outreach and education, which is expected to increase diversity in patient recruitment. • The team has a strong track record of DEI activities and the disease affects across our population without bias. • Yes, the plan is to incorporate prevalent cases, 22q11 microdeletions, and a third microdeletion solicited from family foundations, using human iPSCs and organoids, along with mice incorporating human explants. • The approach can be used for other micro deletions and is independent of gender or ethnicity. • The project is dependent on cells from affected individuals and requires inclusion of patients. The outreach to involve them in being committed to providing cells is very thorough.

Application #	DISC4-16400 #2
Title (as written by the applicant)	High throughput, multi-modal analyses of neuropsychiatric disorder risk genes in a diverse cohort
Research Objective (as written by the applicant)	Drug development for autism and schizophrenia is hampered by disease mechanism knowledge gaps and minimal inclusion of ancestral diversity. We will address both bottlenecks to improve drug discovery.
Impact (as written by the applicant)	We will identify disease phenotypes in stem cell models that are shared between autism and schizophrenia, which will enable future drug screens to help find treatments for these conditions.
Statement of Benefit to California (as written by the applicant)	Autism and schizophrenia are neuropsychiatric disorders that collectively affect 3-4% of people. Thousands of Californian families are impacted, and the estimated annual economic costs are in the tens of billions of dollars. Here, we will use stem cell-derived models of the developing human brain to identify disease mechanisms and nominate drug targets. We will conduct these investigations using human cell lines from ancestral backgrounds that represent the diversity of California residents.
Funds Requested	$14,247,869
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13 **No:** 1	• This proposal addresses the biggest bottleneck in the field right now: moving from gene discovery to etiological understanding. • The proposal's major output is a large number of iPSC (induced pluripotent stem cells) lines with disease mutations of an African American origin. • Interrogating mechanisms of disease deeply will yield important insights into understanding neuropsychiatric disease. This is a good team for this effort. • The project will give important mechanistic insights to gene-to-phenotype relationships. Will establish needed diversity in iPSC-lines. Negative is power for detection of common variants with limited sample size but this might be helped by cell-state specific analysis and increased variability in genetic background. • Arguably the greatest benefit of this project is the diverse cell lines, but given that, applicant could just go all-in on producing them and generate a more likely-to-be useful sample size (for sporadic/idiopathic/polygenic disease). • Novel approach, highly relevant and addressing unmet medical need. However, the applicants expertise and ability to synthesize and analyze obtained data is of concern. • The proposal has a very wide scope so it is very unclear if any impactful conclusions could be made. • The reviewer notes that the applicant will possibly have under-powered data for the case that is of broadest interest - idiopathic/sporadic disease. The applicant will quite likely have an unfinished deep learning model due to insufficient resources, and hence the main piece of this proposal that is supposed to unify the findings is not functional, preventing the extraction of coherent disease mechanisms across diverse lines. • The proposal will likely not be successful for reasons explained. The novel Artificial Intelligence (AI) analysis claims to be 10x+ faster than experts in the field have ever experienced. The approach would violate findings of the largest studies on complex disease with regard to effect sizes. While it might find convergent mechanisms of disease, the capstone analysis does not show any preliminary results, intermediate constructs, or relevant success to support this. • Still potentially under-powered.
GWG Votes	**Is the proposal innovative?**
Yes: 13 **No:** 1	• Yes - very excited about the imaging and electrophysiology components. • The analyses are highly advanced and innovative. • A combination of state-of-the-art methods including iPSC-derived cell models, 3D organoids and cell village. Well designed to work together. • This is innovative in that it builds on new pipelines for production and analysis of iPSC and iPSC-derived neurons. • Not new, but doing so on the largest scale seen for these diseases. • The proposal combines novel technologies but is not innovate as such. • Possibly. A lot of that cross-cutting depends on a highly speculative AI model that lacks any preliminary data.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• The study follows a strong scientific rationale using novel technologies to advance mechanistic insights. The author's rebuttal about the criticism around using cell lines from African American people is very strong. The applicant makes a clear point that this choice addresses a major knowledge gap, is scientifically highly relevant and that nothing is known about genetic background modifying disease risk in European Americans either. • Highly relevant - in fact it's such an important topic and approach that it's worth doing in a way positioned to succeed. • Overall the idea to generate more disease iPSC lines in an African American background is rational. • Yes, overall sound. Reviewer is skeptical of the idea that schizophrenia-related biology/phenotype will be uncovered in iPSC cultures as they represent too early a time point. However, understanding the relationship between gene-phenotype is still important, and what happens in an early neuron might be somewhat related to what happens later. The project is definitely relevant to autism.

	• Model for ASD (Autistic Spectrum Disorders) is clear. Model for schizophrenia is more challenging. • The idea to include two different conditions and diverse studies makes the proposal weaker. • 45 lines for studying idiopathic disease (compared to Timothy syndrome) is quite low and may be underpowered. However, this reviewer feels it is important to start somewhere. • As the authors state, there are no large transcriptional studies for cell lines in these diseases. There are cell line collections for Alzheimer's Disease and Parkinson's Disease from which applicant could draw from data, while adjusting for smaller effect sizes in ASD. Alternatively, the applicant could use postmortem transcriptome studies and determine the proposed number of samples. Currently, the power analysis for the idiopathic cell lines does not adequately reflect complex disease finding with such samples sizes, and given the lack of effects typically seen in the transcriptome with n=45 case/control size, this really does need to be demonstrated with real analogous data. • For power calculation on the transcriptome, the direct citation currently is a paper in which a small minority of the cell lines are from idiopathic disease, and hence are not appropriate. • Although a schematic AI model can be written down, that is miles away from demonstrating that it is possible. Direct evidence from the exact data is what that's needed. Failing that, next step is to move to analogous data sources. When not all data sources are available, then at least benefits from fusing some of them should be shown. However, there are literally no actions taken showing that the members of this grant are processing data (or analogous data) approximately as proposed and showing benefits from that. • Stating that the applicant's sample size is automatically powered because it is larger than some underpowered studies does not mean that it is actually adequately powered.
GWG Votes	**Is the project well planned and designed?**
Yes: 9 **No:** 5	• Project involves global leaders across different areas and has highly synergistic parts. Even if not all aspects will be well powered, this is well positioned to provide mechanistic insights. • Yes, perhaps with the exception of the AI aim, which may be underdeveloped. • There are still questions remaining in the data analysis section. The analysis approach appears moderately generic. • Inadequate preliminary data for Aim 5. • Major strengths are the team and the infrastructure. Weakness is aim 5 which is still under-developed and with little preliminary data. • Aim 5 is problematic. • There is not adequate funding/effort to complete two key and arguably most important components of the project that are going to be of great interest: the cell line transcriptomics and deep learning. Other aspects of the project are very strong, but the issue is these weak areas are rate-limiting for the overall impact of the project. • There is potential for synergy, and the electrophysiology measurements on various lines are an example of exploring new and disease relevant aspects of the lines. However, the most nominally synergistic aim - the deep learning model that will synthesize everything together is very vaguely described. It lacks the preliminary data found in essentially every other grant, even those much smaller, and thus is both relatively and absolutely not demonstrated to be synergistic. • The major weakness is the diversity of the proposal making it less likely to generate impactful findings. • The AI part seems underestimated.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 1	• Authors have provided convincing preliminary data. • Feasible, except aim 5 • Adding the new investigator with expertise in AI is good, and the additional details provided make the approach more feasible for the team. • Yes, aims 1-4 are feasible (infrastructure, preliminary data and scale). Aim 5 is hard to judge. • Concerns about Aim 5; this reviewer would have given a 1 if Aim 5 was removed.

