APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
CLINICAL APPLICATIONS												
CLIN2COVID19-11796	A Phase 1 study to assess the safety of living related donor derived T regulatory cell therapy in subjects with acute respiratory distress syndrome	$750,000	**N**	**70**	67	10	50	80	0	15		
TRANSLATIONAL APPLICATIONS												
TRAN1COVID19-11975	COVID-19 Antiviral Therapy to Block Direct Cell Injury and Associated Tissue Damage	$349,999	**Y**	**85**	84	3	80	90	9	6	Small molecule	Small molecule drug that can block viral replication in AT2 lung progenitor cells
DISCOVERY APPLICATIONS												
DISC2COVID19-11838 #2	Biomaterial vaccine to enhance the formation of SARS-CoV-2-specific T memory stem cells	$149,916	**Y**	**87**	88	3	83	95	13	2	Vaccine biologic	Development of a bioengineered, artificial antigen presenting cell to stimulate T memory stem cell response to SARS-CoV-2
DISC2COVID19-11979	CRISPRa/i CAR-T Cell Technology to Engineer an NKG2D-CAR-T Cell with Conditional IL15 Upregulation to Treat Patients With COVID-19	$149,850	**N**	**80**	75	12	50	90	3	12		
DISC2COVID19-11872	Use of human organoids to identify potential FDA-approved therapies for COVID-19 with metabolic disorders	$150,000	**N**	**75**	77	6	70	86	2	13		
DISC2COVID19-11970	Tailoring of an Existing Dendritic Cell Vaccine for Adaptive Immunotherapy against COVID-19	$150,000	**N**	**75**	70	11	50	84	0	15		
DISC2COVID19-11746	The pathogenesis of SARS-CoV2 infection of the central nervous system	$149,999	**N**	**65**	63	5	52	70	0	15		
DISC2COVID19-11959	Repurposing drugs to inhibit the translation of COVID-19 RNA in stem cells	$150,000	**N**	**-**	-	-	-	-	0	15		

Application #	TRAN1COVID19-11975
Title (as written by the applicant)	COVID-19 Antiviral Therapy to Block Direct Cell Injury and Associated Tissue Damage
Translational Candidate (as written by the applicant)	Berzosertib (VE-822), a safe drug candidate for treatment against COVID-19, will be investigated.
Area of Impact (as written by the applicant)	The outcome of the proposed studies will have a significant health benefit to COVID-19 affected patients.
Mechanism of Action (as written by the applicant)	Our drug candidate, Berzosertib, works as a treatment against COVID-19 by blocking a critical step in virus replication. Moreover, Berzosertib is a selective inhibitor of a key cellular enzyme ATR (ataxia telangiectasia and Rad3-related protein), which can result in disabling DNA repair pathway in damaged cells. Coronaviruses are known to hijack this pathway for efficient replication, thus inhibiting the DNA repair mechanism can block viral growth.
Unmet Medical Need (as written by the applicant)	Currently there is no vaccine or effective treatment to limit the COVID-19 disease caused by SARS-CoV-2 virus, which is an unmet medical need.
Project Objective (as written by the applicant)	Plan to have Pre-IND meeting with FDA in 6 months
Major Proposed Activities (as written by the applicant)	• Testing Berzosertib drug dose course against SARS-CoV-2 using lung stem cell-derived ALI and lung organoid culture models. • Assessing treatment effects of Berzosertib on reducing cell death and inflammation. • Preclinical safety and efficacy testing of Berzosetib in a human ACE-2 transgenic mouse model infected with SARS-CoV-2.
Statement of Benefit to California (as written by the applicant)	Emergence of a highly-contagious novel coronavirus, SARS-CoV-2, precipitated the current health crisis with over 3289 deaths and more than eighty thousand confirmed cases in California. Development of effective antiviral treatment targeting COVID-19 can help benefit the affected patients and reduce the impact on California's health care system and economy.
Funds Requested	$349,999
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	84
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

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	• This is a high-risk application that could produce a valuable drug candidate for COVID19. • Currently there are no approved drug or biological therapies to treat COVID-19. • Interesting platform but concerns about drug accessibility.

	• Novel.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• Preliminary data support the target/pathway as potentially involved in disease pathogenesis. • Therapy looks promising. • Positive control drug comparator has not shown a compelling clinical benefit. • Some concern that preliminary data in lung organoid model currently show only very limited infectivity. • Limited organoid data. • There are concerns about the timing and dosing of patients.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• Application of drug is well-considered. • The applicants have responded acceptably to the initial CIRM review. • Dose and regimen need further refinement. • Successful completion of in vitro and optimized in vivo study should support a pre-IND submission • Major concern is only one dose selected without specific justification and regimen is not provided.
No: 2	• Some issues - key concern about dose, frequency and route of administration for murine study. • Concerns raised in review about use of agent at single dose and insufficient rationale for regimen, route of administration.
GWG Votes	Is the proposal feasible?
Yes: 13	• Revised in response to prior feedback. • Need clinical trialist to help with the IND. • The improvements help make this feasible but there are concerns about licensing from the drug manufacturer. • Assuming sufficient cooperation from drug manufacturer as source of drug. • There are concerns about being able to cross-ref the drug manufacturer filing. I don't think that is necessary at this stage and it would be unusual for that permission to be granted at an early stage of development. I think having access to the drug is good enough for now and to expect more from the drug manufacturer is unrealistic. • The applicants need to have access to the study drug. • The key value proposition is to be able to leverage the data and drug from the drug manufacturer. This means being able to cross reference their IND (unclear). This is also why the in vivo study is so critical as it was a stipulation to provide drug.
No: 2	• Remaining concerns about drug manufacturer support for trial.

