APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
DISCOVERY APPLICATIONS												
DISC2COVID19-11947	Persistent Off-the-Shelf meACE2-CAR-IL-15 NK Cells Derived from CD34(+) Cord Blood Stem Cells to Prevent and Treat COVID-19	$150,000	**Y**	95	94	3	90	100	15	0	Cell therapy	Develop an adoptive NK therapy that uses ACE2 and IL-15 to target SARS-CoV-2 infected cells
DISC2COVID19-11920	Application of PGE2/BPV, a muscle stem cell targeting therapeutic, to the treatment of COVID-19 associated diaphragm atrophy	$149,996	**Y**	90	91	5	80	96	14	1	Small molecule drug	Use FDA approved drug combinations that activate endogenous muscle stem cells to stimulate diaphragm regeneration
DISC2COVID19-11941	Identifying HLA Class I Restricted Peptides That Induce CD8+ T Cells Against SARS-CoV-2	$149,999	**Y**	86	86	3	80	92	13	2	Vaccine development	Identification of peptides for a vaccine that will induce both an antibody and T cell response
DISC2COVID19-11928	Develop MTL-CEBPA by modulating hematopoietic stem cells for the treatment of cytokine storm in COVID-19 patients	$150,000	**N**	83	84	4	80	95	4	11		
DISC2COVID19-11782	Using hiPSC-derived lung organoids, a clinically-relevant system, to validate & winnow a list of approved drugs that inhibit SARS-CoV-2 cytopathy	$150,000	**N**	82	82	4	75	90	4	11		
DISC2COVID19-11781	Advancing COVID-19 Polytherapy to the Clinic by Minimizing Liver and Cardiac Toxicity	$149,999	**N**	82	81	4	70	85	2	11		
DISC2COVID19-11954	Development of monothiol human thioredoxin-1 (ORP100S) as an inhaled treatment for COVID-19 respiratory disease	$149,999	**N**	77	75	6	60	80	0	15		
DISC2COVID19-11953	Mesenchymal stem cell derived exosome repression of SARS-CoV-2	$150,000	**N**	75	74	6	65	80	0	14		
DISC2COVID19-11798	Small molecules to enhance T memory stem cell activity in the elderly to fight Coronavirus infection	$149,500	**N**	65	65	7	50	75	0	15		
DISC2COVID19-11919	Development of a new targeted senolytic drug for the treatment of chronic respiratory conditions in Covid-19 survivors	$149,085	**N**	65	63	5	50	70	0	15		
DISC2COVID19-11910	Engineered mesenchymal stem cell-derived extracellular vesicles for the treatment of COVID-19 cytokine storm disease.	$149,999	**N**	-	-	-	-	-	0	15		
DISC2COVID19-11927	Mesenchymal Stem Cell-derived Mitochondria-rich Microvesicles for Myocardial Inflammation in Cytokine Release Syndrome in COVID-19	$149,999	**N**	-	-	-	-	-	0	15		
DISC2COVID19-11937	Novel Adult Pluripotent Stem Cells for Treatment of COVID-19 by Enhancing Tissue Regeneration and Immune Modulation	$149,820	**N**	-	-	-	-	-	0	15		

Application #	DISC2COVID19-11947
Title (as written by the applicant)	Persistent Off-the-Shelf meACE2-CAR-IL-15 NK Cells Derived from CD34(+) Cord Blood Stem Cells to Prevent and Treat COVID-19
Research Objective (as written by the applicant)	To develop and characterize meACE-2-CAR-IL15 NK cells expressing a mutated ACE2 and IL-15, allowing specific killing of SARS-CoV-2-infected cells and long in vivo persistence of the engineered cells.
Impact (as written by the applicant)	To provide a timely, novel, and effective cell therapy for COVID-19, which has no FDA-approved vaccines and only remdesivir has received an emergency-use approval.
Major Proposed Activities (as written by the applicant)	• To further optimize expansion of umbilical cord blood (UCB) hematopoietic stem cells (HSCs) and engineer the expanded with the meACE2-CAR-IL15 retrovirus. • To differentiate UCB HSCs transduced with meACE2-CAR-IL15 into NK cells, followed by cell expansion. • Proof of concept: In vitro evaluation of meACE2-CAR-IL15 NK cells. • Proof of concept: In vivo evaluation of meACE2-CAR-IL15 NK cells. • Manuscript submission for publication & preparation for an INTERACT meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	SARS-CoV-2 has presented as a major public health threat in the past. A new SARS, COVID-19, started in December 2019 has rapidly disseminated worldwide including California with mortality as high as 20% in the elderly and other more vulnerable populations. At present, worldwide COVID-19 patients have over 3.6 million with over 250,000 deaths. Currently, there are no approved COVID-19 vaccines and only remdesivir has received an FDA-approval for the treatment of COVID-19.
Funds Requested	$150,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 95

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	94
Median	95
Standard Deviation	3
Highest	100
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• If successful, this approach could have a major impact on COVID-19 and would also open up avenues for using this platform against many other diseases. • NK cells are currently being used in COVID-19, this proposal would be an improved version. • Excellent project, great team and significant potential for impact.

No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	● The ACE2 expressing NK cells should be able to target SARS-CoV-2 infected cells with spike protein on the surface. The expectation being an overall reduction of infection. The investigators provide extensive preliminary data to support their proposal. ● Yes, although the data on the CAR construct is limited. ● Strong rationale supported by preliminary data. ● NK CAR-T cells targeted to the spike protein on infected cells is a highly rational approach.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 15	● Very thoughtfully constructed research plan and the investigators have considered alternative approaches if they meet stumbling blocks. ● The milestones approach of moving from stem cell expansion and transduction to product testing to in vivo proof of concept study is very logical and appropriate. ● Well planned - clear logical progression of milestones. ● Significant study with solid rationale. ● Good preliminary data. ● Extensive expertise in NK cell biology and NK Cells. ● Applicant has a history of bringing products to clinics. ● I was impressed by their thorough responses to the pre-review comments. ● Concerns over toxicity and efficacy in the mouse model temper enthusiasm. ● Some changes may need to be made to construct prior to clinical translation e.g. need justification of all components of construct (e.g. marker genes). ● Very logical development plan. ● There is a plan to move towards clinic. ● Considered scaleup. ● Lentiviral vectors pseudotyped with VSV-G do not transduce NK cells - will need to use another pseudotype.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	● Fantastic team of investigators and great environment. They should be able to complete the project in 1 year. ● Great team and environment. ● Previous clinical experience, team can manufacture and scale up. ● Excellent team.
No: 0	*none*

Application #	DISC2COVID19-11920
Title (as written by the applicant)	Application of PGE2/BPV, a muscle stem cell targeting therapeutic, to the treatment of COVID-19 associated diaphragm atrophy
Research Objective (as written by the applicant)	Intramuscular delivery of 2 repurposed FDA approved drugs to activate diaphragm stem cells to augment regeneration and restore strength to COVID-19 patients with diaphragm atrophy from ventilation.
Impact (as written by the applicant)	Currently effective treatments are lacking for diaphragm atrophy due to ventilation to treat COVID-19. Our treatment will promote full recovery of such patients.
Major Proposed Activities (as written by the applicant)	• To establish efficacy of PGE2/BPV treatment to stimulate stem cells to regenerate muscle in a murine muscle atrophy model that mimics the atrophy seen in COVID-19 patients. • To demonstrate sensitivity of human diaphragm muscle stems cells to PGE2 • To assess the efficacy of PGE2:BPV formulation in enhancing stem cell function to counter diaphragm atrophy in ventilator induced diaphragm dysfunction
Statement of Benefit to California (as written by the applicant)	3500 Californian COVID-19 patients have been hospitalized, and 1200 require the Intensive Care Unit (ICU). While in the ICU, many are put on mechanical ventilation (MV) as they cannot breathe independently. Even relatively brief periods of MV result in diaphragm weakness that makes it difficult to wean patients from the ventilator. COVID-19 patients as they spend weeks on MV. Our therapy stimulates diaphragm stem cells to promote regeneration. This will improve recovery and decrease healthcare costs.
Funds Requested	$149,996
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	5
Highest	96
Lowest	80
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: 15	• Ventilator-induced diaphragmatic dysfunction (VIDD) involves muscle atrophy and is a serious complication arising from long-term mechanical ventilation. This is a serious problem for COVID19+ individuals who are placed on mechanical ventilation. They are on ventilation much longer than individuals with other respiratory conditions and more likely to suffer serious adverse effects. • This project aims to develop a treatment as a potent inducer of muscle stem cell proliferation to increase the mass and strength of atrophied diaphragm that occurs when ventilation is used to treat COVID-19. • Targeting muscle atrophy, specifically the diaphragm, compromised in COVID-19 patients requiring ventilator support is a novel approach to improve/restore muscle integrity.

