PDEV AWARDS

6/25/26

$89,618,837 GWG RECOMMENDED

$40,479,865 CIRM TEAM RECOMMENDED

$42,408,250 AMOUNT AVAILABLE

$0 BOARD APPROVED

						Score Range				Number of GWG Votes				
APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Early+Late/ Late Only	Disease Indication
PDEV-19735	Hypoimmune Stem Cell–Derived Islets: A Next-Generation Cell Therapy Toward a Functional Cure for Type 1 Diabetes	$12,480,000	Y	Y	91	92	2	90	95	14	0	Y	Early+Late	type 1 diabetes
PDEV-19727	Regenerating the Acutely Infarcted Heart with iPSC-Ventricular Cardiomyocytes.	$7,499,998	Y	Y	90	91	3	86	95	14	0	N	Late only	acute myocardial infarction
PDEV-19742	Therapeutic Restoration of Immune Function through iPSC-derived Human Thymic Epithelial Cells	$12,999,871	Y	Y	90	88	3	84	92	14	1	Y	Early+Late	congenital athymia
PDEV-19725	Stem Cell-Engineered Off-The-Shelf CAR-NKT Cell Therapy for Multiple Sclerosis	$7,499,996	Y	Y	87	87	3	80	90	12	3	Y	Late only	multiple sclerosis
PDEV-19718	A one-time gene therapy for rare and common forms of fibrotic kidney disease	$12,948,726	Y	N	85	86	6	70	95	12	2	Y	Early+Late	fibrotic kidney disease
PDEV-19835	Allogeneic, Immune-Evasive and Regenerative iPSC-Liver Organoid Therapy for Acute-on-Chronic Liver Failure	$11,679,420	Y	N	85	85	1	80	85	12	3	N	Early+Late	liver failure
PDEV-19729	Durable Islet Transplantation to Bridge Gap in Current Type I Diabetes Therapies	$11,623,155	Y	N	85	83	6	70	87	11	4	N	Early+Late	type 1 diabetes
PDEV-19780	Escape-Resistant Genetic Therapy for CMV Disease in Transplant Patients and Newborns	$12,887,671	Y	N	85	83	3	80	90	8	6	N	Early+Late	CMV disease
PDEV-19751	Autologous ABCD1 ex vivo gene-modified iPSC-derived microglia cell therapy for cerebral adrenoleukodystrophy (CALD).	$12,740,075	N	N	84	82	4	70	85	5	10	N	Early+Late	cerebral adrenoleukodystrophy
PDEV-19728	AAV gene therapy for brain metastases	$12,999,999	N	N	84	81	8	60	88	6*	8	Y	Early+Late	metastatic brain cancer
PDEV-19710	Small non-coding RNA drug for Duchenne muscular dystrophy	$6,484,315	N	N	80	79	8	55	84	0	14	N	Early+Late	Duchenne muscular dystrophy
PDEV-19746	A Regenerative Small Molecule Therapy for Vision Restoration in Glaucoma	$9,495,876	N	N	80	79	3	70	83	0	15	N	Early+Late	glaucoma
PDEV-19715	Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia	$7,499,999	N	N	75	75	2	70	78	0	15	Y	Late only	white matter stroke and vascular dementia
PDEV-19832	A Novel Peptide-MHC Adaptor CAR-T Cell Therapy for Targeted Elimination of Autoreactive T Cells in Type 1 Diabetes.	$12,996,187	N	N	75	73	5	65	80	0	15	N	Early+Late	type 1 diabetes
PDEV-19734	A Safe and Effective Genome Editor for Definitive Therapy of Fibrodysplasia Ossificans Progressiva	$12,022,344	N	N	75	72	7	50	80	0	15	N	Early+Late	fibrodysplasia ossificans progressiva

APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Early+Late/ Late Only	Disease Indication
PDEV-19732	In Vivo Generation of TRAC Locus-Specific CD19 CAR T Cell Therapy for B Cell Malignancies	**$12,231,968**	**N**	**N**	**70**	73	4	70	84	0	15	N	Early+Late	B cell malignancies
PDEV-19744	IND-Enabling Development of a Human iPSC-Derived Cardiomyocyte/Mesenchymal Stromal Cell Organoid Patch for Ischemic Cardiomyopathy	**$5,504,460**	**N**	**N**	**70**	72	2	70	75	0	15	N	Late only	ischemic cardiomyopathy
PDEV-19722	Regenerative iPSC-Derived Liver Graft for Functional Hepatic Replacement	**$12,999,998**	**N**	**N**	**70**	71	3	70	80	0	14	N	Early+Late	liver failure
PDEV-19720	Gene therapy for the treatment of congenital lipodystrophy	**$8,971,749**	**N**	**N**	**70**	70	8	60	84	0	15	Y	Early+Late	congenital lipodystrophy
PDEV-19712	A novel epigenetic gene therapy delivered using lipid nanoparticles to treat advanced HPV-associated cancer	**$12,720,367**	**N**	**N**	**67**	68	8	50	84	0	14	N	Early+Late	HPV-associated cancer
***Minority Report**														