Application #	DISC2COVID19-11838 #2
Title (as written by the applicant)	Biomaterial vaccine to enhance the formation of SARS-CoV-2-specific T memory stem cells
Research Objective (as written by the applicant)	The objective of this project is to develop an injectable biomaterial platform that can induce TMSCs and boost immunoactivation to vaccines against SARS-CoV-2, which will help protect elderly people.
Impact (as written by the applicant)	This approach will boost T memory stem cell production to enhance immunization, and address the low/weak immunoresponses to vaccines, especially in the elderly and patients with immune deficiency.
Major Proposed Activities (as written by the applicant)	• Fabricate artificial antigen presenting cells (aAPCs). (month 1 – month 3) • Enhanced affinity and prolonged release of cytokines. (month 2 – month 4) • Preparation and integration of biomaterial vaccine. (month 3– month 5) • Engineer the fate and functions of murine and human T cells in vitro. (month 5 – month 8) • Perform in vivo immunization assays. (month 8 – month 10) • Study the formation of TMSCs in vivo. (month 9 – month 11)
Statement of Benefit to California (as written by the applicant)	Vaccine will be essential to stop the spread of COVID-19 in California and world wide. However, vaccine may not be effective enough for the people who need them most: elderly population who have declined immunue responses to vaccines. The biomaterial-based vaccine proposed here will boost the effectiveness of the vaccination for the elderly people and patients with other diseases, and will help fight COVID-19 virus, flus and other infectious diseases.
Funds Requested	$149,916
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 87

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	87
Standard Deviation	3
Highest	95
Lowest	83
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	• Highly significant and promising proposal; Artificial antigen presenting cells (APCs) in anti-viral vaccine would clearly be an improvement over autologous DCs as APCs. • This could be particularly relevant in an elderly population which is relevant for COVID-19 where they are most at risk. As such, it could address an unmet medical need not necessarily addressed by traditional vaccines that are more uniformly focused on generating an antibody response.

	• Innovative artificial antigen-presenting cells could have broad impact for COVID-19 and other viral illnesses. • Novel approach for vaccination. • This is a high-risk project to generate durable vaccination responses. • Potential vaccine approach which is broadly applicable and may have specific advantage to elderly.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The scientific rational for bioengineering artificial APCs with co-stimulatory and cytokine signals is well thought out. • Boosting T cell responses is a clear goal of a lot of SARS-CoV-2 therapies • The use of aged and young mice is novel and important. • Novel theoretical approach which differs from current vaccine strategies. • Limited preclinical proof of concept data.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• May have application beyond SARS-CoV-2. • The project is trying to do a lot of things at once: combining materials for direct cell engagement (co-stimulation), the controlled release of multiple cytokines, and the release of multiple vaccine antigens to real DCs. In the revised proposal the applicant has simplified both the vaccine and the cytokine components. • A complex design and many components to this vaccine; their roles are not entirely clear. • The product is complex and high risk. • Outstanding team with clear, if ambitious goals. • Very complicated proposal, but could generate important data. • Product concept was revised based on previous review.
No: 1	• The candidate is still too complex to generate meaningful data on the mechanism of action for this approach.
GWG Votes	Is the proposal feasible?
Yes: 15	• Still a very complex biomaterial. • Applicant has taken feedback from the previous application. • The proposed timeline is still somewhat unrealistic but the applicant has now identified more of the needed reagents making it a little more realistic. • Considered ambitious but simplified from previous submission. • I agree with the comments that it's a complex product concept, but it is early stage and can be simplified later as they learn. • Milestones are likely to be achieved.
No: 0	*none*

Application #	CLIN2COVID19-11796
Title (as written by the applicant)	A Phase 1 study to assess the safety of living related donor derived T regulatory cell therapy in subjects with acute respiratory distress syndrome
Therapeutic Candidate (as written by the applicant)	We intend to test if the transfer of donor immune cells, known as T regulatory cells, can help patients with respiratory failure from COVID-19.
Indication (as written by the applicant)	Acute respiratory distress syndrome from COVID-19 infection
Unmet Medical Need (as written by the applicant)	There is no SARS-CoV-2 vaccine and no specific medical treatment for patients with COVID-19 related ARDS. ARDS accounts for over 75,000 deaths annually in the the United States. The only treatments are largely supportive. Thus this is an area of clear unmet medical need.
Major Proposed Activities (as written by the applicant)	• Final regulatory approval. • Trial initiation and enrollment of 20 patients, with at least 12 treated. Assess feasibility and safety. Determine if there is any potential efficacy. • Correlative science studies to see how Tregs might alter immune and inflammatory state of the patient.
Funds Requested	$750,000
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	67
Median	70
Standard Deviation	10
Highest	80
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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	• ARDS is a dreaded complication of SARS-CoV-2 infection and current treatments are inadequate. • There is a potential for T regulatory cells to impact ARDS. • The strategy could promote healing in the lung and help generate fundamental knowledge about Treg cells. • Primary impact would be from basic immunology; wide applicability is not likely. Major concerns about feasibility. • There are concerns regarding whether this approach is practical and scaleable. • Despite some of the challenges with the application I am supportive of it, although some aspects could be improved. • A major concern is lack of data in active infection and a potential for the treatment to exacerbate disease.
No: 8	• Since this is a Phase I study, the best outcome that can be hoped for is that Treg cell infusion will not cause adverse effects. Efficacy data would have to come from later studies. If CIRM wants efficacy data quickly, then this study may not have the urgency

