APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Lowest Score	Highest Score	Y	N
CLINICAL APPLICATIONS										
CLIN2COVID19-11857	A phase I/II study of human placental hematopoietic stem cell derived natural killer cells (CYNK-001) for the treatment of adults with COVID-19	$750,000	**N**	**84**	82	5	70	85	5	9
CLIN2COVID19-11823	Mesenchymal Stromal Cells for ARDS (COVID positive and COVID negative)	$750,000	**N**	**72**	72	7	60	85	1	13
DISCOVERY APPLICATIONS										
DISC2COVID19-11811	Repurposing Aminoadamantane Nitrate Compounds to Inhibit SARS-CoV-2 Viral Activity and to Protect the Brain from Viral-Related Damage	$150,000	**Y**	**90**	89	3	85	93	14	0
DISC2COVID19-11901	Development of a novel PIKFYVE kinase inhibitor for the treatment of COVID-19	$150,000	**Y**	**85**	84	8	65	99	8	6
DISC2COVID19-11838	Biomaterial vaccine to enhance the formation of SARS-CoV-2-specific T memory stem cells	$149,916	**N**	**82**	82	4	75	88	7	7
DISC2COVID19-11813	Combating COVID-19 using human PSC-derived NK cells	$150,000	**N**	**78**	77	7	65	90	2	12
DISC2COVID19-11770	Mitigating SARS-CoV-2 hyper-infectivity and induced inflammation	$149,998	**N**	**75**	74	4	65	80	0	14
DISC2COVID19-11840	“Accelerating stem-cell based repair of the lung in response to SARS-COV-2 infection.”	$150,000	**N**	**74**	72	7	50	80	0	14
DISC2COVID19-11881	Extracellular vesicles from cardiosphere-derived cells (CDEX) for treatment of Covid19.	$150,000	**N**	**-**	-	-	-	-	0	14
DISC2COVID19-11734	Improving Immune Function via Rejuvenation of Aged Human Hematopoietic Stem Cells to Combat COVID-19	$149,999	**N**	**-**	-	-	-	-	0	12

Application #	DISC2COVID19-11811
Title (as written by the applicant)	Repurposing Aminoadamantane Nitrate Compounds to Inhibit SARS-CoV-2 Viral Activity and to Protect the Brain from Viral-Related Damage
Research Objective (as written by the applicant)	The objective is to screen a series of aminoadamantane nitrate compounds for their ability to protect hiPSC-derived neurons from SARS-CoV-2-related damage and to block SARS-CoV-2 activity.
Impact (as written by the applicant)	If successful, our screen would identify a drug candidate for further development that would protect neurons from SARS-CoV-2-related damage and also inhibit SARS-CoV-2 activity.
Major Proposed Activities (as written by the applicant)	• Screening of nine (9) aminoadamantane nitrate congeners for ability to inhibit NMDAR-mediated current in hiPSC-derived cerebrocortical neurons. • Moderate-throughput screening of nine (9) aminoadamantane nitrate congeners in BSL3 facility for cytopathic effect (CPE) of SARS-CoV-2 live virus in monkey Vero cells. • Moderate-throughput screening of 'hits' of aminoadamantane nitrate congeners in BSL3 facility for cytopathic effect (CPE) of SARS-CoV-2 live virus in monkey Vero cells with full dose-response curve. • Viral plaque assays for SARS-CoV-2 for viral titer and full dose-response curve of drug candidates. Field of view microscope provides dynamic tracking of plaques at individual cell death event level. • Assess synaptic integrity of hiPSC-derived neurons in co-cultures of SARS-CoV-2-infected monocytoid cells and astrocytes with full dose-response curve of drug candidates.
Statement of Benefit to California (as written by the applicant)	Finding a drug that positively affected the course of COVID-19 infections by protecting the nervous system AND limiting viral infectivity or virulence would have tremendous benefit for all Californians as well as everyone in the world.
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	89
Median	90
Standard Deviation	3
Highest	93
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	● Identification of aminoadamantane nitrate compounds as novel anti SARS-CoV-2 compounds is a novel approach for a potential active agent to one aspect of multifactorial COVID-19 disease. ● This class of drugs is important to investigate and it is not clear that any other groups are doing this. So it is important that someone investigate these drugs.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	● Given the stage of development, the rationale is sound. ● Aminoadamantane drugs (e.g., amantadine, rimantadine, and memantine) act as anti-viral agents because they can also block the ion channel found in the envelope of viruses such as SARS-CoV-2. ● Approach is based on efficacy with another virus, influenza. ● There is strong prior experience that drugs of this class have antiviral activity. ● Can the applicant explain if (or why not) aminoadamantane or other adamantane drugs have been identified (e.g., in preprint servers or published literature) in computational or high-throughput screens for coronavirus activity?
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	● Some concern with respect to toxicity associated with product class but should be manageable with dose optimization. ● "PI subsequently found that these aminoadamantanes had activity in the CNS." This is an overstatement. In 1969, amantidine's Parkinson's disease activity was discovered.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	● No concerns noted. ● Drugs are currently available, thus approach is feasible.
No: 0	*none*