Application #	PDEV-19735
Title (as written by the applicant)	Hypoimmune Stem Cell–Derived Islets: A Next-Generation Cell Therapy Toward a Functional Cure for Type 1 Diabetes
Therapeutic Candidate (as written by the applicant)	Hypoimmune stem cell-derived islet cells
Indication (as written by the applicant)	Type 1 diabetes, MODY (rare, genetic form of diabetes that typically develop before age 25), secondary diabetes (caused by pancreatitis or cancer)
Unmet Medical Need (as written by the applicant)	[Redacted] addresses the unmet need for a durable, immunosuppression-free therapy for type 1 diabetes by restoring insulin production using off-the-shelf hypoimmune islet cells, overcoming immune rejection, donor shortages, and exclusion criteria that limit current transplant and device-based treatments.
Major Proposed Activities (as written by the applicant)	• Complete IND-enabling nonclinical safety, biodistribution, and toxicology studies. • Finalize GMP manufacturing, quality control, and release strategy for an IND-ready drug product. • Prepare product-specific pre-IND materials and develop an IND-ready Phase 1 clinical protocol and operations plan.
Statement of Benefit to California (as written by the applicant)	This project advances an immunosuppression-free cell therapy for type 1 diabetes, a condition affecting tens of thousands of Californians. By enabling IND clearance and first-in-human testing, the work accelerates translation of a potentially disease-modifying therapy using California-based research, GMP manufacturing, and clinical infrastructure. The project supports patient access, safety, and equity while strengthening California's leadership in stem cell and gene-edited therapeutics.
Funds Requested	$12,480,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 91

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	92
Median	91
Standard Deviation	2
Highest	95
Lowest	90

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The strengths of this proposal include the robust animal data showing the ability of these cells to function properly in a diabetic animal. While pancreatic endocrine cells derived from pluripotent stem cells that function to control blood glucose in animal models have been available for some time, the issue has been how to protect those cells from the human immune system while maintaining cell survival and function. The applicant's immune evasive cells may finally offer a solution to that problem.
- A small physician sponsored trial in a single patient in another country showed promising results using mature pancreatic endocrine cells from a subject where the cells had been genetically altered to evade the human immune system. While this is an early time point in one patient and it uses cadaver derived pancreatic cells from a donor it is an important first step in demonstrating the exciting potential of hypoimmune cells in treating human disease.
- Key Strengths - the potential for this therapy to provide meaningful and substantial improvement is evidenced by 1) off-the-shelf availability (cryopreserved product), 2) fully suspension based differentiation platform (scalability), 3) no need for immunosuppression, 4) potential for insulin independence, 5) potential for durable effect, 6) relative ease of administration, 7) potential to reach patients through local/community hospital settings.
- Key Weaknesses - the potential for 1) transplanted cells to dysregulate, 2) the theoretical possibility that the immune system will overcome the hypoimmune edits (with no immunosuppression, graft will be lost), 3) it's unclear the route of administration will be clinically effective compared to the established route of administration, 4) the site of administration has the potential to become tumorigenic.
- High off-the-shelf potential.
- Prior platform validates regulatory approach.
- There is an unmet need for Type 1 Diabetes (T1D). Novel approach with a route of delivery which is reasonable and they have a strong preclinical package and supporting data. They have de-risked the platform and program.

Value Proposition

- This application aims to create immune evasive pancreatic endocrine cells for the treatment of Type 1 Diabetes (T1D). T1D is currently treated with insulin therapy and glucose monitoring which is a heavy life long burden for a person with this condition. In addition, insulin therapy is inferior to endogenous control of insulin and other pancreatic endocrine hormones.

- If successful, this product would be transformative for people suffering from T1D. In addition, there are many insulin dependent T2D patients that could benefit from this product.
- There are multiple initiatives to treat T1D with cells derived from pluripotent stem cells. These include encapsulation to protect cells from the immune system and the use of immunosuppressant drugs to allow survival of transplanted cells. There are also other initiatives involving engineering various cell types to protect them from the patient's immune system and treat T1D. Which approach will succeed in supplying pancreatic endocrine cells which are protected from the immune system is not known and all these approaches have benefits and potential problems.
- The applicant's approach will use an intramuscular transplantation site on the forearm which will be attractive to subjects.
- The value proposition is compelling, in particular for patients who suffer from Severe Hypoglycemia (SHE) and Impaired Awareness of Hypoglycemia (IAH) and are challenged to manage their disease with exogenous insulin. A nonimmunogenic, living cell-based transplant, that responds to glucose stimulation and releases insulin in a titrated fashion, without use of mechanical devices or another person's efforts, has high value to the patient and caregiver. The cost of therapy is not near-term comparable to insulin maintenance but should provide ROI over time as insulin-independent patients do not develop/have reduced comorbidities / health issues due to their diabetes.
- The proposal addresses the unmet clinical need and gap in therapy and recognizes the burden of disease.
- An unmet need could be addressed by not inducing an immune response.
- One cannot predict whether this approach will produce cells that evade the human immune system of subjects because it is not possible to recapitulate the complexities of the human immune system in the context of an autoimmune disease which is geared towards destroying pancreatic beta cells.
- The points regarding the differences across the different populations are not as well defined as one would expect. No mention is made whether there are differences in ethnic populations and how the proposal would be able to manage differences if this is anticipated. Limitations of the current standard of care (e.g. lifelong immunosuppression, lack of ample pancreases available for transplants) are chronicled and discussed.
- The affordability question lacks the exact dollar to dollar comparison between the proposed approach and the current available therapies for patients with T1D requiring lifelong insulin, etc.
- The competitive landscape, the risks associated with the proposed approach are fairly well described and mitigation strategies are outlined.
- Concerns about freedom to operate in relation to [redacted].

