APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
CLINICAL APPLICATIONS												
CLIN1COVID19-12023	Dendritic Cell Vaccine for COVID-19	$399,107	**N**	**-**	-	-	-	-	0	15		
DISCOVERY APPLICATIONS												
DISC1COVID19-12047	Development of Anti-COVID RNAi Therapeutics Using Human iPSC-Derived Alveolar Epithelial Cells	$150,000	**Y**	**90**	90	3	85	95	15	0	Biologic	Engineered delivery system for RNAi therapeutics into lung cells
DISC2COVID19-12022	Using hiPSC-derived lung organoids, a clinically-relevant system, to validate & winnow a list of approved drugs that inhibit SARS-CoV-2 cytopathy	$249,999	**Y**	**90**	89	2	83	93	14	1	Small molecule	Screen for drugs that inhibit SARS-CoV-2 using an iPSC-derived lung organoid model
DISC1COVID19-12048	Repurposing drugs to inhibit the translation of COVID-19 RNA in respiratory epithelial primary and stem cells	$149,930	**N**	**75**	75	8	60	90	2	13		
DISC2COVID19-12049	Examining mTORC1 inhibitors as a treatment for COVID-19	$250,000	**N**	**75**	75	3	70	85	1	14		
DISC2COVID19-12045	Engineered human placenta-derived mesenchymal stem/stromal cells (ePMSCs) for the treatment of COVID-19	$249,632	**N**	**70**	70	8	60	85	1	14		
DISC2COVID19-12027	Engineered allogeneic reticulocytes expressing SARS-CoV-2 antigens as a cellular vaccination strategy to prevent Covid-19	$202,500	**N**	**60**	56	7	40	65	0	15		
DISC2COVID19-12053	Fucosylated Cord Blood Stem Cells to Treat COVID-19 Patients with ARDS and Prevent Respiratory and Multi-Organ Failure	$249,728	**N**	**-**	-	-	-	-	0	15		

Application #	DISC1COVID19-12047
Title (as written by the applicant)	Development of Anti-COVID RNAi Therapeutics Using Human iPSC-Derived Alveolar Epithelial Cells
Research Objective (as written by the applicant)	To optimize a new approach to deliver Anti-COVID siRNAs into human iPSC-derived lung cells that can selectively kill the COVID virus
Impact (as written by the applicant)	Our proposal, if successful, will solve the siRNA delivery problem and rapidly open the door to Anti-COVID siRNA therapeutics.
Major Proposed Activities (as written by the applicant)	• Complete synthesis of a new delivery device • Generate a panel of human iPSC-derived lung cells • Test and optimize the ability of the technology to deliver Anti-COVID siRNAs into human iPSC-derived lung cells • Rapidly expand the technology to delivery of Anti-COVID siRNAs in a broader panel of human iPSC-derived lung cells
Statement of Benefit to California (as written by the applicant)	COVID-19 is a deadly health hazard for all Californians, Americans and the world. siRNA-induced RNAi responses are highly selective genetic medicines that have great potential to treat COVID patients and to prophylactically inoculate Californians to prevent their infection. However, due to a delivery problem, we cannot yet deliver siRNAs into lung cells of patients. Our proposal, if successful, will solve the siRNA delivery problem and rapidly open the door to Anti-COVID siRNA therapeutics.
Funds Requested	$150,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

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

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?	15	0	0
Is the rationale sound?	15	0	0
Is the proposal well planned and designed?	15	0	0
Is the proposal feasible?	15	0	0

REVIEWER COMMENTS

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

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

- The proposed technology is somewhat novel, timely, important and could potentially impact an unmet medical need in the treatment of COVID-19 and other disease entities as well. Notwithstanding the potential delivery of the technology to alveolar stem cells in the lung, the technology does not directly address a critical bottleneck to the development of stem cell-based therapies.
- Interesting and new approach make it worth the risk. It may well have much wider applications increasing the potential for impact.
- Potentially exciting new intervention for new treatment.
- Very innovative project which could make a difference.
- The potential aerosol delivery of the siRNA and its long term effect(s) is both exciting and critically important in treating COVID-19.
- New siRNA blocking SARS-CoV-2 replication would have promise as a therapeutic.
- siRNA therapeutics may well be in an important drug for COVID-19. They will likely have to be delivered to the lung. Effectively solving the endosomal escape problem is important. The drugs need to get out of the inhaled medicine and into the cytosol where they will be effective.
- It is conceivable that knockdown of SARS-CoV-2 RNAs and/or genomes by siRNAs delivered to lung epithelial cells could become an effective therapy.
- Solving endosomal escape could be broadly applicable for a large number of medical conditions, not just COVID-19. Also could be a useful tool for investigation of stem cell biology and development of stem cell therapies.
- There could be learnings that could be applied to other stem and progenitor cells.
- Considering that the project falls under the category of Early Discovery, the applicant has not provided a detailed progression from successful candidate discovery to translation. However, the PI acknowledges the importance for delivery of device to alveolar cells in the lung, and the appropriate design of the siRNAs to limit viral replication.
- This is a basic molecular mechanism that is universal across all humans. Inhaled siRNA therapies don't require frequent contact with the healthcare system so may be more likely to be broadly and equitably available.
- The therapy could be delivered every few months and widely accessible.
- Therapy involves iPS-derived lung epithelial cells and is thus relevant for support by CIRM.
- If the pilot experiments described in the proposal are successful in iPS-derived lung epithelial cells, then it is easy to imagine how the procedure could be adapted to virally-infected cells and then animals and humans.
- The relationship to stem cells is reasonable and I don't think the requirement for stem cells should be interpreted too strictly.
- Expert group with outstanding principle of therapeutic.
- Consideration of delivery directly to the lungs is strong.

Is the rationale sound?

- The proposed project is based on sound scientific rationale; and this is presented both as previous publications from the PI's laboratory, and clearly designed figures within the application. The so-called preliminary data is compelling and supportive of the proposed project, and underscores the feasibility of the work, and its successful completion within the allotted timeline.
- The molecular biology is strong and this presents a strong rationale for this mode of action. The candidate is able to get around a trafficking issue for many siRNAs.
- The state of the art of developing molecules to assist in endosomal escape have been evolving over many years, and this current iteration builds upon past experience. It has a decent chance of success.
- The proposal attacks a rate limiting step in siRNA-based therapeutics, that is, delivery of siRNAs from endosomes where they are taken up to the cytosol where they need to act.
- Logical mechanism to deliver RNAi therapies in lung cells.
- Technology is based on strong prior work by this team.
- The idea to transport the siRNA into the cell to knock down SARS-CoV-2 virus using their uEED has reasonable preliminary data.
- The rationale for endosomal escape to deliver product directly to the lungs is sound.
- Well written with good preliminary data.

- In certain ways, the proposed project is enabled by human stem/progenitor cells both within the cell culture dish, and in vivo. The technology is not only enabling for the advancement of stem cell-based therapies (as per the alveolar type 2 cells), but also for treatment of somatic lung cells (alveolar type 1) via siRNAs as a plausible treatment of COVID-19.
- Evidence for synthesis of the chemical components proposed to move siRNAs from endosomes to cytosol is provided. No evidence is provided, however, to show that multimers can actually translocate RNA from endosomes to the cytosol.

Is the proposal well planned and designed?