	• High probability of advancing to translational stage with a strong candidate for a significant unmet need in COVID-19 patients who require ventilation.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• Study is based on the rationale that prostaglandin E2 and Bupivicaine synergize to stimulate endogenous muscle stem cells to participate in a regenerative response that augments muscle force. • The novel proposed formulation of 2 currently approved drugs has been shown to stimulate human muscle stem cells and rodent muscles in vivo. • Directly addresses the need to restore strength of diaphragm muscle (and potentially others) after atrophy due to extended period of ventilation. • The applicant provides extensive preliminary data to support the proposal goals.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• Clarity and logic of progression from milestone to milestone are outstanding. • Well written and logical. • Avoid Aim 1 to move more quickly with the mouse model. • The experiments are well-designed and the aims fit together nicely. • If they could complete Aim 1 quickly, it doesn't matter if it isn't the most efficient plan possible, they could get moving and make the most progress by being funded now, given the 150K budget.
No: 1	• The major strengths of this proposal are the preliminary data generated to support another indication together with the availability of a relevant animal model to mimic COVID-19. • In vitro studies in human diaphragm muscle stem cells are also highly relevant. • Major concerns are the questionable translational value of the in vivo murine model and limited details on study protocol/scope of study in the animal model, which is relevant to the disease indication. • Translation to clinic could be accelerated by focus on the in vitro milestone and by understanding feasibility of ROA, dose and timing in the animal model.
GWG Votes	Is the proposal feasible?
Yes: 15	• Candidate compound already identified, based on prior studies with closely related combination. • Experiments very well designed with good alternatives if problems arise. • The work can be completed within the timeframe and could lead to a drug combination ready for clinical trials. • Milestones are likely to be achieved.
No: 0	*none*

Application #	DISC2COVID19-11941
Title (as written by the applicant)	Identifying HLA Class I Restricted Peptides That Induce CD8+ T Cells Against SARS-CoV-2
Research Objective (as written by the applicant)	A vaccine to help prevent COVID-19
Impact (as written by the applicant)	There is a clear need for a vaccine to prevent the spread of the COVID-19 coronavirus that is effective, can be rapidly produced and can be scaled for worldwide demand.
Major Proposed Activities (as written by the applicant)	• Identify structural regions of SARS-Cov-2 that can inhibit viral entry • Identify potential regions that can induce CD8+ T cell responses • Confirm which regions produce peptides that bind to human HLA Class I molecules • Confirm which peptides induce antibodies inhibit viral entry using hematopoietic and bronchioalveolar stem cells • Identify which peptides induce CD8+ T cells that lyse cells containing Spike protein from SARS-CoV-2
Statement of Benefit to California (as written by the applicant)	This research will result in a vaccine candidate that can be made part of an overall vaccine composition that will protect California citizens from contracting COVID-19, allowing its people to interact freely and resume normal activities.
Funds Requested	$149,999
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	92
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The applicant is taking a novel approach to identifying the best epitopes for vaccines aimed at generating an optimal, long-term CD8 T cell response to COVID-19. This could have great, near-term impact on the optimization of COVID-19 vaccines and for future pandemics. • Targeting of nonlinear epitopes may afford a valuable alternative approach to promote immunity against SARS-CoV-2. • The knowledge of the peptides could be valuable for vaccine development. • Exciting concept. • There is currently a significant need for a vaccine to control the COVID-19 pandemic. Developing CD8-targeted peptide vaccine will be essential to provide protection for long duration from SARS-CoV-2. • A specific focus on cellular immune response would positively impact current approaches to COVID-19.

No: 1	• Interesting project but peptide vaccine responses have not shown robust success.
GWG Votes	Is the rationale sound?
Yes: 15	• The proposal uses proteasome produced fragments from the spike protein to predict better CD8 T cell epitopes. This is based on recent, very interesting insights from their own work in cancer and support the approach. • The concept that CD8 T cells will provide protection against SARS-CoV-2 is demonstrated in animal models of SARS infection. T cells are shown to persist for longer duration than antibodies following recovery. The technology can be used to identify T cell epitopes and improve T cell immunity. • Strong preliminary data with tumor peptide antigens. • TCR responses targeting SARS-CoV-2 is a rational response.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• The project is very well planned and they predict having actionable insights at the end of the project. • Novel approach, high risk, potentially high reward. • History of research on tumor specific peptides to induce response. • Two of the primary reviewers noted a significant concern is the failure to include HLA types representative of minority populations in the US that are being disproportionately impacted by COVID-19. • Excellent team.
No: 2	• Aim 3 seems challenging. • HLAs from minority populations should be included. • The project does not focus upon a candidate that has potential for success.
GWG Votes	Is the proposal feasible?
Yes: 15	• The timeline is aggressive but achievable and the team is strong. • Concern that Aim 3 is not achievable. Limited discussion of pitfalls. • Concern regarding realistic timing for stem cell generation of CD8 T cells. • The data from the study would be interesting even if not candidate focused.
No: 0	*none*

Application #	DISC2COVID19-11928
Title (as written by the applicant)	Develop MTL-CEBPA by modulating hematopoietic stem cells for the treatment of cytokine storm in COVID-19 patients
Research Objective (as written by the applicant)	Our objective is to develop MTL-CEBPA, a small activating (sa)RNA drug that activates C/EBPα and modulates HSC differentiation, for the treatment of cytokine storms in COVID-19 patients.
Impact (as written by the applicant)	By priming early adaptive immunity and targeting a broader range of cytokines further up in the pathway, MTL-CEBPA will mitigate cytokine storm and get better clinical outcome for COVID-19 patients.
Major Proposed Activities (as written by the applicant)	• Evaluate the therapeutic efficacy of MTL-CEBPA in vivo animal model • Establish preclinical safety profiles of MTL-CEBPA to support expedient clinical translation
Statement of Benefit to California (as written by the applicant)	The urgent need for safe and effective drug treatment in California is highlighted by the fact that California ranked 5th among the 50 states in the number of COVID-19 diagnoses. As of May 5, 2020, there are a total of 54,937 positive cases and 2,254 deaths in California. To address the immediate need to reduce the rising mortality, we propose a cutting-edge, targeted strategy that may offer a safer and more effective treatment to suppress cytokine storm in severely ill COVID-19 patients.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 83

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	83
Standard Deviation	4
Highest	95
Lowest	80
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: 15	• Dysregulated inflammation and associated cytokine storm is linked to severe COVID19 and poor clinical outcomes. The current application aims to moderate SARS-CoV-2 induced inflammation using MTL-CEBPA as a broad-spectrum anti-inflammatory agent by altering the differentiation of human hematopoietic stem cells. • Major need to prevent/control cytokine storm associated with COVID-19. • The drug could be repurposed for SARS-CoV-2. • Potential to specifically modulate immune cells would have impact for COVID-19 patients. • Strength: the candidate is already developed for different indications (currently in clinical trials in oncology), has good safety profile and will be repurposed for COVID-19. It may have a significant impact in COVID-19 related ARDS, which is a big unmet medical need. • The presented project is not exactly "stem cell technology", because in the context of ARDS the underlying mechanism of therapeutic action is a direct impact on mature blood cells.