Rationale

- The applicants have good preclinical data supporting their approach.
- The scientific rationale is sound. The product is an allogeneic, next-generation hypoimmune iPSC–derived pancreatic islet cell product (SC-islets) for off-the-shelf treatment of T1D patients. The group has made a major pioneering contribution in this field.
- The available data support the rationale and the applicants have good efficacy data in animal models.
- The rationale is robust (hypoimmune platform-approach, across disease indication lines) and is supported by relevant preclinical and CMC data - using iPSCs as starting material to gene-edit for immune

evasiveness and then to be able to manufacture to scale for multiple patient dosing makes a strong case for proceeding into human trials.

- The approach utilizes CRISPR-Cas for the knockouts and targeted integration via homology-dependent repair (HDR) for the transgenes. There is considerable body of data that is supportive of the proposed approach. There are models that show disease modification.
- They have developed a suspension culture differentiation protocol to produce human pancreatic endocrine cells from a starting iPSC culture. This approach is potentially scalable as it uses suspension based cell culture which is amenable to scale-up in stirred tank bioreactors.
- While the data is robust it is only possible to test the ability of these cells to evade the human immune system in patients that have an autoimmune disease which targets pancreatic beta cells in human clinical trials.
- While the site for transplantation is amenable to removing the graft should this be necessary it would still be a challenge (and potentially disfiguring) to remove the graft. However, I think this is unlikely and it is more likely that any issues encountered would be around cell survival and function.
- Three mechanisms of action for evasion of immune response. The proposed route of delivery is reasonable however regulatory effects with hypoglycemia could still be an issue.
- The route of administration is intramuscular. How this route would fare in the context of regulatory effects considering the requirement for the portal circulation is not clear.
- Limitation: It is unclear whether the hypoimmune-editing will make the engineered beta cells more susceptible to routine infections. This has not been clearly spelled out.
- While the differentiation strategy and protocols are well-defined it is unclear whether the functionality of the beta cells meets the native islet levels and has improved.

Project Plan and Design

- The project plan is sufficiently detailed and complete to envision achieving IND clearance.
- The project plan and design of the proposed activities and studies are well described that are IND-enabling. The process and analytical development/testing is appropriate.
- It is likely the objective will be achieved within the timeframe and the budget is appropriate.
- The CMC activities are well thought out.
- The plan is to take an already established GMP master cell bank (MCB) and make a GMP working cell bank (WCB) (already established) - grow the WCB and perform targeted mutation of the cell line and clonally isolate the mutated cell. Then make a MCB and WCB (from the MCB) from the mutated line and use that bank as starting material after qualifying the cell line.
- This grant will support the production of the hypoimmune master cell bank and working cell bank and all downstream work from there.
- Experienced team CMC and GMP throughout. Have a cell bank and have had a pre-IND meeting. Off the shelf availability - the platform is de-risked.
- The potential project risks and the contingency plans are well articulated. A mitigation approach is provided for the risks to be circumvented.

Project Team and Resources

- The team is outstanding. The manufacturing team are well qualified and have worked on multiple pluripotent stem cell products so there are no concerns about their ability to do the required work.
- The PI and team are the correct people for this endeavor. [Redacted] is an established, reliable, competent manufacturing partner. The senior team is made up of executives from another organization and have worked together for years on these programs. It is unclear from the personnel descriptions and resources section of the proposal who will be responsible for regulatory strategy and IND preparation and submission, including managing interactions with FDA / regulatory authorities.
- These are leading pioneers in the field.
- The leadership and expertise of the team is excellent and the staffing plan is likely to allow navigation to IND clearance. The GMP, expansion strategies and regulatory, clinical functional areas are excellent.
- There is a very clear and sound plan for coordination and execution of the major components of the approach.
- A number of the individuals who are consultants and personnel have a track record in this area of stem cell based approaches.

Population Impact

- The project aims to develop a cell therapy which would be invisible to the immune system and therefore applicable across all populations.
- This treatment may be particularly valuable to patients with SHE / IAH because of the difficulties in managing their condition. Generally, the possibility of receiving an off-the-shelf, one-time, IM injection of immune-evasive cells (no immunosuppression) to achieve insulin independence in a T1 diabetic should be supportive to patients adopting the therapy, caregivers appreciation for a decreased need of their support and, despite initial higher cost than routine insulin injections, attractive to insurers for the potential reduction/removal of consequences that befall long time T1D patients such as comorbidities and medical complications that eventually find their way into the payor environment.
- Concerns about expense because of concerns about freedom to operate in relation to [redacted].
- A large unmet need limitation has been the immune response to transplanted islet cells. This could be a breakthrough therapy. Establish insulin independence - reach more pts in rural setting
- The applicant has a good understanding of the environmental, genetic and associated factors that are necessary for the proposed therapy,
- As written some finer aspects of the different population groups that may be affected is not well documented.
- The applicants proposed activities do include a number of considerations and perspectives from individuals affected by type 1 diabetes.