- The project is well planned and appropriately designed to achieve the expected outcome(s) of the Program announcement...and that is a candidate technology ready to advance to pre-clinical studies and early translation. The general consensus and agreement among the reviewers was that the application was well-constructed and a quality Early Discovery project.
- The team includes an exceptionally qualified PI, postdoctoral fellow and stem cell expert who are all very familiar with the experimental design and required resources to be successful. No significant potential pitfalls and alternative approaches were discussed in part, because the PI does not predict that any will arise....and this reviewer would agree with that notion. The project complements ongoing studies in the two laboratories.
- The project is very straightforward. It should be very clear whether the library-tethered siRNAs can knockdown lentivirally expressed SARS-CoV-2 target RNAs in iPS-derived lung epithelial cells without toxicity.
- Targeting siRNA against stem cell-derived lung cells is appropriate.
- COVID-19 is an emergency and requires an urgency. The project plan and timeline are commensurate with the mission that CIRM serves.
- The team is very strong and has decades of experience in this field.
- The team presents a logical plan based on preliminary data.
- Everything in place to support the project.
- Well laid out and feasible.

Is the proposal feasible?

- The proposed milestones at both 6-months and 12-months are logical and likely to be achieved within the stated timeline of one year. The research team, made up primarily of the PI, postdoctoral fellow, and stem cell expertise is complementary, integrated and outstanding. They have access to all the necessary resources to conduct the proposed studies; and much of the work is a logical extension of both laboratories designed to treat COVID-19.
- The budget as requested is appropriate for the proposed research, and studies. No animal usage is described, and the experiments will be primarily iPSC differentiation and cell culture work, together with conjugate chemistry and siRNA design.
- Experienced lab with strong background - will be relevant for other diseases potentially.
- The milestones are straightforward.
- Should be doable in a 12-month time frame.
- Yes. The proposal is quite modest in scope.
- The assembled team has experience with iPSC-derived stem cells and developed the chemistry.
- Based on prior success of the group the project seems achievable.
- Really good team with complementary expertise.

Application #	DISC2COVID19-12022
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)	Using authentic in vitro models of the human lung, complete with inflammatory cells & vessels, we will validate drugs that might be rapidly repurposed for use in patients with COVID-19.
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)	• hiPSC-derived lung organoid development & baseline cellular characterization from a diverse group of patients (race, gender, HLA type). • Molecular characterization of the above-mentioned organoids that are also invested with isogenic alveolar macrophages & vasculature. • Infect above organoids with pseudovirus & complete SARS-CoV-2 & characterize cellular, genomic, & proteomic changes from baseline. • Determine impact of the narrow-spectrum oral clinical-stage protease inhibitor ONO5344 on "rescuing" infected organoids. • Determine impact of the broad-spectrum oral late-stage protease inhibitor VBY825 on "rescuing" infected organoids. • If 1 or both drugs are effective in this clinically-relevant system, send INTERACT, pre-IND, and/or IND packages to the FDA to expedite redesignation & advancement to clinical trials.
Statement of Benefit to California (as written by the applicant)	This research will benefit Californians by using authentic "mini-human lungs-in-a-dish" to test drugs that already exist & are often being used for other purposes by patients but which must be validated for effiacy against SARS-CoV-2. Until a vaccine is available, a drug that suppresses the severity & contagion of COVID-19 might be the next best thing. If we can bypass animal testing with this system (no good COVID-19 animal model yet exists), we might fast-track these drugs to patients.
Funds Requested	$249,999
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	89
Median	90
Standard Deviation	2
Highest	93
Lowest	83
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	• Applicants are proposing to use a unique model of multicellular human lung organoids with vasculature and immune cell compartments to investigate FDA approved protease inhibitors, one being shown to act synergistically with remedesivir. The model is really exciting and if successful it might be a break through in drug discovery research for respiratory diseases. • The proposal is an excellent system to screen drugs and lessons learned from this work will be useful in other diseases. • Project aims to elevate to status of "candidate" at least one of two "proto-candidates". Both protease inhibitors have already shown in a high throughput screen to have activity against SARS-CoV-2. There remains a significant need for effective antivirals to treat COVID-19. A main goal is to show activity in a relevant organoid model of human lung and to use the model to gain further insight into biological and molecular mechanisms in COVID-19. • This work could move two candidates forward into clinical trials for treating COVID-19. • Project could validate a platform technology of broad utility. The iPS cell-derived lung organoid model containing syngeneic macrophages and endothelial cells represents a stem cell technology well-suited to the type of secondary screen described in the application. It could fill a key niche between high-throughput but biologically "crude" screening of compound libraries and low throughput, slow and costly animal models, and shed light on key mechanisms of pathogenesis by SARS-CoV-2 in lung. • Potential to serve underserved population based upon selection of starting cells for organoid cultures. • The organoid system should be very valuable. • The proposed human organoids can be used to assess viral pathogenesis and antiviral activity. • Molecules identified in a repurposing have potential for treating COVID-19 and warrant further investigation in organoids and other preclinical models. These repurposed molecules could be rapidly evaluated and represent a broadly accessible therapeutic. • Broad spectrum screen for a number of biological and demographic factors. • The applicant makes a good case for the potential impact: "to re-designate fairly rapidly & fast-track to COVID-19 patients the most promising FDA-approved and/or late/clinical-stage drugs, at likely safe & therapeutic doses..." • Thorough response to feedback. • A little concern about the over-ambitiousness of the proposal.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• There is a strong rationale to carry out a secondary screen for effects of an antiviral compound in a biologically complex but tractable system, such as the organoids of this application, in which the key human lung cell types are well represented. • A very attractive feature of the project is the plan to look for biological differences in the SARS-CoV-2-infected organoid model with respect to gender, race, ethnicity, and/or specific HLA haplotypes already associated with increased susceptibility to the coronavirus. The approach represents an innovative, positive response to the CIRM Board's call for inclusiveness in those likely to benefit from funded program. • The characterization of the system and the drug candidates are high. • Clear use of stem cells. Organoid system may be sufficient to expedite translation to clinical candidate into COVID-19 population based on the FDA's increasing interest in utilization of in vitro approaches. • Exceptionally strong preliminary data that the model could be used for drug testing, though I am not sure if there is enough evidence that the proposed drug candidates are strong candidates for the therapy. • Demonstrated ability to grow organoid. • Demonstrated organoids are infectable. • Excellent organoids good preliminary data. • Strong preliminary data showing infectivity in organoids. • Very responsive to the prior critique.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The core of the project - to test antiviral activity of two proto-candidate compounds against SARS-CoV-2 in a biologically relevant human model - is well planned and likely to achieve a candidate ready to advance to translation.

	• Outstanding construction and characterization of the organoid model - very well documented in the application. • The range of ethnic cell sources is responsive to the diversity requirement. • Thorough description of experimental endpoints. • Some endpoints are ambitious but even a partial completion will likely provide useful information. • Although there are still too many variables and a large volume of work, the proposal to address ethnicity, HLA haplotype variation, and gender is recognized as an advantage. To address these all fully would take a whole additional project. The investigators should be encouraged to ensure they can characterize their model fully (intra/interdonor variability for given ethnicity/gender etc) which will improve output of tool. • More focus is needed on generating reproducibility and reliability data. A more rigorous description of the assay variability is needed for this work to have a large translational impact for the human organoid field. • Good milestones for advancing molecules to translation. • Remains a risk of project being overly ambitious; should be careful not to become defocused while pursuing secondary objectives -- even though these are interesting and could yield valuable insights. • The aims around HLA could be distracting, but otherwise, the planning is appropriate. • Applicant very responsive to previous review including providing additional data.
No: 1	• Applicant states that he has "taken to heart" the GWG comment that the initial project was overly ambitious. However, while more focused, this revision remains very ambitious. By focusing even more, applicant could conceivably establish the system baselines for secondary drug screening by showing utility for the two protease inhibitors. • Before undertaking comparative studies of viral infection and drug sensitivity in organoids derived from demographically different populations, applicant needs to demonstrate the reproducibility of data in multiple independent organoid preparations derived from the same donor and also from several donors with similar demographic characteristics. Need to establish what meaningful differences in measured parameters will be. This means reorganizing and extending initial milestones. This approach will be necessary for making a development decision on candidates, especially if data is to be used for FDA discussions. More work looking at variability in susceptibility to virus or efficacy of drugs could follow, but would most likely extend beyond scope of this grant.
GWG Votes	Is the proposal feasible?
Yes: 13	• It looks like the applicants are proposing to do too much within the timeframe, however their strong track record and pilot data are reassuring that the team will be able to deliver the project. • Milestones are laid out logically. Final outcome would be drug ready for pre-IND or equivalent. • This is a lot of work for this time period, but excellent team and resources. • The project milestones are ambitious but will delve appropriately into the biology of the candidates. • Even if they only get through 75 or 80% of the application, it would have been well worth the modest investment. • Experienced team, however very ambitious. Would provide value even if all milestones are not met. • A major issue is that the volume of work remains extensive and unlikely to be achievable in the timeline. If focused on the 2 compounds, the proposal is feasible, but all the other variables are unlikely to be addressed. • Will make good progress, but scope is too broad to meet all milestones. • Good chance of identifying a molecule to advance as a therapeutic. • Looks like a superb team. PI has ca 40 years track record as a leader in stem cell biology, including extensive experience with iPS cell generation and use to create model systems, mainly in neurobiology. Team members bring the necessary experience in lung cell biology, virology, drug screening & chemistry. • Team appears to have access to outstanding resources for the organoid development & characterization and for the compound testing. • The ethnicity/HLA aims are unlikely to be completed.
No: 2	• Concerns about secondary goals being achieved, but primary goal is likely to be feasible. • There remains too much work to be done in the grant period. A lot depends on staffing; see below. Should focus on establishing baseline characteristics and response to drugs [protease inhibitors] of infected lung organoids derived from similar susceptible donors [reproducibility]. If staffing permits, perhaps do proof of concept to see if system can