	• Overall the applicants have relevant background except for the AI part. • Aim 5 is not clear and lacks demonstration of AI experience. Aim 5 should not be supported in its present form. • Looking at what is proposed for Aim 5, which is both novel and speculative, 8% of a professor (+85% of a junior engineer) is insufficient for the inevitable process of refining the base model. Based on related projects, a minimum of three (world-class and experienced) Full Time Equivalents (FTEs) who are not torn in multiple directions are needed to make headway on such a major project. • While Machine Learning (ML) is commonly confused and conflated with AI, they are not the same thing. The repeated assertions that an AI project is feasible based on [redacted investigator's name] ML experience does not follow. While helpful, it is not sufficient. • Applicant has limited AI-related publications and lacks demonstrated technical ability on the specific issue of setting up deep neural network topologies. • There is a persistent problem with lack of rigor in determining number of samples. For number of cell lines, the proposal plans to keep adding lines until an effect is seen. Similarly for the calcium imaging, the proposal states it will select up to 15 neurodevelopmental disorder (NPD) models for high-density microelectrode array (HD-MEA) analysis from those that displayed unusual bursting activities, changes in neural network composition, alterations in oscillatory rhythms, and/or recurrent epochs of high frequency oscillations in Aim 3b, along with five control lines. Cherry picking lines for comparison to controls does not provide generalizable information and could inflate results. • No. The budget allows for some of the aims. At the current budget level, cuts to other areas would be needed to generate an adequate number of idiopathic cell lines that will likely show disease effects, based on appropriate effect sizes drawn from literature.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14 **No:** 0	• Outstanding DEI proposal. • Focus on samples from African Americans addresses a major gap. • The project has a very relevant DEI part. • This is at the foundation of the proposal. • Yes - it would extend the findings from EUR (European) to more diverse ancestries, but applicants do note they're not set up for discovery of ancestry specific factors, so there's a limit - best case scenario everything from EUR is applicable, but without finding anything new.

Application #	DISC4-16360 #2
Title (as written by the applicant)	Patient-derived organoids for early diagnosis and personalized prognosis of intellectual disability (ID)
Research Objective (as written by the applicant)	We aim to identify biomarkers in organoids derived from patients with intellectual disability (ID) and potential correlations with disease mechanism and clinical electroencephalograms (EEG) data.
Impact (as written by the applicant)	Identifying biomarkers reflecting the severity of ID, and correlating patient EEGs with organoid signatures, may transform clinical practice by aiding diagnosis and treatment.
Statement of Benefit to California (as written by the applicant)	This study introduces new technologies and frameworks for early diagnosis and personalized prognosis of ID, impacting California's population and healthcare system. Through our hospital partnership we will generate organoids from ethnically and racially diverse ID patients, reflecting the affected communities across California. Our advances in mental health research through collaborative research and data sharing may change the treatment regimen of ID patients.
Funds Requested	$10,328,056
GWG Recommendation	**Tier 2: needs improvement, could be resubmitted**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 2

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Highest	1
Lowest	2
Count	14
Votes for Tier 1	2
Votes for Tier 2	12
Votes for Tier 3	0

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- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 7 **No:** 5	• This is a technologically exciting proposal with the potential to have high impact. • The proposal includes many potential technological advances in recording, imaging, and fate mapping/lineage tracing of cerebral organoids. These could be foundational for many future studies of neurodevelopmental disorders (NDDs). • The project offers more potential impact on technology development than on the understanding of intellectual disability (ID). • Cell lines from ID-affected individuals from marginalized groups will be generated, along with syngap1 heterozygous individuals. Novel protocols for recording, imaging, and lineage tracing in organoids will be generated. • The proposal has partial potential for impact by generating new iPS lines with altered syngap, but the correlations under study are speculative. • This project will use human organoid models to study ID, specifically to identify biomarkers, disease mechanisms, and correlations to clinical data from patients. The overview goal is to studying and diagnose ID using in vitro models. • Diagnosis and prognosis of human diseases are highly complex. Indeed, the EEG of a person with intellectual disability can be normal and is not a specific test for this condition. In other words, despite many decades of effort, diagnosis/prognosis for intellectual disability could not be established in the clinic based on EEG only. Rather, EEG can be used in combination with various other psychometric tests, which cannot be recapitulated with organoid models. • This project will establish an organoid model and identify biomarkers for intellectual disability by comparing in vitro electrophysiology to clinical EEG data. This approach appears to be highly risky. • The proposal will generate various datasets including single-cell transcriptomics, synthetic RNA exporters, machine learning protocols, and neuromodulation models, and potentially disease mechanism-based classification.
GWG Votes	**Is the proposal innovative?**
Yes: 9 **No:** 3	• This is a highly innovative proposal. • Yes. The combination of e-phys, imaging, and gene expression is innovative. • This is not really a new conceptual framework - but testing whether the organoid system can recapitulate some aspect of EEG abnormalities associated with ID and/or syngap1 +/- phenotypes. • This is an extremely unique approach and topic. • The technology development, e.g., the e-phys platform, is at an average level of innovation for the field. • The technology development for comparison between EEG and ephys is interesting but speculative. • Potentially, yes, but unclear at this point and without stronger preliminary data. • Yes. Correlation of clinical data and in vitro data is of interest and could provide new insights into disease mechanisms. However, it is unclear what the significance of the findings might be. • Potentially yes, and more preliminary work needs to be done.
GWG Votes	**Is the rationale sound?**
Yes: 7 **No:** 5	• For most points, the rationale is sound. However, there are remaining concerns that the scope of the project using 3D organoids may not be justified for studying network activity when a more simplified system and direct approach of synaptic function may be sufficient for some of the same outcomes. • The technology development, and the team for developing it, is outstanding. Cerebral organoids are an excellent system for studying the effect of SYNGAP1 mutations on human radial glial-like cells. • The problem remains that excitatory connectivity within cerebral organoids is not established to bear much if any similarity, let alone be able to model, that connectivity in vivo. Neurons deprived of their normal targets will often innervate aberrant targets, thus the vast majority of connectivity in an organoid will be aberrant since collosal, interareal, and subcortical connectivity is absent. • Thus, while phenotypes are highly likely to be found, and may even correlate with the degree of ID, it is not at all evident why the results should be more useful and amenable