	that is commensurate with CIRM's mission. Even if successful, there are big questions about whether a protocol this complex and expensive could be broadly implemented for an acute disease, especially in underserved communities. ● Use of T reg cells for treatment of ARDS using partially matched donors is unlikely to develop into a therapy to have an impact on COVID-19 patients. There are many feasibility concerns. ● The role of Treg in the recipients with acute viral infection is unclear. Will they be beneficial or harmful? ● A lot of feasibility issues, some things can only be done at the applicant institution, making the program high risk. ● Important problem but significant issues with feasibility in an acutely ill population. Scaleability is a major limitation. ● The challenges with getting a healthy, related donor to the clinical site, or eventually another central manufacturing site, during a pandemic, are too great to be dismissed. ● Not scalable. Expensive. ● The applicants should have done a lead-in study to test feasibility - or proposed it instead. The proposed project is too expensive, and not enough will be learned from doing a full scale study just to see if timing and logistics will work out.
GWG Votes	Is the rationale sound?
Yes: 9	● Treg therapy has reasonable pre-clinical and clinical results to suggest therapeutic efficacy in ARDS. ● Evidence from the literature supports the idea that regulatory T cells can facilitate the repair of lung tissue damage in other models. Use of donor HLA-matched is desirable because these cells are less likely to be rejected by the host or to cause GVHD. But haploidentical cells do not have this advantage. Use of donor HLA-matched or haploidentical allogeneic T regulatory cells is desirable because these cells will be HLA-restricted to the HLA-type of the recipient and thus likely to respond effectively to the antigenic peptides presented by recipient HLA. It is not currently clear, however, whether HLA-restricted recognition is required for Treg cell function. Use of non-expanded Treg cells is desirable. ● Concern remains that the infused Treg cells could suppress clearance of the virus. ● There is some basis for ARDS, but no pre-clinical data in COVID-19 is provided.
No: 6	● Unlike MSCs, there are very few studies supporting the feasibility of this proposal. ● Novel clinical application but uncertain results; may be unexpected, even harmful. ● For this reviewer, the authors provided insufficient support (in this application) for a trial in human critical illness. Eg, are there animal models of sepsis or ARDS where Treg infusions have been studied. Also the failure of other therapies targeted at "lung repair" (GMCSF, eg) in ARDS were not addressed. ● The use of fresh cells is attractive, but there are concerns about the safety of the approach. ● Limited preclinical work provided to support rationale.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	● Although the protocol is complex, the applicants have experience with HLA typing, isolation of human Treg cells, infusion of Treg cells, and monitoring recipients of Treg cells for detrimental effects. ● There are questions about how long it will take to accrue 20 suitable donor-recipient pairs. ● Plans were carefully spelled out but practical issues of timing, transportation, obtaining immune cells from patients etc were problematic.
No: 12	● A run-in phase identifying critically ill patients at one of the hospitals, HLA typing donors, and other study procedures could be done outside of a pandemic to show the ability to do these in a timely fashion in critical illness in the proposed 120 hour window. ● Major concerns raised with feasibility and a need for run in study. ● The study is not designed to produce sufficient data to detect efficacy signal - and nothing is prospectively defined. On p. 16 they describe their plan to use a gene-modified donor-derived Treg if the signal from this study is not strong. They plan to use this study to make decisions when at the same time they state it's a safety/feasibility study not designed to provide effectiveness data. ● Would benefit from a control group. Not sure we will learn anything. ● Donors may be COVID-19 positive and may not be able to travel. ● Concern whether donors would be available in time to manufacture cells to impact the disease. ● Should use the term "first-in-humans" not "first-in-man". ● Project does not use stem cells.

	• Low N (n=20); no control arm - or at least not clearly described. With N this small, matching controls absolutely critical across age, sex, disease stage, co-morbidities, previous therapy, etc.
GWG Votes	Is the proposal feasible?
Yes: 0	*none*
No: 16	• It is likely it will take too long to identify suitable donors, HLA type them, purify the Treg cells, and infuse them into recipients with a potentially rapidly progressing disease to get meaningful results. • This is the major issue with the trial - The time frame for identifying a donor, getting them to travel, get HLA matching data, then apherese, and then return cells to ICU and administer within 120 hours seems unfeasible. • The practicality of actually getting people to travel, access health care facilities during a lockdown in pandemic is not addressed either. • The timelines do not seem realistic for processing and HLA typing. • What would the effect of regulatory T cells from a previously infected COVID-19 donor be compared with those from a previous uninfected donor? • The cells will be immunosuppressive - it is impossible to say these will not potentially pose risk during infection. • The evidence that high level sorting can be achieved is not presented. How would this be delivered outside the applicant institution if the treatment was successful? • Concern that the applicant did not consider FDA's recommendation for control group. • Concern with so few subjects that data will not be interpretable. • Not likely to learn anything about safety.

