APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
CLINICAL APPLICATIONS												
CLIN2COVID19-11857 #2	A phase I/II study of human placental hematopoietic stem cell derived natural killer cells (CYNK-001) for the treatment of adults with COVID-19	$750,000	**Y**	**85**	85	2	80	87	13	2	Cell therapy	Allogeneic stem cell-derived NK cell therapy to enhance immune defense against SARS-CoV-2
DISCOVERY APPLICATIONS												
DISC2COVID19-12052	Identifying HLA Class I Restricted Peptides That Induce CD8+ T Cells Against SARS-CoV-2 (supplement to explore COVID-19 impacted ethnic groups)	$100,000	**Y**	**90**	90	2	85	95	14	0	Vaccine development	Identification of peptides for a vaccine that will induce both an antibody and T cell response
DISC2COVID19-12016	Chimeric Antigen Receptor Targeting Spike Glycoprotein of SARS-cov2	$249,996	**Y**	**90**	88	3	85	95	15	0	Cell therapy	Off-the-shelf iPSC-derived NK cell therapy with chimeric antigen receptor trageting SARS-CoV-2
DISC2COVID19-12014	A treatment for COVID19 and related neurological conditions	$250,000	**N**	**82**	83	4	80	95	6	9		
DISC2COVID19-12007	Pro-healing biomaterial for treating lung inflammation associated with COVID-19	$249,974	**N**	**80**	79	5	70	85	2	12		
DISC2COVID19-12019	A CRISPR-based antiviral for COVID-19 targeting lung progenitors and epithelial cells	$149,999	**N**	**80**	77	9	65	88	6	9		
DISC2COVID19-12021	Development of a new targeted senolytic drug for the treatment of chronic respiratory conditions in Covid-19 survivors	$249,734	**N**	**70**	71	4	65	80	0	14		
DISC2COVID19-12010	Evaluation of neutrophil vesicles derived from ex vivo expanded HPSCs as therapeutic candidates for the treatment of COVID-19 patients	$250,000	**N**	**60**	59	10	40	85	1	13		
DISC1COVID19-12011	A nuclear factor that potentially intervenes cytokine release syndrome	$150,000	**N**	**-**	-	-	-	-	0	15		
DISC1COVID19-11998	In vitro modelling of COVID-19 infection on Alzheimer's Disease brain organoids	$150,000	**N**	**-**	-	-	-	-	0	15		

Application #	CLIN2COVID19-11857 #2
Title (as written by the applicant)	A phase I/II study of human placental hematopoietic stem cell derived natural killer cells for the treatment of adults with COVID-19
Therapeutic Candidate (as written by the applicant)	Human placental hematopoietic stem cell derived natural killer cells
Indication (as written by the applicant)	SARS-CoV-2 positive patients requiring hospital admission and have any 2 out of 3 symptoms: fever, cough, or positive disease-related chest x-ray.
Unmet Medical Need (as written by the applicant)	The primary objectives of the Phase I study is to evaluate the safety, tolerability, and efficacy of the treatment in COVID-19. The co-primary endpoints of Phase II study: A) To determine virologic efficacy of the treatment in COVID-19 by rRT-PCR. B) To assess the impact of the treatment on clinical symptoms.
Major Proposed Activities (as written by the applicant)	• Complete phase I study for 14 COVID-19 patients enrollment • Complete phase II study for 72 COVID-19 patients enrollment • Clinical data record, collection and management
Funds Requested	$750,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	85
Median	85
Standard Deviation	2
Highest	87
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 15	• If effective this could add to various treatments being proposed for COVID-19. • The relative benefit versus risk of exacerbating disease is compelling. • Could be a major breakthrough, but would be expensive. • Unique idea, but concerns about limited correlative studies. • The investigators provided a satisfactory response to prior concerns. • Novel therapy.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• The rationale is sound and may help with T cell immunity. • There remains some concerns about the direct involvement of NK in inhibiting SARS-CoV-2 and the potential for exacerbating disease. But overall it is quite sound • Still have some concerns about safety in this particular indication-- acute myeloid leukemia comparison is not particularly relevant. • Borderline. But there is evidence of lymphopenia in COVID-19 patients.

No: 2	● My primary concern is a further increase in cytokine release syndrome along with GvHD. Is the risk benefit ratio sound? The patients currently treated at this early time point appear to be safe. ● Maybe. It is not clear if NK cells will help treat COVID-19 or exacerbate it.
GWG Votes	Is the proposal well planned and designed?
Yes: 12	● Well designed study. There is a potential to exacerbate disease, but the protocol mitigates risk in this regard. ● The organization of the study seems very well thought out, benefiting from previous clinical trial experience and FDA guidance. ● The applicants should think more carefully about a futility rule in the protocol. Also they should look at ALL serious adverse events (SAEs) regardless of attribution and SAE attribution to treatment should be made on the basis of aggregate analysis by the DSMB, not individual attribution. All SAEs should be reviewed by the DSMB.
No: 3	● Rationale for dose is thin. ● Secondary immune studies are not well-defined.
GWG Votes	Is the proposal feasible?
Yes: 14	● The product is already prepared and could be moved into patients relatively quickly. ● I think it is likely sufficient patients could be enrolled as proposed, so feasibility seems good. ● The requirement to exclude patients on antiviral treatment may limit accrual. ● The team has extensive experience operating similar trials that are highly similar and expertise with handling and preparation of samples. The great team expertise is a strength. ● Adverse event reporting should be modified to report a wider range of outcomes. ● Appears to be well-developed.
No: 1	● Major query of feasibility given exclusion of patients on antivirals - what about remdesivir?