	to therapeutics development than the much more rapid differentiation of patient neurons on control astrocytes with analysis of maturation and synaptic properties, or even MEA, within 60 days and with decreased variability. ● How can closed-loop neuromodulation be clinically useful when derived from a system that features largely if not almost entirely aberrant connectivity? ● The proposal features many opportunities for tremendously impactful technology development - but why not focus more on establishing the connectivity that exists within their organoids, and its correlation to connectivity in vivo? Or perhaps compare 2D and organoid utility for making ID-relevant (prevention or therapeutic) discoveries in SYNGAP +/-? ● The proposal includes outstanding preliminary data. ● It is a bit too speculative that organoid data will be prognostic of ID development. ● The idea that a limited amount of neurons and their limited synaptic connectivity will provide a "window" into brain connectivity in humans later in life is not well supported by any data. ● Yes, but depending on the approach, the project goals can turn out to be highly risky, variable and of unknown significance for diagnostic and therapeutic purposes. It is unclear if subtle electrophysiological differences in organoids will be sufficiently strong and reproducible to serve as diagnostic biomarker. ● The preliminary data are not sufficiently compelling to support such an ambitious goal of diagnosing and prognosticating about ID based on highly variable organoid models that need to be cultured in vitro for several months. ● Potentially yes, but the project goals are not directly relevant and informative for clinical diagnosis of ID.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 4	● The project combines analyses of activity, lineage, and RNA expression. However, it is not likely that novel molecular mechanisms will be discovered. ● The applicant's presentation of additional details of the analytic plan is excellent. ● Yes. The revised proposal provides further clarifications. ● There are potential scientific synergies but of unknown significance and impact.
GWG Votes	**Is the project feasible?**
Yes: 6 **No:** 6	● This is an outstanding team. ● The team provides excellent data in support of the proposal. ● The team has the capacity to carry out the proposal. ● The team is qualified and experienced but unclear how the quality of the large number newly generated iPSC lines will be ensured and then applied to the suggested experiments. ● It is possible or even likely that the team can identify e-phys phenotypes in their syngap iPS models, but it is unclear how that will lead to any progression for ID patients ● Correlating a limited electrophysiological outcomes to a complex disease and making prognostic decision is at this stage not feasible. ● Potentially yes, but the project could take longer or produce conflicting results, which may require additional budget.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12 **No:** 0	● This was acceptable in the initial submission and remains the same. ● The DEI plan is relevant to the disease.

Application #	DISC4-16507 #2
Title (as written by the applicant)	From genes to circuits: leveraging neural assembloids to decipher multi-level mechanisms in neurodevelopmental disorders
Research Objective (as written by the applicant)	Identifying neurodevelopmental pathomechanisms at the molecular, cellular, and circuit level in human neural assembloids will lead to tailored therapeutic approaches.
Impact (as written by the applicant)	Identifying neurodevelopmental pathomechanisms at the molecular, cellular, and circuit level in human neural assembloids will lead to tailored therapeutic approaches.
Statement of Benefit to California (as written by the applicant)	An estimated 2.8% of Californian children are diagnosed with autism spectrum disorder (ASD), 1.6% with intellectual disability, and 1% of adults with schizophrenia. We will determine the role of neural circuits in neurodevelopmental disorders and integrate findings with data about molecular and cellular abnormalities as well as validate our findings across diverse cell lines. A better understanding of how human brain circuits are dysfunctional will point us toward better ways to protect, improve, and treat those symptoms.
Funds Requested	$15,215,281
GWG Recommendation	**Tier 2: needs improvement, could be resubmitted**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 2

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Highest	1
Lowest	3
Count	13
Votes for Tier 1	1
Votes for Tier 2	10
Votes for Tier 3	2

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- A score of “3” means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 9 **No:** 2	• Treatments for neuropsychiatric and neurodevelopmental disorders (NDDs) are hindered by the lack of available human circuitry models. • This project would help allow the identification of genes that are involved in emergent circuit dysfunction in NDDs and point to potential therapeutic targets. • The applicant plans to identify shared genetic nodes across various neurodegenerative diseases and generate valuable resources, such as heterozygous knockout iPSC lines and extensive datasets for AI and machine learning. • The applicant proposes the generation of 45 engineered iPSC lines. 30 lines will be in a single iPSC line engineered to contain mutations in selected genes with suspected roles in NDDs. The top five genes will then be engineered into three additional iPSC lines from racially diverse subjects. • The proposed experiments utilize complex assembloids made from brain region specific organoids that may provide the best model system for accurately mimicking human brain development. • Once assembloids are generated, the role of these genes in NDDs will be comprehensively mapped. The applicant will perform electrophysiology, optogenetic mapping, and single cell RNAseq to determine if any of the selected genes play a role in NDDs and/or affect neural connectivity. • They will also test these genes in vivo by transplantation of the assembloids into animal models. • Heterozygous knockout iPSC lines, extensive datasets, and advanced in vitro models will be utilized. • The data sharing plan is well thought out and appropriate. • Highly relevant, well developed and designed project. However, highly ambitious and likely not (entirely) achievable. • The project will investigate several mutations relevant to NDDs using organoid technology, primarily in White male iPS lines. While this investigation may be interesting, it is questionable how impactful the outcome will be. • The project has potential impact but there are concerns about the ability to evaluate hypoactivity in this system. • No protein analysis is proposed, despite the well known poor correlation of transcripts to proteins.
GWG Votes	**Is the proposal innovative?**
Yes: 10 **No:** 1	• A strength of this study is the in-depth nature in which they will probe the role of the selected genes in neural development and circuitry. • The ability to test the circuitry of NDDs in development is a key aspect of this proposal and one of its strongest features. The biggest challenge of cell culture models is the ability to integrate all the different cell types and spatial and temporal relationships found in an actual organism. This proposal does an excellent job trying to recapitulate all those variables in an in vitro model. • This project may help identify key genes involved in NDDs and may help identify targets for treating these disorders. • The proposal engages a number of different disciplines and sub-disciplines. Broadly, it incorporates cell modes, genetics, animal models and AI. However, even within these broad disciplines numerous sub-disciplines are engaged. • The proposal incorporates diverse disciplines such as machine learning, electrochemical bioengineering, and neuroscience. • The proposal examines human mechanisms across psychiatric conditions and scales of analysis. • The applicants have taken special care to try to ensure the results are consistent among many different genetic backgrounds and this is also an important aspect of this proposal. • The proposal integrates a range of cutting-edge technologies, including bioelectronics, patch-seq, and advanced assembloid production. • The technologies used are world leading. • The proposal applies demonstrated, but novel, methods on new iPS lines.
GWG Votes	**Is the rationale sound?**