No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 10	● The rationale is based on the fact that CEBPa targeting small double stranded RNA is a a priming factor at the HSC level where it actively promotes myeloid differentiation and counteracts lymphoid lineage choice, thus modulating immune response. ● Some questions about whether the product will act quickly enough to treat ARDS. Stem cell targeting may not be the most effective strategy in acute disease like COVID-19 ARDS.
No: 5	● The rationale, presented by authors is a modulation differentiation of hematopoietic stem cells (HSC) and blocking proinflammatory cytokine storm by "pushing the myeloid cells into a non-inflammatory phenotype". However, underlying cause of cytokine storm in COVID-19 related ARDS is a massive rapid acute systemic release of cytokines by mature blood cells. ● Modulation of differentiation of HSC as a mechanism and the rationale for a blockade of acute cytokine release syndrome is not relevant for COVID-19. Development of such acute condition as COVID-19 ARDS takes a few days, but replenishing of myeloid blood lineages from HSCs takes weeks. ● Evidence that hematopoietic stem cells are the best, or even a feasible, target is lacking. ● The stem cell aspects of this proposal are not well motivated. ● The anti-inflammatory effect of MTL-CEBPA was demonstrated in cancer patients, who have chronic inflammation, not acute. Therefore, it could not be extrapolated to the rapid short-term release of cytokines in such acute condition as COVID-19 related ARDS. ● Preliminary data supporting cancer indication.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	● Based on mechanism of action in ARDS, the focus of the first milestone experiments should be shifted from CD34 cell-based assays to testing the impact of the drug on mature immune cells, such as granulocytes and monocytes. CD34 cell differentiation platform could also be used but as supplementary. ● Where MTL-CEBPA treatment mediated accumulation of neutrophils and macrophages will increase inflammatory response is not well understood.
No: 4	● Cumbersome, complex approach, and may not impact cells most important to achieve desired effect. ● Data on acute inflammation needs to be included. ● Proposed animal model may not be relevant to acute disease.
GWG Votes	Is the proposal feasible?
Yes: 14	● This application will be strengthened by including a virologist/viral immunologist to support infection studies. It appears that the applicant institution BSL3 facility is only equipped to carry out in vitro studies. Thus, it is unclear how and where animal studies will be carried out. ● Capacity to do in vitro but not in vivo COVID-19 virus studies at applicant institution. ● Addition of viral expert recommended for the project team. ● I was impressed that this could be translated quickly if these studies were successful. ● Drug is currently available. ● The project looks feasible.
No: 1	*none*

Application #	DISC2COVID19-11782
Title (as written by the applicant)	Using hiPSC-derived lung organoids, a clinically-relevant system, to validate & winnow a list of approved drugs that inhibit SARS-CoV-2 cytopathy
Research Objective (as written by the applicant)	We will derive hiPSCs and differentiate them into 3D lung organiods, macrophages and endothelial cells which will be co-cultured into a multi-tissue organoid.
Impact (as written by the applicant)	The impact will be the avoidance of an animal model once an approved medication hit has been verified by our model. The medication can then be immediately used in a clinical trial.
Major Proposed Activities (as written by the applicant)	• Human iPSC derived lung organoid development from different genders and ethnicities and characterization. • Human iPSC derived macrophage and endothelial development and co-culture. Exposure to vaping chemicals. Baseline molecular characterization of multi-tissue organoids. • Infect iPSC derived multi-tissue organoid with live SARS-CoV-2 and characterize genomic and proteomic effects. • Determine cytotoxic profile of drug 1 after infection of iPSC derived multi-tissue organoid. • Determine cytotoxic profile of drug 2 after infection of iPSC derived multi-tissue organoid. • Determine cytotoxic profile of drug 3 after infection of iPSC derived multi-tissue organoid.
Statement of Benefit to California (as written by the applicant)	This research will benefit the State of California and its citizens by utilizing an authentic human multi-tissue organoid model to test approved drugs that showed decreased cytotoxicity after infection with SARS-CoV-2 in a primary screen. This allows us to bypass an animal model since safety profiles have already been tested in these approved drugs. If the secondary screen is successful, we can immediately use it in a clinical trial in California.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 82

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

Mean	82
Median	82
Standard Deviation	4
Highest	90
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: 14	• Lungs represent the main organ damaged by the SARS-Cov-2 virus. However, the mechanisms by which the virus affects lung function is not really clear. Indeed, it is unclear which lung cells express the virus receptors ACE2 and under which circumstances (age,smoking etc.). In addition, we don't know the mechanisms by which the virus damages the lung. It could be a secondary effect induced by the cytokine storm. In addition, the virus could target the vascular system.

	• Targeting lung for COVID-19 makes sense. • The organoid cultures could be used for many other purposes. • If successful, the proposal could help identify new drug candidates for translation. • Important to screen drugs in human system. • Novel testing method using human cells. • This is an exciting idea linking the immune component with lung model. • Use of lung organoids to validate HTS of potential antiviral compounds against SARS-CoV-2 offers a significant benefit compared to cell culture models. • Incorporation of immune cells into multicellular organoids is exciting. • Efficacy of organoid infection by SARS-CoV-2 or pseudovirus is not well established. • Might not be representative of SARS-CoV-2 infection. For example, does not emulate vasculature.
No: 1	• Question over whether vasculature can be modeled using this system.
GWG Votes	Is the rationale sound?
Yes: 12	• Conceptually the project is very interesting. • The proposal is based on the rationale that lung organoids offer more relevant models to test antiviral compounds for further development for clinical use in humans. • Organoids may be better than cell lines or animals for testing. • It is not clear if organoids represent the lung epithelium well (e.g. no vasculature modeling). • Some concern that epithelial cells used were not tested for ACE2 expression. Vasculature important but it is not clear that it can be modeled in this model. • It may take several days to weeks to generate the organoid and the cells to express ACE2 and TMPRSS2. • The model is not validated. • Excellent team with good background in organoids and HTS. • Exciting HTS data. • Good preliminary data.
No: 2	• The preliminary data is not strong enough for the proposed aims. The organoid system is not developed well enough. • Minimal preliminary data to support proposal.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• Very solid team. • Sound scientific basis. • Very good team. • Development of AT2 cells is challenging.
No: 7	• Unclear whether proposed models will adequately address disease complexity. • Unclear the cells in the organoid express ACER or TMPRSS2 - is this not in the RNA-seq already available? Therefore it is unclear virus infection can be established. • The data on vascular structures in the distal organoids are not compelling - unorganized cells • The choice of immune cell is questionable and missing key other components of the lung. • Too many variables being introduced to allow this to be delivered in 12 months (age, gender, vaping, ethnicity) • Not possible to complete in 12 months. No priorities set. • Strong group. • The project plan seems unrealistic for the proposed timeframe. • The proposal needs to be streamlined and more focused for this funding mechanism. • Too ambitious for one year - even with high level resources • Too ambitious. Lab and staffing with funding does not appear to be sufficient to generate necessary throughput. • The volume of work is unrealistic.
GWG Votes	Is the proposal feasible?
Yes: 5	*none*
No: 9	• There is concern that not all the proposed work can be completed in time. • The project is too ambitious for the one year timeline. • Ultimately very interesting scientific questions but overly ambitious to achieve this in a 12 month period. • Very ambitious proposal; unrealistic amount of work. • Completion of range of studies proposed unlikely in the requested timeframe. • The volume of work makes this project not feasible.

	• Would like to see a more modest proposal, with careful attention to scientific design elements such as inclusion of controls (e.g., proof of concept with known antiviral against another virus). • Given that they are an experienced lab with good expertise, and there was enthusiasm about the many of the aspects of the award, I lean towards giving them a 150K opportunity. • Donor source not identified. • Budgets are not adequate.