	detect difference in viral infection or drug response in one other demographic group. Other groups can be added later. ● It is not clear who will do the large body of work proposed. The Co-PIs will dedicate ~20% effort; they most likely will not be in the lab. The budget requests salary Research Associate (20% effort) and a Post Doc (10%) with specific tasks. Several other people are listed as participants in the application, but their time commitment to the project is not specified. Applicant says in response to GWG review that he has 10-12 "volunteers" involved. Their roles and experience are not defined. ● Senior researchers and their laboratories are all highly experienced in the areas covered by the application and appear to have already established productive working arrangements.

Application #	CLIN1COVID19-12023
Title (as written by the applicant)	Dendritic Cell Vaccine for COVID-19
Therapeutic Candidate (as written by the applicant)	Vaccine to prevent COVID-19 infection.
Indication (as written by the applicant)	Prevention of COVID-19 infection in adults.
Unmet Medical Need (as written by the applicant)	Currently, there is no existing preventative therapy to protect from contracting COVID-19 infection.
Major Proposed Activities (as written by the applicant)	• Manufacturing validation. • Anti SARS-CoV-2 vaccine production. • Clinical study start-up activities.
Funds Requested	$399,107
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 2	• There is a clear global need for an effective COVID-19 vaccine.
No: 11	• The personalized vaccine approach is unlikely to be a universal anti-COVID-19 approach, but may be appropriate for certain high risk populations. • Technology may be useful for other diseases, including cancer. • Although the vaccination approach, based on the use of ex vivo loaded dendritic cells is well established in the cancer field, and indeed is beneficial in some specific groups of cancer patients, I am not sure that this approach will be feasible for COVID-19, when mass vaccination is required. In addition, it is still not clear if the antibody response only is enough to clear infection, when development of long lasting T cell immunity is desirable. • This is an individually produced autologous cell product and has an extremely high price point and no evidence that dendritic cell (DC)-loaded vaccine is likely to be superior to vaccine alone. This could be a niche product for individuals at very high risk. However, the applicant has not provided a clear definition of who that would be and whether this product specifically would mitigate risk for such individuals. • Not clear an autologous DC vaccine is significantly more efficient to justify the cost of production.

	• Cell therapy is not well suited for prophylaxis as it would be cost prohibitive. It would be impossible to impact a large number of people, and very challenging based on current knowledge to define a small group highly likely to benefit. • An individualized vaccine is not going to be a realistic strategy for a pandemic organism - even for focused groups of "high risk" persons. Very high costs and impracticality of manufacture and delivery make this not feasible. Giving it with GM-CSF adds huge cost as well. • Autologous manufacturing is too costly to be feasible to have a large impact. • Very high cost is a barrier to accessibility. • Unclear how this technology could be rolled out to the larger patient population.
GWG Votes	Is the rationale sound?
Yes: 3	• Rationale of vaccination is likely to work. • Strong preliminary data in melanoma. • Sound rationale for immune response boost with DC loaded vaccine, but may not be associated with long lived response. The absence of preclinical study of DC-loaded vaccine vs vaccine is key. In the background info, the melanoma vaccine trial took many years to recruit 9 patients - this is a concern. • There are no data on what protective immunity to COVID-19 would be defined as. • No virus vaccine experts on study. • In vitro secretion of cytokines as correlate of immunity is not defined. • Whether DC vaccination is better than cheaper more standard forms of vaccination is unclear. • Manufacturing is well-considered.
No: 10	• The applicant proposes to leverage previous preclinical and clinical data from cancer trials. • The selection of multiple antigens makes sense and there is some preliminary data showing antigens react with immunoglobulins in serum from patients who have recovered from COVID-19 infection. • Supporting anti-viral data are from published literature and not with the proposed product (or similar virus) to justify use in COVID-19. • Insufficient preliminary data with viral antigen(s) to justify clinical trial. • Insufficient preclinical data. • The data in melanoma is not directly applicable to this cohort of patients.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	• Concerns about lack of preclinical studies for efficacy. • Likely to meet their endpoints.
No: 12	• Limited preclinical studies are proposed. • Insufficient preclinical data. • Completed trials of these vaccines for cancer haven't been published; this is a concern. • There is no discussion of activity/efficacy in the 190 cancer patients that have been studied with an analogous product using tumor antigens and/or discussion of doses used in these studies. • Hexa-histidine tags on the antigens are a concern. • Safety question raised about whether (His)6 tag is removed from antigens. • Poorly designed trial. • The clinical trial protocol is too complex. • Clinical trial design is not appropriate (should be vaccine vs ex vivo loaded dendridic cells) • It isn't clear that this study will establish that dendritic cell loading is better than direct immunization. • Clinical protocol is too complicated. • DC loaded vaccine versus vaccine alone is important to establish for this disease. • There are no data (sufficient rationale) to support proposal not to use GM-CSF as GM-CSF was used in the cancer trials.
GWG Votes	Is the proposal feasible?
Yes: 3	• The proposal is feasible if they could find sufficient funding for an expensive clinical study. • It is likely feasible to deliver the preclinical work in the time allocated. • The trial protocol is too complex.
No: 10	• Feasible in principle to accomplish the goals of proposal, but unlikely to be feasibly expanded for a large population. • Too many variables in clinical trial, resulting in a large and complex study. • Clinical trial design is too large and complex.

	● While the proposed study may be safe there are not sufficient data to support that the study will generate protective immunity. ● There is no data to support in vitro secretion of cytokines from autologous lymphocytes correlates to immunity. ● There does not appear to be sufficient expertise in the team in COVID-19 infections or other anti-viral indications. ● There is no justification for proposed clinical doses, which are stated will be derived from in vitro experiments i.e. correlation of an in vitro concentration with in vivo dose.

