APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
DISCOVERY APPLICATIONS												
DISC2COVID19-12020	Battling COVID-19 Using Off-The-Shelf HSC-Engineered iNKT Cells	$250,000	**Y**	**86**	86	3	80	90	9	5	Cell therapy	Engineered HSC-derived NKT cells for treatment of COVID-19
DISC2COVID19-12007 #2	Pro-healing biomaterial for treating lung inflammation associated with COVID-19	$249,974	**Y**	**86**	85	5	70	92	14	1	Biologic	An extracellular matrix-containing, soluble biomaterial that recruits progenitors cells for treating lung inflammation
DISC2COVID19-12059	Development of TMPRSS2 antibody as an antiviral treatment for SARS-CoV-2 (COVID-19)	$249,997	**N**	**80**	81	3	75	87	4	11		
DISC2COVID19-12083	Shelter in Place COVID-19 Vaccine	$250,000	**N**	**80**	79	5	75	91	2	13		
DISC2COVID19-12014 #2	A treatment for COVID19 and related neurological conditions	$250,000	**N**	**70**	72	5	60	80	0	15		
DISC1COVID19-12050	Investigating the pathogenesis of cardiovascular complications in COVID19	$149,998	**N**	**60**	57	6	40	65	0	15		
DISC1COVID19-12079	Targeting a key regulator in naïve CD4+T cells to treat cytokine release syndrome	$150,000	**N**	**-**	-	-	-	-	0	15		
DISC2COVID19-12071	Study of anti-inflammatory and anti-viral adipose-stem-cell secretory factors as potential treatment for the respiratory syndrome induced by COVID-19	$199,700	**N**	**-**	-	-	-	-	0	15		

Application #	DISC2COVID19-12020
Title (as written by the applicant)	Battling COVID-19 Using Off-The-Shelf HSC-Engineered iNKT Cells
Research Objective (as written by the applicant)	Allogeneic HSC-engineered iNKT (HSC-iNKT) cells
Impact (as written by the applicant)	Treatment for COVID-19
Major Proposed Activities (as written by the applicant)	• Milestone 1. Production of AlloHSC-iNKT and UHSC-iNKT cells • Milestone 2. Characterization of the AlloHSC-iNKT and UHSC-iNKT cells • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	The novel SARS-CoV-2 is the cause of the coronavirus disease 19 (COVID-19) pandemic, which is responsible for over 10.3 million cases and 500,000 deaths worldwide. There are over 2.6 million COVID-19 cases in the US, including over 217,000 cases in California. The proposed off-the-shelf allogeneic HSC-engineered iNKT (HSC-iNKT) cell therapy, if successful, may provide a treatment and save lives of COVID-19 patients at California.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 86

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	86
Median	86
Standard Deviation	3
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	5

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 proposed technology will address unmet medical need if successful. There is no approved highly effective treatment for COVID-19. A couple of repurposed drugs demonstrated very modest improvements so far. • The proposed therapeutic candidates are developed from hematopoietic stem/progenitor cells. It addresses some current bottlenecks in cell therapy, for example immediate availability of the drug (off-the-shelf) in acute conditions. • Killing infected lung epithelial cells via NKT cells could be helpful. • An allogeneic iNKT cell-based therapy to target and repair damaged cells/tissues in COVID-19 patients is a promising new idea. • This is a potentially highly impactful proposal.

	• For this early stage application, I think the proposal is reasonable and while it is a lot of work, they seem like a motivated group. It is impressive that they were able to quickly generate data in response to the prior CIRM review. • Excellent revision from the initial submission. • Possible impact. Way forward to clinic, if any, could be clarified by the proposed studies. But some major issues will be difficult to clarify. • Very high cell doses may be needed at the highest numbers used for cell therapies. • There is a concern about cytokine release and practicality of manufacture.
No: 1	• Cytokine release/storm could be a serious side effect. High doses seem to be required.
GWG Votes	Is the rationale sound?
Yes: 12	• The authors did a great job addressing the earlier concerns, and provide new supportive information and a focus on the generation of universal iNKTs. • The new preliminary data supports the rationale. • The scientific rationale is sound. The authors presented new preliminary data, which provide a rationale and possible mechanism of action. • Addition of preliminary data strengthens the proposal. • Activation of iNKT cells as a therapy to kill target (infected) cells is a potentially impactful approach. • Preliminary data on killing infected cells strengthens rationale, but potential clinical use given possible safety issues will need to be very carefully considered. The proposed efficacy studies will not give much information on safety considerations. • Reasonable rationale but still extreme concern which isn't addressed by resubmission that activation of NKT cells will cause significant cytokine release. • There is significant concern that the use of this strategy could lead to a hyper-cytokine reactions further complicating cytokine storm problems known to be problematic with COVID-19 disease. • Direct killing effect of SARS-CoV-2 infected cells still maybe speculative. It will depend on biodistribution of infused cells and efficiency of selective killing. • Is a two-fold reduction in virus as shown in preliminary data evidence of a substantial anti-viral effect? • The mechanism by which the iNKT cells act is not clear. • Potency of the cells in a preliminary data appears low.
No: 1	• The safety of the product needs to be studied in more detail.
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• The project is well planned and designed. • The organoid model is useful to ascertain the efficacy of the cells. • Addition of new complementary model systems to evaluate the iNKT cells is strong. • In vitro studies and GVH studies are well designed. Efficacy models all have different issues, as discussed by the applicant. The applicant understands these issues well, but how to overcome them and get information that will inform dose as applicant considers clinical use is not clear. Dose will be very important concern, as always, but may be critical with iNKT that secrete multiple cytokines. • Manufacturing issues seem to be taken for granted even though preliminary data shows sizeable subpopulations of cells in both product candidates. No discussion of this issue, potential product characterization or release, or impact of heterogeneity on important function metrics or potential immunogenicity. This is important. • Not enough evidence on product heterogeneity or release criteria despite apparent significant manufacturing experience - the flow data suggest there are cellular subpopulations.
No: 1	• Heterogeneity of the cell product (CD8 flow and MHC I expression) is a concern.
GWG Votes	Is the proposal feasible?
Yes: 10	• The proposed milestones are logical and well described. • The proposal is well thought out and highly feasible. • Excellent discussion of feasibility. • Even if they do not complete all the work proposed, they will learn and add to the field with original research.