Application #	DISC2COVID19-11781
Title (as written by the applicant)	Advancing COVID-19 Polytherapy to the Clinic by Minimizing Liver and Cardiac Toxicity
Research Objective (as written by the applicant)	Integrated human cardiac and liver microphysiological systems (MPS) for screening the toxicity of viable COVID-19 therapeutics.
Impact (as written by the applicant)	Reduction of patient risk with improvised COVID-19 polytherapy treatments. Minimize the time and cost to bring COVID-19 drugs to patients.
Major Proposed Activities (as written by the applicant)	• To use our cardiac tissue chip and in silico workflow to predict drug-induced proarrhythmia of FDA-approved drugs currently being clinically tested for COVID-19 therapy. • To use the liver tissue chip to define the hepatic toxicity of FDA-approved drugs currently being clinically tested or considered for COVID-19 therapy. • To use our integrated cardiac and liver tissue chips to predict drug-induced proarrhythmia of FDA-approved drugs currently being clinically tested or considered for COVID-19 polytherapy.
Statement of Benefit to California (as written by the applicant)	We will create a patient specific heart and liver microphysiological systems (i.e., tissue chips) that will have a significant impact on the development and safety of COVID-19 drugs, especially in combination therapy. If successful, we can reduce the cost and time needed to bring new COVID-19 drugs to clinic, thereby improving the lives of many Californians and significantly reducing the cost to California's healthcare system.
Funds Requested	$149,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 82

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

Mean	81
Median	82
Standard Deviation	4
Highest	85
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	2
(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	• Investigators propose to use human induced pluripotent stem cell (hiPSC)-based in vitro microphysiological systems (MPSs) of cardiac muscle and the liver on a microfabricated and fluidically integrated platform to test safety and toxicity of the compounds that have potential therapeutic value. • An assay that could screen COVID-19 drug candidates for toxicity could be very beneficial in eliminating promising compounds from clinical trials. • We need to understand the cardiotoxicity and hepatotoxicity of drugs in order to prioritize them for clinical advancement. • The application is mainly technology based rather than providing any prophylactic and therapeutic options. • Understanding drug-drug interactions is important.

No: 3	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• Project is based on the rationale that the cardiac and liver MPS serve as tools to predict cardiac and hepatic toxicity, including drug-drug interactions. • The drugs that investigators are planning to test have either been examined for safety or currently in trial. • The potential application of these tools is well described. • Significant preliminary data are presented. Ability to translate iPS-derived cardiomyocyte results to mature cardiomyocyte conduction abnormalities is appealing. • Preliminary data focuses on drugs that already have really well known effects. Can this system predict effects that are not already known? Consider building something like a "training" and "test" set to evaluate whether there is any predictive utility. • It is critical to have a discussion of the limitations on throughput of this technology, both during the funded period, as well as the eventual upper limit on throughput when deployed translationally. • It seems unlikely that the throughput will ever rise beyond several dozen. That means this cannot be seen as a "screening" technology. Rather it is a method to eliminate well-established candidates from a pipeline. • Because of lack of throughput, true drug-drug-interaction screening cannot be done. The only interactions that can be tested are those that are already highly suspected to interact, so unexpected interactions will no be picked up by this technique. • Testing a wide range of doses also requires high throughput. • The computational sub-aim probably isn't necessary, particularly given the amount of funding offered by this funding mechanism. • If the computational aim is retained, it needs to be described in more detail, without jargon. In particular, the phrase "inverting the data" is unclear, even if the cited reference is read. Do the authors mean "inferring model parameters from the data?" • The computational aim lacks experimental validation and controls. For example, in the cited paper, only known cardio-modifying drugs are used. No controls that are known not to affect the heart are used. This lack of good experimental control in published works makes me desire to see more clear emphasis and detail on experimental design and controls in the proposal.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• The overall design is clear and endpoints for milestones are quantifiable. • The applicants should describe the system throughput (numbers of different drugs that can be screened, replicates and different donors) and how population variability is incorporated.
No: 5	• Please reduce the number of acronyms, they make the proposal difficult to read. For example, it is unclear whether "cardiomyocyte maturity" needs to be abbreviated, and if so, why MM is used as the acronym. Watch capitalization (e.g, Verapamil <-> verapamil).
GWG Votes	Is the proposal feasible?
Yes: 12	• The applicants should describe how these assays fit into the drug development process. • Staff effort may not be sufficient for this project. • It might be understaffed and underfunded to achieve all the aims.
No: 1	*none*

Application #	DISC2COVID19-11954
Title (as written by the applicant)	Development of monothiol human thioredoxin-1 (ORP100S) as an inhaled treatment for COVID-19 respiratory disease
Research Objective (as written by the applicant)	We want to investigate if ORP100S can be used as therapeutic drugs against SARS-CoV-2-induced cytokine storm on alveolar epithelial type 2 cells, the stem cells in the lung.
Impact (as written by the applicant)	This would validate the ORP100S as a potential treatment against SARS-CoV-2-induced cytokine dysregulation.
Major Proposed Activities (as written by the applicant)	● Establish ORP100S's efficacy against SARS-CoV-2 pseudo-virus and live replication competent SARS-CoV-2 virus infection in human pluripotent stem cell (hPSC)-derived 2D lung cultures. ● Establish ORP100S's efficacy against SARS-CoV-2 pseudo-virus and live replication competent SARS-CoV-2 virus infection in hPSC-derived lung 3D organoids.
Statement of Benefit to California (as written by the applicant)	There is current no vaccines or treatments available for COVID-19. The proposed research will provide a potential treatment for patients who suffers from elevated cytokine levels due to the SARS-CoV-2 infection. Completion of the proposed research will benefit the State of California and its citizens enable Californians to live without social distancing requirements.
Funds Requested	$149,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 77

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	77
Standard Deviation	6
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: 11	● SARS-CoV-2 induced inflammation plays a major role in the pathogenesis of COVID-19 and a dysregulated inflammatory response is associated with poor clinical outcomes. Since antiviral agents must be effective, their efficacy is greatest when applied during early stages of infection. Consequently, strategies to reduce virus induced inflammation are critical to moderate excessive inflammation and provide protection from lethal disease. ● Directed delivery of an effective therapeutic to the lung of COVID-19 patients should impact the disease. ● Promising approach. ● This study is limited in its investigation of anti-inflammatory effect of ORP100S to in-vitro tissue culture and stem cell derived lung organoids. Preclinical and or clinical assessment of this anti-inflammatory agent is not proposed.

No: 3	*none*
GWG Votes	Is the rationale sound?
Yes: 8	• Rationale is based on the preliminary studies that show thioredoxin/ORP100S reduced inflammation upon virus infection and during cystic fibrosis. • Milestones are well arranged.
No: 6	• The cellular target of the drug may not be in the AT2 model. Immune cells may be required. • Some pilot toxicity data. • No preclinical data showing infection by COVID-19.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• The investigators first proposed to test ORP100S in-vitro, which will then be extended to test efficacy in lung organoids. The study, however, falls short in advancing the candidate drug to translation as no preclinical studies are proposed to test its efficacy in vivo. • Insufficient preliminary data to show that AT2 cells can be infected. • Limited assessment of anti-inflammatory activity. • Concerns over suitability of model. • Useful to know if vesicles affect viral activity, but not properly assessed. • Milestones clearly laid out. • Good team.
No: 7	• The preliminary data on SARS-CoV-2 infection of AT2 cells is needed to motivate the design. Without this data, the work is very risky.
GWG Votes	Is the proposal feasible?
Yes: 10	• The proposed milestones are feasible and can be achieved within timeline. However, lack of preliminary data showing infection of AT2 cells and lung organoids is a limitation. • PI has access to BSL-3 facility. However, both PIs lack virology expertise. It would be ideal to add a virologist to the team.
No: 4	• Complex aims that may be difficult to execute. • Concern whether there will be sufficient impact on cytokine modulation.