Application #	PDEV-19727
Title (as written by the applicant)	Regenerating the Acutely Infarcted Heart with iPSC-Ventricular Cardiomyocytes
Therapeutic Candidate (as written by the applicant)	Heart muscle cells derived from human induced pluripotent stem cells.
Indication (as written by the applicant)	Patients with recent myocardial infarctions (heart attacks) who are in shock and require mechanical circulatory assistance.
Unmet Medical Need (as written by the applicant)	Heart failure due to ischemic heart disease is the number one cause of death in the US and California. Cardiogenic shock following acute myocardial infarction (AMI-CS) is one of the most lethal conditions in cardiovascular medicine, with a 50% one-month mortality rate.
Major Proposed Activities (as written by the applicant)	• Completion of IND-enabling studies (manufacturing and preclinical pharmacology/toxicology) • Prepare clinical protocol and clinical operations plan • Prepare and file IND with the FDA, achieve IND clearance
Statement of Benefit to California (as written by the applicant)	Ischemic heart disease is the leading cause of death in CA. Patients with recent myocardial infarction complicated by cardiogenic shock face ~50% mortality within one month despite optimal medical and device therapy. Our approach addresses the root cause—loss of cardiac muscle—by remuscularizing the heart with stem cell-derived cardiomyocytes. This scalable therapy has the potential to be broadly accessible, including to underserved populations disproportionately affected by heart disease.
Funds Requested	$7,499,472
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	3
Highest	95
Lowest	86
Count	14

(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The strengths of the application are that it addresses a large unmet medical need in a patient population where only supportive therapies are currently available. The product is allogeneic, which will allow many patients to be treated with the same product and may make it more affordable.
- The weaknesses are the need to use immunosuppression (albeit somewhat mild in nature) in a fairly sick patient group. In addition, despite the fact that the product is allogeneic, there will be some cost challenges in producing a large number of cells in a cost-effective manner. Over time, costs may come down as large-scale technologies are developed for the expansion and differentiation of pluripotent stem cells. In addition, there are multiple efforts to develop cell lines that evade the human immune system. If successful, these cell lines will obviate the need for immunosuppression.
- Key strengths: restorative therapy; potential to remuscularize cardiac tissue up to normal metabolic function; off-the-shelf product; addresses the cause of cardiac disease; tailored immunosuppression.
- Key weaknesses: need for immunosuppression; potential for engraftment arrhythmias.
- Strong biology and development of the cell suspension to date. Effective development of approaches to mitigate key factors related to rejection, cardiac integration kinetics, and longevity. A clear product and MOA have been developed over years. The new indication of AMI/cardiogenic shock is positive. It is perhaps a difficult population for immune suppression, but there is an urgent need and value in pursuing this population. There is a clear delivery approach to achieve localized delivery. FDA interactions have been good to date, albeit in a different patient population from previous iterations of the clinical positioning, but the current approach is aligned. Excellent PI and track record for this innovative approach.
- Strengths: world-class team; MCB and WCB established; well-designed development program; clear unmet need and value to affected patients with high mortality; unique patient population distinguishes the program from others; Type C meeting in Q2 2026 prepared to inform study design; the field has advanced substantially with scalability and a clear chance for reduced COGS; adequate risk mitigation strategy backed by significant institutional funds.
- Weaknesses: the pre-IND was focused on chronic heart failure, and the change in indication may raise flags. Immune suppression is not established in the target patient population and may be questionable in patients with cardiogenic shock. Clinical trial measures may need to be refined: (1) PET may be difficult to perform in patients with cardiogenic shock; (2) 6MWT, pVO2, and KCCQ are neither possible nor meaningful at baseline (and are also not suggested by the applicants). The relevance of the first data assessment at 6 months is not clear. In addition, the potency assay shows 20-25%, which is rather low and would imply low seeding efficiency.
- The cardiogenic shock patient population is fragile and has a high unmet need.

- Some of the clinical endpoints should be reconsidered based on feedback, practicality, and feasibility. Patients may have difficulty performing the functional outcome measures, and these should be reconsidered with clinical and patient input.
- Functional restorative product.
- Strengths: large unmet need; strong scientific rationale; and proposed solutions for key product risks, including immunosuppression/rejection and arrhythmias, which have been de-risked preclinically.