	• The isolation of NKT cells from hematopoietic cells (to be engineered subsequently) seems reasonable. • There are minor concerns about the scope of investigating multiple cell products, but overall the project seems feasible. • With addition of second product-candidate the project maybe too ambitious overall. • The team is qualified and can perform the work.
No: 3	• The proposal to test both the primary and universal candidate seems unlikely to be manageable within the timescale and budget of the project. • The manufacturing of this product may need some significant work. • Unlikely to be able to accomplish all the efficacy models discussed in the application with the staff available. Should be able to do the in vitro characterization work: 2 manufacturing runs and characterizations of the allo and universal products from the same cord.

Application #	DISC2COVID19-12007 #2
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 improve lung function in rodent model ● Evaluate biomaterial for ability to recruit human stem cells
Statement of Benefit to California (as written by the applicant)	In late-June 2020, there are more than 5,700 Californians who are currently hospitalized because of COVID-19 (tested positive or suspected) with over 1,300 confirmed COVID-19 patients 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	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 86

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	86
Standard Deviation	5
Highest	92
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

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 injectable biomaterial has potential to prevent or decrease the severity of Acute Respiratory Distress Syndrome (ARDS) associated with COVID-19, a significant unmet medical need. ● Development of a biomaterial to promote lung repair in COVID-19 patients has the potential for significant impact on recovery from the disease. ● Potential for this close to clinic intervention to be efficacious in injured lungs. ● A unique project that could have a big impact. ● The extracellular matrix (ECM)-based regenerative material has high translational approach and is easy to deliver. ● The path to translation is rapid and accessibility may be high.

	● The product has already entered testing in humans for another clinical indication. This makes the plan for progression to translation relatively straightforward, as the applicants already have considerable experience with issues of manufacturing and toxicity testing for human use. ● The stem cell component is underdeveloped and not relevant to the success of the project.
No: 1	● I don't think that there is really much novel about this biomaterial and think it's a long shot.
GWG Votes	Is the rationale sound?
Yes: 14	● The basic finding that certain decellularized ECM materials can dampen inflammation and promote remodeling of damaged tissue has been established in a variety of contexts, including prior work from the applicant team. ● The reduction of inflammation in the ARDS setting by this technology is sound. ● The grant is responsive to previous critiques and proposes lung and cardiac ECM matrices for use as protective and therapeutic treatments. ● The applicant has compelling evidence in the cardiac system that may translate to the lung. ● The ECM may attract progenitor cells and reduce inflammation. ● The most compelling preliminary data come from characterization of the biomaterial, the soluble fraction of digested ECM hydrogels, demonstrating that it is hemocompatible and can be delivered intravascularly. ● Evidence that the ECM material can recruit endothelial progenitor cells (EPCs) is a positive feature for therapy for a viral disease that increasingly is recognized to damage blood vessels. ● Sound rationale but likely not necessary to test both lung and cardiac-derived ECM. The rationale for the pulmonary MSC experiments is not good, it would be better to focus on known lung epithelial progenitor cells, eg. AT2 and basal cells. ● No preliminary data presented on activity of the ECM hydrogels on well-recognized stem cells for lung epithelial cells (e.g. Type 2 alveolar epithelial cells). Focus on mesenchymal stromal cells (MSCs) as potentially significant source for regeneration of lung epithelia, as for other epithelial tissues, is not compelling. ● Rationale for retention of tissue specificity of ECM materials after treatments that include use of harsh detergents (SDS), digestion, etc. (especially conditions expected to strip out proteoglycans) is not compelling. The cardiac-derived ECM has already passed manufacturing and toxicology hurdles for human testing -- why not focus on this material and only consider lung-derived ECM as an alternative if the cardiac material proves ineffective?
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 15	● The program is well-designed to enhance the ability of the lung or vasculature's endogenous stem cells to repopulate injured areas. ● Applicants have revised the animal model per CIRM recommendations. ● Overall the lung aspect of the project is well-designed. ● Key to the project will be in achievement of Milestones 1 and 3 - reduction of inflammation and improvement of pulmonary function in a model relevant to ARDS. Choice of the in vivo model appears a significant improvement over the bleomycin model proposed in an earlier iteration of the application. This should achieve a candidate ready to advance to translation. ● The project has been revised to use a more relevant lung injury model. It's a bit unclear at what stage in the patient pathway they are modeling intervention - before severe injury but after initial insult? Would the investigators envisage giving pre-ventilation? ● Generally, the proposal is well planned but the sample size calculation is not based on any actual measurements. Ten is a reasonable indicative size, but like a clinical trial, it would be important to understand the primary measurements that will be your go/no go criteria, understand the variation in these, the expected Rx effect size and therefore to know whether 10 per group was likely to answer the question. ● The assay of inflammatory markers in response to treatment seems reasonable.