Application #	DISC2COVID19-12052
Title (as written by the applicant)	Identifying HLA Class I Restricted Peptides That Induce CD8+ T Cells Against SARS-CoV-2 (supplement to explore COVID-19 impacted ethnic groups)
Research Objective (as written by the applicant)	Recent studies suggest both T cells and antibodies are needed for an effective COVID-19 vaccine. We will use breakthroughs in identifying peptides that stimulate T cells to produce a better vaccine.
Impact (as written by the applicant)	A vaccine is needed to prevent the spread of COVID-19 that is effective, can be rapidly produced and can be scaled for worldwide demand. This supplement work will help serve impacted minorities.
Major Proposed Activities (as written by the applicant)	• Proteasome digest 50 amino acid regions of the spike protein and identify the fragments produced • Assemble a database that encompasses potential proteasome catalyzed splicing products • Perform HLA Class I precipitations to purify the peptides that bind HLA-I • Perform de novo sequencing using the database to identify the fragments that bind; test these fragments in an in vivo assay to confirm binding • Identify which peptides induce CD8+ T cells that lyse cells containing Spike protein from SARS-CoV-2
Statement of Benefit to California (as written by the applicant)	This research will help contribute to a vaccine candidate that can be made part of an overall vaccine composition that will protect California citizens from contracting COVID-19, allowing its people to interact freely and resume normal activities. This supplemental work will specifically address finding peptides that will benefit impacted ethnic groups.
Funds Requested	$100,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	90
Median	90
Standard Deviation	2
Highest	95
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 14	• The applicant is taking a novel approach to identifying the best epitopes for vaccines aimed at generating an optimal, long-term CD8 T cell response to COVID-19. This could have great, near-term impact on the optimization of COVID-19 vaccines and for future pandemics. • The application now also addresses underserved minorities, including African-American. • It is important to add these additional HLA types in order to cover a greater percent of the population.

	● Exciting extension to MHC that represent a breadth of the population ● This added capability will increase the impact of the studies. ● Will address other alleles and therefore other populations especially those at risk of poorer outcomes from COVID-19. ● It will explore a neglected arm of the immune system in preventing SARS-CoV-2 infection.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	● The rationale is sound and done in response to feedback after initial application. ● The proposal uses proteasome produced fragments from the spike protein to predict better CD8 T cell epitopes - including non-continuous epitopes. This is based on recent insights from their own work in cancer as well a previous publications. ● This is an exciting, novel approach that could impact the discovery of COVID-19 therapies as well as future pandemics. ● Yes, based on their previous work in glioblastoma. ● Builds on the expertise of this group.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	● The proposal is well planned and should add depth of knowledge to the wide field. ● Yes, except Milestone 3 may be very challenging, especially with the addition of 6 other HLA alleles. ● The project is very well planned and they predict having actionable insights at the end of the project. ● No concerns.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	● Feasible and addresses previous concerns. ● I am a little worried about completing milestone 3 but believe it will generate valuable data even if milestone 3 is not fully completed. ● The timeline is aggressive but achievable. ● No concerns noted.
No: 0	*none*

Application #	DISC2COVID19-12016
Title (as written by the applicant)	Chimeric Antigen Receptor Targeting Spike Glycoprotein of SARS-CoV-2
Research Objective (as written by the applicant)	We expect to generate iPSC derived NK cells expressing a CAR against SARS-CoV-2 that could be used as an off-the-shelf therapy for COVID-19
Impact (as written by the applicant)	The proposed studies will provide a novel therapeutic approach to boost the cellular immunity against SARS-CoV-2, especially for high risk populations.
Major Proposed Activities (as written by the applicant)	• Construction of SARS-CoV-2 CAR constructs • Generation of iPSC-derived NK cells expressing CARs • Differentiation of iPSC-CAR cells into hematopoietic progenitors • Derivation of human NK-CAR cells • In vitro studies of iPSC derived NK-CAR cells • In vivo studies of iPSC-derived NK CAR cells
Statement of Benefit to California (as written by the applicant)	The SARS-CoV-2 is the etiological agent of COVID-19, a global pandemic that has caused more than 4200 deaths in California. The proposed studies will provide a novel therapeutics to improve the immune response to COVID-19.
Funds Requested	$249,996
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	88
Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 13	• The technology is based on the use of stem cells, namely iPS cells. If successful, it will be a good example of using stem cell-based technology and it will improve patient care. • The technology addresses multiple bottlenecks, including one of the biggest ones - the large-scale production of off-the-shelf cell therapy. • The iPSC-NK-CAR product could have a significant impact as an off-the-shelf product. • Interesting use of iPS CAR NK cells to target COVID-19 - potentially a very novel NK. • Given the global need for alternative therapeutics in COVID-19 patients, if successful this could be highly medically applicable. However this is obviously a more expensive treatment compared to say antivirals or antibody based therapeutics, where the benefit of this type of therapy may not be better. • Very good approach, although many technical details remain to be solved. • The product would be complex to manufacture and thus expensive compared to antivirals, which dampens the potential for impact. However, a very interesting approach and potential for wider application.