Value Proposition

- This application is aimed at developing an allogeneic iPSC-derived cardiomyocyte product (SCM-101) for the treatment of acute myocardial infarction with cardiogenic shock.
- This condition affects about 10% of acute myocardial infarction patients and has a high mortality rate. Survivors often develop progressive heart failure.
- The product is allogeneic in nature, which allows cost-effective scaling of manufacturing. However, the product will require immunosuppression to allow the allotransplanted cells to survive, and this may impact very sick patients.
- If successful, this product could see widespread adoption in affected patients, as currently only supportive therapies are available and they do not address the root of the problem.
- This product has the potential benefit of restoring heart function in patients who have suffered an acute myocardial infarction. Thirty-day mortality is approximately 50%, and survivors often develop progressive heart failure over time. Replacement of damaged or dead cardiomyocytes with off-the-shelf functional cardiomyocytes that remuscularize damaged infarct areas could mitigate disease progression.
- This cell therapy has a strong opportunity to become a new and compelling therapeutic in the target indication. The target population has changed recently from chronic heart failure to post-MI cardiogenic shock shortly after MI, with the goal of replacing lost myocardium and cardiomyocytes. This is an allogeneic product that could provide substantial benefit. Accessibility and distribution may be challenging and will depend on cost analysis and the ability to broadly deliver a cell therapy of this kind.
- Remuscularization or protection from cardiomyocyte loss in a subacute setting of myocardial injury promises to prevent or delay disease progression to advanced heart failure.
- Cardiomyocyte injection under concomitant immune suppression in cardiogenic shock with mechanical circulatory support (ECMO +/- Impella) will be feasible, but difficult to evaluate because of the highly variable baseline and outcomes. After the first proof of concept, a large clinical trial will likely be required unless mortality can be reduced dramatically.
- Clinical feasibility will depend on the acceptance of (1) immune suppression in instrumented patients (ECMO + Impella) with cardiogenic shock and (2) engraftment arrhythmia, which will likely be dose dependent.
- The cardiogenic shock patient population is fragile and has a high unmet need.
- Strong value.
- Cardiogenic shock following myocardial infarction has a high mortality rate (40-50% after 30 days) and affects a large patient population. Prior cell therapies have relied on transient paracrine effects, whereas the proposed product aims to restore contractile mass and address the dominant mechanical deficit underlying this disease in order to prevent or delay progression to end-stage heart failure. High unmet medical need.

- An allogeneic, off-the-shelf therapy with a specifically tailored immunosuppression regimen, distinct from whole-organ immunosuppression, to balance graft durability with patient tolerability and clinical practicality increases the likelihood of accessibility and uptake.
- The proposal notes that this is the only group attempting to replace lost cardiomyocytes at disease onset.
- There is an unmet medical need, since this condition has a high mortality rate within 30 days and long-term quality of life is diminished.
- Although this study will initially be a safety study, the end goal is to remuscularize the heart and greatly improve patient outcomes.

Rationale

- The applicants have devised a protocol to develop cardiomyocytes with ventricular specificity from human iPSCs. This differentiation protocol appears robust and scalable.
- Treating patients acutely is important for the potential for positive outcomes. The cells are delivered by trans-epicardial injection, which allows precise delivery.
- From a manufacturing perspective, the program is well advanced. A large cGMP MCB and WCB have been produced. These banks will supply starting material for the foreseeable future.
- The scientific rationale for using iPSCs to create new myocardial cells makes fundamental sense. Loss of myocardial tissue due to injury is replaced by nonfunctional scar tissue. Intervening prior to scar formation by providing cardiomyocytes that engraft, mechanically synchronize with the heartbeat, and replace the damaged area has the potential to return heart function to pre-AMI performance levels.
- Despite changes to the reprogramming approach, the manufacturing process has been under ongoing development and appears to deliver a pure product, with minimal undifferentiated cells and no teratomas, in sufficient quantities for FIH studies. Previous animal studies have demonstrated cell engraftment, improvement in contractile function, and synchronization with host myocardium, although transient engraftment arrhythmias have been seen in large animals. This suggests that the ability to detect arrhythmias may relate directly to the rapid heart rates seen in small animal models versus large animal models.
- Evaluation of arrhythmia and associated pharmacological management is part of the clinical study safety analysis. A reduced-intensity immunosuppression regimen has been developed to permit use of an allogeneic product. This has been vetted in large animal studies and will also be evaluated during the clinical study.
- Extremely strong scientific evidence of efficacy has been demonstrated in rodents and large animals. This has been a long journey for the PI, with longstanding evidence of safety and efficacy. The work has highlighted the potential to replace damaged myocardium effectively.
- Several safety issues have been managed well and predicted appropriately for a first-in-human study, including teratoma risk, arrhythmia, and rejection. If effective, this product would generate substantial interest.
- The applicant's track record is best in class, with a series of top-tier publications on cardiomyocyte injection in animal models, ranging from rat to macaque, of subacute myocardial infarction.
- Cell retention remains a major challenge. The potency assay has a base case estimate of >25% and a best-case estimate of >35%. This would convert to an effective dose of 50-160 million cardiomyocytes and may be on the lower end of an assumed effective dose. However, preclinical data with similarly low retention demonstrated efficacy. Considering engraftment arrhythmia as potentially dose limiting, it seems prudent to start with a low dose.

- Although only reported anecdotally by groups investigating similar cardiomyocyte injection approaches, including HeartSeed, HelpTx, and HECTOR, engraftment arrhythmia and immune suppression in this high-risk patient population may be challenging.
- Strong preclinical animal data.
- The preclinical data are sound and supportive. Whether these patients can tolerate immunosuppression could be discussed further with the FDA.
- CMC: demonstrated yield and purity up to a 3L scale. The approximately 20% off-target cells should be identified. The team has already obtained a GMP MCB and WCB, and has demonstrated production of up to 14 billion cells in PD.
- It is unclear whether the differentiation process has been performed using the GMP WCB, which will be important to test and de-risk. Based on pre-IND feedback, some additional analytics will also be needed on the cell banks.
- Preclinical: 10 studies were presented overall. These studies show efficacy, demonstrate electrical coupling and synchronization with the host EKG, and include pharmacologic means for controlling arrhythmia. The pre-IND feedback supports the GLP toxicology study design.