	• There are some concerns about the feasibility of the stem cell effects to be assayed upon treatment with ECM matrices. • Milestones 2 and 4 are potentially interesting but do not seem essential elements of the critical path for translation. Timeline presented in the application is generic and task-oriented and doesn't lay out a clear critical path. • Milestone 4, in particular, adds little. If damaged blood vessels are repaired in vivo, the in vitro migration assay for EPCs adds little value for a project on such an urgent timeline. Study of the migration of MSCs in vitro seems almost irrelevant, especially when there is notable omission of comparable study of known epithelial stem/progenitor populations for the lung. • Migration of progenitors of specialized lung epithelial cells seems to be of low relevance to potential clinical success. • The cardiac comparison and stem cell components detract from the focus of the proposal.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• There is some data to show that the ECM material can transit to lungs, a point of promise. • The team has expertise in development of ECM-based regeneration. • The team is well qualified for work on the biomaterial and to carry out the in vivo experiments. • The applicants have lots of experience and should be able to complete the project. • Probably yes - although I doubt that both ECM therapies are likely to be achievable in the time frame. • Despite reservations, the core in vivo experiments are worthwhile and a positive outcome would justify the project. • The in vivo experiments are the crux - and those alone could fill the 6 months on a tight timeline. • The team appears well qualified for biomaterial development and studies in an in vivo ARDS model. The stem cell biology does not reflect an equally high level of expertise in either lung or endothelial cell lineage biology.
No: 0	*none*

Application #	DISC2COVID19-12059
Title (as written by the applicant)	Development of TMPRSS2 antibody as an antiviral treatment for SARS-CoV-2 (COVID-19)
Research Objective (as written by the applicant)	We want to investigate if TMPRSS2 antibody can be used as an antiviral against SARS-CoV-2 infection on alveolar epithelial type II cells, the stem cell of the distal lung.
Impact (as written by the applicant)	Although broad spectrum protease inhibitors blocks SARS-CoV-2 infection, their toxicities are high and half lives are short. We would validate a novel TMPRSS2 antibody for the treatment of COVID-19.
Major Proposed Activities (as written by the applicant)	• Determine the cytotoxicity of TMPRSS2 antibody. • Determine if TMPRSS2 antibody blocks SARS-CoV-2 infection in vitro. • Investigate the mechanisms by which the antibody inhibits TMPRSS2 that could prevent SARS-CoV-2 cellular entry.
Statement of Benefit to California (as written by the applicant)	There is currently no vaccine and treatments available for COVID-19 and California currently is the 3rd state with most confirmed cases. The development of vaccines might take longer than a year. Antivirals, on the other hand, are likely to be developed and approved faster and are potential treatments for the COVID-19. Here we proposed to investigate the possibility of developing a TMPRSS2 antibody as antivirals for SARS-CoV-2. If successful, we will have a potential treatment for COVID-19.
Funds Requested	$249,997
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	81
Median	80
Standard Deviation	3
Highest	87
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

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	• Targeting the co-receptor is a novel approach to control SARS-CoV-2. • A study of approaches to inhibit activation of spike protein with an antibody approach could provide a useful antiviral therapeutic agent, which may inhibit viral entry into cells. • Targeting viral entry and activation via a monoclonal antibody is a promising approach to limiting SARS-CoV-2 infectivity. • I think it sounds like a reasonable first step to do novel research in an early stage project. • The project represents a first step. There are concerns with antibody delivery and cost. The project might lead to development and testing of small molecule protease inhibitors.