Application #	DISC2COVID19-11953
Title (as written by the applicant)	Mesenchymal stem cell derived exosome repression of SARS-CoV-2
Research Objective (as written by the applicant)	We will develop a Mesenchymal Stem Cell based therapeutic consisting of anti-SARS-CoV-2 exosomes that block virus infection or target virus infected cells to repress virus expression and disease.
Impact (as written by the applicant)	We will develop a mesenchymal stem cell based exosome therapy to treat COVID-19 disease caused by SARS-CoV-2.
Major Proposed Activities (as written by the applicant)	• Generate and assess siRNA containing mesenchymal stem cell (MSC) exosomes for repression of SARS-CoV-2 in vitro. • Develop and validate a single round infectious virus that expresses the full-length SARS-COV genome but with a luciferase/GFP replacing the spike gene for in vitro and in vivo work. • Generate and assess ACE2 virus receptor targeted MSC exosomes for blocking of SARS-CoV-2 and targeting virus infected cells. • Generate and assess ScFv protein S spike targeted MSC exosomes for blocking of SARS-CoV-2 and targeting virus infected cells. • Assess spike ScFv directed siRNA containing MSC exosomes for targeting SARS-CoV-2 infected cells in vitro and in vivo.
Statement of Benefit to California (as written by the applicant)	This project will benefit the State of California by developing a therapeutic to treat COVID-19 disease by utilizing mesenchymal stem cells to generate a biological treatment that can either (1) target and neutralize free virus or (2) target virus infected cells and inhibit virus expression, pathology and ultimately disease.
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	74
Median	75
Standard Deviation	6
Highest	80
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• COVID-19 caused by SARS-CoV-2 is a significant global health burden. Prophylactic and therapeutic agents are essential to control and treat COVID-19. The approach proposed to suppress virus replication is novel and interesting. • If successful, exosome derived siRNAs can be used to treat COVID-19. Considering several high throughput screening studies have identified anti-SARS-CoV-2 drugs, use of an exosome-derived siRNA is approach is cumbersome.
No: 2	• The product seems too complicated for scale up.
GWG Votes	Is the rationale sound?

Yes: 7	● The rationale that exosome-derived siRNA targeting viral RNA suppress SARS-CoV-2 and other RNA virus replication is based on published and new preliminary studies. ● The results from HIV studies are encouraging. The investigators plan to extrapolate the technology to inhibit SARS-CoV-2 replication and treat COVID-19. ● Targeting multiple viral protein to overcome resistance.
No: 7	● Requires more information about the ScFv that will be used. ● Several issues with the preliminary data were noted.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	● Aim 1 is well planned and designed to identify anti-SARS-CoV siRNA candidates for targeted inhibition of SARS-CoV-2 and determine any off-target effects. Aim 2 is rather complicated. The goal to develop receptor targeted exosome that incorporates a SARS-CoV-2 spike protein specific ScFv into the exosome, to inhibit SARS-CoV-2 in infected cells and free virus is ambitious. ● SARS-CoV infection dose and route of administration are not provided.
No: 8	● What is the source of MSCs? How are they made? ● The design of the experiments still needs more focus.
GWG Votes	Is the proposal feasible?
Yes: 7	● The changes seemed to make the proposal more feasible. ● Path for successful translation not considered. ● The application is ambitious, but the investigators have the expertise and resources to complete it within the timeline.
No: 7	● It appears to be a challenging manufacturing process.

Application #	DISC2COVID19-11798
Title (as written by the applicant)	Small molecules to enhance T memory stem cell activity in the elderly to fight Coronavirus infection
Research Objective (as written by the applicant)	We will target a novel stem cell pathway in immune cells to address the age-related mortality of COVID-19 patients and restore a youthful immune response.
Impact (as written by the applicant)	Mortality by COVID-19 is age-dependent and immune responses to vaccination are weak or defective in the aged. We propose an adjuvant therapy restoring a youthful immune response in the elderly.
Major Proposed Activities (as written by the applicant)	• Genetic engineering of COVID-specific immune cells to increase the stem cell reservoir and improve virus-specific cytotoxicity • Test selected compounds for their ability to enhance stem cell self-renewal, reduce exhaustion and increase virus-specific cytotoxicity • Test clearance of infected lung tissue by COVID-specific immune cells treated with selected small molecules
Statement of Benefit to California (as written by the applicant)	COVID-19 pandemic has greatly affected the health of Californians and threatens the State's economy. The proposed research will benefit the State of California by providing a novel therapeutic strategy to combat the deadly COVID-19 pandemic which has greatly affected the Californian citizens.
Funds Requested	$149,500
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	65
Median	65
Standard Deviation	7
Highest	75
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	• If successful, the work would address an important question. • The idea of promoting the stemness of T cells to improve virus-specific T cells using proposed small molecule inhibition is innovative and has potential to improve virus-specific T cell response in the elderly, but it is not know if this approach will succeed. • Interesting concept.
No: 3	• If project is successful it is unclear how potential impact would be specific to COVID-19. It may have broad implications for any kind of viral infection, immune system boost in aging, and cancer. • Overall, although the application addresses an important topic - how to improve immune fitness in the elderly. However, major weaknesses in the proposed experiments render this project unlikely to succeed. • Not clear how experimental results will translate into the clinic.
GWG Votes	Is the rationale sound?

Yes: 8	• The scientific rationale, described by the authors justifies use of small molecule inhibition for modulation of adults stem cells and "stemness"/fitness of naive T-cells. • Proposal to use small molecule inhibition to improve stem like T cell function is rational. • Reasonable concept to test. • Applicants do not present compelling evidence to choose their hypothesis over other models for immune exhaustion with increasing age. • The data provided is not sufficient to support the rationale and conclusions. • Methodologies to improve T cell fitness and stemness are highly desirable, but the lack of strong preliminary data decreased enthusiasm. • Preliminary data are lacking of experiments with human T-cells (for example, transduction efficiency and parameters). • The project is not specifically enabled by stem/progenitor cells but it relies on the modulation of naive T-cells and an increase of the pool of T-stem cell memory cells.
No: 7	• Previous studies from the applicant have shown that reducing levels of the inhibitor expands number of stem cells in BM, brain and breast tissue as well as reduced levels of p16 a hallmark of cellular senescence. While the applicants provide preliminary data that p16 expression is increased in highly differentiated T cells, there is no evidence that inhibitor expression or activity is increased with T cell differentiation or age, nor that repression of inhibitor activity in T cells will maintain their naïve phenotype. • Many technical issues are a problem. • Expansion of the T cells seems too challenging for the work. • Lack of supportive preliminary data. • No clear path to a translational intervention.
GWG Votes	Is the proposal well planned and designed?
Yes: 2	*none*
No: 13	• Concerns regarding feasibility of experiments. • Some important potential pitfalls are not mentioned. For example problems with transduction, lack of donors, lack of T-cells derived from donors, lack of Interferon-gamma producing cells. • The most substantial issue is the peripheral blood mononuclear cell (PBMC) collection. First the applicants do not provide all the needed information regarding the subjects from whom PBMC will be collected (such as how long post COVID-19 diagnosis will subjects be recruited). Also undisclosed is how many milliliters of blood will be obtained (as these experiments require a large number of starting cells) or whether the donors will be HLA-typed (since the applicants will be using other cell lines to measure anti-viral functions). • Aging of COVID-19 donors should be considered. The number of tested samples will be increased then. • The number of samples (N) in the experiments is too low for sufficient statistical power. • The numbers of samples are too small to generate meaningful knowledge from the proposed studies. • With such a small n, it is unlikely that the applicants can account for age, sex, and other factors known to impact immune fitness – even for a discovery application, these limitations should be discussed. Same concern for healthy donors where PBMC from only 4 subjects will be used. • A substantial issue with this application is the lack of preliminary data that supports the scientific premise of this application as well as the feasibility of the experiments proposed. Insufficient details are provided for expanding T cells lines. Only the PI has experience with human T cell work and that work did not involve virus-specific T cells. • The applicants propose a very large number of experiments to characterize T cell function. In all cases the applicants will expand SARS-CoV-2 T cells using stimulation with peptide pool followed by IFN gamma capture assay and then expansion of the T cells. However, (1) not all antigen-specific T cells make IFN gamma, (2) it is unclear how they will expand the cells for 15-20 days, and (3) how will the HD samples be treated? • T cells will be stimulated with various antigen presenting cells – some are very technically challenging (DC and B-LCLs), the availability of others is unknown (K562 transfected with specific HLA molecules). Unclear how T cells from COVID-19 naïve individuals will be treated in these experiments. • Goal 3 calls for testing killing of virus infected cells but the applicants seem to be unaware that cultured epithelial cell lines don't express ACE2, and again the HLA matching will be an issue. • Describe the planned serology test including false positive and false negative rate. • No clear path to the clinic described.
GWG Votes	Is the proposal feasible?