	• May have some issues with broad applicability but could definitely have utility and would be informative of protective mechanisms.
No: 1	• Translational plan is underdeveloped. How will it be moved to human studies? There are concerns about cost and access even if the project is scientifically successful.
GWG Votes	Is the rationale sound?
Yes: 14	• Yes, the rationale is generally sound. The investigators seem to have identified a scFV targeting the spike protein that should work with their CAR NK cell constructs. The specificity of this targeting is a strength. • The rationale is scientifically sound. • The authors provide good preliminary data, which significantly support the project. • NK-CAR approach is innovative. • Identified a good scFv for anti-spike targeting. • The scFV has already been identified. • iPSC is a good way to reduce cost of goods and solve some of the logistical problems of engineered cell therapies. • Significant preliminary data. • Good rationale. • Strong team. • It would be important to understand the use of human cells in a mouse model and the use of immunocompetent mice. • There are questions on persistence and IL-15 could be added to the genome engineering strategy.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• Clear and appropriate milestones and success criteria. • The proposal is well planned but it will be important to monitor closely what the fate and duration of persistence of the NK cells would be in these models. • The investigators present compelling data that their approach can generate scFV that will bind spike protein on target cells. • The project is well planned and designed. • Well-considered, mouse-adapted virus available. • In general yes. It is sometimes unclear how certain time points were chosen (i.e., time of infusion). Animals will be monitored for virus replication, pathology, and inflammatory markers, but more detail could be given and other ex vivo analyses considered. They will monitor persistence of the CAR NK by flow cytometry and their assay. Not clear how each of these measures will be considered for defined success in the in vivo arm. • There is some concern about using immunocompetent mice which they suggest wont be an issue but indicate they could irradiate the mice if it is. I think other approaches could be identified here. It is also not clear how much experience they have with this infection model. And even though I appreciate the mouse model, they list it as their safety evaluation which is really hard to extrapolate from murine models. • The immunocompetent mouse model may have an issue, and clear translation plan is needed. • Translation plans need work. • The investigators do indicate a plan to have an FDA meeting, but any real detail on how this could be moved into human translational studies is lacking.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• The proposal is feasible. The team is strong and the environment should be able to execute all the studies. It is possible that that the timeline may be a little ambitious though. • The proposal is feasible. • Very ambitious - tight timeline particular for in vivo work that may limit the number of in vivo experiments that can be done. • Major concerns that all of the proposed work will not be completed in 12 months. • The ACE2 mice might be hard to get. Understandably tight timeline. • Overall the pieces are in place; some concerns about experience with the mouse model. • The BSL3 studies may need to be planned with more detail. • The timeline seems too ambitious especially for the in vivo work.
No: 0	*none*

Application #	DISC2COVID19-12014
Title (as written by the applicant)	A treatment for COVID-19 and related neurological conditions
Research Objective (as written by the applicant)	We propose to determine the impact of the SARS-CoV-2 virus in the human brain and to test a FDA-approved therapeutic candidate to treat COVID-19.
Impact (as written by the applicant)	A novel drug to treat/cure COVID-19 and for neuroprotection.
Major Proposed Activities (as written by the applicant)	• To determine the molecular and cellular alterations caused by the SARS-CoV-2 virus in the human brain. • To validate a potential treatment for COVID-19 and strategies for neuroprotection. • To prepare and design a clinical trial for COVID-19 using a repurposed FDA-approved anti-viral candidate.
Statement of Benefit to California (as written by the applicant)	Repurposing an available FDA-approved drug that treats COVID-19 and protects the nervous system would have a dramatic medical, social, and economic positive impact for California and all the World. Moreover, our experiments will inform us how SARS-CoV-2 affects the human brain.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 82

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	83
Median	82
Standard Deviation	4
Highest	95
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	9

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 12	• The approach involves a translatable drug, although there are concerns about cost and access. There is a lack of novelty associated with studying this drug as a SARS-CoV-2 treatment. • Potential to understand the effect of COVID-19 on the developing brain and potential to test an antiviral - but why limit to one antiviral? • Drug is very expensive, but the science is good. • Relevant question and expert investigator--compelling idea. • I am on the fence about the potential for impact. If we think about availability and access, no cellular or related therapy could enter widespread use and help a wide range of patients because of the high cost. But, that doesn't stop us from trying to find an efficacious therapy and hope that the cost issues are worked out somehow down the road. • There is much to like in this proposal. The science is largely strong, and the problem is an important one. The question of whether there is infection of fetal brain of COVID-19 is