Application #	DISC1COVID19-12048
Title (as written by the applicant)	Repurposing drugs to inhibit the translation of COVID-19 RNA in respiratory epithelial primary and stem cells
Research Objective (as written by the applicant)	A screening platform to discover drugs which can be repurposed to inhibit COVID-19 in respiratory epithelial primary and stem cells.
Impact (as written by the applicant)	Successful completion of the project will identify repurposed compounds that inhibit COVID-19 in respiratory epithelial primary and stem cells and provide a rationale for clinical investigation.
Major Proposed Activities (as written by the applicant)	• To generate a fluorescent reporter system for studying COVID-19 function in respiratory epithelial primary and stem cells. • To identify repurposed drugs for inhibiting COVID-19 in respiratory epithelial primary and stem cells.
Statement of Benefit to California (as written by the applicant)	Since the emergence of COVID-19, 17 million jobs were affected in California as the state expects $50 billion loss in tax revenues due to business closure. Despite strict shelter-in-place measures, the total case count is at 81,911 with new cases emerging daily. As we face a potential second wave of the pandemic, an effective anti-viral will not only alleviate the burden on the state's healthcare system and prevent further spread of the disease but also expedite California's economic recovery.
Funds Requested	$149,930
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	75
Median	75
Standard Deviation	8
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

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?	7	8	0
Is the rationale sound?	10	5	0
Is the proposal well planned and designed?	4	11	0
Is the proposal feasible?	12	3	0

REVIEWER COMMENTS

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

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

- This is a simple proposal to do HTS to test 14,000 compounds from the ReFRAME Calibr library using an established translation inhibition assay.
- Applicants are evaluating a unique area (translational regulation) to screen compounds for SARS-CoV-2 activity.
- The potential for impact is unclear. Innovative approach. However, impact, if any, likely to require considerable time as output from DISC1 stage is likely to be "hits" not very close to a drug candidate. Probably 3 years out before this would have much of a chance to get to clinic.
- May have impact in identifying drugs that help to reduce lung damage caused by other viruses as well.
- Unlikely to have significant impact to meet current urgency of COVID-19.
- The concept is sound, but there are concerns about the likelihood of finding a hit and developing a tool.
- Concerns about the likelihood of getting a relevant hit in this library -- the mechanism of action is limited in the chosen library.
- No info on what the cell targets are in the in vitro models proposed.
- Insufficient new understanding of virus will arise from this study.
- Relatively unlikely they are going to have impact on current pandemic with this work - no discussion in the proposal of doing a viral screen on successful hits.
- The library has already been looked at by other groups by other ways.
- If effective, the already approved therapeutics can be identified, they are likely to be inexpensive, and broadly available to a wide range of people, with fairly quick development time.
- It just doesn't sound like there is enough novel work here that will add to work others are doing. Rather it seems like it will be a modest duplication of efforts, which is not a good investment of limited resources.
- Unlikely to find a hit in the screen, and there's no impact without a hit.
- The library for the screen is not novel, and the project is not uniquely enabled by stem cell technology.
- Stem cells are not required for the proposed work.
- The project is not enabled by stem cell technology nor is it addressing a bottleneck in stem cell field.

Is the rationale sound?

- A similar approach has been used to identify translational inhibitor Silvestrol for use in coronavirus and other RNA viruses such as Ebola.
- Screening approach to inhibit transcription and translation is appropriate for a high risk/high reward project.
- Inhibition of transcription and translation of SARS-CoV-2 is not a high impact target.
- The rationale is sound, but there is very little preliminary data or evidence that the compound library is likely to have molecules useful for the proposed mechanism.
- It is not clear that cells that are used for screening will identify COVID-19 relevant compounds.
- The standardization of the epithelial biology in the platform may be important.
- Not validating compounds on the appropriate test system--need to target intact coronavirus with the appropriate host modifiers (could be another beta-coronavirus)
- No stem cells used in screen.
- Unlikely that stem cells are major site of drug target.

Is the proposal well planned and designed?

- They have done high throughput screening before for translation inhibition. The basic approach here is to substitute the IRES from SARS-Cov-2 into their existing vector, so the work seems straightforward.
- Since original submission as a DISC2 application, in this DISC1 application: they repositioned and simplified their application appropriately to either address or avoid the criticisms of the previous proposal.
- The panel wanted to see more validation of the best hits from the initial screening. The superficial and cursory description of cellular assays in Figure 4b was unsatisfying, and it was the only location where milestone 2.3 was discussed.
- The panel wanted to see a collaborator with expertise in SARS-CoV-2 biology. The nuances of coronavirus transcription and translation may make it difficult just to "plug and play" with vector molecular biology without fully understanding the function of each viral protein.
- The panel wanted more discussion on the pros and cons of using a "diversity" molecular library to explore the full range of biochemistry or of using an "approved compound" library, and the approved compound library may not have a lot of drugs with the right properties for inhibiting translation.
- Lack of basic virology and understanding of SARS-CoV-2 biology in their background. Still insufficient collaboration or understanding relevant to the virology of SARS-CoV-2. No clear sense of how applicants would plan to progress from "hit" discovery to a drug candidate.
- Strength of proposal is in HTP screening but not sufficient expertise in COVID-19 biology.
- Not targeting the appropriate model systems.
- Why no viral screen planned with the outputs of the HTS?
- HTS should have a simple, clear readout - ideally more usefully done on a basic cell line.
- Proposal lacks virology expertise.
- Investigators need to look at entirety of viral system.

- The project does not uniquely use stem cell technology.
- They have an MTA with institution holding the library.

Is the proposal feasible?

- This is a high throughput screening proposal to be implemented by a company that has experience in high throughput screening.
- Initial screen is feasible; but downstream steps absent and no detail on how to actually get to a candidate therapeutic.
- The group has experience with HTS and viral systems and potentially can complete the proposal.
- Lack of sufficient resources to optimize chemistry of "hit" if needed to optimize a lead candidate.
- As described, the screen is likely to proceed successfully.
- Mechanisms of action are complex and difficult to target.
- Translation from a hit to the next steps for this group will be a challenge.

Application #	DISC2COVID19-12049
Title (as written by the applicant)	Examining mTORC1 inhibitors as a treatment for COVID-19
Research Objective (as written by the applicant)	We will use two adult stem cell derived lung models in this research. These mimic the cell types and architecture of the human lung and are readily infected by SARS-CoV-2.
Impact (as written by the applicant)	Our studies will test whether our candidate therapeutic limits SARS-CoV-2 replication in stem cell derived lung models, which could lead to rapid translation as a treatment for COVID-19 patients.
Major Proposed Activities (as written by the applicant)	• Confirm that SARS-CoV-2 activates our drug target in human stem cell derived lung cultures. • Confirm that our candidate therapeutic reduces viral replication in stem cell derived lung cultures. • Compare our drug target activity in lungs from matched COVID-19 and non-COVID-19 patients. • Perform and analyze scRNA-seq on 10 COVID-19 patient lung aspirates. • Write a paper summarizing our results, and apply for funding of a clinical trial to investigate the use of our candidate therapeutic as a treatment for COVID-19.
Statement of Benefit to California (as written by the applicant)	Although the State of California led the nation in responding to SARS-CoV-2, there will still be health and economical costs until a therapy or vaccine is discovered. If successful, our research offers the hope of a rapid therapy to treat COVID-19. This could have a large impact for Californians, especially those in socioeconomically deprived areas where the risk of COVID-19 is highest; reduced virus levels could lower the risk of infecting people in the same household and community.
Funds Requested	$250,000
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	75
Median	75
Standard Deviation	3
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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: 11	• Obvious need for better antivirals against SARS-CoV-2. Repurposing existing drugs can give a fast path to clinic. • I think it is a unique enough approach that CIRM should fund, despite some of the limitations brought up in the review.