Yes: 7	• Overall, the project is feasible as presented. • The plan is not well articulated.
No: 8	• The cell manufacturing aspects of this proposal seems too ambitious. • Limited experience in producing specific T cells. • Anticipated problem of HLA matching.

Application #	DISC2COVID19-11919
Title (as written by the applicant)	Development of a new targeted senolytic drug for the treatment of chronic respiratory conditions in COVID-19 survivors
Research Objective (as written by the applicant)	We propose to ascertain if SARS-CoV-2 infection increases AT-II stem cell senescence and demonstrate efficacy of senolytic molecules in driving apoptosis in infection-induced senescent AT-II cells.
Impact (as written by the applicant)	Preventing or mitigating respiratory conditions (such as lung fibrosis) resulting in COVID-19 survivors.
Major Proposed Activities (as written by the applicant)	• Demonstrate SARS-CoV-2 mediated senescence induction in human AT-II cells in 2D and 3D in vitro models • Demonstrate presence of pulmonary senescent cells in COVID-19 patient biopsies and/or pre-clinical models with a focus on AT-II stem cells • Evaluate effectiveness of experimental senolytics for the elimination of infected human AT-II cells in vitro • Evaluate effectiveness of experimental senolytics for the elimination of senescent AT-II cells in preclinical models for pulmonary fibrosis
Statement of Benefit to California (as written by the applicant)	As of May 3, 2020, there are a total of 54,937 positive cases and 2,254 deaths in California. While long-term complications in COVID-19 remain to be determined, pulmonary fibrosis was observed in SARS patients who had recovered and were recently discharged from hospital care. Patients exhibiting pulmonary fibrosis was 62%. We expect that our proprietary compounds can reduce respiratory complications, ameliorate and possibly reverse lung fibrosis in COVID-19 survivors.
Funds Requested	$149,085
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	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: 7	• There is a strong need to ameliorate chronic respiratory conditions in individuals who have had moderate-severe COVID-19 infections. • Interesting hypothesis to use senolytics; certainly worth testing. • If successful, the work could develop a therapeutic for COVID-19. • Interesting idea, but no data to indicate whether SARS-CoV-2 induces senescence.
No: 8	• The current proposal aims to investigate whether alveolar type II cells undergo senescence during COVID 19 infection and whether removing senescent ATII cells using senolytics will reduce rate of ARDS.

	• It isn't clear that there is senescence in the alveoli in these patients, and it is unclear whether you could demonstrate this in vitro in the epithelial cells in the absence of immune cells. • Unclear whether this is a relevant target for COVID-19 to have impact. • We do not know if senescence is a major factor for COVID-19. • Information about the senolytic compounds is not provided.
GWG Votes	Is the rationale sound?
Yes: 3	• Senescence of AT-II cells is well-documented as a risk factor for long-term lung dysfunction and enhanced clearance of senescent cells via senolytic molecules is associated with mitigated progression of pulmonary fibrosis. Investigators propose to ascertain if SARS-CoV-2 infection increases AT-II stem cell senescence, to demonstrate efficacy of senolytic molecules in driving apoptosis in infection-induced senescent AT-II cells and demonstrate efficacy. • Rationale is speculative. • Unproven with weak preliminary data.
No: 12	• Interesting hypothesis, but no direct evidence offered that senescent AT-II cells are implicated in chronic effects of SARS-CoV-2 respiratory system infection. • No evidence yet that SARS-CoV-2 induces senescence. • Need to prove that senescence is a key factor for COVID-19. • The preliminary data seems weak. • Preliminary data weak. • No rationale or information is given regarding the compounds to be tested -- it appears (based mainly on published patent and comments in one of the bio summaries) that the proposed compounds are mainly prodrugs that depend for activation on cleavage by senescence-associated beta-galacosidase. If so, why would this be a superior approach? • There is no evidence presented as to the nature of their senolytic, or evidence that it even works in their existing models of lung disease. • Specificity and selectivity of senolytics is limiting.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The plan is not supported by preliminary data. • Weak link to COVID-19. • Only evaluating senescent cells in COVID-19 patient in second milestone. • Complete experimental details are not provided. • Unclear whether the applicants have an optimized list of potential senolytics. • No description of the compounds. • Milestone 3 lacks info on chemistry. • Milestone 4 has poor support for the assumption that the fibrosis model is directly relevant to SARS-CoV-2 infection. • The animal models of bleomycin and LPS are of highly questionable significance for modeling senescence in response to virus. • Some of the studies, especially those related to fibrotic tissue, are not relevant to COVID-19 therapy. • Animal model is not relevant. • One concern of the panel was how difficult it would be to get biopsies. I am not sure I agree, however, more detail needs to be provided to enable the panel to better evaluate this capability. • Strong PI with track record in regenerative medicine. • High quality collaborators.
GWG Votes	Is the proposal feasible?
Yes: 5	• It would be helpful if collaborators more experienced with SARS-CoV-2 and AT-II cell biology provide substantial input.
No: 1	• Pure AT-II culture is high risk. If the applicants get to the second milestone and no evidence of senescence in patient samples there is no point in progressing, regardless of what is demonstrated in an in vitro culture. • Getting AT2 cells in a short time is challenging. • Unlikely to induce senescence in 5-7 days via viral infection. • Getting lung tissue may not be easy. • Difficulty getting lung samples resonated with me. • Will likely not be able to get relevant/reliable biopsy materials to test for COVID-19 patients. • The animal model does not appear relevant for COVID-19. • Strong collaborators.

Application #	DISC2COVID19-11910
Title (as written by the applicant)	Engineered mesenchymal stem cell-derived extracellular vesicles for the treatment of COVID-19 cytokine storm disease.
Research Objective (as written by the applicant)	Engineered stem cell-derived extracellular vesicles as an immunotherapeutic for COVID-19 cytokine storm.
Impact (as written by the applicant)	A safe and cost-effective treatment for COVID-19 cytokine storm disease and ARDS. Our EVs have the potential of greater specificity, bioavailability, and bioactivity than whole stem cells.
Major Proposed Activities (as written by the applicant)	• Engineer stem cells to produce engineered extracellular vesicles (EVs) with enhanced therapeutic potency. • Establish clinically compliant, scalable production of the therapeutic EVs. • Deploy a clinically compliant, scalable bioprocess for concentration, purification and formulation of therapeutic EVs. • Generate a composition and identity profile for the therapeutic EVs. • Asses bioactivity and therapeutic mechanism of EVs using human immune cells. • Test therapeutic potential of EVs using a mouse model for lung inflammation.
Statement of Benefit to California (as written by the applicant)	As of writing, California has seen nearly 50,000 cases of COVID-19 and nearly 2000 deaths, with no signs of abating. New therapeutic approaches are desperately needed. The proposed research is aimed at developing a novel stem cell derived biologic for the acute pulmonary phase of the disease. The value goes beyond COVID-19 as over 10% of Californians suffer from lung diseases.
Funds Requested	$149,999
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: 7	• The application proposes to use MSC-derived extracellular vesicles engineered to modulate the host response to COVID-19 and limit cytokine storms (CRS) that may harm patients. • Engineered MSCs with vesicle secretion are an attractive modality for potential treatment of COVID-19. • Activity of MSCs used in COVID-19 has been related to their "secretomes". • Appealing concept.