	scientifically important. At the same time, it seems to me the project is missing its potential in important ways. ● Mother to child transmission of SARS-CoV-2 during pregnancy to address neurological defects is a significant need.
No: 3	● There is limited benefit for the studies outside of using this particular drug. ● The drug is already approved for HCV, and can be used off label for COVID-19 immediately. ● The drug is mentioned as a treatment for flaviviruses in UpToDate. And there is a decent body of in vitro and in mouse studies showing efficacy for Zika. But it nevertheless is not a mainstream drug for Zika. So despite all the success of the previous work, the drug does not seem to be a breakout success. If success for Zika was so limited, will it really be of great impact for COVID-19? ● The cost of using the drug for Zika treatment in the US is many thousand dollars. This high cost could limit availability to the most privileged communities. ● The potential impact is unclear. Good science for studying basic viral pathophysiology in CNS. Not clear that a candidate will emerge. Or that the system will provide a unique screening tool for new drugs. The candidate discussed is not unique although it could be used for proof of concept. Need letter of support from the drug manufacturer.
GWG Votes	Is the rationale sound?
Yes: 14	● The proposal would benefit from mapping a path to get the drug from the organoid models to patients. ● Extrapolates from their work on zika virus, asking important questions about the interaction of virus, placenta and brain. Not clear that placenta is a target for SARS-CoV-2? ● Proper cell targets, some concern that it might be "overkill" for the question asked. ● I think it's sound, but not overwhelmingly so. ● The rationale for using organoids with this drug is sound. ● The proposal is designed to validate the drug as a treatment for SARS-Cov-2 infection in two human models, placenta and brain organoids. The rationale for brain organoids is reasonable. The rationale for Aim 2 (placenta) is missing. Also, it seems like the main goals of this proposal could be met more efficiently by testing drugs on cells in a monolayer. In other words, why should one test the effectiveness of this drug first in brain and placenta, rather than first in a monolayer of another cell type? ● "The SARS-CoV-2 RdRp shares high sequence and structural homology with HCV, supporting..." - What do you mean by high? Be numerically and quantitatively specific. ● Preliminary data showed that different cell populations in cortical organoids are susceptible to SARS-CoV-2 infection.
No: 1	● Not clear; this could be better done with cell lines. ● The significance of the placental cell work is not clear.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	● Excellent science. ● Straightforward plan. ● Acknowledged alternative approaches. ● The advantages of brain and placental organoids are not clearly defined. ● Although the applicant could test other drugs in this system, the rationale for this specific drug over others is not well justified (or indeed testing one vs a range of antivirals is not justified).
No: 4	● No alternatives considered, some other similar drugs used against Zika may be more effective, so it would nice to test one of the alternatives. ● It is an interesting way to test this antiviral. Why not test it in a mouse or hamster model to see if it works as an antiviral against SARS-CoV-2 and then see if it affects the brain tissue or other tissues? ● I was not convinced of any need to use organoids rather than monolayer cultures. All of the endpoints being studied are more easily studied in monolayer cultures, and there is no evidence that the expression of ACE2 (for example) is different in organoids. ● Monolayer cultures also would facilitate addressing another concern, which is that they are more suitable for large scale drug screens. This is a proposal that bets on a single drug, when even reviews on which the applicant is a co-author speak to more effective drugs for Zika (and potentially, from the rationale of this proposal, for COVID-19). ● A stronger proposal, from the point of view of this reviewer, would have been using this as a starting point for screening other candidates and/or drug discovery. That cannot be

	done with organoids easily, but it can be done in monolayer cultures of embryonic brain cells or iPSC-derived monolayer cultures. ● Alternative approaches are not considered, and comparators are not included. ● Vasculature is missing from the organoids, and more detailed studies of cell-cell interactions are needed. ● The basic structure of this proposal is similar to the applicant's previously successful CIRM grant completed in 2019 that resulted in multiple publications and IP disclosures associated with this award to date. Has had other multiple CIRM awards, with an excellent publication track record for these awards. ● PI has a strong track record. ● Not clear that investigators have economical access to the drug. Would like to see a LOS from the drug manufacturer. ● There is scant background literature support. There are many papers on the drug & COVID-19 on the preprint servers. Only two of these show up in the bibliography and only one of these is actually cited in the proposal. Recent review articles on the proposed drug and other drugs used to treat Zika should be cited. Critically, a case needs to be built as to why this drug is chosen out of many hundreds if not thousands of other reasonable candidates to test. Why not include some of these as controls? ● Adequate statistical methodology is described, but it would be nice to see a power estimate. ● "using several readouts, such as gene expression, cell proliferation and death, and synaptogenesis." Please be specific as to exactly what these readouts are. ● There are some next-generation compounds mentioned in review articles that are more effective than the proposed drug against Zika. Would it make sense to include at least one of these as a control? ● Would it make sense to include Zika virus infection as an additional dimension to the study design (i.e., additional control). If the drug mitigates COVID-19 infection less than it mitigates Zika infection, maybe it is a dead end.
GWG Votes	Is the proposal feasible?
Yes: 14	● The proposal is feasible although it is likely to take more than 6 months to get as much information from this model system as it may yield. ● The team appears be capable to run these experiments. ● Would like to see commitment from the drug manufacturer to provide drug. ● This is a good team with a good plan. ● This is basically a repeat of their previous work on Zika, so I have every expectation it would be successful from a technical point of view.
No: 1	● The feasibility lies in the translational relevance of the project. First, there is no letter of support from the company. Adding to this is the enormous cost of this drug. Unlike dexamethasone, which can be prescribed off-label at little cost, that is not the case here. So how would this actually be brought from interesting laboratory findings to clinical studies? ● In addition, it's already clear that the particular drug of choice is of active interest in the COVID-19 arena. Whether the proposed study would impact on this interest is not clear, but it is hard to see how this would change things even if they hit all their endpoints. ● There is also the question of underserved populations. A nod is given to iPSCs from different groups, but there is no evidence that this is relevant. The costs of the drug make it very problematic for use in underserved populations.