	• It is important to explore novel mechanisms and viral targets, as it may ultimately be necessary to use combination therapy to achieve the best results against SARS-CoV-2.
No: 4	• It's unlikely the antibody, especially at the concentrations required, will catch up with small molecule protease inhibitors delivered orally during this pandemic. • Concerns about drug delivery strategy. • Monoclonal antibodies (mAbs) are unlikely to compete against small molecule inhibitors targeting the same molecule.
GWG Votes	Is the rationale sound?
Yes: 12	• Targeting the co-receptor is a sound approach. • Inhibition of spike protein activation is an attractive target. The use of an antibody to inhibit TMPRSS2 seems helpful. Toxicity and safety will also be assessed. There are some concerns of how an antibody would be delivered to lung effectively in a future therapeutic. • There is good evidence of targeting TMPRSS2. • The proposal is missing TMPRSS2-deficient cells to show that it is critical for viral entry to the cell. Other proteases may potentially facilitate this, ie. need to show there is no redundancy of function. • It is not clear that organoids are needed to show that the antibody actually works. • The SARS-CoV-2 infection of the organoids in preliminary data is not highly convincing. • The use of mAbs do not seem potent enough to warrant this type of treatment.
No: 2	• No evidence was given that TMPRSS2 is required for viral entry and how the antibody effectiveness would be at best if the protease was absent. • Not clear if they have the right lead molecule.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• The proposal is rational and reasonable using a pseudoviral organoid model. • Not clear an organoid system is necessary.
No: 7	• The preliminary data raise some concern that the current lead candidate may not actually be the best candidate. • Lead candidates appear to have low potency. The project would benefit from lead optimization. • There is little rationale for using organoids. • The organoid model system may be overkill for what they need to demonstrate in this application. • Why no animal model? The progression through pre-clinical models is not well described and focuses only on humanization of the antibody. • Knockout models should be used to validate their hypothesis.
GWG Votes	Is the proposal feasible?
Yes: 14	• This work is feasible. • Generally, well designed. • The preliminary data indicates that the planned research is feasible. The high concentration levels needed to inhibit the virus with the current antibody is a concern. • The research plan seems feasible and is clearly presented. There is some concern that the antibody titers required for effective inhibition are rather high. • Very high antibody concentrations are expected to be needed which may reduce feasibility beyond laboratory testing. • The team has all the necessary resources and could execute their proposed activities.
No: 0	*none*

Application #	DISC2COVID19-12083
Title (as written by the applicant)	Shelter in Place COVID-19 Vaccine
Research Objective (as written by the applicant)	A Shelter in Place COVID-19 Vaccine
Impact (as written by the applicant)	To make a competitive and cost-effective COVID-19 vaccine available throughout the world
Major Proposed Activities (as written by the applicant)	● Produce 31Kd RBD. Formulate the vaccine, print the vaccine on the microarray in varied doses, and vaccinate animals using different prime and boost schedules, and assess immune response. ● Determine the optimum antigen and adjuvant dose. ● Determine the optimum dosage schedule
Statement of Benefit to California (as written by the applicant)	In addition to furthering a potential COVID-19 vaccine candidate for the residents of California, the proposed research utilizes a novel delivery system. This delivery system offers room temperature stability for up to 4 months and can be potentially shipped in the mail and administered by the patient at home. These features would enable vaccinations to reach underserved communities in California, the United States, and throughout the world.
Funds Requested	$250,000
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	91
Lowest	75
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: 11	● A safe, effective, and affordable vaccine for SARS-CoV-2 would be a boon to humanity. ● Would be inexpensive and could be used by underserved populations as well. ● New vaccine delivery technologies will be important in preventing COVID-19. ● Accessibility of the delivery technology is high and doesn't require cold storage. ● There is good rationale for using the delivery technology given lack of need for cold chain supply. ● The technology could help increase access to SARS-CoV-2 vaccines. ● A "deliver-it-yourself" at home vaccine could be immensely valuable in a pandemic. ● Relevance to stem cells is not apparent.

No: 3	• I like the novel aspects of the technology but philosophically question the wisdom of putting vaccination of a highly contagious disease in the hands of patients with varying levels of compliance and experience, if I am understanding the shelter in place concept correctly. • Needle technologies have been tried many times and they have failed. There is no innovation here to overcome the physical limitations of such technologies. • Seems like very low stem cell connection - rationale relayed from the applicant is unconvincing. Why should CIRM fund this?
GWG Votes	Is the rationale sound?
Yes: 9	• Another group has shown that the delivery method coated with a MERS protein and adjuvant induced the production of antibodies against the virus. The applicant provides promising preliminary data showing that their technology induces SARS-CoV-2 S antibodies. Needle-less delivery, low production cost, and cold chain-independence are very desirable features of the technology. Could be an advantage for delivery to underserved or vaccine-hesitant communities. • Overall the concept is fine, but this system is not robust. • The technology has been around for a long-time and is well-established. • The rationale is sound, with the caveat regarding the discussion of whether this is relevant to the stem cell purpose of CIRM. • The applicant makes minimal if any effort to justify the idea that this CIRM-relevant research. • But probably has no relationship to stem cells.
No: 5	• Why is the applicant testing vaccine response of all these animal models without any challenge? The rationale not clear. What's the evidence these specific models get infected with COVID-19? • This is not dependent in any convincing way on stem cells. • Unclear if there is any relationship to stem cells. • The work does not investigate stem cell biology. • No relevance to stem/progenitor cell makes eligibility of this proposal questionable
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• The overall plan is reasonable. • Animal models are not infected by SARS-CoV-2, limiting the ability to test the vaccine. • The plan will establish immunogenicity. Disappointing that no virus challenge studies are proposed. The applicants clearly have expertise with the FDA and pre-clinical testing of antibody based vaccines, which is a strength. • It would be preferable to do challenge experiments in animals susceptible to the virus. • Delivery technology is independent of the actual vaccine. • Focus on manufacturability and vaccine delivery is appropriate. • The work would help with cold-chain storage and experiments logically explore this.
No: 3	• No emphasis on the study to analyze for mucosal immune responses and their relevance in neutralizing immunity. • No challenge experiments.
GWG Votes	Is the proposal feasible?
Yes: 13	• The plan involves simple immunogenicity and toxicity studies in several types of animals. • The standard endpoints make sense. • Feasible but won't answer the question if the vaccine works.
No: 1	• The proposed technologies have not been shown to be robust for delivery of vaccines. There is no indication that this team has overcome these limitations.