	• I liked this application because it is novel and for a modest investment, we could learn something new and impact the field. I don't see that it will directly lead to a treatment but it could perhaps inform other efforts. • Drugs exist to target the Tor pathways and are in clinical practice - if they could be repurposed for COVID-19 this would have potential impact. • Repurposing drugs such as mTORC1 inhibitors represents a rapid pathway to translation. • Accessibility of this treatment (if effective) is a strength. • Interesting concept and good principle of action, but details need to be drawn out. • The path to clinical trials is unclear. • This is a high risk, ambitious project. • The applicant mentions applying for funding to do a clinical trial with a candidate if one emerges from the work. No consideration is given to how to work with the company that owns the drug that becomes the candidate. This is a critical issue.
No: 4	• The idea of testing mTOR inhibitors is promising. • It is unclear whether intervening by this mechanism will have sufficient impact in COVID-19
GWG Votes	Is the rationale sound?
Yes: 10	• The preliminary data is convincing. Good use of positive and negative controls in the preliminary data. • Rationale is sound in parts--needs clarification on the mechanism of action. • mTORC1 inhibitors have been demonstrated to have effects on viral replication and warrant further study in treating COVID19. • Preliminary data are very strong. • Weak "Yes": Some preliminary evidence presented for (mild) antiviral effect of mTORC1 inhibitors in vitro, but not compelling that these are likely to have a major impact on SARS-CoV-2, to extent needed for significant therapeutic benefit. • Concern: Compounds chosen have significant side effects. • Preliminary data, although limited [and difficult to see!] is supportive of the proposed project. Quantitative assessment of the immunofluorescence and immunoblots would be more compelling. The proposed research will greatly expand these early studies and are set up to provide quantitative data.
No: 5	• The rationale is somewhat weak, I would like to see data from COVID-19 patients that mTOR pathway is activated and its activation is associated either with disease severity or mortality. It is likely that information on the role of mTOR activation in pathogensis of COVID 19 is already available in the literature or open data bases on scRNAseq of lung tissue of COVID-19 patients. • The relevance of mTOR biological pathways to COVID-19 lung disease is less clear. Deprivation of lipids to virus might reduce viral survival but maybe more in a chronic than an acute infection. • A drug to prevent spread in asymptomatic individual is unlikely to be acceptable • The metabolic premise is not very strong. • Limited preclinical supporting data.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• Likely to succeed in the described work--need clarification for how it will be applied. • Plans appears reasonable.
No: 10	• The project will evaluate the class of compounds for which applicant has some preliminary data. Multiple approaches to considering whether inhibitors are viable as a candidate for the clinic based on limited, but consistent, preliminary data. • If early experiments in Aim 1 are negative, applicant suggests moving to an alternative approach involving metabolomics to look for new targets. This is possible, but unlikely to be fruitful in time frame of grant. Project is basically yes or no on this type of inhibitor as a candidate. • Aim 2 does not seem on critical path for therapeutics development - ultimately, it just comes down to whether the inhibitors exert a sufficiently strong antiviral effect or not. • The first aim of the project is to investigate the ability of FDA approved mTOR inhibitors to prevent SARS-CoV-2 infection of primary human lung epithelial cells in two models. Organoids and ALI cultures are well-designed and will produce clinically relevant data, however the second aim is to validate mTOR activation in patients with COVID-19- I think that this should be done first before starting testing of mTOR inhibitors in the pre-clinical models. • Applicants propose to do scRNAseq of samples of COVID-19 patients, I am a bit surprised as to why they want to do this if such a study has already been published. • I think it would be better to jump right to an animal model and go for the home run hit.

	● A short term course of rapamycin might be OK, but it can have lots of side effects. There are a number of mTOR inhibitors that could be tested alongside rapamycin. Rapamycin may not act fast enough to impact the virus. ● The plan is underdeveloped. The lung organoid composition requires more study. ● It is unclear how experimental outcomes/endpoints using lung organoids will inform translation to the clinic. ● The construction and analysis of the stem cell-derived models is underdeveloped. ● Quantitative milestones are provided but it's unclear what is needed to warrant the next step in clinical development. ● Reasonable qualitative approach in human cell systems, but no comparison with other antivirals or clear sense of the degree of inhibition that would qualify for progression.
GWG Votes	Is the proposal feasible?
Yes: 11	● Strong letters of support/collaborations. The team appears to have all the pieces in place to carry out the proposed experiments. ● Likely to succeed. ● Seems feasible. ● Does the BSL3 have approvals and are the individuals experienced in BSL3 work? ● Strong team with good expertise, access to necessary resources is in place. ● Team has clear expertise in viral effects on metabolism and cell biology. Might benefit from input from translational side in pharmacology/drug development. ● Studies as designed should be achievable. ● Research plan is clearly articulated and specific. Work towards different aims with different collaborators overlaps. ● Excellent team with each of the key members providing complementary skills and resources. ● Team has secured institutional approval and priority access to autopsy and bronchial lavage samples for the project. All other facilities and resources are in place in team members' laboratories.
No: 4	● Aim 1 is feasible whereas Aim 2 (which incurs most of the costs) seems non-essential - this is not a research grant. ● The activities are too ambitious (e.g., scRNA-seq).

Application #	DISC2COVID19-12045
Title (as written by the applicant)	Engineered human placenta-derived mesenchymal stem/stromal cells (ePMSCs) for the treatment of COVID-19
Research Objective (as written by the applicant)	We aim to compare the therapeutic effects of ePMSCs to the well-established bone marrow MSCs (BM-MSCs) leading to the development of an effective stem cell product for treatment of COVID-19.
Impact (as written by the applicant)	If successfully achieved, this project will lead us to identify an effective cell therapeutic product for the currently evolving COVID-19 pandemic.
Major Proposed Activities (as written by the applicant)	• In vitro comparison of the therapeutic functions of ePMSCs and BM-MSCs in the context of COVID-19 • Evaluate the therapeutic function of ePMSCs and BM-MSCs for the treatment of COVID-19 in the K18-hACE2 transgenic mice
Statement of Benefit to California (as written by the applicant)	California is seeing a steady increase in the number of COVID-19 cases. Thus, this proposed research has the potential to ameliorate the ARDS associated symptoms of COVID-19, and help in reducing the burden on the healthcare system. As the state of CA and the US is moving towards reopening, there is great potential for a second spike in the number of patients, and thus there is an unmet urgent need to develop efficient therapeutic products for COVID-19.
Funds Requested	$249,632
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	70
Median	70
Standard Deviation	8
Highest	85
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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: 8	• This project is seeking to develop a novel MSC cell product (placenta derived MSCs, grown in defined medium which is supporting MSC neurogenic potential) towards application in COVID-19 induced ARDS. Due to their potent immunomodulatory properties, MSCs are regarded as promising candidates for treatment COVID-19 induced cytokine storm and more than 10 registered clinical trials investigating MSCs are already recruiting patients. • The proposed MSC product is likely to be superior in efficacy to the commonly used BM-derived MSCs. Applicant provides strong pilot data demonstrating superiority of their cell product in terms of secretion of key paracrine factors important for MSC therapeutic mechanism. Placenta derived MSCs have several advantages over the BM-derived: non invasive procedure of isolation, almost unlimited supply of tissue source (as this is discarded material), reduced variability due to donor age, low donor age.