Application #	DISC2COVID19-11901
Title (as written by the applicant)	Development of a novel PIKFYVE kinase inhibitor for the treatment of COVID-19
Research Objective (as written by the applicant)	Alveolar type II cells are the stem cells of the lung, and they are killed by SARS-CoV-2. We will determine if a novel PIKFYVE kinase inhibitor prevents SARS-CoV-2 infection of type II cells.
Impact (as written by the applicant)	Although PIKFYVE inhibition blocks SARS-CoV-2 infection, no known PIKFYVE inhibitors have suitable drug-like properties. We would validate a novel PIKFYVE inhibitor for the treatment of COVID-19.
Major Proposed Activities (as written by the applicant)	• Confirm ASR-149's efficacy against SARS-CoV-2 in human iPSC-lung type II cells • Use antisense oligonucleotides to verify that PIKFYVE inhibition blocks entry of SARS-CoV-2 pseudovirus and live replication competent SARS-CoV-2 virus in human iPSC-lung type II cells
Statement of Benefit to California (as written by the applicant)	If successful, these studies could lead to an effective treatment for COVID-19 that would reduce suffering from COVID-19 and enable Californians to live without social distancing requirements.
Funds Requested	$150,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	8
Highest	99
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The proposed technology will further test the role of a phosphatidylinositol-3-phosphate 5-kinase (PIKFYVE) inhibitor, which blocks endosome maturation, in the prevention of SARS-CoV-2 infection. There is a high level of potential benefit and significance. • Effective treatments for COVID-19 is an unmet medical need. Anti-SARS-CoV agents are urgently needed to control and prevent current and future CoV infections. • The proposed candidate has potential to intervene in two key disease pathways of COVID-19 patients. • It is important to continue work on compounds that are lead candidates out of large small-molecule screens. Otherwise there is little point in having people do large screens in the first place. This proposal meets this challenge by following up on one of the promising compounds identified in a high-throughput screen. • The main premise for this work was recently published, and proposed work will extend these findings. Unfortunately, the PI does not properly cite the work shown in the figures (except for figure 2) as not being from their research group, rather lifted from published

	work by others. This is an egregious way to provide preliminary evidence in support of the proposed work. ● The proposed work does not directly deliver a human stem cell based therapy, rather it makes use of PSC-derived lung organoids to test the effectiveness of the PIKFYVE inhibitors. ● This compound could have a profound effect on the virus.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 11	● The proposed project is based on the sound scientific rationale that PIKFYVE blocks early endosome maturation and fusion with lysosomes, and thereby prevents SARS-CoV-2 entry into the host cell cytoplasm. PIKFYVE inhibitors also suppress Th1 immune cell mediated inflammatory response, thereby moderating T cell mediated inflammatory response during virus infection. ● The proposed candidate was shown to be 25 times more potent than remdesivir, currently the only drug shown to be active in COVID-19 disease. ● Drug needs to be tested. ● Excellent preclinical data.
No: 3	● The fact that the evidence they provided was not credited properly is problematic. ● The main strength is the improved stability of the kinase inhibitor. ● Some of the preliminary data seemed lacking.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	● Supportive in vitro data were provided with SARS-COV-2. ● Supportive data were provided showing in vitro efficacy in human PBMCs with analogue. ● While the proposed iPSC-lung culture system has not as yet shown susceptible to SARS-COV-2, the system was shown susceptible to RSV. ● There is pilot safety data showing target selectivity, acceptable PK properties, in vivo target engagement and safety at 2x therapeutic dose.
No: 4	● The proposed work would have been strengthened by using SARS-CoV-2 or pseudotyped viruses in testing the efficacy of the compound. ● To directly show the requirement of the PIKFYVE kinase in viral infection, the PI will use an antisense oligonucleotide approach to knock-down the gene. This experiment should be moved up as an early aim, as it is critical to establish the role of this pathway and for later on to test off-target effects. ● At some point they need additional virology consulting support. ● Would be nice to test in infected mice.
GWG Votes	Is the proposal feasible?
Yes: 14	● Based on the preliminary data, and the work done by other groups, there is good support for the proposal as being feasible. ● This is an excellent team, with expertise in the necessary areas. ● Excellent primary team including consultants. ● 1) No preliminary data provided to show how efficiently pseudovirus and SARS-CoV-2 infect iPSC derived type II lung cells. 2) PIKFYVE inhibitors are shown to have anti-SARS-CoV-2 properties. As a result it is not novel. However, development and testing ASR-149, a stable PIKFYVE inhibitor is novel and worth further consideration. ● Rationale for not proposing virus-titration assays is not provided. ● Antiviral efficacy of ASR-149 in a preclinical model of SARS-CoV-2 infection is not provided. ● Back-up molecules are available as risk mitigation.
No: 0	*none*

Application #	CLIN2COVID19-11857
Title (as written by the applicant)	A phase I/II study of human placental hematopoietic stem cell derived natural killer cells for the treatment of adults with COVID-19
Therapeutic Candidate (as written by the applicant)	Human placental hematopoietic stem cell derived natural killer cells
Indication (as written by the applicant)	SARS-CoV-2 positive patients requiring hospital admission and have any 2 out of 3 symptoms: fever, cough, or positive disease-related chest x-ray.
Unmet Medical Need (as written by the applicant)	The primary objectives of the Phase I study is to evaluate the safety, tolerability, and efficacy of the product in COVID-19. The co-primary endpoints of Phase II study: A) To determine virologic efficacy of the product in COVID-19 by rRT-PCR. B) To assess the impact of the product on clinical symptoms.
Major Proposed Activities (as written by the applicant)	• Complete phase I study for 14 COVID-19 patients enrollment • Complete phase II study for 72 COVID-19 patients enrollment • Clinical data record, collection and management
Funds Requested	$750,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 84

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	84
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	9

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• There is no therapeutic available to prevent and treat COVID-19. This proposal aims to use an allogeneic, culture-expanded NK cell population derived from human placental hematopoietic stem cells as a therapy to control SARS-CoV-2 replication. • Adoptive transfer of antiviral NK cells to control virus infection is novel and strength of this application. • NK administration has potential to positively impact adverse immune system presentation of COVID-19 patients. • An interesting idea to combat a viral infection, but if successful it would be important. • If effective, this could add to various treatments being proposed for COVID-19. • This treatment strategy is more complex and likely more costly than antiviral drug treatments being proposed.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 8	• Weak rationale but sufficient to support a pilot clinical study. • It is unclear if NK cells as a therapeutic is relevant in COVID-19. • The rationale is based on the fact that NK cells kill their target cells by cytotoxic molecules, and via death receptor-mediated apoptosis.