Yes: 9 **No:** 2	• The applicants have chosen to focus on three NDDs – intellectual disability, autism and schizophrenia. • The selection strategy behind the selected genes is well thought out. The initial strategy to screen for circuit defects in all selected genes and then do in depth analysis of the top five candidates in diverse backgrounds is a very sound plan. • Each of the investigators in the proposal are experts in their fields and have provided excellent preliminary data. • Not only is the project extremely relevant to human biology and disease, but the investigators have excellent plans to help ensure the project is relevant to the greatest range of people possible by creating the NDD cell models from iPSC from racially diverse subjects. • Yes, this addresses a critical need for a systematic, multi-level infrastructure for comparing many NDD genes in a human-specific experimental platform. • The team's capability to generate heterozygous knockout hiPS cell lines with an >75% success rate helps. • The use of the animal transplantation experiments to provide additional mechanistic insights is well justified and the investigators worked with a bioethics team to create guidelines for the transplantation experiments. • The rationale is a standard proposal of convergence and E-I imbalance. • It is rational to generate more NDD lines but it is unclear why the specific background is chosen. • The emphasis on electrophysiology raises major questions in outcomes where activity is expected to decrease (hypoactivity).
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 3	• The subprojects are very well organized and are well planned to accomplish the aims of the proposal. • A strength is the way each aim builds on the one before it in order to fully map the role of the selected NDDs in neural development. • The applicants do an excellent job discussing the potential pitfalls of each milestone and providing alternative approaches. • Nice addition of alternatives for the heterozygous knockout iPSC generation. • The application would be stronger if the expected outcome for each aim and sub-aim was explicitly stated. • Some concerns about not examining protein, and no discussion of expected outcomes about what constitutes phenotypic convergence. • Electrophysiology is not adequate to detect hypo-connected cells as spontaneous activity is typically very low at baseline. • Major concerns about electrophysiology experiments; signal will already be low, and when looking for hypoactivation, they will miss out on functional changes. Several experts on the panel were very concerned about the ability to do these experiments and get meaningful results. • Unclear why such low density electrophysiology tools are suggested. • Again unclear why a more diverse iPS background is not the primary target.
GWG Votes	**Is the project feasible?**
Yes: 7 **No:** 4	• The proposed team is very well qualified, each having the necessary expertise to accomplish their goals. • The plans for organizing the project are appropriate. The PI has past experience managing similarly large projects and communication between all team members is ongoing. • The team is very competent and can carry out the proposed studies. • The amount of work to be accomplished is very ambitious, but the preliminary data go a long way to establish that it is feasible. • Most of the necessary resources are in place. The budget does plan for some additional equipment, but it is well justified and the lab space for each of the groups is appropriate. • There were some serious concerns raised about the feasibility of the planned electrophysiology experiments. • The proposal needs an alternative to looking for hypoactivation.

	• The project is ambitious, but the work on hyperconnected phenotypes should succeed. There is reviewer concern about detecting hypoconnected phenotypes. • Some minor concerns remain regarding technical measurements.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 10 **No:** 1	• The project does an excellent job attempting to ensure the findings are applicable to a very diverse population. Once the applicants determine the genes most involved in the emergence of neural circuitry, these mutations will be engineered into a few additional iPSC from diverse subjects, ensuring that the phenotypes seen initially are not limited to a single population. • The applicants plan to enlist the help of family and advocacy groups to disseminate the results to the public. • The proposal includes minimal effort to study diverse iPSC lines, making it just adequate for DEI. • The experimental plan does not consider DEI sufficiently.

Application #	DISC4-16283 #2
Title (as written by the applicant)	Prenatal Marijuana Exposure and Neuropsychiatric Predispositions: from Single Cells to Neuronal Circuitry
Research Objective (as written by the applicant)	This study will explore how maternal marijuana use during pregnancy may disrupt fetal brain development, potentially increasing the risk of neuropsychiatric disorders later in life.
Impact (as written by the applicant)	This study aims to resolve the debate on marijuana's safety in pregnancy, using mechanistic findings to guide community support and shape informed public policies.
Statement of Benefit to California (as written by the applicant)	In California, approximately 19% of young women use cannabis during pregnancy, with marijuana commonly seen as safe. Yet, studies consistently show that prenatal cannabis exposure is associated with increased neuropsychiatric risks in children. By identifying the biological mechanisms at play, this study aims to guide evidence-based policies and expand support for underserved communities, ultimately working to improve birth outcomes and address health inequities.
Funds Requested	$10,330,051
GWG Recommendation	**Tier 2: needs improvement, could be resubmitted**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 2

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Highest	2
Lowest	3
Count	14
Votes for Tier 1	0
Votes for Tier 2	12
Votes for Tier 3	2