Application #	DISC2COVID19-12007
Title (as written by the applicant)	Pro-healing biomaterial for treating lung inflammation associated with COVID-19
Research Objective (as written by the applicant)	Pro-healing biomaterial to treat lung inflammation and promote recovery.
Impact (as written by the applicant)	COVID-19 associated acute respiratory distress syndrome
Major Proposed Activities (as written by the applicant)	• Evaluate biomaterial for ability to reduce lung inflammation in rodent model • Evaluate biomaterial for ability to recruit stem cells in the lung • Evaluate biomaterial for ability to prevent lung fibrosis in rodent model • Evaluate biomaterial for ability to recruit human stem cells
Statement of Benefit to California (as written by the applicant)	As of Mid-May 2020, there were more than 4,500 Californians who were hospitalized because of COVID-19 (tested positive or suspected) with over 1,300 in the ICU. A significant number of severe cases involve a negative inflammatory response in the lungs leading to respiratory failure. We aim to develop a new therapeutic that can treat this inflammation and promote lung healing thereby having potential benefit to thousands of Californians.
Funds Requested	$249,974
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	79
Median	80
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 10	• Highly translatable approach. Addresses key issues associated with lung regeneration. Good accessibility potential. • The proposal addresses regeneration of damaged lung tissue in response to severe COVID-19. • ECM may act as an important repair mechanism. • Exciting potential application for ECM therapeutics. • Novel product that has been in the clinic already is a big plus. • Bleomycin is not a relevant model for the damage associated with COVID-19 disease.
No: 4	• A new model is needed for the testing of these products.
GWG Votes	Is the rationale sound?
Yes: 8	*none*

No: 5	• Treating lung pathology with ECM restoration has a strong justification. • Yes, it is rational to consider using ECM proteins to to help regenerate damaged tissue, but not rational to test it in this way for COVID-19. • Does deposition of clumps of protein in the areas of injured lung risk further microthrombi formation/emboli? How will you assess this in the murine models? • The bleomycin model may not be appropriate for COVID-19. • Not a relevant model for COVID-19 disease. • A more appropriate model should be considered.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 11	• Concerns with bleomycin model. • The major issues are the bleomycin model is not a good model for COVID-19 - an epithelial injury and sterile, and lacks lymphocytic and plasmacytoid components. If the aim is that these hydrogels could target endothelial leak then this should be modeled in the animal model of injury - flu would be a better model. • The choice of model does not initiate a lymphocytic response which is important for COVID-19. • The proposal focuses on chemically-induced lung injury. We do not know how relevant this is for COVID19 disease lung tissue. • Although the bleomycin model is not the best, as it doesn't model SARS-CoV-2, it will shed some light on if the product can repair damaged lung tissue. So I think it is a good starting point. • At some point, other physiological measurements will need to be made to ensure safety of infusion of product in a diseased lung. For example, changes in BP would be helpful during and immediately after infusions. • Questions around power and the ability to account for the variation between animals. • It is unlikely that the studies are adequately powered with n=6 per group/time point. There is no consideration given to the variability in these measurements in the bleomycin model. • Inflammatory aspects of the response are not well studied. • The product is close to the clinic.
GWG Votes	Is the proposal feasible?
Yes: 11	• Strong group. Consider alternative models. • This is a logical extension of their other work. • Proposal needs expertise on virology. Links to COVID-19 should be stronger. • It is likely feasible to complete these experiments. They will not readily say whether you should progress to COVID-19 experiments. • The role of the pulmonary MSC is unclear. • Consideration to having an ARDS investigator inputting to this project should be given. • Animal numbers may be low. • The proposed number of measurements on lung tissue seem difficult to perform with a small amount of lung tissue. • This is a lot work for this timeline. • Model and materials available.
No: 2	*none*

Application #	DISC2COVID19-12019
Title (as written by the applicant)	A CRISPR-based antiviral for COVID-19 targeting lung progenitors and epithelial cells
Research Objective (as written by the applicant)	We seek to use a CRISPR-based antiviral to specifically target and cleave SARS-CoV-2 RNA sequences. By targeting this antiviral to lung stem cells, we can achieve prolonged protection.
Impact (as written by the applicant)	There are currently very few ways to improve the prognosis of COVID-19 patients. This tool could reduce viral load, cell toxicity, and improve COVID-19 patient health.
Major Proposed Activities (as written by the applicant)	• Test the effectiveness of our CRISPR-based antiviral against SARS-CoV-2 in upper respiratory tract cells and lung stem cells. • Test whether downregulating virus-essential host genes using CRISPR-based tools can inhibit SARS-CoV-2 in upper respiratory tract cells and lung stem cells. • Test whether our CRISPR-based antiviral can inhibit coronavirus in a mouse model of infection. • Test whether our CRISPR-based antiviral can inhibit SARS-CoV-2 in a Syrian hamster model of infection.
Statement of Benefit to California (as written by the applicant)	California has had over 100k cases and 4k deaths confirmed from COVID-19 since the pandemic started. The toll on human lives and health, the hospital system, and the economy in California has been immense. Any antiviral that can help patient prognosis would help to lessen the toll of this disease to individual patients and to California as a whole. Our proposed CRISPR-based antiviral has the potential to reduce infectivity and toxicity from SARS-CoV-2, and thus help Californians thrive.
Funds Requested	$149,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	77
Median	80
Standard Deviation	9
Highest	88
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	9

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 8	• Very interesting approach. • A very new method to alter RNA. Off target effects appear to be unknown at this point, however, it could be a game changer if it works. • Likely expensive. The proposed technology is unlikely to provide prolonged protection for individuals exposed to SARS-CoV-2.
No: 6	• This is a prophylactic strategy and is too high risk to pursue as a prophylactic therapy for a virus that has low impact for the majority of sufferers.