No: 8	● It is not clear that the system will be of clinical significance. ● It is unclear if this treatment would affect late stage COVID-19 patients. ● Scientific rationale and preliminary data are insufficient to demonstrate that proposed modification of MSCs and their EVs would result in the enhancement of the MSC EVs therapeutic efficacy in ARDS, or any other disease indications. It is not clear why and how the proposed candidate would result in a significantly more effective therapy for ARDS or COVID-19. ● The mechanism of action is not well understood. ● No clear primary target.
GWG Votes	Is the rationale sound?
Yes: 2	● MSC EVs have therapeutic potential for ARDS as an alternative to mesenchymal stem cell therapy,. However, currently there is no evidence that proposed modification of MSC EVs would enhance their therapeutic efficacy in any indications.
No: 13	● Although MSC EVs are recognized to hold significant therapeutic potential for ARDS as an alternative to MSC whole cell therapy, currently there is no evidence that proposed modification of MSC EVs would enhance their therapeutic efficacy in any of the disease indications. ● The science behind this approach to immunomodulation is still emerging. ● The biological activity of the exosomes is not well understood. ● Preliminary data provided demonstrate the experience of the applicant to generate modified EVs from HEK cells and also that HEK-derived EVs convey protection in the in vivo rat model of autoimmune uveretinitis. However MSCs are a very different cell type and data obtained from HEK cells do not automatically suggest that MSC-derived EVs will have similar properties. Also, this in vivo model is not relevant to ARDS or to COVID-19. ● Need preliminary data from relevant models. ● They are too far behind with MSC expertise to make a timely impact on COVID-19. Other groups are much better positioned. ● Preliminary data is not relevant to COVID-19 induced ARDS. ● Conceptually interesting but expression of the proposed genes can inhibit T cell responses.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 14	● No preliminary data that they have a suitable model system. Assays to demonstrate efficacy in patients is unclear. ● The preliminary data is not with MSCs. ● The applicant proposes first to optimize the process of manufacturing and characterization of the product and only then (in the last 2-3 months) to test the efficacy of their product in the pre-clinical models. There is a big risk that after 7 months of work on optimization of EV production, their biological effect will be modest. ● Manufacturing before proof of concept. ● The clinical relevance of the in vivo model of Poly-IC induced lung injury for ARDS is not clear and the data from just one pre-clinical model would not be enough for clinical translation. ● No specific experience with MSCs. ● The timelines are too optimistic and some aspects of the project are likely more complicated than the applicant thinks (e.g. lentiviral transduction of MSCs). ● The proposal is not well thought out. EV delivery to the lung is not trivial. ● There are no contingency plans.
GWG Votes	Is the proposal feasible?
Yes: 2	● The project seems possible but likely not in the timeframe indicated and also unlikely to be successful.
No: 13	● The plan for optimization of production process and EV characterization is good, however testing of therapeutic efficacy in the clinically relevant models is not sufficiently developed. ● The team has limited resources. ● Company has limited resources. ● Unclear where MSC experience lies in company. ● Concern regarding sufficiency of proposed team size and resources to meet CIRM timeline. ● Lack of experience with MSCs decreases enthusiasm for this proposal.

Application #	DISC2COVID19-11927
Title (as written by the applicant)	Mesenchymal Stem Cell-derived Mitochondria-rich Microvesicles for Myocardial Inflammation in Cytokine Release Syndrome in COVID-19
Research Objective (as written by the applicant)	Efficacy of mesenchymal stem cell derived mitochondria-rich microvesicles will be investigated in reducing cytokine storm and related myocardial inflammation.
Impact (as written by the applicant)	The specific role of cellular secretomes will validate cell-free therapy to treat the cardiac complication of cytokine storm, which results in high morbidity and mortality.
Major Proposed Activities (as written by the applicant)	• Robust culture of mesenchymal stem cells (MSCs) and collection of MSC-derived mitochondria-rich microvesicles (mM-EVs). • Reliable culture and viral transfection of bone marrow-derived macrophages (BMDMs) to establish a genetically defective BMDM cell line. • Evaluation of the effects of mM-EVs on mitochondrial damage associated immune response in BMDMs and genetically defective BMDMs. • Examination of the effects of mM-EVs in a systemically infected mouse model, which provides an established model for inflammation-mediated multi-organ failure. • Examination of the therapeutic efficacy of intravenous (IV) vs. intramyocardial (IM) injection of mM-EVs on cardiac function in mouse acute heart inflammation model. • The therapeutic mechanisms of mM-EVs will be studied by performing high resolution molecular analysis of white blood cells and heart cells isolated from the mouse heart tissue
Statement of Benefit to California (as written by the applicant)	Successful completion of this proposal will address a critical pathophysiology underlying COVID-19. The cytokine storm and related multi-organ complication, including the heart, result in significantly higher mortality. Mesenchymal stem cell-derived mitochondria-rich microvesicles' efficacy to reduce the hyper-inflammatory response by COVID-19 patients will be investigated in a reliable mouse model of systemic infection and heart injury.
Funds Requested	$149,999
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: 11	• The investigators propose to test the efficacy of mesenchymal stem cell (MSC)-derived mitochondria rich microvesicles (mM-EVs) in treating myocardial injury and cytokine storm that occur during COVID-19.

	• The project focuses on an important component of COVID infection, mainly cytokine storm and myocarditis. • This is an exciting idea that could be impactful. • MSCs have been used in COVID-19, component "enrichment method" could improve efficacy. • Interesting innovative approach.
No: 4	• While the area of research is important and the research team is highly qualified, this proposal is likely to have modest impact. • The overall hypothesis and the experimental plans are not clear. The in vivo and in vitro studies are disconnected, the clinical relevance of the models for the COVID-19 is unclear so it is unlikely that specific findings from in vivo or in vitro models will be linked to mechanisms or clinical effects. • The match of their exosomes for COVID-19 is not appropriate. • The pathway to translation is not discussed in this proposal.
GWG Votes	Is the rationale sound?
Yes: 3	• The proposed mitochondrial rich EVs appear an attractive tool. • There is limited preliminary data showing a direct functional link to the proposed disease mechanism. • The study is based on fact that the mitochondrial DAMPs induce inflammatory responses. mM-EVs that target the DAMP inflammasomes generated from the injured cardiomyocytes suppress the cytokine storm from the activated monocytes/macrophages to promote myocardial stability. • Role of mitochondrial damps during COVID-19 is unknown.
No: 12	• The mechanism of action does not seem strong. • The rationale is somewhat weak, the authors state that 'pathophysiology of myocardial inflammation is unknown. mM-EVs may target the DAMP inflammasomes generated from the injured cardiomyocytes while also suppressing the cytokine storm from the activated monocytes/macrophages to promote myocardial stability' • The preliminary data demonstrate improvement in cardiomyocyte function in vitro , however there are no data on therapeutic effect in the clinically relevant in vivo model. • The idea to use mitochondria-enriched MSC microvescles is novel and relatively unique (there are other groups working on that), however it is not clear how authors achieve mitochondrial enrichment in their EV product. • Unclear. Existing data fragmentary and not particularly relevant to COVID19. • Lack of preliminary mouse model of viral myocarditis. • Too far from translation; logical steps in progression of the application and connections between the experiments are missing. • Model is not appropriate to obtain necessary data to move to next phase.
GWG Votes	Is the proposal well planned and designed?
Yes: 2	• Preliminary data is not sufficient to support the rationale.
No: 13	• The experimental plan is extremely unclear and difficult to follow. What is the overall aim of this proposal? The project design is unfocused and it is unclear how the proposed studies will inform further translational development of the MSC EV towards COVID-19. • The aims of the proposal are disconnected. Aim 1 is focused on the ability of EVs to inhibit inflammasome activation in monocyte/macrophages in LPS-induced intraperitoneal sepsis and in murine BMDMs. Aim 2 is focused on the route of administration of vesicles in the acute myocarditis model, mechanistic studies will be investigating differences in the cardiomyocyte transcriptomes between experimental groups without plans to validate NGS results. • I do not see how Aim 1 and Aim 2 are linked to each other and to MSC EVs application to COVID-19. • The development plan is poorly designed. • There are significant concerns related to the mouse model. There is no preliminary data for the proposed models and whether those mouse models are established. • The proposal lacks preliminary data for the proposed mouse model. There is only limited data for a rat model. It is not clear whether the proposed cell models and animal models are established. Given the ambitious timeline that is a major concern. • There are virus induced models of myocarditis. Those might be closer to the underlying disease mechanisms and therefore more appropriate. • Preliminary data in a mouse model would help. • Have not established mouse models. • May not achieve goals in 1-year time frame.