Project Plan and Design

- The applicants have already shown their ability to manufacture the product in a format that is amenable to scaling.
- The starting materials have been produced in a GMP facility. While large cell numbers will be required to treat humans, the applicants have recognized this and are working in a 3D format that is amenable to scaling in bioreactors.
- Disposable bioreactors are available for scaling cell manufacturing. It is too early to determine what the cost will be for a product of this nature, but cost will be an important consideration because a large number of cells will be required for a successful therapeutic outcome.
- There is minimal risk of tumor formation, although the subjects will be immunosuppressed, so careful assessment in preclinical testing will be required.
- Given that the patients will be quite sick, challenges associated with immunosuppression need to be a consideration.
- The applicants have considered access and affordability. This condition is overrepresented in underserved communities. Any new cell therapy is going to be expensive, especially when a large number of differentiated cells will be required for treatment. Over time, costs may come down, as they do with most new therapies after widespread adoption.
- The pre-IND meeting sufficiently supported the clinical study design for the previous indication such that use of the same design for cardiogenic shock is reasonable, although this still needs to be confirmed by the FDA. Direct injection of DP into the infarct and peri-infarct areas raises different safety issues than the previous ROA and requires clear surgeon training, which is provided for in the clinical operations plans, even if the mini-thoracotomy is minimally invasive.
- Master and Working Cell Banks have been prepared and released. The cells have not yet been adapted to suspension culture, which presents a potential risk, and this will need to be accomplished before clinical DP can be manufactured. Adaptation may be complex; however, the applicant states that they have performed multiple development runs and do not foresee difficulties in achieving suspension culture.

- Potency testing is included in the DS/DP testing; however, it is unclear whether this will be sufficient to demonstrate mechanism of action without additional assays.
- All changes from the previous pre-IND, including CMC, nonclinical design, route of administration, and clinical indication, are to be discussed with the FDA in a follow-up meeting. The proposal states that a Type C meeting is planned before PDEV starts, while the cover sheet on the briefing book indicates that a Type B meeting will be requested.
- Regardless, there is a great deal of work to be done and information to be reviewed. Since the Type C meeting is on the critical path, having the meeting in Q2 2026 seems optimistic, although doing so would support sufficient time to address feedback and file the IND in Q3 2027.
- The proposal is based on final rodent studies to assess biodistribution and other characteristics of the product, as well as planning for regulatory activities, the clinical trial, CMC, and related efforts. This approach seems effective.
- Well-outlined and prepared IND-enabling studies and clinical program preparation, including GLP toxicology, tumorigenicity, and biodistribution studies with CDMO/CRL over 24 weeks; non-GLP efficacy studies in nude rats injected 4 days post-MI with 12 weeks of follow-up; GMP Suspension Cell Bank development; stability testing of MCB, SCB, and DS for up to 60 months; clinical protocol and operations planning; patient engagement; IND clearance; market landscape and patient demographics; and reimbursement and affordability planning.
- The preclinical and CMC plans were adapted in response to information obtained in a pre-IND meeting in Fall 2024.
- There has been a critical change in clinical planning from chronic heart failure to cardiogenic shock patients, which is to be discussed with the FDA in a Type C meeting planned for Q2 2026.
- The budget is adequate and backed by contingency funds secured from the hosting institution. A $2.3M letter of support was included.
- Scalable off-the-shelf product. COGS appear favorable compared to HTX and LVAD treatment.
- No concerns.
- The clinical trial is well planned, but some of the measures may not be able to be performed or collected.
- The plan is very clear and well thought out. The nonclinical plan is appropriate and can incorporate pre-IND feedback as necessary.
- CMC: manufacture of a suspension cell bank, if successful, could simplify routine manufacturing.
- Risks: main risks include arrhythmia, with a pharmacologic management strategy proposed; immunosuppression, using a regimen specific for transplanted cells rather than organs in order to balance patient tolerability with efficacy; and product purity, including identification and assessment of the risk of off-target populations.

Project Team and Resources

- The team is excellent. The manufacturing facility and team at the applicant institution have produced many iPSC cell banks and products developed for clinical trials.
- The PI is well known and respected in the cardiac cell therapy area.
- The project team possesses the expertise to launch this clinical study. The applicant institutions provide experienced CMC facilities and testing coordination, and the research and clinical team have evolved over

more than 10 years through different manufacturing processes and FDA interactions to streamline their clinical design, TPP, and manufacturing process.

- Very strong PI. The overall team seems adept, with strong long-term track records in this area.
- Excellent team led by a pioneer in the field and supported by expert clinicians.
- Excellent manufacturing facilities at the applicant institutions.
- Experienced multidisciplinary team across all of the areas required to develop this type of product, with consultant support. Established plan for communication and coordination.
- Fantastic team.
- Excellent group with a strong history.