Application #	DISC2COVID19-11979
Title (as written by the applicant)	CRISPRa/i CAR-T Cell Technology to Engineer an NKG2D-CAR-T Cell with Conditional IL15 Upregulation to Treat Patients With COVID-19
Research Objective (as written by the applicant)	Achieve conditional IL15 upregulation using NKG2D/BBz IL15 CAR-T cells to control specific cytotoxicity against virally infected human cells while sparing uninfected cells
Impact (as written by the applicant)	Improve the prognosis of COVID-19 infected cells
Major Proposed Activities (as written by the applicant)	• Engineer and test lentiviral vectors to express the proposed three NKG2D CAR designs • In vitro mechanism of action studies • In vivo efficacy • In vitro model of virally infected human cells
Statement of Benefit to California (as written by the applicant)	This proposal offers opportunities to identify and develop diagnostics and treatments that can effectively control this disease and present the potential to reduce the gravity of a second wave of COVID19 or similars that may arise in the future. It also represents potential benefit to California by attracting scientists to California helping to bolster the economy. The intellectual property generated from this project can also promote California-based biotechnology in the stem cell technology.
Funds Requested	$149,850
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	75
Median	80
Standard Deviation	12
Highest	90
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(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	• A treatment for SARS-CoV-2 would be of important impact but the pathway to impact here is unclear with no near-term potential discussed. • Targeting the NKG2D ligand on damaged cells is a highly attractive approach. • NKG2DCART cells producing IL-15 for therapy of COVID-19 infection are a very good, novel idea.
No: 4	• It is not clear that this technology will have any near-term impact on COVID-19 therapy. There is no proposal how to translate this quickly to the clinic. • This project is far too risky for this application. • Unclear whether construct could have sufficient impact on COVID-19 patients.

GWG Votes	Is the rationale sound?
Yes: 7	• CAR-T cells with a novel NKG2D CAR is highly feasible. • Spectacular gene editing effort likely to rapidly provide the desired product; plans for translation of this technology to the clinic should be provided.
No: 7	• The rationale for using IL-15 secretion to support T cell engraftment, and activate NK cells, etc. is strong. • Insufficient preliminary data on some key points to support rationale and feasibility. • Sparse preliminary data for this application. • There is not enough preliminary data to support this high risk application. • Lack of sufficient preliminary data to support proposed construct as well as disease indication. • It is unclear the the NKG2D will recognize ligands on only virally infected cells. Will they recognize NKG2D on other stressed cells (there will be many in COVID patients)? • The relationship to stem cells is less than clear. • Concern about using a T cell allogeneic product. • The rationale for using CART to treat COVID-19 is not well thought out. How would this be implemented clinically? There is really no suggestion for how to proceed beyond creating the conditional CAR CRISPRa construct. • Not clear how a product will be made from this.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	• The gene editing and expected results are well described. Some examples of success in vitro need to be provided, e.g. IL-15 production by engineered NKG2DCAR-IL-15 cells. • Experienced team.
No: 4	• The plan for creating a conditionally activated IL-15 expression construct is well planned. • There is no plan outlined for how to bring this to the clinic. Would this be an autologous or allogeneic T cell therapy? • There is no discussion of pitfalls such as immunogenicity of the construct or the challenges of manufacturing T cells for treating patients in an acute setting. • There are potentially immunogenic components in the genome editing strategy. • Concerns with aspects of constructs which could be immunogenic.
GWG Votes	Is the proposal feasible?
Yes: 11	• The investigators are experts and have a very strong record of developing new gene engineering platforms, so feasibility is not an issue. • The functionality of the final product remains an unknown element of this project. • Timelines are aggressive and it's a good team. • Good team and corporate backing.
No: 3	• The timelines are too short for the applicants to complete their milestones.

Application #	DISC2COVID19-11872
Title (as written by the applicant)	Use of human organoids to identify potential FDA-approved therapies for COVID-19 with metabolic disorders
Research Objective (as written by the applicant)	Human islet like organoids and intestine organoids differentiated from human pluripotent stem cells.
Impact (as written by the applicant)	Providing the immediate drug candidate for clinical trial of COVID-19 patients with diabetic complication.
Major Proposed Activities (as written by the applicant)	• Construction of visualized system for SARS-CoV-2 infection. • Establish human pluripotent stem cells with NF-kB-luciferase reporter. Infection of lentivirus of NF-kB-luciferase in human pluripotent stem cells and pooled selection. • Modeling SARS-CoV-2 infection in intestine and pancreatic organoids from human pluripotent stem cells. • High-throughput Drug Screening in human Intestinal organoids and pancreatic islet organoids. Identifying the target small molecules which suppress both infection and inflammation. • Identification of the transcriptional pathway which inhibits pL-SARS-Cov-2-GFP infection and NF-kB activation. • Public announcement of the results.
Statement of Benefit to California (as written by the applicant)	The drug discovery by proposed study for COVID-19 in diabetic complication in California maximize the benefit for future treatment in the citizen of California, include vulnerable populations such as Hispanic, African-Americans, men, older populations, homeless people, those from lower socioeconomic status. It may also provide the research assistant jobs with highly educative research program in South Bay area of Los Angeles.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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	75
Standard Deviation	6
Highest	86
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(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: 12	• Use of the stem cell-derived organoid models of various tissues (pancreatic islets and intestine in the case of this proposal) for drug screening and/or study of infectious mechanisms is innovative and represents a potential major strength. Project has strongly innovative elements and PI is a promising young investigator. • Ability to modify the state of the organoid and evaluate the infectivity of the virus under different metabolic conditions is innovative. This may provide novel insights about the