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KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 8 **No:** 5	• Nearly 20% of pregnant women in California use cannabis during pregnancy. While epidemiological studies show a negative impact of cannabis and birth outcomes, these data thus far have failed to convince large part of the public and are often dismissed as "anecdotal". While the applicants for the proposed study cannot guarantee that additional data will lead to a better appreciation of the risk of cannabis for the developing brain, it will provide additional data as to the specific impact to the fetus. • Spatially resolved transcriptomics may yield new biological context to the understanding of neuropsychiatric disorders. • As many as 20% of women use marijuana during pregnancy. The successful completion of this project could have substantial positive impact. • They will collect millions of single cell data (mostly transcriptional) from ex vivo treated, in vivo collected (control and users) and treated organoid models. Assuming the generally shallow single cell data capture relevant gene expression signatures, one may learn more about the effect of THC on gene regulation and possibly cellular effects. This may also provide molecular hints for the developmental consequences or link of the exposure to the developing fetus. • The application does not directly test whether cannabis use leads to neuropsychiatric disorders. The identification of potential pathways or cells that might be affected by cannabis is a good start, but it is far from allowing extrapolation to neuropsychiatric disorders. • The premise for the project is that the study will identify an easy to understand mechanism that is disrupted by cannabis and is directly linked to a disease. Such an outcome is highly unlikely, and thus, effective messaging of the data to the public will remain a challenge. • The association of genes that respond to cannabis with other know genes that are found to be disrupted in neurodevelopmental disorders is interesting. However, many of these genes are considered a risk factors rather than being directly causative. It will be challenging to determine which genes are risk factors and which genes are causative to formulate an intervention strategy. The applicant does not provide a discussion of this issue. • The proposal is based on an interesting and impactful idea, but the experimental planning and preliminary data do not give evidence that the outcome will be significant. • Conceptually, it is not clear that adding functional data will substantially improve the impact of public messaging. Aim 4 is underdeveloped and lacks preliminary data.
GWG Votes	**Is the proposal innovative?**
Yes: 4 **No:** 9	• Generation of a large-scale single-cell human brain atlas available to researchers could be broadly impactful, allowing the scientific community to derive new insights that go beyond the scope of the proposal and have potential benefits for years. • Spatially informed gene expression may yield new biological context for approaching how expression relates to neuropsychiatric disorders. • Novel organoid model brought by one of the investigators sounds intriguing. Study of networked excitatory and inhibitory neurons is potentially exciting. What will interpretation look like from such a synthetic system? • Aim 4 is perfect as is and needs no additional consideration in this reviewer's opinion. Aims 1-3 are the primary areas to add more detail on how the science to be done is innovative. • The proposal is not focused on inventing new approaches but rather optimizing existing approaches. • Combining state of the art approaches to interrogate the impact of cannabis in a suitable human model is novel and will generate informative scientific data. • Access to great (novel) technologies is not necessarily innovation per se, the proposed project does not bring new concepts. • The idea behind the proposal is innovative but the tools used and planning are not. • The project has some innovative aspects as highlighted by the applicants, but most of the data will be generated with commercial kits (Parse, Vizgen) and run through existing analysis tools (Seurat). The access to special and expensive instrumentation is great, but does not count as innovation.

	• The applicants claim this is first use of many of these techniques in the specific tissue under study was helpful. However, a primary weakness of this application is innovation. More specific detail is requested beyond the idea that some of the aspects are innovative and more on how this project is innovative.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 4	• Feasibility and rationale are sound and seen as a strength of the application by this reviewer. • Yes, the rationale is strong, and the subprojects tie together well. • Preliminary data reported on cell-type characterization is in press at a high impact journal. • The hypothesis is based on epidemiological data that suggest an impact of cannabis on the developing brain. • As stated elsewhere, many of the protocols have been applied to other traits and conditions. This diminishes the innovation somewhat but shows the investigators are capable of delivering high quality research derived from this proposal. • The focus on the disruption of the excitation/inhibition (E/I) balance is logical as it is already well established that a large number of intellectual or developmental disorders (IDD) show E/I balance disruptions. • The rationale to focus on the central ganglionic eminence (CGE) is driven by the idea that CNR1 expression is associated with CGE interneuron (CGE-INs) migration and maturation in the cortex. However, co-expression of COUPTF2 and CNR1 in cortical CGE-INs is not identifiable from the data shown in Figure 8, and single cell data confirm absence of CNR1. This is confusing. • The rationale to use advanced neuronal in vitro / ex vivo models to study cannabis exposure is rational, but the planning must improve. • The molecular rationale is generally fine with some caveats. The social impact is still not convincing.
GWG Votes	**Is the project well planned and designed?**
Yes: 9 **No:** 4	• This is a solid, well explained project with multiple areas of expertise incorporated in synergistic ways to accomplish the study aims. • A strong panel of diverse expertise is assembled by the applicant. The most notable weakness is an apparent expected contribution from investigators. They bring letters of support, but they are not well integrated into plans or the budget other then to say they 'will collaborate' or 'join data analyses'. • At a high level, all three experimental aims will measure the possible impact of THC in different ways, and all are imperfect in some aspects. Naturally, the perfect system does not exist, and hence simplified models/samples are a reasonable compromise. However, they may also not lead to the crystal clear answers that may be needed to communicate back to the community. • Key details for the experimental design of Aim 1 are missing. For Aim 2, the applicant did a good job to try to improve selection criteria, but the small numbers at play remain a challenge. Aim 3 takes advantage of distinct organoid models to zoom into cellular details and long term effects, and Aim 4 should translate these insights back into community impact. • In Aim 1 there is still the confusion about "samples" versus conditions. • Considering that Aim 1 and 3 rely on relevant exposure doses, it is surprising how little information is provided to set up the ex vivo system. Aim 2, which is focused on "real-life" exposures is not utilized to benchmark the organoid work. Thus, the model itself is not well defined to warrant the massive omics analyses. • The pitfalls and alternatives seem to be adequately detailed for each of the grant aims. The exception is the concern over the validity of the THC exposure. The response is simply that they will extend the exposure but this doesn't fully alleviate concerns that this may not resemble or replicate prolonged developing brain's exposure. This limitation/pitfall could use a more scholarly approach. • The major weakness is the lack of discussion and rationale for exposure doses and times. • It is not clear how and whether the proteomics data will be integrated. As shown by the applicant, inhibitory neurons, the focus of the study, display the lowest correlation between RNA and protein. It is not clear how this insight is integrated into the data