	Might be better repurposed to a treatment strategy. ● Major concerns about translatability and likelihood of use as a prophylaxis. ● The prophylatic strategy is not appropriate for such a risky technology.
GWG Votes	Is the rationale sound?
Yes: 9	● Prophylactic approach is not very feasible. ● Could be useful for other viral diseases. ● Targets both the SARS-CoV-2 virus and inhibits replication once in the cell. A very novel approach. ● This may be hard to control and if it has overlap with other RNA replications could be really problematic. ● Preliminary data suggests the concept works in terms of degrading the viral RNA--it's not clear that this would be therapeutically enough to make a clinical difference. ● Concerns about off-target effects.
No: 5	● This is a relatively new discovery - has potential to have significant off-target effects and it is not yet clear that it does not target DNA. The RNA editing effects on host transcription are not yet known. ● The delivery aspects and lung stem cell targeting aspects need to be motivated better. ● There needs to be more information regarding translatability, delivery, and safety.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	● Delivery method will be key to making this work and this will be tested here. Important to test after the disease has taken hold, rather than purely as a prophylactic therapy.
No: 4	● No evidence that these can be delivered to the lung. ● The proposal should include work to understand potential toxicity and off-target effects of the CRISPR reagent. ● There are potential bottlenecks in translatability of the treatment in disease application. ● The focus on stem cell biology and stem cell targeting would be more appropriate.
GWG Votes	Is the proposal feasible?
Yes: 10	● The ability to deliver to lung raises concerns about feasibility. The move to a prophylactic strategy is untenable. ● Hamster model at this point appears to be feasible and a good choice. ● Team and environment are excellent. ● No letters of support and it is clear some work will be done in other labs.
No: 4	● Highly innovative but there are questions about delivery and translational feasibility. ● Concerns about modality and delivery--translatability seems very far off. ● The work is too ambitious for a 1 year timeline.

Application #	DISC2COVID19-12021
Title (as written by the applicant)	Development of a new targeted senolytic drug for the treatment of chronic respiratory conditions in COVID-19 survivors
Research Objective (as written by the applicant)	Investigation of SARS-CoV-2-induced senescence of AT-II progenitor cells and efficacy of targeted senolytics to treat COVID-19 survivors with respiratory conditions driven by senescent AT-II cells.
Impact (as written by the applicant)	Preventing or mitigating respiratory conditions (such as lung fibrosis) resulting in COVID-19 survivors.
Major Proposed Activities (as written by the applicant)	• Demonstrate SARS-CoV-2 mediated senescence induction in human AT-II cells in 2D and 3D in vitro models • Demonstrate presence of pulmonary senescent cells in COVID-19 patient biopsies and/or pre-clinical models with a focus on AT-II progenitor cells • Evaluate effectiveness of experimental senolytics for the elimination of infected human AT-II cells in vitro • Evaluate effectiveness of experimental senolytics for the elimination of senescent AT-II cells in preclinical models for pulmonary fibrosis • Evaluate effectiveness of experimental senolytics for the elimination of senescent AT-II cells in preclinical models infected with SARS-CoV-2.
Statement of Benefit to California (as written by the applicant)	As of May 31, 2020, there are a total of 90,631 positive cases and 3,708 deaths in California. While long-term complications in COVID-19 remain to be determined, Pulmonary fibrosis was observed in SARS patients who had recovered and were recently discharged from hospital care. Patients exhibiting pulmonary fibrosis was 62%. We expect that our proprietary compounds can reduce respiratory complications, ameliorate and possibly reverse lung fibrosis in COVID-19 survivors.
Funds Requested	$249,734
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	71
Median	70
Standard Deviation	4
Highest	80
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 5	*none*
No: 8	• The role or occurrence of senescence in COVID-19 is unclear. • This is a substantial revision and responsive to the previous critiques. They have improved the animal model, added evidence that the SARS-CoV-2 infection may cause

	senescence, but it is still not clear about which drugs will be tested, but they do have several in their pipeline. Still high risk and I think likely moderate reward. ● Questions about whether senescence is a good model for the pathology in COVID-19. ● The rationale is too weak to have high significance. ● Not clear involvement of senescence.
GWG Votes	Is the rationale sound?
Yes: 1	*none*
No: 12	● We still do not have convincing evidence that senescence occurs in COVID-19 or what the impact of that senescence is. The RNAseq data is supportive but by no means conclusive. ● Link between senescence and COVID-19 is not supported sufficiently. ● The link between AT-II cell senescence and pulmonary fibrosis is not well established. ● Makes sense from a role of overall fibrosis, but unlikely to be COVID-19 relevant--concerns about reaching COVID-19 milestone. ● The connection between fibrosis and senscence could be stronger. ● Will the mice survive long enough to develop fibrosis (and therefore to be able to show an inhibitory effect with the drug? ● There is still minimal information about the senolytics being used. ● More information is required on the senolytic drugs to be tested.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	● Overall plan is straightforward. ● Good effort to respond to criticisms.
No: 8	● Question about need for all 3 models. ● The underlying science is not spelled out very well. ● Models are a concern.
GWG Votes	Is the proposal feasible?
Yes: 5	*none*
No: 8	● 3 animal models seem unmanageable and it is not clear that the project is achievable in the time frame. ● Not clear what relevance to bleomycin and IT models add to the SARS-CoV-2 model for the purposes of this grant. ● Unlikely to be completed in the time allotted. ● Concerns about accessibility of tissue. ● Concerns about number of collaborations required for success. ● The plan has a heavy reliance on collaborating labs.