	● Preliminary data have not shown activity against other viruses SARS COV-1, MERS. ● No specific data on SARS COV-2.
No: 6	● The investigators indicate expression of CXCR3 and lung trafficking of the product. However, there is some concern that NK cell infiltration could exacerbate disease in the lungs and this is not clearly considered. Obviously that is the point of the safety testing, but it would seem the product could be tested in a mouse infection model. NK cells are major correlates of control for respiratory viral infections and the investigators cite one study where SARS may be inhibited by NK cells. However, several studies also suggest NK cells are not involved or at least dispensable for control of related SARS and MERS (Zhao Proc Natl Acad Sci U S A 2014; Glass J Immunol 2004; Yasui et al Virology 2014). This diminishes some enthusiasm. ● This therapy seems to have a potential for high risk (hypersensitivity reactions, potential neurotoxicity and graft vs. host disease) for this indication unless patients are very sick. In particular, the cytokine release syndrome that could happen with this therapy may be the largest issue. ● NK cell transfer has never been demonstrated to work for treating any infectious disease. More preliminary data in other systems, including animal models and human studies is needed. Otherwise this is a huge leap of faith. Such a leap might be justified if there were no other concerns, such as toxicity. ● No pre-clinical data is presented which demonstrates potential efficacy. ● The rationale is tenuous.
GWG Votes	Is the proposal well planned and designed?
Yes: 13	● The organization of the study seems very well thought out, benefiting from previous clinical trial experience and FDA guidance. ● Study is well designed. ● The number of cells planned for infusion is higher than previous clinical trials of the similar product, but the rationale for this is not clear. How were any of these numbers determined? ● Other than improved outcomes there is no real evaluation of the function of the transferred NK cells. Could other assays to measure anti-SARSCoV2 activity be evaluated for this product? The proposed K562 assay is really insufficient. Virus inhibition, ADCC, and related assays are recommended. ● The investigators state the product may persist in the lungs for up to 21 days. If the presence of the expanded NK cells are pathologic, how would this be handled? ● The study design takes into account the possible safety issues. With the stopping rules and treating a few patients at a time, this should mitigate risks related to the immune response to the NK cells.
No: 1	● No data were provided showing NK cells are not susceptible to virus. ● Major concern is that increase in NK cells could exacerbate disease.
GWG Votes	Is the proposal feasible?
Yes: 13	● The product is already prepared and could be moved into patients relatively quickly. It is likely sufficient patients could be enrolled as proposed, so feasibility seems good. The team has extensive experience operating similar trials that are highly similar and also has expertise with handling and preparations of samples. ● The great team expertise is a strength. ● Good team and necessary resources. ● Interesting concept that needs to be tested. ● Protocol has been approved by FDA to initiate the clinical trial. ● The feasibility of allogeneic NK cell transfer in treating any virus infection is unknown.
No: 1	*none*

Application #	CLIN2COVID19-11823
Title (as written by the applicant)	Mesenchymal Stromal Cells for ARDS (COVID positive and COVID negative)
Therapeutic Candidate (as written by the applicant)	Novel testing of a cell based therapy (Mesenchymal Stromal Cells) for respiratory failure from ARDS.
Indication (as written by the applicant)	COVID-19 positive or negative ARDS patients
Unmet Medical Need (as written by the applicant)	There is an unmet need for more effective treatments for ARDS both COVID-19 positive and COVID-19 negative.
Major Proposed Activities (as written by the applicant)	• Assess clinical efficacy of MSC treatment for ARDS in this double-blind, randomized, placebo-controlled trial.
Funds Requested	$750,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 72

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

Mean	72
Median	72
Standard Deviation	7
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• No current treatment exists for COVID-19 ARDS. • There is a need for anti-inflammatory agents in COVID-19 associated ARDS. • ARDS caused by SARS-CoV-2 is a cause of fatal pneumonia and death during COVID-19. • Addressing ARDS using MSCs is a rational approach. • This treatment may work against ARDS, for which there are no good therapies at this time. • The focus on ARDS seems significant.
No: 4	• Impact on COVID-19 is not clear in the context of the larger study and ongoing development. • Key concern is that COVID-19 patients may not actually enroll into the trial. • Currently no supportive data that there have been any positive outcomes in lung diseases. • Use of allogeneic mesenchymal stem cells is a novel potential therapy for ARDS associated with COVID-19. • The approach is not unique—at least one other trial using a commercially prepared product has been proposed/is underway.
GWG Votes	Is the rationale sound?
Yes: 7	• The rationale that MSCs moderate lung inflammation, microvascular injury and protect lungs from virus induced ARDS is sound. • The rationale is sound, but the outcome for the clinical trials are unlikely to be achieved.