Population Impact

- The applicant intends to develop the product for clinical trials. Because the product is allogeneic, it is not geared toward any specific population.
- The applicants are well aware that this condition disproportionately affects minority populations and will take that into account when developing and testing the product.
- The PI and team understand their target patient population and are developing a restorative therapy that addresses the potential for permanent injury caused by AMI.
- The plan is for two clinical trial sites with diverse patient populations, which is reflective of the California population.
- The applicant has a good understanding of these factors, and the intended population appears to be appropriate.
- Outreach will be very limited since patients will present with a sudden-onset condition.
- Consent forms will be translated into a number of languages, and the team will have bilingual coordinators. Budget will be set aside for logistics and travel, patient navigators, dependent care, and a small stipend.
- The potential cost savings to the medical system could be substantial, as traditional interventions can run into seven figures. However, the proposal alludes to some form of dynamic pricing without a clear link to a market price range.
- Engagement with advocacy groups is planned to help shape trial design, patient recruitment, and access strategies.
- The applicant articulated a framework for future patient enrollment with comprehensive support.

Application #	PDEV-19742
Title (as written by the applicant)	Therapeutic Restoration of Immune Function through iPSC-derived Human Thymic Epithelial Cells
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate comprises iPSC-derived thymic epithelial cells, the first cell therapy to treat thymic (non-hematopoietic) immune defects.
Indication (as written by the applicant)	PoC: Congenital athymia, a lethal orphan disease. Further: Immune augmentation in the context of thymic injury from e.g. HSCT, GVHD & Immunosenescence.
Unmet Medical Need (as written by the applicant)	Congenital athymia's only treatment is HLA-unmatched thymic tissue transplant, but it faces severe barriers: 1) scarce tissue availability, 2) U.S. access restricted to Duke University, and 3) HLA-mismatching causing poor graft function and nearly 100% autoimmune complication rates.
Major Proposed Activities (as written by the applicant)	• CMC: manufacturing process, potency and release assay development, and APS and validation runs. • Regulatory: pre-IND and IND preparation and conduct of meetings • Clinical planning: development and finalization of clinical protocol and trial start-up activities
Statement of Benefit to California (as written by the applicant)	In addition to congenital athymia patients, many others could benefit from restored thymic function, providing economic benefit to California by decreasing societal costs: 1. allogeneic HSCT recipients (>2000/year in CA) who are exposed to numerous thymic insults. 2. cancer patients (>200,000 new cases/year in CA) receiving immunotherapies that require functional immune system, 3. solid organ transplants (~5,000/year in California) to induce tolerance and diminish lifelong immunosuppression.
Funds Requested	$12,999,871
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	88
Median	90
Standard Deviation	3

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- Ultra rare condition with a large unmet need. Compelling application and experienced team. Very positive FDA Interact meeting.
- The applicant had a successful INTERACT meeting in December of 2025 with written responses provided that included concurrence of the development approach in general and additional specific recommendations to which the applicant agrees. This should aid in the preparation of a successful preIND, assuming the identified concerns are adequately addressed.
- The need to make many different iPSC lines to accommodate the many different HLA subtypes in the human population is a longer-term concern/weakness. A reviewer is not certain if others working with hypoimmune cells that escape the human immune system will present a possible alternative to producing these multiple cell lines, but it is worth considering in the longer term.
- The number of animals in the proposal's study designs do not align with those costed in the budget. Given the expected duration of the tumorigenicity study, it would seem more efficient to design a single chronic toxicity/tumorigenicity study. The multiple early time points and proposed animal numbers will likely be insufficient for assessing toxicity or tumorigenicity.
- IND-enabling studies are not well designed.
- Unusual selection of preclinical models to advance the therapy; the designs do not seem to make sense.
- There are concerns that personalized cell therapy approaches are not affordable.
- Costs are exceptionally high. Please recheck them.

Value Proposition

- The applicant's customized, allogeneic HLA-matched approach has the potential to improve immune reconstitution and reduce complications relative to current standard of care. This approach could be extended from congenital athymia to additional populations, including patients with primary thymic disorders, secondary thymic injury (e.g., following chemotherapy or radiotherapy), transplant recipients, and aging individuals with immune decline. These groups currently lack curative options. As such, a scalable thymus replacement therapy could have transformative clinical and healthcare system impact.