	• Authors already have established protocols for GMP manufacturing of their cell product and generated cell bank of GMP grade PMSCs to be used in the proposed study. If successful, there is high likelihood that the product might indeed result into effective therapy. • Because the applicant has already generated GMP grade cell product it will accelerate progression to clinical trial. The applicant mentions an IND submission upon completion of the proposed work. • A path for MSCs to clinical trials is well-paved. Accessibility to broad populations is feasible. • New treatments for respiratory distress syndrome associated with COVID-19 are needed, especially as some patients acquire significant long-term deficits. • Other MSC-based therapies are already well ahead of the ePMSC product in clinical testing for same indication. • MSC-based cell therapies have been advanced as a spotential treatment for COVID-19.
No: 7	• Ambitious proposal but concerns about defined endpoints and how success will be evaluated. • There are multiple MSC trials already underway for COVID-19 ARDS. It is unlikely the proposed project can catch up with/overtake these to impact on this pandemic. • The cells are unlikely to distribute broadly in the body. • It could lead to the selection of an ePMC (or possibly a BM MSC) cell line for use in the clinic for treatment of COVID-19 ARDS, but the decision tree for promoting a candidate for clinical use is not clear. Close to 30 clinical trial using some sort of MSC for treatment COVID-19 ARDS are underway or close to enrolling around the world. This potential use of this general type of adult "stem cells" is well established. The idea of comparing different lots and/or different types of MSC for several activities elated to potential MOA is excellent, and careful, but criteria for selection of the best lot (really MOA based potency) are unclear. • Not clear what the applicant will do with the data in terms of making a decision to proceed. If BM-MSC end up to be better or as good, will applicant try to advance ePMC? Indeed, from a drug development perspective, why is the applicant studying the bone marrow derived if different lots of ePMC vary in the various activities measured, which would advance the therapeutic? Applicant says they will weigh "immunomodulatory" activities more in choosing lots for studies with infected hACE2 mice. How will this be done?
GWG Votes	Is the rationale sound?
Yes: 7	• Strong preclinical data suggest that MSCs have strong therapeutic potential for treatment of ARDS and their safety is already established in patients with ARDS • Applicant demonstrated that their cell product is characterized by higher then BM-MSCs level of secretion of number of key biologically active factors which were previously demonstrated to be important for the MSC mechanism of action in multiple disease settings. Additional benefit of ePMSC is their neuroprotective effect which might be important for COVID-19 patients. Authors also demonstrate that ePMSC have a strong protective effect in 3 different in vivo models of neurological diseases. • MSCs have been proven safe. This source of MSCs are likely more consistent and potent than other sources of MSCs. • MSCs have anti-inflammatory properties so it does make sense. • MSCs have strong therapeutic potential for treating ARDS, and thus COVID-19-induced cytokine storm. • Placental MSCs have advantages over bone marrow-derived MSCs. • Other groups are much further along with MSC therapy, so this product would need to be much better to move past this stage. • While the placental stromal cell product has some advantages over MSCs derived from adult bone marrow or adipose tissue, especially for neurological conditions (e.g., because of high BDNF secretion), no compelling evidence is presented that for lung disease the ePMSCs would be better than others. • Neuroprotective effects of IV-administered cells are not well-justified. • Suggestions that these cells would also help avoid neurological deficits resulting from COVID-19 are not well supported. Seems likely the large majority of injected cells would wind up in the injured lungs.
No: 8	• The proposed assays for characterizing lots are based on widely accepted ideas for how MSC might impact inflammatory states. Again, dozens of on-going trials invoke the same rationale for using MSCs in COVID-19 ARDS. • There are concerns about the generation of interpretable data outcomes.

	• Skepticism of whether cell models will faithfully reflect the underlying biology. • The rationale for MSCs is sound and already well explored. This project pivots around using a ePMSC that is enhanced to be particularly effective in CNS disease. The rationale for this in COVID-19 ARDS is therefore less clear since the cells will be trapped in the pulmonary microcirculation and not reach CNS/PNS. • Preliminary data with animal models is needed to support this rationale. • There are no preclinical data to justify use of this cell product in lung disease. • The preliminary data reviewed indicates that the ePMSC do differ in some regards from the types of BM-derived MSC tested by the applicant in the past. Whether these differences will result in more biological activity against COVID-19 ARDS is not clear. • The application does not mention that large corporate clinical trials of BM-MSC in different lung inflammatory states, including ARDS, while raising no safety concerns, have not met efficacy endpoints. Also, while BM-MSC are approved in a few countries for steroid resistant GVHD in children, approval for GVHD in the US is still pending.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• Applicant proposes clear, well structured and thorough experimental plan, using clinically relevant in vitro and in vivo models which will allow to obtain useful information about therapeutic effect and gain insights into the mechanisms of action. • Clear strength is the use of K18-hACE2 mice to model CoV-SARS-2 infection. • All in vitro models and assays are well established within the groups of the applicant. The colony of K18-hACE2 mice is already established. In case difficulties would arise in the work with this mouse strain, applicants have identified an alternative to use recombinant virus which could use mACE2 for entry so risks are minimal. • How much better are these cells than other MSCs? I would skip the first aim and move right to animal studies. • Additional endpoints on the animal models should be added. • Well-designed study that uses appropriate preclinical models of ARDS. • Outcome measures need to be better defined. • Studies as designed should support translation.
No: 10	• Endpoints not defined. • The milestone 1 in vitro data have all been done before on a wide range of other MSCs. It's unlikely they will generate much new data. • No info on what success criteria are for the animal studies: ie. estimated treatment effect size. measure variability, etc. • The ACE2 transgenic model is relevant but limited as it expressed ACE2 only on epithelial cells. It might therefore be useful to have an additional model where virus can target a range of cells. • Plan is not really clear on how in vitro test or animal model would reveal potential unique/superior properties of the ePMSC product for the ARDS indication. To some extent this reflects structure of application around qualitative Aims rather than more rigorously defined Milestones for progression to a validated candidate. A "me too" MSC product should not be a priority for CIRM funding at this time. • Not sure how much we are going to learn by comparing these MSCs to BM-derived MSCs. • If applicant really wants to advance the ePMSC as a product and already has characterized the lines with the assays, why wait for comparison with BM lines to go to in vitro and animal models? • It is not clear what their specific target in the body is (e.g., CNS). • No discussion of using human MSC in immune competent mouse model.
GWG Votes	Is the proposal feasible?
Yes: 11	• Yes, the plans are clear, realistic and likely to be achieved within proposed timeline. • The applicant has assembled a stellar team of collaborators, consisting of world leading experts in clinical translation of MSC based therapies, virology, immunology and mouse models of disease. • This is a good team and have the resources in place to carry out the aims of proposal. • Likely to succeed in proposed experiments. • Should be feasible in the time frame of the grant.
No: 4	• There may be difficulty in initiation of clinical trials based upon the current number of clinical trials in COVID-19 using MSCs.

Application #	DISC2COVID19-12027
Title (as written by the applicant)	Engineered allogeneic reticulocytes expressing SARS-CoV-2 antigens as a cellular vaccination strategy to prevent COVID-19
Research Objective (as written by the applicant)	Engineering allogeneic reticulocytes to produce SARS-CoV-2 antigens for vaccination against COVID-19.
Impact (as written by the applicant)	Overcoming the barriers that exist in eliciting anti-viral cytotoxic T cell responses from vaccination by cell-associated antigen transfer of reticulocytes.
Major Proposed Activities (as written by the applicant)	• Demonstrate effective technology-mediated delivery of eGFP-mRNA into reticulocytes • Demonstrate effective technology-mediated delivery and expression of SARS-CoV-2 spike protein mRNA into reticulocytes • Measurement of perturbation and differentiation of reticulocytes • Gene editing/insertion of SARS-CoV-2 spike protein/eGFP expression cassette into a Rosa26 locus using CRISPR/Cas9 and Homology Directed Repair (HDR) • Assessment of SARS-CoV-2 antigen presentation • Demonstration of disease modifying activity by engineered cells
Statement of Benefit to California (as written by the applicant)	Not only is COVID-19 a public health crisis but it has had a massive impact on California economy. The budget proposal for the state of California has projected a revenue decline of 22.3%. Vaccination is critical for both the health of Californian citizens and the restoration of the economy, allowing tourism and large events to resume.
Funds Requested	$202,500
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	56
Median	60
Standard Deviation	7
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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• In theory a vaccine would be beneficial. However, it is unlikely that this vaccine, even if successful, could be mass produced and delivered. There is no discussion about whether HLA matching is required or not and this would be key to understanding whether it could be used as a mass vaccine. • The potential cost is also a concern.
No: 11	• The idea of ex vivo genetic modification of HSC for expression of SARS-CoV spike protein is exciting, however more pilot data are required to reassure the panel that the approach is feasible.