	● This proposal is an extension of a trial with ongoing enrollment and funding. ● The rationale seems good.
No: 7	● It is unclear if the potential immunomodulatory effects of MSC will work. The applicants don't present much evidence how their product might work better than what has already been studied in other similar models. ● The rationale seems weak. Given that the proposed mechanism of action is the effect of immune modulatory factors (various cytokines); why not treat directly with those agents and/or inhibitors, as is currently being done in dozens of trials? ● A clear rationale was not provided. ● Unclear if any type of signal will be detected with 20 patients.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	● Excellent team. ● 15 years of planning has moved into this project.
No: 10	● Piggy-backing onto an existing trial not specific for COVID-19 makes no sense. Without adequate numbers of patients with COVID-19 in experimental and control groups, no useful data will emerge. ● The trial design does not seem optimized for current COVID-19 care strategies. ● Needs a sample size calculation for the 20 patients. ● No supportive data provided. ● The endpoints for the clinical trial will not result in a product. ● On the plus side, modest incremental cost with co-funding.
GWG Votes	Is the proposal feasible?
Yes: 7	● Enrollment period seems really long given the number of COVID-19 patients and only 20 patients, so hard to understand what they expect to find. ● MSCs for treating ARDS is feasible, although the plans are not well thought through. ● Should be possible.
No: 7	● It is unlikely that data will be interpretable with only 20 subjects, i.e. so few patients in an uncontrolled study would at best confirm safety. ● Small sample size. The true primary end points are unclear. Unclear control group. ● The trial design does not seem optimized for current COVID-19 care strategies. ● This trial has had difficulty enrolling nationwide and needed to expand to include patients with trauma-associated ARDS. How likely is it that this site will enroll 20 participants in the required timeframe?

Application #	DISC2COVID19-11838
Title (as written by the applicant)	Biomaterial vaccine to enhance the formation of SARS-CoV-2-specific T memory stem cells
Research Objective (as written by the applicant)	The objective of this project is to develop an injectable biomaterial platform that can induce T memory stem cells (TMSCs) and boost immunoactivation to vaccines against SARS-CoV-2, which will help protect elderly people.
Impact (as written by the applicant)	This approach will boost TMSC production to enhance immunization, and address the low/weak immunoresponses to vaccines, especially in elderly people and with other disease backgrounds.
Major Proposed Activities (as written by the applicant)	● Fabricate artificial antigen presenting cells (aAPCs). (month 1 – month 2) ● Enhanced affinity and prolonged release of cytokines. (month 1 – month 4) ● Preparation of viral components in vaccine. (month 3 – month 5) ● Preparation and integration of biomaterial vaccine. (month 2 – month 5) ● Engineer the fate and functions of T cells in vitro. (month 4 – month 6) ● Perform In vivo Immunization Assays. (month 7 – month 10)
Statement of Benefit to California (as written by the applicant)	Vaccine will be essential to stop the spread of COVID-19 in California and world wide. However, a vaccine may not be effective enough for the people who need them most: elderly population who have declined immune responses to vaccines. The biomaterial-based vaccine proposed here will boost the effectiveness of the vaccination for the elderly people and patients with other diseases, and will help fight SARS-CoV-2 virus, flus and other infectious diseases.
Funds Requested	$149,916
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	88
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

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	● A very interesting proposal using a very unique approach and if successful may have wide application. ● The immunological approach is promising and could help patients including the elderly. ● The concept is intriguing and could have a high impact. ● Novel approach potentially high-risk high-reward. ● The project aims to establish a biomaterial-based vaccination against SARS-CoV-2 by promoting the formation of SARS-CoV-2 specific memory stem cells. The impact of memory stem T cells in controlling acute COVID infection is not known. Also, the role of T cells in antiviral immunity is not well understood.
No:	*none*

0	
GWG Votes	Is the rationale sound?
Yes: 12	● The formation of T cell memory cells could be important in the context of a vaccine. ● There is need for a T cell based vaccine that can protect the host for a longer period of time as antibody response wanes after 2-3 years. ● Biomaterial based vaccination is not well established. ● Preliminary data was provided although not with specific SARS-CoV-2.
No: 2	● The mechanisms of action are unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	● Very detailed plan with milestones. ● The steps are logical, although difficult. ● Very clear milestones and success criteria. ● Good team in place to execute.
No: 3	● The milestones are well detailed.
GWG Votes	Is the proposal feasible?
Yes: 7	● Unique approach that should be supported. ● Biggest concern is complexity of the construct, ultimate manufacturability.
No: 7	● The complexity of the biomaterial and the 7+ different biological materials is huge. In addition, the activity and/or release of the different agents needs to be temporally coordinated. This will require a lot of optimization that will be difficult in this timeframe. ● The work seems quite complex and the preliminary data does not inspire confidence for meeting the milestones. ● It's a challenge but worth the risk for a small investment. ● There is a lot of work to get to a final approval, but I feel this needs to be attempted.

Application #	DISC2COVID19-11813
Title (as written by the applicant)	Combating COVID-19 using human PSC-derived NK cells
Research Objective (as written by the applicant)	We propose to generate NK cells from gene-edited human PSCs and use the resultant NK cells to combat against COVID-19.
Impact (as written by the applicant)	The use of gene-edited hPSCs as a source for genetically engineered NK cells will allow us to generate effective immunotherapy for COVID-19 that has no approved treatment thus far.
Major Proposed Activities (as written by the applicant)	• Generation of gene-edited hPSCs • Differentiation of hPSCs into NK cells • Characterization of hPSC-derived NK cells • Testing the effect of hPSC-derived NK cells on SARS-CoV-2-infected cells
Statement of Benefit to California (as written by the applicant)	As of April 18th, 2020, 30,333 confirmed cases of COVID-19 have been reported in California, which resulted in 1,166 deaths. Besides the tremendous emotional and physical pain that this disease inflicts on families, it produces a huge medical and fiscal burden and halts economic growth in California. Thus, there is a real need to develop a strategy of treatment for this disease. Our study will address the needs by proposing to establish a hPSC-based cell therapy for COVID-19.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 78

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

Mean	77
Median	78
Standard Deviation	7
Highest	90
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The overarching premise of this study is that NKG2A-devoid NK cells could contribute to controlling SARS-CoV-2 infections. If it could be demonstrated that NK cells have a more prominent role in SARS-CoV-2 control, this approach could be considered a straightforward medical approach. Although it should be noted that other similar concepts with NK cells exist, this does have some innovation with the knockout of NKG2A. • This a long way from patients, but this work is necessary to understand if NK cells might be an effective therapy against viral infections. • The iPSC approach with NKG2A editing is very interesting and could impact COVID-19. • It is not clear if NK cells are a major effector in SARS-CoV-2 control or clearance. • NK cells have the potential to impact COVID-19 related immune dysregulation. • It should be noted that there could be major side effects with such a therapy. It is unclear if this therapy would do more harm than good. • The lack of inhibitory receptor may exacerbate immunity and cause pathology.