Application #	DISC2COVID19-12010
Title (as written by the applicant)	Evaluation of neutrophil vesicles derived from ex vivo expanded HPSCs as therapeutic candidates for the treatment of COVID-19 patients
Research Objective (as written by the applicant)	We propose to evaluate the capability of stem cells to expand ex vivo and differentiate into neutrophils in order to find a cell source enabling the production of a new drug delivery nanodevice.
Impact (as written by the applicant)	Cell-derived nanodevices are challenging to mass produce for clinical evaluation and commercialization. The studies will identify a sustainable and appropriate cell source for that purpose.
Major Proposed Activities (as written by the applicant)	• To establish the experimental conditions for stem cell expansion that are suitable for large-scale production of cell derived vesicles • Load drugs into cell derived vesicles to generate drug delivery nanodevices • Assess the functionality of drug delivery nanodevices in preclinical models to validate the use of stem cells for their future manufacturing
Statement of Benefit to California (as written by the applicant)	The stem cell derived product will first be evaluated as a drug candidate to treat COVID-19 patients presenting with medical complications. Furthermore, the research will contribute to validate a technology platform with application in a broad range of medical conditions characterized by uncontrolled inflammation including neural and heart diseases as well as cancers. Hence, the drug candidate may provide new treatment options for the current pandemic as well as other major endemic conditions.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	59
Median	60
Standard Deviation	10
Highest	85
Lowest	40
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal have the necessary significance and potential for impact?
Yes: 4	• The proposed candidate could in theory impact pulmonary inflammation in COVID19, and might impact other disease states as a versatile platform. The likelihood that this will happen is extremely hard to assess from the information in the application. • High potential for translation if proposal is successful. • The proposed general type of candidate, membrane vesicles manufactured from neutrophils generated from HPSC, is a stem cell technology and would provide a new way to utilize primary sources of these cells, especially cells from cord blood banks.

	• Applicant has considerable experience with clinical development of related products and briefly outlines a reasonable way to proceed if this project is successful. The proposed animal experiments would provide reasonable POC for further development.
No: 10	• No pilot data at all. • Manufacture would be time consuming and difficult and expensive. There are likely better, more economical, ways to treat the inflammation. • There is a lack of a clear work plan justifying the proposal. • The potential of the vesicles is difficult to determine.
GWG Votes	Is the rationale sound?
Yes: 2	*none*
No: 12	• Lack of preliminary support is concerning. • There is no description of the pro-resolving mediators to use to help us assess if the rationale for using them is sound. • No information given about yield of cells, success in vesicle prep from neutrophils, purity assessment, ability to load vesicles and exclude unwanted components. • Preliminary data are lacking, so very difficult to assess the likelihood of success. • Application of the vesicles is not justified. • The rationale is hard to determine without preliminary data or a workplan.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 13	• There is no preliminary data. • Lacks concrete plan of work. • No clear work plan to define the neutrophil phenotype - this is potentially a limitless piece of work. • The proposed modification of the microvesicles does not define which proteins will be increased and which will be suppressed. • Lack of detail and resolution of experimental plan. • The yield and purity of cells is not well described. • The gene editing description needs to be strengthened. • Missing key experiments in in vitro models - epithelial cells not addressed, wound repair, toxicity. • Where are the in vivo studies being done? By whom? • Minimal description of the planned in vivo work or the outcome measures, or how this study is powered • No justification for use of a human cell derived vesicle in a mouse model.
GWG Votes	Is the proposal feasible?
Yes: 5	• Likely feasible based on group's expertise.
No: 9	• Unlimited amount of work described for neutrophil surface phenotype. • No information on ethics approval. • No information on yield from a cord blood donation or human blood donation. • Some resources in place, but no mention of resources to do the animal work in the grant. • The letter of support is not on letterhead. • There is no detailed work plan. • It is a very ambitious project, unlikely to be completed at the proposed time. • Investigators are highly qualified.

Application #	DISC1COVID19-12011
Title (as written by the applicant)	A nuclear factor that potentially intervenes cytokine release syndrome
Research Objective (as written by the applicant)	We aim to test the genome organizer SATB1 and its specific modified form as new therapeutic targets for cytokine release syndrome (CRS).
Impact (as written by the applicant)	Because there is no effective treatment for the severe cases of CRS from Covid-19 infection, the introduction of a new regulator for proinflammatory cytokine production will be highly significant.
Major Proposed Activities (as written by the applicant)	• We will knockdown SATB1 levels and inhibit the enzyme that modifies SATB1 to see if these lead to downregulation of cytokine production in human peripheral blood and in naïve CD4T-derived Th17 cells.
Statement of Benefit to California (as written by the applicant)	If the proposed research is successful, it will introduce a new target for therapeutic intervention for cytokine release syndrome (CRS). There is a serious need to treat CRS because many patients with severe symptoms from infection of Covid-19, for instance, can be saved if effective treatments are available. It is also useful for CRS treatment for some cancer patients who received immunotherapy and with autoimmune diseases.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

SCORE INFLUENCES

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	1	14	0
Is the rationale sound?	2	13	0
Is the proposal well planned and designed?	7	8	0
Is the proposal feasible?	10	5	0

REVIEWER COMMENTS

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Does the proposal have the necessary significance and potential for impact?

- There is no stem/progenitor cell-based product or technology in application. The eligibility of the proposal is questionable.