Application #	DISC2COVID19-12014 #2
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: 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	72
Median	70
Standard Deviation	5
Highest	80
Lowest	60
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: 7	● Determining an effect of the drug on COVID-induced cell death in brain cells i potentially quite interesting, and the preliminary data are very promising. ● Treatment of neural dysfunction by the proposed drug may be a helpful treatment. ● Potentially, but apparently would not impact pulmonary disease.
No: 8	● The application focuses on a particular antiviral drug that has promise based on its development to treat Zika. ● I don't understand the target population and when this would theoretically be used in the disease course. ● Who would the target patient population be? Patients with central nervous system involvement? Pregnant women?

	• The work is too focused on the drug effects without considering the indirect effects (e.g., blood clots and cytokines acting at a distance). • Cost of the drug may be prohibitive and would limit accessibility of the treatment, even if it is effective. • The Underserved Population Impact statement is a bit lacking. They state that they could use iPSCs lines from underserved populations, but do not say that they will. They do not address the cost of delivery of their drug, which could be prohibitively expensive. • In response to the criticism that the drug is too expensive, the applicant claims that the drug is cheap outside the United States. However, it is easy to verify that the cost of the drug is astronomical in at least one international country. Furthermore, the manufacturer pricing of another drug is quite high, so it is hard to see how the price of this drug could become low. • This drug is too expensive to ever be a deliverable therapy for patients with COVID-19 globally - $80,000USD for a course in an international country. • There is concern about the lack of involvement of the drug manufacturer in this study. • Still no letter of support from the drug manufacturer. This suggests that the manufacturer has no interest in this drug. It could be an uphill battle to move this drug forward translationally.
GWG Votes	Is the rationale sound?
Yes: 6	• The drug may have some use in treating brain dysfunction as a somewhat frequently observed complication of COVID-19 disease. • Preliminary data are promising. • The scientific rationale for the proposed experiments is sound, but the greater relevance to COVID-19 is less clear. Analysis of lung cells would have been of great importance to include, for example. • In addition, the drug costs and the lack of demonstration of interest by the manufacturer are seriously problematic.
No: 9	• The investigators suggest the drug will only become active in brain (neuronal) and placental cells. This would have a low level impact on COVID-19 globally where infection is predominantly in the respiratory tract. The effect on developing fetuses is unclear - this is not the same as Zika. • It is not clear whether trans-placental transmission is as important as suggested by the applicant. • It makes a ton of sense to target brain and placenta in Zika. However, Zika didn't kill and it affected the brain and placenta. It doesn't make sense to JUST target the brain and placenta in COVID-19, because the main problem is that COVID kills. So the argument here is perhaps that this is a drug for those who are otherwise asymptomatic, but would have long term neurologic consequences or have pregnancy issues. Currently, that would mean giving this drug to everyone who is asymptomatic. There is no way that's going to happen given cost, side effects, and availability issues. • Unclear if they will be able to obtain drug from manufacturer. The drug could easily be tested in phase 1 since it is already approved. • No letter of support from manufacturer which is where the drug would be sourced from.
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• Study design is clear and well-considered. • The proposed studies are well-designed. • The applicants add controls. ZIKV and Flu, compared to last time. This strengthens the proposal. • Targeting the brain and placenta raises concerns about the broad potency of the drug. • If it only inhibits replication in neurons and placenta, that's great, but it still seems to me the key tissues are lung and blood. If you protect the placenta and brain but the lung and blood are overrun, the brain and the placenta will die too. • The claims of limited enzyme expression seem weak. All of the three critical enzymes appear to be expressed in the lung, per public databases. Therefore it would make more sense to include a new lung cell rather than a new neuronal cell into the protocol. One enzyme appears to be expressed in the lung more than it is expressed in the brain (e.g., UCSC Golden Path server data), the second enzyme more highly expressed in lung than in placenta or brain, and the third is widely expressed.

	• "The drug was negative in previous screenings because this is a pro-drug that requires expression of enzymes are not expressed (or expressed at lower levels) in classical cell types used for screenings, such as Vero cells." So why not use something other than Vero cells?
No: 7	• The plan was not well designed. • There is some concern that the grant was not responsive to previous reviews. • Scientifically, the plan is well designed. But not so on translation.
GWG Votes	Is the proposal feasible?
Yes: 12	• The proposal is scientifically feasible, but the prospects for successful translation do not seem feasible. • Feasible to study in this way. • Did very similar work before; could almost certainly do the work proposed here. • The team is excellent. • Strong team.
No: 3	• There is concern that this notion that this drug has not been shown to have protective effects beyond treatment of brain dysfunction, leading to narrow utility. • The interactions with the drug manufacturer have not been initiated, and thus the future of the project may be in jeopardy.