	biology of virus-host interactions. I doubt there is a noticeable metabolic influence, but there is a chance it will provide such insight, so this a worthy area of investigation. ● Development of a tool that may be useful in accelerated drug screening. ● If the screen is successful, new drugs could be discovered using stem cell technology. ● Well established organoid system. Unique system for studying pancreatic function in the context of relatively high throughput screening. ● The potential of finding an effective antiviral in the proposed screen is reduced significantly, as are significance and potential for impact, by limiting the search only to drugs that can block interaction of one protein with its receptor, or processing by the protease. If this were taken simply as a proof-of-concept for use of organoids, that might be mitigated somewhat, but the proposal was not presented that way. ● Establishment of a BSL2 to accelerate screening of potential COVID-19 therapeutics would be valuable. ● Avoiding need for high containment facility by using a reporter system delivered in pseudotyped lentivirus with a protein of SARS-CoV-2 essential for infection of organoids is clever and increases potential impact. ● Very poor presentation of the application -- failures in simple spelling, grammar, proof-reading -- and more substantive weaknesses in project design probably reflect PI's relative inexperience as lab head and grant applicant. This would be correctable with appropriate mentoring and perhaps addition of active collaborator(s) experienced in virology & drug screening. However, as presented this limits potential for impact. ● Taken as an application focused on tool development rather than finding a candidate therapeutic compound, the score improves -- however, impact is still limited by factors discussed in other sections. Lots of potential here, and hope the applicant makes improvements and resubmits. ● I believe there is enough of interest (investigators, concept, etc.) for an early stage development effort to warrant a modest investment. I continue to keep in mind the modest amount of the funding. ● Some focus of CIRM's funds on developing better tools is a good idea and could have a long term impact. Take the opportunity to develop a tool now that could be beneficial later.
No: 2	● Limited assays system that only assays for spike protein drug targets. Limited potential to find a useful candidate.
GWG Votes	Is the rationale sound?
Yes: 12	● There is good rationale for studying different metabolic states. ● Testing metabolic aspects of organoid culture is an innovative approach. ● Rationale for screening in organoid systems is sound. Less support is presented for specifics of application of the tool to the question of whether SARS-CoV-2 infection of pancreatic islets and/or intestinal epithelium is key to pathogenesis in COVID-19, either with respect to direct damage of corresponding organs or to induction of cytokine storm. ● Nice concept to study effects of metabolic factors on the organoids and response to the model challenge. Unfortunately, this is not well developed in the proposal. ● Focusing on epithelial cells in islet or intestinal organoid models as key cells for inflammatory response leading to cytokine storm seems narrow and probably misses the boat - more likely effects through endothelial and/or immune cells. Use of NF-kappaB reporter system in the stem cell-derived epithelial cells as only measure of inflammation is thus too limiting. ● The application does not describe the intestinal organoids at all -- only by reading a published patent application for which PI is a co-inventor does it become clear the organoids do contain endothelial cells, but provided by exogenous HUVEC cells, not derived from the pluripotent stem cells that will be engineered with the NF-kappaB-driven reporter. ● It is stated in the Introduction that "normal culture conditions, high palmitate and dexamethasone treated conditions (in vitro insulin resistance induction)" will be used as conditions. But in the methods, only "high glucose and low glucose" is written. Please be consistent, clear, and detailed in describing methods so that the panel can evaluate them.
No: 2	● Only a small part of the virus biology is considered in the screening approach.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 11	● The pancreatic organoid is well described with preliminary data. More details giving the panel confidence in the intestinal organoid would be appreciated.

	● Major concerns around feasibility.
	  ● 4 months to make the constructs, then 2 months to show the system can work.
	  ● Does the team have any experience in screening? Planning to screen "hundreds" (but how many? impacts feasibility) and then do dose response.
	  ● The constructs won't necessarily be present in all the cells in the organoid.
	  ● It will take a month to make the organoids.
	  ● The metabolic state is interesting - I wonder why the applicant is not focusing on respiratory epithelium.
	● No clear statement on how many of the ~2000 compounds in the purchased screening library (FDA approved drugs) actually will be tested. No evidence that the screen will actually be high-throughput. Do the investigators have access to appropriate automation & detection systems (especially for 3D cells in culture), and does anyone on the team have adequate experience in carrying out drug screens?
	● Application would benefit from more comprehensive screening and also testing of more compounds.
	● The throughput of the screen and statistics are not well described.
	● Experimental design lacks controls and specific assay of COVID-19 biology.
	● More careful and detailed description of controls & control experiments needed.
	● More careful and detailed description of statistical analysis needed.
	● Please perform a literature search (including preprints) on the 1971 compounds in the DiscoveryProbe library. Presumably automated (or could be as simple as searching for the keyword DiscoveryProbe in the COVID-19 literature). Have any of these compounds been identified as positive in any published screens already? What other HTS experiments are being done (to public knowledge) or have been done with this library?