- If studies of proposed drug-candidate are successful, it is unclear how it may compete with currently available drugs for therapy of CRS. There are a few drugs on a market, which are used successfully for therapy and mitigation of CRS after CAR-T therapy. These drugs have also been used in COVID-related CRS. A new candidate will not address the unmet medical need.
- No major link to stem cells and unlikely to impact ADRS cytokine storm.
- No stem cell biology; all targets are around mature cells.
- The potential to treat cytokine storm seems low.
- Not clear it has anything to do with stem cells.
- The proposed in vitro gene knockdown and inhibitor experiments will determine whether the global chromatin organizer SATB1 plays a role in cytokine production and Th17 cell differentiation in a human system. But it is not made clear how this information would be used to generate a safe and effective treatment for SARS-CoV-2-induced ARDS or be applied to stem cell biology. The upstream kinase inhibitor is likely to have many off target effects given the tissue distribution of SATB1.
- Underlying hypothesis is potentially flawed--not clear this pathway is really critically involved in COVID-19 disease.
- Lack of clear significance on stem cells. Focus on cytokine release syndrome rather than COVID-19
- It is not clear if TH17 cells play a role in ARDS or COVID-19.

Is the rationale sound?

- The rationale for studying Th17 cell biology is sound. However, there is no information supporting the role of stem/progenitor cells.
- The target is widely distributed. Off target effects are likely, including inhibiting CD8 cells which are likely to be key in killing virus. It is incredibly unlikely this will result in a clinical therapy for SARS-CoV-2
- The prevalence of CRS as a complication of SARS-CoV-2 is unclear and is a contested concept. There are already several drugs to treat CRS.
- There is no link to stem cell biology.
- Although the proposed plan will yield information about the role of SATB1 in human Th17 cell biology, connections to SARS-CoV-2-induced ARDS or stem cells are not made. Thus, the rationale for CIRM support is weak.
- The Th17 pathway is not especially implicated in COVID-19 (a few references mention these cytokines as noted, but as key and uniquely pathological it is not established).
- Other much more targeted drugs can address this pathway--the off target effects of this drug could be profound.
- This idea would appear to have a lot of off-target effects.
- It is not clear that this factor can control CRS and unlikely to impact COVID-19.

Is the proposal well planned and designed?

- The application does not meet the objectives of the program announcement.
- Potential pitfalls and alternative approaches are not presented.
- Yes in terms of the experiments described, but not realistic target.
- Off-target effects in other cell types is not well studied.
- The proposed experiments to inhibit SATB1 expression by shRNA knockdown or activity by inhibition of an upstream kinase in human T cells and then measure downstream effects on cytokine production and Th17 formation are straightforward.
- The scope is very limited.
- No concerns about the execution of the proposed studies.

Is the proposal feasible?

- The team is qualified and has access to all resources to perform experiments.
- Feasible to do the experiments; impact unlikely.
- The experiments are straightforward and the scope is limited.

Application #	DISC1COVID19-11998
Title (as written by the applicant)	In vitro modelling of COVID-19 infection on Alzheimer's Disease brain organoids
Research Objective (as written by the applicant)	Alzheimer's disease patient cerebral organoids to model Covid-19 infection
Impact (as written by the applicant)	The proposal will provide evidence on how the Covid-19 will impact the progression of Alzheimer's disease. It may enhance drug development of treatment
Major Proposed Activities (as written by the applicant)	• Amyloid beta measurements in Alzheimer's disease (AD) organoids vs control, infected with L-GFP-S (lentiviral vector pseudotyped with CoV2) and No infection control. • pTAU levels in AD organoids vs control, infected with L-GFP-S and No infection. • Amyloid beta measurements in Alzheimer's disease (AD) organoids vs control, infected with L-GFP-S, L-Nsp13, L-M, L-Orf6 (lentiviral vector overexpressing CoV-2 proteins). • pTAU levels in AD organoids vs control infected with L-GFP-S L-Nsp13, L-M, L-Orf6 at any of the time point described in the research strategy.
Statement of Benefit to California (as written by the applicant)	The proposal will help understand how Covid-19 impact Alzheimer's disease patient. It will also provide a model system for drug development.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

SCORE INFLUENCES

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	1	14	0
Is the rationale sound?	0	15	0
Is the proposal well planned and designed?	2	13	0
Is the proposal feasible?	6	9	0

REVIEWER COMMENTS

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Does the proposal have the necessary significance and potential for impact?

- Model and target is not appropriate.
- Relevance of Alzheimers in a specific interaction with COVID-19 is unclear. People with COVID-19 die of pneumonia not brain failure.
- Organoids are not hypoxic. This model takes no account of multi-organ failure.
- The linkage between the two diseases is not compelling.
- It is not clear why it would be important to know whether COVID-19 has any effects on AD-related issues.
- Improper model for the question being addressed.
- Not at all clear how knowledge gleaned from this proposal would impact the disease or move the field forward in any way.

Is the rationale sound?

- This seems to be a misuse of organoids.
- Unclear how AD organoids are going to lead to insights into COVID-19 disease in the more general population.
- The case made for conducting the research is not compelling.
- Concerns about the applicability of the studies.
- The AD model is not an appropriate model for SARS-CoV-2.
- The lack of a vascular component is concerning.
- The role of direct infection of brain cells by SARS-CoV-2 is still unclear and so how this might help is not clear. Even once infected would this change the course of the disease or the aftermath of the disease?

Is the proposal well planned and designed?

- There is a lot of literature in coronaviruses in the brain but this application did not build on any of this existing data.
- The experiments will not generate generalizable knowledge.
- Aside from concerns about causation hypotheses in Alzheimer's disease, it is hard to imagine an outcome that would change anything in medical practice.
- Major concerns about experimental design.

Is the proposal feasible?

- It's technically feasible, but making it to a translational outcome evades this particular reviewer.
- Potential problem with qualifications of applicant and planned approaches.