	● There is no indication of go/no go milestones and no outline of how the results from these studies will be used to inform the next steps of clinical translation. ● Experiments do not show a developmental path towards the clinic. ● Characterization of the product not considered. Translation of manufacturing not considered. ● Proposed development plan for ultimate translation not well designed.
GWG Votes	Is the proposal feasible?
Yes: 7	● The timelines seems ambitious since many of the proposed experiments are not supported by preliminary data and the animal model has not been established. ● The milestone seem appropriate. ● Overall the concept is feasible and interesting.
No: 8	● The proposed aims are not logical and it is difficult to do all the proposed work in just 1 year time. ● It is not clear if sepsis model is established within the group. ● May not achieve goals in 1-year time frame. ● Not clear how ultimate product will be used clinically.

Application #	DISC2COVID19-11937
Title (as written by the applicant)	Novel Adult Pluripotent Stem Cells for Treatment of COVID-19 by Enhancing Tissue Regeneration and Immune Modulation
Research Objective (as written by the applicant)	A new type of adult pluripotent stem cells (APSCs) derived from peripheral blood with superior tissue regeneration and immune modulation capabilities for treatment of COVID-19.
Impact (as written by the applicant)	APSCs represent a new type of pluripotent stem cells from adult peripheral blood, proven to be safe and non-tumorigenic, and have angiogenesis, immune modulation and anti-inflammation capabilities.
Major Proposed Activities (as written by the applicant)	• To induce epithelial differentiation of human APSCs to obtain high quality and quantity of epi-APSCs, and to characterize epi-APSCs. • To optimize the protocols of isolation, expansion, and differentiation of APSCs derived from adult human donor peripheral blood. • To evaluate the efficacy of human epi-APSCs in an ARDS mouse model induced by Oleic Acid, with human MSCs or saline as controls. • To evaluate the efficacy of human epi-APSCs in a lung injury model of respiratory syncytial virus (RSV) infection contracted with a CRO, using human MSCs or saline as controls.
Statement of Benefit to California (as written by the applicant)	The proposed research will promote the development of novel stem cell therapies for treatment of COVID-19 in addition to many difficult-to-heal diseases, including diabetic ulcers, late stage liver diseases, and virus induced diseases. This proposal will benefit the citizens by enhancing the general health and life quality, and reduce financial burdens to the CA health system. The proposal, if successfully achieved, will promote a new stem cell industry branch to boost CA economy.
Funds Requested	$149,820
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: 6	• The idea of using newly discovered adult pluripotent stem cells (APSCs) from peripheral blood to treat COVID-19 patients by enhancing tissue regeneration and immune modulation is novel and if successful can potentially have beneficial effects. • Idea that stromal cells could modulate ARDS could be important. • MSCs are being used in COVID-19, value proposition is potential better engraftment of APSCs

No: 9	• The project is not defined enough to have a potential impact. The target cells are not well described. • The cell product is not well characterized. • Starting cell population is poorly described; very weak data does not provide convincing evidence the starting population comprises pluripotent stem cells. No compelling evidence for ability to achieve even the first key step towards a therapeutic cell product for lung. • There is no evidence that APSC cells are pluripotent. • There is no evidence that APSC cells or epi-APSC cells can make lung. In fact the application suggests that epi-APSCs are epithelial (ecotoderm), whereas lung is derived from endoderm. • There is no evidence that epi-APSC cells or their derivatives are immunomodulatory. • The background information does not support a role in supporting damaged lung. • If the cells have potential to engraft does this mean the cells would have to be autologous? Would this be a practical therapeutic in the setting of an acute disease process requiring urgent therapy? • No clear discussion for long term clinical development.
GWG Votes	Is the rationale sound?
Yes: 1	• General concept to test these cells is valid.
No: 14	• APSC cells are almost certainly not pluripotent. Pluripotent cells can contribute to chimera formation in mice, form teratomas and form embryoid bodies in vitro. • There is no evidence to suggest APSC cells can make lung epithelium or any lung cell type. • They do not provide convincing evidence that the cells are pluripotent (only a few immunological markers are shown). Lung epithelial cells arise from endoderm - why driving the cell to an "epi" type? The nature of the cells is entirely unclear and no characterisation. • Pluripotent nature of these cells is questionable. The evidence provided is not satisfactory. • Not clear that the key cells for this project are indeed pluripotent stem cells. Need better evidence in support of this claim. • No convincing data that their cells are superior to MSCs, even though they claimed as much. There is already considerable study of MSCs as a potential COVID-19 treatment- no clear explanation how this would offer any improvement. • Unclear mechanism of action for the cells. • No clear preliminary data supporting the project. • Preliminary data on liver and skin likely not relevant to lung. • Need better preliminary data. • If this is envisioned eventually as an autologous cell therapy, that would be a non-starter. • RSV model is not the correct model to test for ARDS.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• Another reviewer categorized the application as uninterpretable and I would agree with that comment. • I think the differentiation protocol is untested and it is unknown if it will work or not. • The differentiation protocol using conditioned media from epithelial cells seems very simplistic and there is no evidence this would work. • Protocols are not well defined. • The growth and characterization studies in milestone 1 lack any detail. • The characterization studies are not well designed. • Unclear whether the adult pluripotent stem cells are mesenchymal stem cells. • Model of ARDS does not seem appropriate. • The RSV model is not relevant to ARDS. No anti-viral effect being measured. • No preliminary data showing immunomodulatory activity. • COVID-19 has a different impact on lung than that induced by RSV model. • Irrelevant models. • No evidence provided to show that these cells can moderate inflammation. • Use of RSV model as a surrogate to SARS-CoV-2 is not appropriate. • Proposed animal model is not a relevant model of ARDS. • Several key experimental details are missing, particularly with reference to cell dose and duration of treatment. • They don't plan to measure anti-viral effect.

	● Lack expertise in lung biology.
GWG Votes	Is the proposal feasible?
Yes: 3	● It would be feasible in theory, however there are persistent concerns about the strength of this particular team. ● Feasible to do the animal models. ● Feasibility of the first part is unclear as there is no detail.
No: 12	● The whole premise is based on APSC cells being pluripotent and possessing certain properties - there is not any evidence to support that thesis. ● This project is at a very early stage and there are many unknowns and also many claims which are not supported by data. ● Not clear these are stem cells. ● Lack of specific expertise in lung models. ● Lack of expertise of lung biology significantly increases the risk for failure.