GWG Votes	Is the proposal feasible?
Yes: 11	● There are some feasibility issues. ● The proposal is feasible but with major limitations: Milestones and time line have major flaws. First 2 milestones should be carried out in parallel, not sequentially, this would save 2 of 12 months. Milestone 5 - transcriptional characterization - is poorly explained/justified and seems off the point of either screen development or identification or candidate therapeutic compound in the screening set chosen. Milestone 6 could simply be deleted - this would strengthen the proposal, allow more time for the research component. ● Need to describe current throughput. Writing that "several hundred" compounds will be screened is too vague (is it 201? or 999? there is a big difference). Please provide an exact number an/or a very considered discussion of the constraints or uncertainty on this number. Why not all 1971 compounds in the drug library?
No: 3	● Major concerns about time frame for delivery. ● Convincing data were not provided to ensure that the assay is set up to be high throughput enough to achieve screening goal.

Application #	DISC2COVID19-11970
Title (as written by the applicant)	Tailoring of an Existing Dendritic Cell Vaccine for Adaptive Immunotherapy against COVID-19
Research Objective (as written by the applicant)	Pluripotent stem cell-derived Sars-CoV-2 antigen presenting dendritic cell vaccine.
Impact (as written by the applicant)	COVID-19 has been shown in many cases to elicit a weak antibody response and long term immunity is uncertain. APC driven adaptive immunity is hypothesized to provide more robust and lasting immunity
Major Proposed Activities (as written by the applicant)	• Prototype drug substance (mDC) R&D process • Prototype drug product (SARS-CoV-2 APC) R&D process • SARS-CoV-2 APC drug product functional characterization • VAC COVID-19 CTAP meeting
Statement of Benefit to California (as written by the applicant)	The proposed antigen presenting dendritic cell-based vaccines could provide a complement to the overall vaccine arsenal for the state. Because drug substance (dendritic cells) can be banked in large number and that the required antigen loading is a simple step at end of process to generate drug product, dendritic cell banks could be deployed more rapidly than other vaccine technology for better preparedness to future emerging threats.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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	70
Median	75
Standard Deviation	11
Highest	84
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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	• A vaccine would be critically important in the fight against COVID-19. • This is a significant allogeneic vaccine to be made in bulk to be administered to individuals at risk of COVID-19 with no restrictions for MHC compatibility, race, color or sex. • "Off-the-shelf" dendritic cells, derived from pluripotent stem cells, would represent an attractive concept to induce immunity to SARS-CoV-2 and in other contexts. • An allogeneic dendritic cell therapy could be significant for COVID19. • Proposed construct could serve as both a therapeutic and preventive vaccine for COVID-19. • Construct may have limited applicably to high risk populations. • The technology will result in a therapeutic product candidate because an analogous product already developed by the company has been tested in an oncology clinical trial.

	• As prophylaxis, this approach is not as promising (especially in terms of cost and scaling up global manufacturing) as other vaccine-candidates in development for COVID-19 and less likely to succeed.
No: 3	• Flawed proposal using a line with single HLA type. • Major concerns that they will not elicit protective responses in the context of allogeneic vaccine. Preliminary data are focused on traditional, antigen-specific responses which would require MHC matching. • Described as potentially working in syngeneic A0201 individuals--a very common assertion in the field not unique to these applicants, but a continual problem as it reinforces the exclusion of studies and potentially therapeutics for populations that do not have high A0201 carriage, including African-Americans. • Intended for only a minority of the world's patient population.
GWG Votes	Is the rationale sound?
Yes: 6	• The rationale is not adequately explained: the potential mechanisms of this unorthodox allogeneic vaccine (how and why it works) need to be explained and some preliminary data provided on mechanisms. • The proposal does not discuss how antigen presentation by HLA-mismatched DCs will be affected in vivo and if there will be a sufficient "window" for irradiated DCs to elicit strong anti-viral T-cell response. • Preliminary data is summarized in table 3, but not presented.
No: 9	• The rationale seems to claim both allogeneic and syngeneic effects but the allogeneic mechanisms are unclear and the validation appears to be focused on syngeneic traditional peptide-MHC stimulation. • "Fatal flaw" of design around a single HLA type, commonly used in immunology studies. Review session included an interesting debate of what mechanisms might enable successful immunization with allogeneic dendritic cells, unmatched for major histocompatibility loci which in conventional understanding of immune response must be matched for recognition of antigen by effector cells. However, application neither discussed the mechanism proposed by one reviewer (no mention of potential role of exosomes to bypass normal requirement for MHC matching), nor provided data supporting immunization in entirely allogeneic context. • Insufficient understanding of MOA. • The mechanism of action seems inconsistent with the classical HLA pathways, and therefore the nonclassical mechanisms of action (e.g., exosomes) need to be better described. • Alternate MOA not discussed which could be more relevant to broader populations.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• Production and testing of the vaccine for its broad availability are well designed. • Potential mechanisms responsible for potential responses to the vaccine were not included.
No: 10	• Limited preclinical data to support use in COVID-19. • Missing information about whether the preliminary data used irradiated/cryopreserved product. • Concerns about nature of product, e.g., irradiation of cells, not validated in preliminary studies. • The mechanism of efficacy and the correlates of protection are not well-described. • The diversity of cell lines does not seem to be addressed by their design. • Concern about the focus on HLA A0201 restricted epitopes, and applicability to populations other than Caucasians. • Since this project will utilize previously developed technology of generating DC from human ES cells, it is unclear why milestone 1 work is necessary. The authors can utilize master cell banks of DCs, generated for oncology clinical trial and start right from milestone 2. • Potential pitfalls, related to DC functionality after irradiation, the immunogenicity of mismatched cells, failure in specific anti-viral T-cell response in vitro, electroporation of mRNA, cell viability and others are not described.
GWG Votes	Is the proposal feasible?
Yes: 12	• Vaccine production, testing and release criteria are well presented but could use specific examples of positive results. • The project is unlikely to succeed, unless conventional understanding of adaptive immune response does not apply in this case. • As described it is feasible. • Appears feasible.