	• Proposal is based on unsupported assumption that humoral response will not be sufficiently effective in COVID-19. • Main technology doesn't address a fundamental delivery bottleneck. • As designed, the strategy could pose serious safety concerns. • This could be a potential use for driving HSC expansion technology going down the erythroid pathway. Several companies have tried doing this to make enough RBC for transfusion. It has proved a difficult task to do in a commercially feasible way. This could use some of the expertise developed in that undertaking for an indication that requires manufacturing of fewer cells. However, more straightforward vaccine approaches are still likely to be more commercially practical. • Applicant has sketched moving to animal studies for POC, but nothing beyond that. In particular, no discussion of dosing and scale up issues which are significant.
GWG Votes	Is the rationale sound?
Yes: 3	• Reticulocyte engineering is a sound approach for vaccination. • The proposed delivery of mRNA and transgenes is appropriate.
No: 11	• Preliminary data demonstrate better effectiveness of the technology compared with electroporation in transfection of eGFP mRNA in HSC, however I would like to see successful delivery of CRISPR/Cas9 ribonuclear complex. Also, the process of HSC differentitation towards reticulocytes is not easy and applicants should demonstrate that they can actually do this after HSC modification. • Data shows that the technology preserves HSC viability and colony forming potential, and that reporters can function. • Limited supporting preclinical data to support use in COVID-19. • Mechanism of action unclear. • Lack of info on whether HLA matching matters here or cross priming - no discussion of this. • More thought on the HLA mismatch and cross priming is required. • Applicant does not discuss impact of HLA class I matching for antigen presentation by reticulocytes. Although reticulocytes can present antigen in some cases as cited, most likely that reticulocytes would present through macrophage or DC after phagocytosis rather than directly to T cells. How this would impact generation of Class I restricted cytotoxic T cells compared to Spike proteins presented in other formats is unclear. • Applicant's discussion of potential benefits to elderly of augmenting direct presentation to T cells to generate cytoxic T cell responses is confused. Immunosenescence due to thymic involution impacts T cells broadly. • In connection with point above, applicant's microarray data should give information about expression by reticulocytes of co-stimulatory molecules and of factors needed to load and transport Class I after treatment. Nothing said about this. • Applicant does not discuss issue of HLA restriction of any responses engendered by direct presentation to T cells by erythrocytes. • Except for mentioning use of Type O blood, applicant does not discuss possible role of other alloantigens and of alloimmunization with engineered reticulocytes. • The characterization of the engineered cells is not described. What exactly is the cell readout of efficacy?
GWG Votes	Is the proposal well planned and designed?
Yes: 2	*none*
No: 12	• Appropriate milestones. • Insufficient characterization of engineered cells. • The details of the studies are poorly described, and the planning and design are difficult to evaluate. • How long would the cells last in recipient? About a day? Is this enough to cross prime? • Insufficient characterization of engineered cells; silent on impact if any of HLA type. • Their statement of inclusion didn't really address anything other than to say they would include minorities. Not clear if HLA matching will matter the way the proposal is written, thus would need to include many different sources for the cells. This would increase costs. • Issues with the animal experiments are not considered in any detail. In particular, applicant does not discuss whether immunity to xenogeneic human engineered erythrocytes in hamsters or ferrets will impact this as a model for human immunization. • I could not find any risk mitigation strategy.

GWG Votes	Is the proposal feasible?
Yes: 3	• It is potentially feasible to do this study and the group has experience in transfusing cells efficaciously.
No: 11	• The details of the studies are poorly described. • There is no justification of a read out/endpoint to assess efficacy. • Milestones 1-3 are with "reticulocytes", apparently isolated with beads from peripheral blood. Applicants say nothing about source of blood and feasibility of getting enough material for this work. If possible, it seems to make sense to find out early in the program if engineered reticulocytes can present antigen [Milestone 5] before undertaking HSC modification. Or one could start the HSC expansion project simultaneously. Again, there is little discussion of scale or expected amounts of material. • Milestones 4 uses purchased HSC. There is no discussion of scale. The kits used for HSC expansion and differentiation expands erytbroblasts and a mixture of other cells in the lineage unless EPO is added to drive formation of reticulocytes. Issues of culture purity or yield are not discussed. • No details are given on how APC or T cell killing assays will be done. In particular the issue of HLA restriction is not addressed. However, as applicant is using using commercial sources of HSC [and non- specified sources of T cells and airway epithelium] how will restriction be studied? • Manufacturing may need to be considered early on to improve chances of success. • Lack of alternatives and pitfalls raises feasibility concerns. • Team appears to be missing a stem cell expert. • Team is strong and has relevant expertise. • Short bios in the application budget suggest that staff is experienced with the technology and has already worked with HSC using the technology. Only one detailed biosketch was uploaded. • Applicant says nothing about access to facilities to handle virus safely in briefly discussed studies on virus killing. • Most of material seems to be from commercial sources. But reticulocytes will come from peripheral blood. Source and human subject infrastructure/approvals are not specified. • The budget appears appropriate, although it is not clear how many animals are included in the line items for the animal models.