Application #	DISC1COVID19-12050
Title (as written by the applicant)	Investigating the pathogenesis of cardiovascular complications in COVID-19
Research Objective (as written by the applicant)	This proposal investigates the pathogenesis of cardiac involvement in COVID-19 and identifies therapeutic targets to attenuate cardiac damage.
Impact (as written by the applicant)	The proposal will shed insight into the pathogenesis of cardiac damage in COVID-19, identify effects of SARS-CoV-2 in a cell specific manner and identify novel targets for treating cardiac involvement
Major Proposed Activities (as written by the applicant)	• To study the effects of SARS-CoV-2 on hPSC derived cardiac muscle cells and non-myocyte cells including endothelial cells, smooth muscle cells, cardiac fibroblasts and macrophages. • To study the effects of SARS-CoV-2 infection on the heart and cardiac inflammation in vivo. • To determine the effects of modulating inflammatory response on cardiac injury secondary to SARS-CoV-2 infection.
Statement of Benefit to California (as written by the applicant)	California has been hit hard by COVID-19 and cardiac involvement in COVID-19 is thought to affect 20% of hospitalized individuals and leads to significant increase in mortality. As such, our proposal investigating the pathogenesis of heart involvement in COVID-19 will shed insight into this severe complication of COVID-19 and potentially identify therapeutic targets for attenuating cardiac involvement in COVID-19.
Funds Requested	$149,998
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	57
Median	60
Standard Deviation	6
Highest	65
Lowest	40
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?	6	9	0
Is the rationale sound?	4	11	0
Is the proposal well planned and designed?	4	11	0
Is the proposal feasible?	6	9	0

REVIEWER 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.

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

- The proposal focuses on a clinically important aspect of COVID-19 infection, namely the role of cardiac abnormalities. There is growing evidence that cardiac and more specific myocardial involvement either as a myocarditis phenotype or secondary inflammatory changes contribute significantly to disease progression and outcome. Therefore the project has potentially a high impact.
- If successful, the project could shed light on an important aspect of COVID-19 infection.
- The focus on treating the cardiac phenotype of COVID-19 disease is relevant.
- Although cardiac complications occur in COVID-19 they are not the major cause of death (unlike the investigators' claims). Papers citing underlying heart disease as risk factor have been retracted. It's not clear there is direct cardiac injury rather than cardiac injury secondary to systemic inflammatory response/injury.
- The impact of this work for the treatment of cardiac pathologies resulting from SARS-CoV-2 infection, particularly the interpretations from the animal model, is questionable.
- The significance and impact are somewhat doubtful depending on the association of COVID-19 and cardiovascular injury.
- The proposal may shed some light on the pathogenesis of cardiac injury in COVID-19 disease.
- I do not think cardiac injury is where we should focus in developing treatments for COVID-19. It seems more important to treat the upstream inflammation, which leads to complications including cardiac.
- Infectivity of hPSC-derived cardiomyocytes by SARS-CoV-2 has been reported by multiple groups.

Is the rationale sound?

- Greater insight into the cardiac damage associated with COVID-19 is needed.
- The overall studies are reasonable although the proposed experiments are diffuse and lack clarity.
- The study of a variety of cardiac cell types after infection will yield some useful data on cellular pathology.
- It's not clear that the proposed experiments clearly reflect potential disease mechanisms.
- The proposal lacks a more detailed discussion whether cardiac complications are caused by a primary cardiac infection or secondary to the systematic inflammatory response.
- What is the evidence that cardiac stem cells are infected in patients? Many stem-like cells are resistant to other RNA viruses.
- The use of stem cell-derived cardiomyocytes is well described and justified.
- Pilot data on infecting cells is only for the cardiomyocytes. The different cell types are likely to be differentially susceptible to infection and this will require substantial optimization.
- The proposal lacks data for Aim 2, specifically the generation of an animal model over-expressing ACE2. There will be some significant effort towards generating the construct. It is not clear that there is sufficient expertise or the associated work is sufficiently recognized.
- Not sure the cardiac ischemia model in Aim 3 is valid for COVID-19.
- The selection of the gene for Aim 3 is not well supported in the context of COVID-19 infection. It appears the PI proposes this model because of convenience since it is available in the lab.
- The linkage between the proposed gene and COVID-19 cardiac damage is not well established.

Is the proposal well planned and designed?

- Overall, this will be challenging to complete this work, but some advances in understanding infection mechanisms in cardiac cells will occur.
- The proposal is reasonable but the ability to obtain reasonable data is questionable.
- There is only preliminary data for the infection of cardiomyocytes. The other cell types proposed as part of Aim 1 would need significant optimization. It is not clear how cardiac fibroblasts will be differentiated or obtained.
- Novelty of Aim 1 is low.
- While the proposed platform is available at the institution for Aim 1, the experiments need to be conducted in a BSL-3 environment. The PI should explicitly state that this equipment is available for the duration of the

grant in a BSL-3 lab. Preliminary data demonstrating that the PI can generate data with this platform and a data analysis approach should be described.