	• Construct is available and has been used clinically. • The proposal looks feasible within the timeline.
No: 3	• Not feasible for immunization for large populations.

Application #	DISC2COVID19-11746
Title (as written by the applicant)	The pathogenesis of SARS-CoV-2 infection of the central nervous system
Research Objective (as written by the applicant)	Our research is designed to better understand mechanisms contributing to both host defense and disease following SARS-CoV-2 infection of the CNS and test a novel anti-viral drug.
Impact (as written by the applicant)	Results from our work can assist in the development of CNS penetrant drugs that inhibit viral replication and disease progression.
Major Proposed Activities (as written by the applicant)	• We will identify what cell types of the CNS are targets for SARS-CoV-2 infection and potential anti-viral and neuroinflammatory responses. • We will evaluate the ability of a novel RNase inhibitor in blocking SARS-CoV-2 replication within the CNS as well as affecting proinflammatory gene expression.
Statement of Benefit to California (as written by the applicant)	SARS-CoV-2 is the causative agent for COVID-19 resulting in numerous deaths. California has one of the highest incidences of COVID-19 patients in the US highlighting the need for better understanding of how this virus affects people. Indeed, an increasing number of COVID-19 patients exhibit signs of neurologic disease with evidence of SARS-CoV-2 entering the central nervous system. Our proposed work will provide insight into SARS-CoV-2-induced CNS disease and treatment.
Funds Requested	$149,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 65

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	63
Median	65
Standard Deviation	5
Highest	70
Lowest	52
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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: 2	*none*
No: 12	• The applicants have not shown sufficient data to overcome tremendous risk for taking a single drug into clinical trials. High chance for failure and the opportunity is marginal. • Impact is unclear; the specificity of the drug is questioned. • It focuses on a subset of interesting questions, but is too limited in its scope. • Focus on single agent and lack of proper recapitulation of SARS-CoV-2 associated pathology/inflammation is a concern. • The drug candidate they propose to test may not be utilized in practice, and therefore the studies utilizing this compound seem less significant. • Concern that execution of the proposed studies will translate to use in COVID-19.

GWG Votes	Is the rationale sound?
Yes: 2	• Viral replication in brain has been shown in animal models, and clinical evidence for the virus in the brain of patients is available. This could add more detail on types of cells infected, but how this would map into a clinical setting is unclear.
No: 12	• Rationale is not well presented. • Preliminary data are not compelling for the drug candidate. • It would have been easy to determine if the drug of interest altered viral replication in a candidate cell line (e.g., endothelial cells). • Organoids are a strength but difficult to model an immunotherapeutic in an organoid system. • Relevance of the CNS organoid system is not clear in relation to SARS-CoV-2. • The focus on cytokine storm does not seem on point for this condition. • The drug specificity is questionable and therefore the risk for toxicity is high.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• The planned experiments are straightforward. • Aim 1 of the project is basically designed as a research project to establish whether the virus will infect any of the brain cells in the organoids and cause changes in cytokine release that could explain neurologic effects of COVID-19. No candidate will emerge from that, but some interesting basic biology of the disease could be elucidated. Aim 2 will test one candidate anti-viral if Aim 1 is successful in showing viral replication. • The proposed drug is a potentially interesting agent. Several agents that modulate the unfolded protein response are in the clinic or headed there for a variety of indications. Using this drug to block viral replication, with consequent alteration in neuroinflammation, is a reasonable idea. But it could be tested more directly in other systems.
No: 8	• There are limitations in design; not clear what this drug will ultimately do to the virus. • At a technical level, yes. But there is no backup strategy if this particular drug does not work. • Alternative approaches not provided. • Proposed test system unlikely to sufficiently recapitulate disease.
GWG Votes	Is the proposal feasible?
Yes: 10	• The project is feasible but high risk without concomitant reward. • It is technically feasible. Without a demonstration that the drug would actually inhibit viral replication, however, it seems completely speculative. • Science is good, but they are only studying one potential drug. • All labs have strong experience with the organoid system and the disease models. Systems are in place. • Applicants can handle virus based on previous experience with murine models and are equipped for proposed studies. Strong institutional resources.
No: 4	• Concern with completing all aims in specified timeline.