No: 2	• It is not known whether the progression of COVID-19 disease and the reduction in NK cell numbers is correlative or causative. • There is already a clinical trial underway with unaltered NK cells. I would want to see how that one pans out before doing gene knockout and a complex differentiation of pluripotent stem cells.
GWG Votes	Is the rationale sound?
Yes: 8	• This is necessary and a very interesting approach. • The rationale is strong although there are some concerns that NK cells might do harm in COVID-19 - especially with the NKG2A removed. • The rationale is sound but there are some concerns about inducing cytokine release syndrome with this edited product. • The level and role of NKG2A on NK and T cell is not known during COVID-19.
No: 6	• Circulating NK cell numbers and increased NKG2A expression (as a potential indicator of exhaustion) has been shown in SARS-CoV-2 infection. However, it is unclear if NK cells contribute to control of SARS-CoV-2 in a meaningful way. • The investigators present preliminary data on their ability to expand NK cells from hPSC which are clear and effective. However, the investigators do not yet apparently have a system where they are evaluating SARS-CoV-2 infected cells. • The investigators have experience using CRISPR and state they have generated gRNA specific to KLRC1, but do not show these data and have presumably not validated the approach yet, although CRISPR data is shown for other targets. • The authors have an NK cell killing assay established and present data, but do not yet know how feasible this assay will be for the proposed SARS-CoV-2-susceptible lines hACE/293T/hHuh-7. • Since there has not been a causative relationship established between NK depletion and disease progression the rationale does not appear to be sound. • It is unclear if the addition of NK cells will help or exacerbate inflammation. • No relevant preliminary data were provided that were specific to SARS-CoV-2. • The investigators note that exhaustion of cytotoxic lymphocytes has been shown to promote disease progression. This is a correlation, not a causation. It is also less clear that this has been shown for NK cells than for T-cells. • It is not clear that there are any examples of successful use of adoptive NK cell therapy for infectious diseases.
GWG Votes	Is the proposal well planned and designed?
Yes: 9	• Yes. The project is straightforward and streamlined and if found successful could be moved to patients quickly. However, there is little consideration of potential negative off-target effects once this is moved in vivo. Will the knockout (KO) of NKG2A result in side effects due to improper NK cell education and/or off-target killing? This is generally not an issue in NKG2A blockade or mouse studies, but unknown in humans. • Much of the research plan lacks depth. For example, NKG2A KO is only to be verified by surface antibody stain with no proposed molecular validation. Similarly, the phenotypic evaluation of the derived NK cells could be more extensive. For example, the activating NKG2C is not even evaluated and how this KO really impacts CD94 stabilization is ignored. Overall more detailed analyses of the KO NK cells should be conducted. • Although it is recognized that the simplicity of the proposed approach does contribute to how this could be quickly moved to patients, other NK cell modifications could be considered. • The proposal is lacking details on replicates or statistical evaluations. • The application does not make clear what an adequate amount of killing will be defined as. How robust above background is considered sufficient to proceed with the KO? Similarly, how robust above background would be sufficient to consider efficient killing of infected cells? • The stem cell approach is well designed. • Additional pre-clinical data would need to be generated before translating this to patients. • There is some duplicated text in the proposal between significance and objectives section.
No: 5	• While the application says that GMP iPSCs will be sourced it is unclear if the genetic manipulations would be performed under GMP conditions. That would be essential if this were to be a therapy for human use. • While spin EBs give a uniform size cell aggregate it will be hard to scale this technology for human use. • No specific studies are described to support clinical translation.
GWG Votes	Is the proposal feasible?

Yes: 11	● The project is relatively straightforward and the timeline seems logical and reasonable. The team presents reasonable milestones to accomplish generation of the KO NK cells in the first 8 months and this seems achievable. The remaining 4 months are for in vitro testing against SARS-CoV-2-infected cells, and assuming the team can develop a reproducible assay, this timeframe is reasonable. ● The PI is a very experienced stem cell biologist and the other investigators bring complementary expertise in cell biology and experience working with SARS-CoV-2 and BSL3 studies. ● The facilities and equipment should be able to support the proposed studies without issue. ● The budget seems mostly appropriate. However, it is not clear if a 50% effort staff scientist will be able to conduct the experiments as described in 1 yr. Further, the small consultant allocation to the collaborating institution may not be sufficient given the depth of BSL3 work. ● A lot could be learned about the basic science of NK cells and potentially applied to other diseases. ● It is unclear if the group could carry out the project. This reviewer is not convinced it is warranted at this time and is also concerned that if one did undertake the project that at least the production of the KO cell line should be performed under GMP conditions. ● Translation to patient is missing, but it is early. ● The project is feasible, but more consideration needs to be given to cell line generation and manufacturing scale-up. ● Adaptive transfer of NKG2A -/- NK cells is a cumbersome process. Instead one can choose to use anti-NKG2A antibodies.
No: 3	● The timeline to develop lead candidate is likely to exceed current urgency for response to pandemic.