	analysis. The statement that "we will ask whether dysregulated genes/proteins in each cell type and at each developmental stage ...are involved in neuropsychiatric diseases" does not clarify how the disconnect will be integrated. ● The applicant states that Aims are independent of each other. While this is correct on a technical level, it is not clear whether and how the outcomes inform the design of other aims. For example, if Aim 2 does not point to a change in CGE neurons, would Aim 3 still be focused on that circuitry? ● Organoids in Aim 3 are generated by spontaneous assembly and are thus highly variable. It is not clear how the applicant will determine (perhaps small) changes in the contribution and percentages of specific cells across highly variable organoids. This is especially concerning as only a small subpopulation is expected to respond to TCH in the first place.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 2	● The applicants have the background and tools necessary to carry out the proposed studies. ● There is an adequate team of experts to allow this project to work. ● They appear to have the appropriate access based on the application and letters. ● Yes, the project brings together a great team and adds letters of support to potentially round out the team (though they're not budgeted)? ● Yes, with a caveat regarding the letters of support and budget. New letters of support pledge collaboration, but this reviewer found no funding support within the application or budget justification for these collaborations. The new investigators could be an asset for feasibility, design and rationale, but they don't seem to be as well integrated into the application as the original investigators. ● It is not clear whether the analyses 10,000 cells per treatment are sufficient to provide a true representation of cells in the tissue that is being analyzed. ● The generation of the CGE organoids is not clear and not compelling. How different are these organoids from well established ventral organoids that also express Nkx2.1 and CoupTF? Expression of the synaptic markers (VGAT, VGLUT3, Synapsin, Gephyri) and more mature markers like label deep-layer (CTIP2) and upper-layer (SATB2) neurons are not shown. Quantification and consistency of generation of more mature specific CGE-derived cells is not demonstrated ● In Aim 3, how will morphological complexity and synaptic alterations be evaluated in the mixed organoids? Feasibility of Aim 3b is not shown, and the sensitivity of the system to observing excitability shifts and changes in spontaneous activity patterns post Cannabis exposure is not established. Considering that this aim is critical in establishing a mechanistic outcome of all the omics data, preliminary data that show feasibility are needed. ● There are no concerns regarding the technical side and data collection. Pitfalls include that brief descriptions are provided, though typically not of the hardest/most challenging issues. For instance, data analysis and integration remain less convincingly outlined. Over 2 million single cells will be transcriptionally profiled (with not much information provided on expected genes captured) and 100k proteomic measurements (ideally some thousands of proteins captured). Key details are missing. ● How interpretable and translational insights will prove remains unclear.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12 **No:** 1	● The applicants have a relevant DEI plan, and the idea is very relevant to DEI principles. ● Many DEI aspects are addressed. ● Tissue samples have an over representation of white females. While the samples might be representative of population diversity in the inpatient population, it is not clear whether the samples best represent women who are at risk for high cannabis use. This issue is not addressed. ● Samples are very limited. Male and female samples are included, but full diversity cannot be controlled. ● Yes, this is built into the very nature of this project. No concerns.

Application #	DISC4-16336 #2
Title (as written by the applicant)	Human neural organoid models for opioid, cocaine and alcohol substance use disorder to identify pathomechanisms in addiction
Research Objective (as written by the applicant)	We will establish in vitro human neural organoid models for substance use disorder (SUD) that recapitulate human substance SUD subjects and rodent addiction model that the field is lacking.
Impact (as written by the applicant)	We anticipate finding novel therapeutic targets for SUD. Preliminary results indicate NAD+ could be a potential therapy for withdrawal symptoms. We anticipate finding additional gene candidates.
Statement of Benefit to California (as written by the applicant)	Substance abuse disorder is a condition with medical outcomes associated with large racial and ethnic disparities, with individuals of African American and Native American descent disproportionately affected. Our study aims to clarify the molecular mechanisms that are common and specific to different substance abuse disorders to identify novel therapeutic targets, thus directly addressing an urgent unmet medical that disproportionately affects California's underserved populations.
Funds Requested	$12,608,943
GWG Recommendation	**Tier 2: needs improvement, could be resubmitted**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 2

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	2
Lowest	3
Count	13
Votes for Tier 1	0
Votes for Tier 2	8
Votes for Tier 3	5

- A score of "1" means that the application has exceptional merit and warrants funding.
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 8 **No:** 4	• Given the current opioid crisis, there is an urgent need for innovative approaches to develop new medications for substance use disorder (SUD). In this proposal, applicants plan to develop human organoid models for SUD that replicate molecular changes observed in SUD patients, which will be used for mechanistic and treatment studies. This is a timely and important question given the opioid crisis. • Several important data sets will be generated. • The current opioid crisis in the US and our limited understanding of the complex biology of substance use disorder (SUD)/addiction in general represents an unmet medical need. This project is aimed at using brain samples from patients, human iPSC-derived organoids and animal models to characterize the effects of various addictive agents (including morphine/heroin, cocaine, alcohol), and will identify novel treatments, including testing the role of NAD+ as a potential therapeutic strategy. • This highly ambitious project will generate large amounts of molecular, cellular, and functional data from patients, organoids, and rat models. If successful, a better understanding of disease mechanisms could lead to new hypothesis testing and future therapeutic interventions. • Strengths include technical advancements and new insights into brain biology which could eventually lead to better treatments for neuropsychiatric disorders. Data and resources from the project include human organoid models (cortex and striatal), single-cell analysis datasets (transcriptome, translatome, epigenome) after treatment with SUDs. • The proposal includes a CRISPRi screens to uncover new mechanisms and potential drug targets. • Although highly relevant, the direct effects of the expected project findings upon understanding and treating substance use. disorders are not likely to have a very broad impact due to limitations of the organoid models. • Establishing reproducible in vitro models and assays using human cells is of great relevance. However, the approach presented here lacks focus. Many different models and analytical methods will be used, but it remains unclear how significant and impactful the findings will be. • Finding common signatures across different models and SUD models could lead to unexpected findings. However, the proposal assumes that different addictive drugs with different mechanisms of actions will somehow converge in the models used. This is highly speculative and not well developed for a proposal of this caliber. • The project outcomes include large datasets, potentially new in vitro models if convincingly validated, cell lines from patients, technological innovation, CRISPRi screening data, candidate genes, novel disease mechanisms, and therapeutic interventions. The significance of the findings appears highly risky. • The application focuses on a very relevant question, but, given the limitation of organoids in maturation, it is unlikely that this approach will point to relevant treatments of SUD.
GWG Votes	**Is the proposal innovative?**
Yes: 10 **No:** 2	• The proposal demonstrates a high degree of innovation through its application of a novel technology for single cell RNA binding protein and translatome analysis. The proposed combination of human organoid models, a rat model, and diverse technologies enhances its robustness. • Yes, it's innovative through application of novel technologies such as single-cell RNA binding protein, translatome analysis and organoids. • The proposal combines human organoid models, a rat model, and diverse technologies, using a multidisciplinary approach. • The proposal focuses on integrating human and non-human models, but it lacks efforts to directly relate these findings to molecular changes in living individuals. • Yes, the techniques and data to be acquired are innovative and novel. • Yes, this highly ambitious project will employ new technologies (e.g., single-cell analysis, translatome analysis, different organoid models) for the study of several SUD models. • The proposal used partly novel technology in a new field. • The methods and approach used are not novel.