Application #	DISC2COVID19-11959
Title (as written by the applicant)	Repurposing drugs to inhibit the translation of COVID-19 RNA in stem cells
Research Objective (as written by the applicant)	A stem cell-based screening platform to discover drugs which can be repurposed to inhibit COVID-19.
Impact (as written by the applicant)	Successful completion of the project will identify repurposed compounds that inhibit COVID-19 in stem cells and provide a strong rationale for clinical investigation.
Major Proposed Activities (as written by the applicant)	• To generate a fluorescent reporter system for studying COVID-19 function in stem cells. • To identify repurposed drugs for inhibiting COVID-19 in stem cells.
Statement of Benefit to California (as written by the applicant)	Since the emergence of COVID-19, 17 million jobs were affected in California as the state expects $50 billion loss in tax revenues due to business closure. Despite strict shelter-in-place measures, the total case count is at 81,911 with new cases emerging daily. As we face a potential second wave of the pandemic, an effective anti-viral will not only alleviate the burden on the state's healthcare system and prevent further spread of the disease but also expedite California's economic recovery.
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

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: 2	• It is important to do high throughput screening of approved drug libraries to look for compounds to treat COVID-19. • It is relatively innovative to screen specifically for translation suppression, as few other groups are doing that.
No: 12	• Lack of understanding of viral life cycle. • Repurposing of drugs is a tricky path and it may end in the desert; it is a risky proposal. • The grant seems to be poorly written. • Concern whether relevant to impact COVID-19. • It could lead to a candidate re-purposed drug for COVID infection based on a new mechanism. No other discussion of translation.
GWG Votes	Is the rationale sound?
Yes: 1	• The dual cistronic reporter allows each intervention to essentially control for itself in a number of ways, as typically inhibition occurs at only one class of translation initiation site.

	● "In the preliminary data, we have demonstrated the bicistronic dual-fluorescent reporter system can be successfully used to measure both human and viral RNA translation (Figure 1)." Figure 1 is a cartoon that does not "demonstrate" anything. ● "The SARS-CoV-2 5'UTR sequence will be inserted into the vector followed by GFP while keeping human gene 5'UTR followed by RFP to observe general human mRNA translation." I don't understand why you put two 5' UTRs back to back. Could you explain that better? ● I would like to see much more detail on the vector, more preliminary data, and a better exposition of what already exists and what will be created. ● I would like more detail on the target stem cells and how they will be derived, maintained, conditions, etc. ● I don't think stem cells are needed for this proposal. Or even desirable. The experiments would be better with non stem cells, which would likely make the proposal ineligible for CIRM funding.
No: 13	● There is no evidence of stem cell depletion in patients. They make no coherent argument for screening stem cells and provide no information about cell lines to be used (source, scale of production, ease of transfection) ● Neither the rationale or specific goals are clearly defined. ● The rationale for limiting screening to stem cells is not clear. ● The premise seems attractive, but the biology of the virus life cycle is not well considered. ● Lack of understanding of MOA of coronavirus. ● The literature they cite only tangentially suggests that stem cells are important targets in lungs or in the olfactory system. The persistence of clinical problems months after virus testing becomes negative is hardly hard evidence for that. In the olfactory system, stem cells have not been directly identified as being infected; many other types have. In the lungs an almost terminally differentiated progenitor may be very susceptible to virus, but so are many other cell types. Thus, why use stem/progenitors for re-purposing screening, even if the "stable lines" they propose to make do reflect the properties of stem/progenitors infected in patients, which is completely unclear in the application? ● No information is given on the two "stem cell" systems they propose to use for screening. If they are really interested in treating virus in lung and olfactory tissue "stem cells", how would lines they intend to make compare to these? Application seems to be focused on molecular biology of readout with little of no discussion of the biological context of lines or disease. ● Preliminary data suggests they can monitor translation with technology on hand.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 13	● Publications to show their preliminary data about the dual cistronic vector are needed. ● Limited preclinical data to support proposed targets. ● Inadequate budget for personnel or supplies; this is not meant to be an equipment grant. ● Time frame of the experiments is not defined. ● Nothing novel here that someone else isn't already doing better. ● It is not clear that the applicant has spent much time researching and understanding the proposed library to be screened. It has been years since REFRAME had 12,000 compounds. Now it has 14,000. Both of these numbers are used in the proposal without consistency. ● The experimental design includes efforts to determine human toxicity. Why? These drugs are already all approved, so presumably human toxicity not that bad. ● The proposed 11-point dose-response curve is a strength, it is good to test a variety of doses when screening drugs. ● No stem cell relevance. ● The grant seems to be poorly written. ● There are a vast number of grammatical and spelling errors. Acronyms like RFP not introduced. Proposal has not been proof read to remove phrases like "just a wild guess". ● Some sentences are hard to understand. "The amino acid sequence indicates that both strains contain residues linked to angiotensin-converting enzyme 2 (ACE2)" Do the authors mean covalently linked? That would make no sense. ● Letter of support is needed from the partnering institution.
GWG Votes	Is the proposal feasible?
Yes: 3	● The project is pretty straightforward. ● "... is a computational biologist and will spearhead the machine learning and bioinformatics analysis. He has more than 10 years of experience in biological data

	analysis and has extensive experience with building, maintaining and executing machine learning pipeline." But there is no machine learning anywhere in the proposal. Please clarify the role of this personnel. ● Concerns about ability to publish and disseminate results, and to explain them clearly. ● Only 2 first author papers in CV of PI. ● Clarity of this proposal is weak. ● It is unlikely the applicants will complete the timeline as proposed. The applicants leave one month for establishing the stable "stem cell" lines containing the reporter construct. ● Small organization in shared lab space, but application suggests they have necessary equipment. ● Participants resumes have experience in pertinent drug screening technologies. Little detail given on cell culture, specifically establishing and maintaining stem/progenitor cell lines. ● Applicants claim to have access to the compound library, but no letter of support provided.
No: 11	● There were serious feasibility issues. ● The grant seems to be poorly written. ● Timeframe is not feasible.