Application #	DISC2COVID19-11770
Title (as written by the applicant)	Mitigating SARS-CoV-2 hyper-infectivity and induced inflammation
Research Objective (as written by the applicant)	We propose to design and develop inverse-translocation peptides (ITPs) that inhibit SARS-CoV-2 entry and shedding, and dampen inflammation associated with COVID-19.
Impact (as written by the applicant)	The proposed studies would lead to development of broad-spectrum antiviral peptides, which can act as both prophylactic and therapeutic treatment as they target both early and late viral processes.
Major Proposed Activities (as written by the applicant)	• Identify AMP-like sequences in SARS-CoV-2 membrane envelope proteins. • Investigate the potential of ITPs of different compositions to turn off viral entry and cytotoxicity from NETs-based inflammation using model membrane systems. • Determine whether AMP-mimicking SARS-CoV-2 derived peptides can enhance SINV infection. • Determine whether ITPs can be used prophylactically and therapeutically to suppress SINV infection. • Assay for cytotoxicity of SARS-CoV-2 derived peptides and ITPs in the human lung organoid model. • Demonstrate inhibition of SARS-CoV-2 infection by ITPs in the human lung organoid model.
Statement of Benefit to California (as written by the applicant)	This research will benefit the State of California and its citizens greatly as they are proof-of-principle studies to demonstrate and characterize the antiviral activity of engineered inverse-translocation peptides (ITPs), which can potentially be used to block SARS-CoV-2 and other enveloped viral infections and COVID-19-associated inflammation. As a result, the findings will help mitigate the current COVID-19 crisis.
Funds Requested	$149,998
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	4
Highest	80
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Effective antivirals are essential to control COVID-19 infection. The project aims to identify and characterize peptide candidates unique to SARS-CoV-2 that remodel host membrane curvature to facilitate viral entry and shedding, and design ITPs that can counteract these viral processes and block SARS-CoV-2 infection.

	● The proposed technology has the potential to yield a new set of anti-viral peptides, which could act to inhibit SARS-CoV-2 entry and shedding from infected cells. ● The development of ITPs is supported by initial preliminary evidence of one candidate that appears to affect model membranes, and when given to 393T cells in vitro at high concentrations can block SINV viral replication after infection. Thus, there is some early evidence in support of the notion that ITPs directed to SARS-CoV-2 may have the desired effect. However, a question whether SINV is an appropriate model for a coronavirus like SARS-CoV-2 lessens the enthusiasm. ● The main goal of testing whether ITPs can affect inflammation will only be indirectly tested by measuring cytokine production. ● If it works it would be helpful. The approach may also be helpful for other viral infections but would need to be customized for each virus. ● If successful, the impact would be important for treating COVID-19.
No: 2	● No specific data with SARS-COV-2 to assess impact.
GWG Votes	Is the rationale sound?
Yes: 4	● The innovative uses of 'big data' based machine learning platform, the state-of-the-art synchrotron x-ray diffraction techniques and human lung organoid model are strengths of the proposal.
No: 9	● The proposed work is based on careful consideration of viral proteins and peptides effects on membrane curvature and susceptibility to viral infections. The use of machine learning is well justified. ● The preliminary data provided supports the further development and search for new ITPs; but preliminary evidence using SARS or a SARS pseudo typed virus would be more supportive. ● The proposed work is not directly enabled by human stem cells, but rather human stem cells are used to generate lung organoids for testing the effectiveness of the ITPs. ● It is unlikely to work by only targeting the spike region, but the approach is interesting. ● The entry into SARS-CoV-2 mechanism may not be relevant in vivo. ● There is a concern whether the selected target (S1 antigen region) will impact downstream viral release. ● There are too many steps strung together, each of which needs to succeed, makes this a risky overall strategy. A simpler project design would be preferable.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	● The project has a clear set of milestones and deliverables. ● The proposal considers pitfalls and alternative approaches. In particular for Aim 3, the use of macrophages as a future add-on will be important, as would be the use of monocytes to test NET formation and further delineate inflammatory outcomes. ● There is minimal information on how the candidate would be transitioned from discovery to translation in the next stage of project.
No: 7	● It is not entirely clear when the therapy would be given and route of administration. ● The SINV studies may be tangential. ● Additional experience is needed with in vitro model systems including lung organoids. ● Additional discussion is needed on in vivo experiments including intended route of administration. ● Provide more complete reference information to allow easy identification and access.
GWG Votes	Is the proposal feasible?
Yes: 11	● The research team brings together an excellent combination of expertise, the PI with viral and interferon stimulated gene know-how; the co-PI with antimicrobial peptide and TLR expertise, plus the Co-I for lung organoid development. ● The proposed work is laid out with a clear set of milestones and deliverables. ● Timeline should allow selection of lead candidate. ● The project is too ambitious and cannot do all three aims for $150,000.
No: 2	● The cytotoxicity testing should occur earlier in the process. It seems like these compound could be toxic and would sink the project.