- There are concerns about the novelty of Aim 1 since infectivity of cardiomyocytes has been established, although the relevance of this in COVID-19 is not yet clear.
- Technical issues related the generation of the delivery construct. It is not clear if the construct has been generated. This will require some work and the proposed timeline is very ambitious.
- ACE2R transgenic mice don't get cardiac involvement. How relevant is over expression of ACE2R in the heart when it doesn't usually express much ACE2R?
- The preliminary data are modest and it is not clear how the ischemia model would be relevant to COVID-19 disease.
- Will the transgenic ACE2 be immunogenic in mice? Will that complicate interpretation. The transgenic mouse model could delay the project.
- The ACE2 model will permit cardiac tissue infection, but cardiac damage may not result from infected cardiac tissue. There are concerns about how accurately this mouse may model the disease.
- There is not sufficient justification for the experiments using the KO mouse model. It is not clear that this mouse model and more generally Aim 3 will provide important novel insights.
- The Aim 3 study is well designed, with the caveat that the mouse model may not recapitulate the disease.
- No preliminary data for Aim 3.
- The proposal lacks a description of the data analysis. How will the different types of data be integrated and interpreted?
- No information on how the data will be analyzed or interpreted.

Is the proposal feasible?

- Overall, the proposal is unlikely to yield interesting findings that would be useful for the treatment of cardiac related SARS-CoV-2 pathologies.
- The proposal is overly ambitious as it relates to all three aims.
- The project consists of 3 fairly distinct aims that are not sufficiently integrated for this early stage discovery mechanism.
- Milestone 1 is feasible; not sure about the other two.
- A huge volume of work using very complicated models is proposed for a one year period.
- The project is likely achievable if the mouse model can be established and infected.
- There is some concern that infection in animal models will feasible, and it will depend upon how well ACE2 can be exposed in mice using the proposed delivery approach, and whether this delivery of ACE2 will create enough target cells in cardiac tissues.
- It is not clear the investigators have the vector and there is no description of the ACE2 receptor in the different tissues in this mouse model in their hands.
- The applicant doesn't describe clear mechanisms for delivery of vector - in the published paper by another group this was given directly to heart.

Application #	DISC1COVID19-12079
Title (as written by the applicant)	Targeting a key regulator in naïve CD4+T cells to treat cytokine release syndrome
Research Objective (as written by the applicant)	We aim to devise a potential treatment of patients with COVID-19 suffering from a cytokine storm by targeting a key gene regulator in T-helper progenitor naive CD4+T cells.
Impact (as written by the applicant)	The proposed treatment strategy is expected to be robust and specific in reducing massive production of cytokines and efficient in saving lives of patients with COVID-19 on ventilators
Major Proposed Activities (as written by the applicant)	• Using human peripheral blood mononuclear cells, we will study and evaluate the effects of targeting the gene regulator on T cell activation and cytokine production. • We will disrupt the function of the gene regulator in isolated naive CD4+ T cells and study the effects on cytokine production and differentiation into multiple lineages
Statement of Benefit to California (as written by the applicant)	Although dexamethasone has shown some positive effects in saving lives of patients with severe COVID-19, there are still a large percentage of patients who cannot be saved. When patients suffer from a cytokine storm, we need to quickly turn off massive cytokine production to save normal tissues, including lungs from injury. The methods we proposed, once fully validated, most likely stop cytokine overproduction and save lives of patients regardless of their sex, age, and ethnic background.
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	13	0
Is the rationale sound?	2	12	0
Is the proposal well planned and designed?	4	9	0
Is the proposal feasible?	9	5	0

REVIEWER 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.

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

- The concept of cytokine release syndrome/storm (CRS) is not well validated in humans with COVID-19, and is certainly not a feature in most patients. There are already drugs in trials to target CRS.
- Targeting this pathway to reduce cytokine storm and SARS-CoV-2-associated ARDS is a novel idea. If correct, it could be translated to a therapy since inhibitors are already known as long T cells are the major sources of the cytokines that cause SARS-CoV-2-associated ARDS. But a big weakness is that the connection between T cells and SARS-CoV-2-associated ARDS has not been established.
- The idea explored in the proposal is novel. However, if successfully realized it will not address an unmet medical need. A few therapeutic agents on a market and in clinical development have successfully demonstrated efficacy in combating CAR-T cell therapy associated CRS.
- Only a minor part of COVID-19 is addressed, and there may be significant toxicity.
- Could be useful in controlling CRS.
- Concern about specificity of the pathway and the extent of the applicability to COVID-19.
- It is not clear that existing cytokine release system drugs are not effective for treating COVID-19.
- Little focus on stem/progenitor cells.
- The connection with stem cell science is somewhat of a concern. There are concerns that the approach will cause broad side effects.

Is the rationale sound?