	• Yes, the proposed approach and technical plan is highly interdisciplinary and comprehensive. At the same time, the proposal is likely too ambitious and coordinating all proposed approaches and collaborations will be challenging. • The proposal appears to have some novel ideas but mostly relies on the current concepts in the SUD field.
GWG Votes	**Is the rationale sound?**
Yes: 3 **No:** 9	• Yes, the overall project is based on sound scientific rationale, current scientific understanding, cross-species validation and a mechanistic focus. • The use of non human models in this project is vital as the applicants are addressing substance abuse, which cannot be solely addressed in vitro. This aspect of the project is well developed and argued. • Yes, the systematic generation of comparative data is sound, but modeling withdrawal and substance use disorder (SUD) using organoids is still highly speculative. • The new data are helpful, but the criteria for selecting differentiated cell types need further justification. • The overall scientific rationale is sound, but major parts of the proposal and potential outcomes remain extremely ambitious and speculative. The proposal is based on many assumptions, for instance, that SUD is a similar condition despite use of different drugs, different model systems, and different analytical methods. Integrating the various datasets and arriving at careful and convincing conclusions will be a huge challenge. • It is not convincing that testing of one NAMPT activator from a collaborator will have major impact on therapeutic development relevant for SUD. Please note that the targeted mechanism is associated with significant adverse effects. • Preliminary data are interesting and extensive but also difficult to connect and interpret given the enormous complexity of the multiple topics versus the assumptions that may or may not be correct. • Yes the rationale is sound, but with limitations in the sense that the authors might be overreaching with their overall approach and assumptions. • It is unclear if actionable data will be acquired for impact. • The limitations of the organoids used limits the rationale of this proposal. • The rationale that different drug addictions will converge on a common pathway is not well supported.
GWG Votes	**Is the project well planned and designed?**
Yes: 5 **No:** 7	• The aims and objectives of this proposal are logically designed and not mutually interdependent. In the revised proposal, the applicants have adequately addressed previous concerns related to potential pitfalls. However, the concern related to organoid variability is still pertinent. • This aspect is improved in the revision. • Yes, but the lack of focus and diffuse nature of the proposal remains an issue. • Despite the revisions and clarifications, this project is extremely ambitious and risky. It is unclear how relevant and actionable the massive amount of data will be for the broader scientific community. For instance, despite their addictive nature, the mechanisms of action of opioids, cocaine, and alcohol are different and will likely not converge on the same pathways and candidate genes, but the proposal is written in that way. • Some of the technical pitfalls are described, but key questions remain about the validity of the models that will be used. • The authors did not consider the outcome that treatment with opioids, cocaine and alcohol may not converge on the same pathways with different cell types, neurotransmitters, receptors etc. • The proposal aims to cover too many topics. There is a lack of focus, which makes it challenging for creating scientific synergies. • The project is too broad and tries to cover SUD that are not clearly related. • Some of the preliminary data figures are difficult to assess; this appears not well supported. Power analysis is unclear and power appears low given the limited sample size. • Too broad and unfocused. • Many unfounded assumptions.
GWG Votes	**Is the project feasible?**

Yes: 8 **No:** 4	• The applicants have addressed previous panel concerns and have added a new team member ensuring that the team is well qualified and appropriately staffed to achieve project's aims. • Yes, but it is not clear that the resulting data will be useful/actionable. More preliminary data to reduce the number of assumptions is needed. • The proposal remains quite broad. • The applicants have the competence to carry out the proposal. • The project is very broad which takes down the feasibility. • It's not very clear how the investigators will work together. • The team is experienced and qualified; however, it appears that there has not been sufficient communication and intellectual leadership to define a focus area. Instead, the team offers to work on a vast number of topics, models, mechanisms, and analytical methods that are currently available to the team. • It's unclear how the collaboration can be effectively managed given the very broad and ambitious approach. • Yes, it's feasible to some extent. However, given the highly ambitious goals it, might require more resources and a longer timeline for completion. • The budget is likely not sufficient to address all the ambitious goals laid out in the proposal.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11 **No:** 1	• This aspect is much improved following revision. • Consideration of DEI is much improved. The team will use iPSC lines from diverse ethnic backgrounds, leveraging the iPSCORE resource to increase genetic diversity. • Yes, they described prior efforts and proposed plans for outreach, partnership, and educational activities to inform the development of DEI. • No changes. • The topic is highly related to DEI. • Multiple reviewers agree the project upholds DEI principles.

Application #	DISC4-16378 #2
Title (as written by the applicant)	Mechanistic understanding of neuronal maturational timing
Research Objective (as written by the applicant)	We explore the overlap between genes involved in the timing of neuronal maturation and psychiatric disease, and explain mechanistically the origins of psychiatric disease.
Impact (as written by the applicant)	We will have solved the problem of neuronal timing, and shown that the pathogenesis of severe mental illness has its roots in this mechanism for establishing brain structure and function.
Statement of Benefit to California (as written by the applicant)	Current treatments for serious psychiatric disease are relatively ineffective and none cure disease. By identifying the mechanistic basis of psychiatric disease we will be in a position to develop novel, effective treatments.
Funds Requested	$8,568,852
GWG Recommendation	**Tier 3: sufficiently flawed, cannot be resubmitted for 6 months**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 3

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	2
Lowest	3
Count	15
Votes for Tier 1	0
Votes for Tier 2	6
Votes for Tier 3	9

- A score of "1" means that the application has exceptional merit and warrants funding.
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 8	• The application will generate a potentially novel set of genes that are involved in neuronal maturation in their system, which is valuable. • Yes, but more from a fundamental neuroscience perspective.