Application #	DISC2COVID19-11840
Title (as written by the applicant)	"Accelerating stem-cell based repair of the lung in response to SARS-COV-2 infection."
Research Objective (as written by the applicant)	This work will optimize an identified drug class to promote alveolar stem cell-based repair of the lower airway.
Impact (as written by the applicant)	The developmental candidate enabled by the proposed studies will promote reparative recovery from acute respiratory distress syndrome induced by SARS-CoV-2 infection.
Major Proposed Activities (as written by the applicant)	• Evaluate the ameliorative effects of stem cell-based repair in small mammalian models of SARS-CoV-2 infection. • Establish a lung localized inhibitor candidate with sufficient potency and pharmacokinetics. • Determine the protective efficacy of an optimized lung localized stem cell-expanding agent in animal models of SARS-CoV-2 infection.
Statement of Benefit to California (as written by the applicant)	At present, there are no approved medicines to help Californians combat SARS-CoV-2 (COVID-19). The proposed research aims to develop a lung localized small molecule drug candidate which promotes stem cell-based repair of the lower airway to overcome the harmful effects of SARS-CoV-2 infection.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 74

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

Mean	72
Median	74
Standard Deviation	7
Highest	80
Lowest	50
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: 8	• This is a novel approach which may impact some aspect of one of the many proposed disease pathways. • If it works, it appears to shorten the time of recovery, but hard to tell at this point how much. This would likely reduce hospitalization costs. Not clear at this point if it would reduce mortality. • May be effective against indications other than COVID-19, such as other causes of ARDS. • The inhibitors may reduce ARDS caused by SARS-CoV-2. However, the inhibition may cause other cardiovascular side effects.
No: 6	• The path to translation does not seem clear.
GWG Votes	Is the rationale sound?

Yes: 8	● The preliminary data is strong, with both in vitro and in vivo data which provide some hint at efficacy. However, the dose required is too high for oral use, therefore they need to develop a high dose local delivery system, which is the premise of this application. ● The drugs to be tested may be excessively toxic. ● Augmenting the rate of AEC2 self-renewal would likely help repair the damaged alveolus and restore barrier function in ARDS during COVID-19.
No: 6	● Hard to see this being successful given the large number of unknowns. ● Unclear whether appropriate cell type is being targeted.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	● Yes - no concerns noted.
No: 8	● Concerns with relevance of proposed animal models to COVID-19. ● High risk grant and questionable impact as it is currently written. ● They state that "at least 20 signaling molecules are substrates." This may present a wide range of side effects. The lung restricted compounds may reduce side effects and to address this they offer a suggestion to test other molecules, but essentially it would be starting over. ● Details on dose timing as compared to disease induction are missing. ● The animal models proposed will recover on their own which can make it difficult to discern between treatment and spontaneous recovery. ● Additional consideration is needed with respect to toxicity of product class.
GWG Votes	Is the proposal feasible?
Yes: 8	● Preliminary data shows a reasonable mechanism, using pre-approved drugs. Since the drugs will need to be reformulated, it may not speed approval too much. They propose additional safety, toxicity and efficacy testing which should be enough data to have a pre-IND meeting.
No: 6	● The proposed in vitro system is difficult and will impact timelines.

Application #	DISC2COVID19-11881
Title (as written by the applicant)	Extracellular vesicles from cardiosphere-derived cells for treatment of COVID-19.
Research Objective (as written by the applicant)	The translational candidate is cell-secreted nanoparticles called extracellular vesicles (EVs) from a cell therapy called cardiosphere-derived cells.
Impact (as written by the applicant)	If successful, the proposed studies lead to therapy for COVID-19. More broadly, it would provide relief for overwhelmed hospitals and ICU units by shortening hospital stays and need for ICU care.
Major Proposed Activities (as written by the applicant)	• Evaluate the effect of EVs on COVID-19 infection in a cell culture model of SARS-CoV-2 infection. • Evaluate the effect of EVs on SARS-CoV2-infected cells in a cell culture model of SARS-CoV-2 infection. • Evaluate the effect of EV-treated macrophages on SARS-CoV-2-infected cells in a cell culture model of SARS-CoV-2 infection.
Statement of Benefit to California (as written by the applicant)	The state of California is currently the fourth most affected state by COVID-19 pandemic. Developing a therapeutic will save lives of people in the state of California and elsewhere. If successful this therapeutic has the potential to save the lives of people in the state. by reducing the need for hospitalization, length of hospital stays and the need for ICU care, it would also provide relief to hospitals, ICU units and staff across the California's healthcare system.
Funds Requested	$150,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• The hyperinflammatory response, pulmonary epithelial damage and renin angiotensin system (RAS) dysregulation are all serious drivers of morbidity and mortality. Therefore, a regenerative medicine therapy that can reduce inflammation is essential to treat COVID-19 induced inflammation. Cardiosphere-derived cells are a population of heart-derived stromal progenitors with known anti-inflammatory properties could be of value in treating SARS-CoV-2 induced inflammation. • If it works it would be impactful. • The proposed grant has the necessary significance and potential for impact.
No: 9	• The proposal was poorly written. • No preliminary data provided to assess potential impact. • There is really not enough detail in this proposal to allow evaluation.

GWG Votes	Is the rationale sound?
Yes: 3	• The rationale for the use of the product in cardiomyopathy is sound but still not solid. However, the rationale for the use in COVID-19 is really shaky. No real preliminary data are provided.
No: 11	• Unclear rationale and method of systemic delivery. • A clear rationale was not provided. • Using EVs to treat COVID-19 may be possible, but little direct evidence it would be effective for this or other viruses. • The proposal was poorly written.
GWG Votes	Is the proposal well planned and designed?
Yes: 2	*none*
No: 12	• The research plan is very spare and poorly developed. More details are needed. • The proposal was poorly written. • Experiments were poorly designed. • Insufficient details. • The application is missing details (MOA? stats? other experimental details). • Please define acronyms the first time they are used in the text of the proposal documents, such as EV and the product name.
GWG Votes	Is the proposal feasible?
Yes: 7	• The grant proposal is feasible in the time table provided by the PI. • Project should be feasible based upon the proposed collaboration. • Test article has been characterized.
No: 7	• Although the proposed experiments could be conducted, it is unclear how they will facilitate future develop of the product. • Likely safe, but hard to tell as written. • The proposal was poorly written. • The timeline has no text.