- Preliminary data support the rationale.
- Preliminary data supports role for the pathway in T cells.
- The ability to modulate chromatin in T cells and T cell activation has some bearing on COVID-19 immune responses.
- The rationale for the mature T cell response is not extensively supported by the literature.
- There are significant concerns about broad toxicity as the proposed therapeutic should affect a broad (if not all) cell types.
- The global mechanism of action of this pathway makes it likely that blocking it will cause off target effects. The real possibility that inhibition will reduce the capacity of CD8+ T cells or NK cells to kill the virus was not addressed.
- Some cytokines may not originate from T cells; this may have wide ranging pleotrophic effects on immune cells.
- The rationale does not significantly supports a role of stem/progenitor cells, because it relies mostly on a function of mature T-cells. Even though the pathway is described in naive T-cells, it is not clear if drug will act in vivo mostly on mature T-cell types or T-cells with progenitor/stem cell qualities.
- There is minimal relevance to/dependence on stem cell technology.
- The connection to stem cell science is only tangential.

Is the proposal well planned and designed?

- The project appropriately planned. However it is less likely to meet the objective of the program announcement.
- It is far from clear that this approach is likely to result in a reduction in SARS-CoV-2 associated ARDS, or to be safe.
- This drug will have multiple off-target effects.
- Toxicity should be addressed more centrally in the plan.
- Not clear there is stem cell relevance.
- The range of individuals and populations to be tested is responsive.

Is the proposal feasible?

- The project is feasible as described.

- The team is qualified to perform the work.
- Feasible to do.
- They should be able to carry out the experiments.
- The plan has a very limited scope. It should determine whether inhibition blocks cytokine production by human naive T cells or Th17 cells.
- The application (translation) of this therapeutic approach may be greatly difficult due to anticipated prevalent side effects.

Application #	DISC2COVID19-12071
Title (as written by the applicant)	Study of anti-inflammatory and anti-viral adipose-stem-cell secretory factors as potential treatment for the respiratory syndrome induced by COVID-19
Research Objective (as written by the applicant)	We propose to derive, standardize, and scale up secretory factors from adipose stem cells through a technology that allows us to obtain consistent levels of anti-inflammatory and anti-viral factors
Impact (as written by the applicant)	Anti-inflammatory and anti-viral factors derived from human adipose stem cells will be used to treat severe acute respiratory syndrome (SARS) induced by COVID-19 infection
Major Proposed Activities (as written by the applicant)	• Isolation and expansion of adipose stem cells (ASCs) from human donors • Plating ASCs in plastic disks that will be placed into controlled and dynamic systems such as bioreactors to optimize production of secretory factors • Quantification and characterization of secretory factor patters using methodologies that quantify the factors through specific antibodies • Testing the toxicity and effectiveness in the laboratory using sensitive cells and in animal models of COVID-19 infection
Statement of Benefit to California (as written by the applicant)	The sate of California has reported about 220,000 cases of people infected by COVID-19. About 6,000 patients have died because of a severe acute respiratory syndrome (SARS). The objective of this proposal is to produce, standardized, and test the anti-inflammatory and anti-viral effects of soluble secretory factors derived from adipose stem cells (ASCs) and, in this way, treat the respiratory syndrome induced by COVID-19 and reduce the mortality.
Funds Requested	$199,700
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: 0	*none*
No: 15	• This is not a good field for an application of their technology.

	• There is no evidence presented that this product has any biological activity or anti-viral effect on any virus. • There is no information about any product specification. • There is concern that the proficiency of this group for stem cell research is not strong, nor the ability to complete aspects of the cellular assays demonstrated. • The path to translational impact is unclear.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 15	• There is no pilot data that is relevant to their hypotheses. • There is next to no rationale presented for why the investigators think this is superior biologically to any of the existing cell-based therapies, especially MSCs being tested. • There is little evidence that the secreted cytokines have any relevance to SARS-CoV-2 infection. • There is no evidence that the investigators understand lung biology or the pathogenic mechanisms of SARS-CoV-2. They confuse SARS-CoV-1 and 2 throughout the application. • Not clear what product they are trying to develop. What is a "physiological balanced" cytokine mix? • The plan to rigorously assess secreted factors from adipose stem cells seems problematic.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• There is no experimental detail on either the in vitro or in vivo studies. • There is no info regarding product specification/release criteria. • There is no info regarding numbers of experimental replicates. • Very difficult to follow this application. Many details are missing. • The presentation of the grant is confusing, and therefore there is concern about the organization and completion of proposed research. • Relevant models are not being used. • The experiments do not directly address the key questions in the field.
GWG Votes	Is the proposal feasible?
Yes: 0	*none*
No: 15	• Unclear that the applicants know enough about SARS-CoV-2 to carry out the work. • Expertise in virology and stem cells is lacking. • There is no information that the authors understand lung biology/ARDS or SARS-CoV-2 infection. • No information to suggest they have access to a BSL-3 lab to do the in vitro work (nor indeed any info to suggest they realize that they need access to BSL-3 to work with this pathogen). • There is no access to BSL-3. • No correspondence from CRO to confirm agreement to undertake the work.