Application #	DISC2COVID19-12053
Title (as written by the applicant)	Fucosylated Cord Blood Stem Cells to Treat COVID-19 Patients with ARDS and Prevent Respiratory and Multi-Organ Failure
Research Objective (as written by the applicant)	Fucosylation-enhanced homing of cord blood stem cells to sites of lung inflammation, to improve the outcome of COVID-19 patients with acute respiratory distress syndrome (ARDS) and respiratory failure
Impact (as written by the applicant)	Poor engraftment is a major limitation of stem cell transplantation, due in part to a defect in the cord blood or mesenchymal stem cells' ability to home to sites of inflammation and bone marrow
Major Proposed Activities (as written by the applicant)	• Optimize the fucosylation of cord blood and mesenchymal stem cells, evaluated by post-treatment flow cytometric analysis using anti-CLA antibody to assess fucosylation of the various cell components • Using established methods, compare the efficacy of fucosylated cord blood vs. mesenchymal stem cells to attenuate ARDS induced in mice using the H5N1 HALO flu virus model of virus-induced ARDS • Using established methods, compare the efficacy of fucosylated cord blood vs. mesenchymal stem cells to attenuate ARDS induced in hACE2 transgenic mice in a SARS-COV-2 model of virus-induced ARDS. • Based on the results of Activities 2 & 3, determine the mechanism(s) of action, immunoproteomics and other pharmacodynamic metrics of efficacy vs. ARDS induced in mice infected with either viral model • Assuming positive results, initiate activities that will facilitate a Phase 2 clinical trial of TZ101-treated cells in human COVID-19 patients, including drug manufacturing and obtaining IND clearance
Statement of Benefit to California (as written by the applicant)	To date California has 145,643 confirmed cases of COVID-19, with a staggering 4,989 deaths. Approximately 15-20% of COVID-19 patients require hospitalization, ~5% require advanced care in Intensive Care Units (ICU), with many requiring mechanically assisted ventilation. All COVID-19 ICU patients require respiratory support; many need multi-organ and neurological support, straining the California health care system. Effective therapy would reduce hospitalization burden and medical intervention.
Funds Requested	$249,728
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: 3	• A new therapy for COVID-19 ARDS would be valuable. However, is it feasible to match, fucosylate cells, characterize them and deliver them to patients with ARDS in a realistic time window? • ARDS is a significant problem.
No: 12	• The main problem of this proposal is that the data on the effectiveness of the whole cord blood transfusions in the setting of ARDS are very limited (I could find only 1 publication). Although cord blood (CB) indeed contains Tregs and MSCs which could be beneficial for patients with ARDS, it also contains neutrophils and other inflammatory cells which might become activated and further exacerbate the cytokine storm. • Before proceeding to modifications, one should establish first that the cell product can provide therapeutic benefits in the disease of interest. • Not clear what the products will really do in this application. • Unclear how cells will enhance healing in injured lungs. • The work is unlikely to yield a clinical product that would have a high impact. • Safety concerns regarding mixture of cells (not characterized) for use in COVID-19. • The MOA of such a highly heterogeneous product in the context of COVID-19 ARDS is unclear, and critical product characteristics are not likely to be controlled well. Many other approaches to COVID-ARDS are being developed. • This proposal involves a cell therapy, but not a stem/progenitor cell therapy. Stem and progenitor cells constitute less than 1% of the cells in cord blood. The vast majority of the cord blood cells that are fucosylated are mature leukocytes, as noted by the applicant. • Applicant has brought the product into the clinic for a cord blood transplant and has found collaborators with relevant animal models, and has experience with FDA processes. Applicant does not address what regulatory strategy it might pursue given that TZ-101 already has an history with the Agency.
GWG Votes	Is the rationale sound?
Yes: 2	• Fucosylation can enhance homing to site of inflammation.
No: 13	• Applicant and academic collaborators have provided evidence that fucosylation of whole cord blood samples can enhance hematopoeitic engraftment in animal models and that fucosylation of in vitro expanded regulatory T cells from cord blood can suppress 3rd party GVHD in mice. Other workers have shown that fucosylation of MSC augments suppression of 3rd party GVHD in mice. Although fucosylation is associated with better binding to selectins, the actual MOA for the augmented activities remains unclear. • There is no solid evidence that cord blood infusions are beneficial in patients or pre-clinical models of ARDS. • The preliminary data are sketchy, difficult to read, and do not support the hypothesis that cord blood infusions will be protective in patients with ARDS. • There's no proof of concept for lungs. We have no idea of the effect of a cord blood donation's neutrophils, monocytes/other cellular components on the lung. • It isn't clear that increasing cell delivery to the injured lung is necessary since cells tend to accumulate in the lungs. • Limited supportive data to justify use in COVID-19. • It has long been known that >90% of iv administered cell products used for transplant, including cord blood, is removed in the lungs during the first circulatory pass. Some cells can then re-enter the circulation and go to other tissue sites like the marrow. Whether or not CB cells are fucosylated, most of them will be in the ARDS inflamed lung. Applicants present no data suggesting fucosylation will make a difference in this context. • Weak rationale, minimal relevant preliminary data. • Unclear how the various cell components will contribute to treating ARDS. • The clinical product is not well designed. • Table 1 makes no sense to me. What are the historical controls in figures 3, 5 and 6? Not sure what happened to Figure 4. • Applicants cite the potential activities of cord blood Treg cells on suppressing inflammation. Most studies have been done with GVHD. ARDS has a GVHD-like component, but also many other features. Also, cord blood Tregs are low in number. Clinical trials showing the activities of cord blood Tregs have involved in vitro expanded Tregs to increase cell numbers from those available in cord blood. • Cord blood monocytes have also been shown to have anti-inflammatory activities, but how these cells would respond in the context of the inflamed lung is not clear. The general issue is that each cord blood unit is different in terms of the number of each type of leukocyte [and senescent CB RBC] it contains, and each type of leukocyte could

	contribute to the activity of the unit. Cord blood banks only bank units on the basis of total nucleated cells, CD34+ counts and HLA type. ● The applicant does not discuss or consider the impact of HLA mismatch on the activity of the proposed product. Applicant's previous work in the clinic in the transplant setting has involved partially matched cords. Mismatching could lead to rejection of the product, with consequent increase in inflammation. Mismatch could also lead to GVHD. Cord blood T cells are less likely to cause GVHD than PB cells in some combinations, but still cause the major morbidity associated with transplant. ● The previous work cited by applicant in transplant is not relevant to the proposed indication for many of the reasons given above. I could only find one previous clinical trial with this material listed in ClinTrials, in the published literature, or on the applicant's website. This phase 1 trial was published in 2015, applicant's reference 29. If a phase 2 has been done, it has not been published. The website appears to call the published trial a phase 2. ● Figure 6 in the the application is drawn from the phase 1 trial. Importantly, in that double cord transplant trial, fucosylated and control cells become the dominant cord that prevailed long term in recipients at equal frequency. Treatment of the cord blood did lead to faster neutrophil and platelet engraftment compared to a historical control [Figure 6 of application]. ● In contrast to statements in the application text and the figures in Table 2 and Figure 3, the data in reference 29 show that the incidence of toxicities and GVHD in between the fucosylated cells and the historical control were not statistically significant. No statistical metrics are given in the application. Again, the application discusses a phase 2 trial, and reference 29, a phase 1 trial. I do not understand the discrepancy. ● This is not a stem/progenitor cell project. Such cells would contribute little, if anything to the proposed MOA of the product.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 14	● The design of the proposed experiments is not clear. There is no information on how exactly the product will be tested in various animal models (dose, controls, timeframe, endpoints, mechanism of action, etc). ● The animal studies are missing too many details. Dose/timing in relation to infection with either model. Sample sizes? Primary endpoints? Cell source? Human cells? ● The preclinical experiments are lacking in details. ● No details on how candidate will be tested in animal models. ● Animal model characterization of ARDS is insufficient. ● Not enough preclinical detail. ● I am concerned about using human cord blood cells in immunocompetent mouse models of viral infection. The issue is similar, or perhaps more acute as a xenogeneic combination, to the potential issue in clinical use discussed above. The applicant has not discussed issues of timing, dosing, or previous experience with cellular products in this regard. ● There are many issues with the product concept and the plan. No pitfalls are mentioned: Alloreactivity of mismatched stem cell products, exacerbation of inflammatory responses in the lungs due to alloreactivity in either direction, exacerbation of debris in the pulmonary circulation due to intravenous injection of thawed cord blood containing dead cells and damaged erythrocytes. ● No info on HLA matching/ABO matching. Is it feasible to (match), fucosylate cells, characterize them and deliver them to patients with ARDS in a realistic time window? ● No info on how the cells would be characterized - this should be available as already used in a clinical trial before. ● HLA matching not discussed. ● No info on assessing the antiviral effect of the cells. ● Heterogeneous cell population is a concern. ● There is not a sufficient discussion on the potential to exacerbate disease. ● The plans seem too ambitious.
GWG Votes	Is the proposal feasible?
Yes: 7	● Aim 1 should be readily accomplished for cord blood as the applicant and collaborators already have considerable data in this regard. It is not clear what additional information they need to optimize or what criteria they will use. Is it simply "All cells get fucosylated?" This is what they have attempted to do in the past and Table 1 suggests they are pretty close.

	● With regard to Aim 1, on p. 8, applicant includes "hemopoietic and mesenchymal stem cells and cord blood." Subsequently in the application, the applicant only refers to cord blood cells. Given the rarity of HSC and MSC in cord blood, why these populations are called out for cord blood optimization is not at all clear. ● Manufacturing the product is very simple and proposes no risk to feasibility. ● The applicant team has been working together, with the product, and with academic collaborators for an extended period. However, previous work has centered on transplant related matters associated with indications in oncology. The primary issues have been engraftment, GVHD, and related outcomes in immune ablated patients. They have found a good collaborator for viral infections and pulmonary pathology but could use related clinical expertise on the team as they prepare for an FDA process. ● The team is very complete including a regulatory affairs person. Excellent letters of support. ● Outstanding team. ● Some questions on what is established in investigators' labs already. ● The letter of support suggests that the animal models of virus infection are in place, but no specifics about availability during the proposed 6-month time window are given. ● The collaborators are experienced in the animal models they propose to study. ● The team is well qualified.
No: 8	● Project lacks strong preliminary support in treating lung injury. ● Lack of anticipated translation value for COVID-19. ● It is not clear if the animal models are established in the applicant's laboratory or at least colonies of transgenic mice are in place. ● The work package does not describe the planned work in enough detail to ascertain feasibility.