Application #	DISC2COVID19-11734
Title (as written by the applicant)	Improving Immune Function via Rejuvenation of Aged Human Hematopoietic Stem Cells to Combat COVID-19
Research Objective (as written by the applicant)	The objective of this project is to develop a highly potent secretome product derived from PSCs cultured in a perfusion bioreactor that is capable of rejuvenating the function of aged HSCs.
Impact (as written by the applicant)	Currently no therapies exist to restore functional benefits to aged HSCs. This strategy would be the first of its kind to improved the yield and function(s) of immune cells derived from aged HSCs.
Major Proposed Activities (as written by the applicant)	• Determine the effect of PSC-secretome treatment on human HSC lymphopoiesis and subsequent T cell antiviral activity. • Determine if rejuvenated aged HSCs can generate more functional innate immune cells. • Determine the antiviral response of T cells, monocytes and neutrophils generated from aged human HSCs towards SARS-COV-2 infection.
Statement of Benefit to California (as written by the applicant)	COVID-19 has caused a global pandemic that led to a shelter-in-place order for the entire state of California, tens of thousands of confirmed cases, and more than a thousand deaths statewide. Older individuals (>60 years old) exhibit a much greater incidence of severe complications and mortality than younger people, likely due to a weakened immune system. This project seeks to test an approach that could help protect the vulnerable, aged population by rejuvenating their immune system.
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	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• Age associated increase in COVID-19 severity is a major public health issue. Age related decline in host response to SARS-CoV-2 is believed to cause severe disease. This proposal aims to address improved immune response in the elderly through soluble factor mediated rejuvenation of aged stem cells and tissues.

No: 8	• The proposed work will investigate the ability of human pluripotent stem cell (PSC) derived secretome (secreted proteins, excluding exosomes) to affect the function of aged hematopoietic stem cells (HSCs) ability to give rise to lymphocytes, in particular T cells. • The proposed technology is based on early preliminary work showing that HSCs from aged mice appear to respond favorably to the PSC secretome, by showing transcriptional changed and improved lymphoid differentiation in vitro and in vivo. Albeit, both myeloid and lymphoid outcomes were improved. • The proposed technology will be tested on human HSCs, >65 yr old, using in vitro assays, looking at T and myeloid differentiation outcomes. Future work will focus on characterizing a key soluble component(s) that mediates the effect. • The main strength is the preliminary evidence showing some effect by the PSC-secretome on aged mouse HSC in vitro and by transcriptome analysis. • The main weakness of the proposed work is that even if the effect on HSCs can be improved by culturing with PSC-secretome, there is little evidence that these HSCs will be able to improve T cell generation in the aged, as the main culprit thymic atrophy will still be present, and the main reason why young HSC in old mice do not lead to increased T cell outcomes. This is a major flaw in the logic behind the proposed work. • It is way too early to tell whether the candidate would accelerate the development of stem cell technology. • This is an interesting project and has merit if you can reverse immune function aging, but since aged patients have a limited thymus function, this approach may not boost T cell function. • While the technology could have long-term uses for improving the immune system for the aged population, it is unlikely the technology will produce a useful robust candidate in the foreseeable future. • PSC-secretome should be well characterized and tested in disease models in order to present it as a therapeutic product candidate. • Scale up of this type of product (once defined) doesn't seem practical to treat patients in a timely manner. • It is not clear from the proposal what kind of product candidate will be created. • There is no clear clinical translation path presented in the proposal.
GWG Votes	Is the rationale sound?
Yes: 4	• Study is based on the rationale that a novel stem cell derived therapeutic approach can improve the overall immune function in the elderly population to combat viral diseases, such as COVID-19, and other infectious pathogens. • In theory the idea could work, however there would be too much variability to develop into a commercial product.
No: 8	• The authors provide good preliminary data to support a basic science project to study HSC aging. • The scientific rationale is presented for studying of PSC-secretome on the aging of HSC, but not for the development of novel therapies for COVID-19. • The preliminary data offer support for the notion that some factor(s) in the PSC-secretome is influencing the behavior of aged HSCs, whether a similar effect is also seen in young HSCs was not clarified. • It is not clear how this project will enable the advancement of stem cell-based therapies for COVID-19. • There is initial evidence presented to provide enthusiasm for some of the proposed work. • The proposed work uniquely relies on PSC-derived factors, and thus is enabled by stem cells. • The project does not propose a definite candidate. The project does not provide a rationale on how to use such a candidate - eg prophylactically and how such a candidate would be applied clinically.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	• The project outline is reasonable, but the potential output is not compelling. The investigator did not describe how the work will translate to a candidate product that would reproducibly produce the secretome proteins with little lot to lot variability using the bioreactors described in the proposal. • It is a well-described and structured project. • Very few potential pitfalls and mitigation strategies are described in the proposal. There could be many more.
No: 8	• Progression from discovery to translation options were not presented. • Not sure how this could be translated to a therapeutic. • Pitfalls are considered, but the notion that the thymus in the host will still be a major drawback was not considered.

	● The proposed timelines are aggressively conceived, as human HSC to T cell development take much longer than that of mouse T cell differentiation. ● This seems like a very complicated approach.
GWG Votes	Is the proposal feasible?
Yes: 3	● The proposed milestones are reasonable and likely to be achieved. ● The team is well qualified and staffed to perform proposed work. ● The team is well resourced with equipment and tools enabling this work.
No: 9	● Unlikely to achieve milestones within proposed timeframes. ● The proposed team and collaborators have the necessary expertise to carry out the experiments. However, expertise in T cell generation in vivo could be added. ● This has reasonable basic science, but a final candidate is unlikely. ● Major gaps in the ability to translate this into an ultimate treatment. ● The project is not feasible to deliver a candidate in 6 months.