No: 5	• The application tests a novel hypothesis that evolutionary genomic changes specific to human are involved in both timing of neuronal maturation and neuropsychiatric disorders. • The study may not have immediate impact but may enhance our understanding of disease in due course. Not clear how the findings would lead to new therapeutic interventions. • The proposal is focusing on the role and mechanisms of neuronal maturation as a major contributor to neuropsychiatric diseases. While it might be possible to identify pathways for maturation control and find new genes that have as of yet not been considered linked to Intellectual Developmental Disorders (IDDs) is not clear and entirely speculative. • Mutations in *[gene name redacted]*, although seen in autism relatively frequently, are not per se causing autism; their penetrance is not complete. At the end of this project, the applicants expect to have a list of genes that they believe alter maturational timing. Only then will the experiments to check those beliefs be done. • The impact is overstated. Identifying gene sets in the early embryological organoid system will not recapitulate the impact of the immune system, myelination, insults during pregnancy or postnatal development. The balance of maturation and neurogenesis is likely to be highly dynamic and not a static process that determines a given outcome. • This proposal, although interesting as it proposes to look into neuronal maturation, does not directly addresses any disease, let alone neuropsychiatric ones, although the applicants argue that it may have some relevance to autism, schizophrenia etc. The rationale is, at best, unclear. • The proposal is very unclear. The applicants state that the relevance of their findings to human disease is speculative and unpredictable. • The applicants' statement of project significance is an overstatement - it is not supported by the possible proposal outcomes. • The applicants also argue that maturational timing mechanisms are likely shared across cell types, extending the significance of their finding. This is too optimistic. Furthermore, maturation mechanisms in some other cell types are not completely unknown. • There is so much of the unknown and/or not sufficiently well hypothesized in this project that, combined with some overstatements of the impact, unfortunately makes this project unlikely to have any broad impact. • The proposal is largely hypothesis generating in nature - near-term impact is not to be expected. • Data are the main output, utility to the community rests heavily on the quality of the experimental design, which has some significant flaws. • This proposal is too preliminary. It would benefit from repackaging as a much smaller pilot study to demonstrate feasibility prior to a large scale application. The overall concept is interesting but highly speculative. • The proposal could have an impact as a basic science project, but not for the focus of this call. The proposal is very speculative and has too little clear preliminary data. • Impact relevant to disease is unclear and overstated. • The authors are not highly responsive to reviews.
GWG Votes	**Is the proposal innovative?**
Yes: 9 **No:** 4	• Study brings together experts in neuropsychiatric disorders, stem cell technologies, computational approaches. • Previous studies have examined neuronal aging but have not made a link between this phenomenon and human evolution and disease. • The importance of timing is already appreciated but the applicant will increase the gene candidate pool that might play a role in this process. • This is, but other groups also have published or and are working on a similar topic. • There are innovative aspects of the proposal and the technologies applied but the suggested outcome is too speculative. • Innovation somewhat diminished by recent publication from Studer lab on the use of pluripotent stem cells (PSC) to analyze neuronal maturation and genes that affect the process. (Reference 116 in current application). This study used 2D cultures, synchronized cells, and carried out morphological and functional assessment. • Actually no. The applicants argue that, unlike most other researchers starting with genetic aberrations and then working its way down to mechanisms, they will take the vice versa approach - which, although reasonable, is not innovative nor has direct implications for

	any specific disease. In other words, this is an interesting and important question, but the proposal in its current form is not suitable for this funding call. ● The complete elimination of Aim 3 has decreased the engagement of different disciplines but the proposal still involves organoid differentiation, neural development and bioinformatics.
GWG Votes	**Is the rationale sound?**
Yes: 5 **No:** 8	● The hypothesis on which this project is based is scientifically sound, but this is not a project suitable for this funding call, mainly due to its more basic character and no strong links with neuropsychiatric disorder(s). ● The rational is sound and based on published data that support the idea that neuronal maturation and psychiatric disease are linked. ● The applicant rightly points out that the mechanisms involved in neuronal maturation are only in part cell intrinsic. It is well known that while genes might be risk factors, exogenous insults can contribute to a given pathology. Thus neuronal maturation is a complex interplay of carefully orchestrated events that involve other cells. It is not clear how such events are integrated into the proposal. ● The applicant make some sweeping statements about [redacted gene], which has a complex presentation of multi organ defects including seizures, weak muscle tone, hyperactivity and ASD. In fact a study by Mignoit et al(2015) found that only 50% of patients had ASD (total of 16). It is thus not correct to state that "[redacted gene] is a gene that causes autism" and it is even more a stretch to assume that changes in maturation account for the ASD syndrome in some patients. The premise is thus not accurate. ● Too speculative. Didn't really address reviewer comments. ● There is a lack of strong foundation provided, there is a lot of speculation regarding the approach. ● The rationale that this approach will give meaningful findings for NDD is not well motivated. ● There is a good deal of speculation in this proposal around the general hypothesis of neuronal maturation, human evolution and disease. Little concrete data exists on this topic (number of genes for which evolution impacts neuronal maturation or neuronal maturation impacts disease can be counted on one hand). Proposal is highly speculative. ● This proposal would benefit from more preliminary data.
GWG Votes	**Is the project well planned and designed?**
Yes: 5 **No:** 8	● After removal of Aim 3, the project is well designed. ● Overall, the plan is sound and the removal of Aim 3 makes the project focused. ● Removal of Aim 3 is helpful. ● The project is rather well described but the rationale for some of the planning is too suggestive and not well founded by preliminary data. ● Deeper phenotyping of maturation would improve the design. ● The team was not very responsive to previous reviews. ● Comments raised during the previous review have not been that well addressed and remain. ● The application addresses the potential outcomes of finding "little evidence for an overlap between the genes from the maturation screens and genes believed to be involved in psychiatric disease". In this case, applicant proposes to test the relationship "of whether polygenic risk scores influences maturation". This is a completely different question that asked whether genes affect maturation instead the other way round which is the novel aspect of the application. ● A perhaps more informative alternative approach would have been to add relevant insults to the organoid model (infection, hypoxia, toxicants, drugs etc) to test whether such insults now drive changes in maturation genes. ● It is far from clear that the organoid system is the best approach here. Data on inter-experimental variation in timing of expression of *[redacted gene name]* or other proposed reporters is missing. A positive control to test the screen's ability to pick up genes affecting maturation is needed. Organoid cultures are variable and become more variable as they mature. Nothing proposed here could not be done in 2D cultures. ● Project focuses on single-cell RNA sequencing (scRNA-seq) validation. Neuronal maturation is not simply a matter of gene expression - it involves profound changes in

	structure and function of neurons, neither of which are examined here. (See reference 116) ● Many factors apart from neural maturation might affect the timing of the expression of the reporter genes chosen - not just changes to neurogenesis, but alterations in timing of reporter through dysregulated expression that have nothing to do with overall neuronal maturation.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 4	● The applicants have experience in the approaches described. ● Yes. However, the concern that the outcome of this project we be identification of neurogenesis associated genes rather than neuronal maturation ones is still not addressed sufficiently. ● Yes, but there is a lack of preliminary data of synchrony of neuronal maturation markers across organoids. ● The applicants have the competence to carry out the experimental plan but the suggested outcome is very unclear. ● Aim 1 screens and validations are large time consuming experiments which may not yield much of interest. ● Enhancer analysis of HRA; human ancestor quickly evolved regions (HAQER) and integration of this analysis into studies of maturation and disease genes is interesting but a huge task. It requires identification of bonafide enhancers, establishing linkage of enhancer activity with disease genes, then assessment of activity on maturation using cumbersome and flawed assays from Aim 1. Definitive identification of roles of non-coding variants is not trivial. This is a separate project in itself.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13 **No:** 0	● DEI plan is well described. ● The plan for DEI is comparatively well described. ● The insight would be applicable to many disorders although it is not clear who any intervention would look like. This proposal is not clinical but rather addresses a fundamental biological problem. ● DEI statement refers mainly to team and lacks clarity on how project outcomes will reflect DEI concerns.