- If the approach proposed works in congenital athymia, it would only be a starting point. Multitudes suffer from thymic dysfunction because of other illnesses, treatment side-effects and advancing age. In this case, the effects on the unmet needs of patients, caregivers and the health system would be substantial.
- Validating proof of concept and safety in the initially proposed clinical population will support expanding the technology to other clinical presentations of immune insufficiencies.
- The treatment proposed offers a clear advantage over current therapies, such as Rethymic, or others in trial in terms of safety, efficacy and healthcare system burden. The comparison of potential cost savings to families and the system are particularly notable.
- The applicants believe that their product would save up to $10,000,000 per patient.
- While congenital athymia can be treated with cultured thymic tissue, this is mostly from a mismatched donor. Material is also extremely limiting; this means that most children are not treated. Untreated children die young, so there is an urgent need for treatment options for these kids. Uptake by patients, caregivers and the healthcare system is likely to be enthusiastic. The current treatment is given to only a small proportion of patients and is very expensive.
- The applicant's approach, if successful, would provide an easier, more convenient and more practical treatment solution for patients and families, especially since it could be administered in most hospital settings.
- The product is designed to be allogeneic with at least a 6/8 HLA match. This allows manufacture of many doses of product to treat patients with HLA matches.
- The proposed allogeneic, HLA matched, scalable, cultured thymus tissue is a significant therapeutic advancement for congenital athymia patients. The current treatment option is a sole approved product, and it's only available at two centers worldwide.
- Strong value proposition addressing an unmet need.
- Applicants illustrate that regenerating thymic function shows great therapeutic promise. The plan is to begin by focusing on children with congenital athymia. This form of the disorder cannot be treated with current stem cell transplants. The applicants describe severe limitations in efficacy, safety and cost-benefit of the currently available treatment marketed in the USA, Rethymic.
- The team describe in some detail how their product would be superior in all respects to those products currently available such as Rethymic and those in the developmental pipeline.
- The initial personalized approach is likely to be associated with high costs, potentially limiting accessibility. However, the proposed evolution toward an off-the-shelf product represents a more scalable and potentially cost-effective strategy that could substantially enhance accessibility over time. Given the severity of the target condition and the lack of effective alternatives, uptake by patients, caregivers, and clinicians is expected to be strong, provided safety and efficacy are demonstrated.

Rationale

- The rationale is strong and supported by the available preclinical data in addition to clinical experience with allogeneic thymic cultured tissue.
- The preclinical data, including in vitro and in vivo work in humanized rodent models, support further development of the product.
- Sound rationale. Feasibility, scalability, and affordability pose risks.

- To this panelist, the scientific approach to therapy and route of administration seemed very robust.
- The evidence of disease modifying activity was compelling.
- The data presented were compelling for the indication. Thymic regeneration would have a seismic effect.
- The application is supported by a strong and well-articulated scientific rationale, underpinned by an extensive and high-quality research program led by the principal investigator.
- The development of a directed differentiation protocol to make thymic epithelium from pluripotent stem cells is a novel aspect of the work. Multiple iPSC lines will be made that represent multiple different HLA subtypes. The differentiation protocol has been shown to work across multiple different iPSC lines; the protocol is robust.
- While the initial patient population is very small, targeting them in the first instance is the correct strategy because of the dire clinical need. Once POC is established, there are many different and larger patient populations where this product may be useful.
- The proposed two-tiered development strategy is scientifically, clinically, and ethically well justified.
- The lack of direct evidence supporting the need for an allogeneic HLA-matched cell product in congenital athymia is an important gap. Comparative studies in humanized models assessing matched versus mismatched hematopoietic stem cell and cell product combinations would strengthen the rationale. A partially HLA-matched approach warrants consideration and could represent a more practical and scalable strategy, while still offering a theoretical advantage over the current fully mismatched standard of care with Rethymic. Importantly, such an approach for athymic patients may also improve affordability and accessibility, which are key limitations of existing therapy. Incorporating this strategy earlier in development could therefore strengthen both the scientific and translational rationale.

Project Plan and Design

- The applicants have been guided by a successful INTERACT meeting with FDA in December 2025. From a manufacturing standpoint there were no major issues raised by the FDA. The issues that were raised will be addressed in future FDA submissions.
- A reviewer sees no show stoppers that would impact the budget or timeline, and believes the proposal can be completed in a timely fashion.
- In general, there are no manufacturing issues which stand out either from the proposal or the INTERACT meeting. The manufacturing proposal is sound and achievable within the budget period.
- Animal studies will be done with implantation under the kidney capsule while patients will be treated by intramuscular injection (current route of administration for the current approved product). This did not seem to raise any concerns with FDA.
- The applicant had a successful INTERACT meeting in December of 2025 with written responses that include concurrence of the development approach in general and additional specific recommendations which the applicant agreed with. This should aid in the preparation of a successful preIND, assuming identified concerns are adequately addressed.
- The Agency has accepted an alternative ROA for the animal studies than the intended clinical route. Initial clinical dose and dose escalation will be justified/better informed by previous clinical experience with allogeneic cultured thymus tissue.

- The number of animals and costing of IND enabling studies as presented in the application are unclear. It is expected that the proposed tumorigenicity study will need to be longer than proposed. It would seem more efficient to design a single chronic toxicity/tumorigenicity study.
- IND-enabling studies are not well designed.
- Sound and positive interactions with FDA.
- The budget is sufficient, but preclinical study designs may need to be reconsidered, redesigned and addressed with new timelines.
- The proposed activities seem appropriate and necessary for both the immediate and longer-term goals of the study and the IND. The pre-IND activities appear to be well-managed. The team has enlisted impressive, quality partners as part of the developmental plans.
- The proposer did a good job of describing potential risks (which is why they plan to start with the individuals most endangered without treatment) and developed clear strategies for mitigating and tracking risks both in the short-term and the long-term.
- The access and affordability aspects of the proposal were among the most compelling components of the proposal. Their description details how their product has the potential to completely upend the market for thymic treatment.
- Overall, the proposed project plan is well structured, clearly justified, and aligned with the objective of achieving an active IND.
- The CMC strategy is thoughtfully designed. However, the proposal to generate iPSC banks from two PBMC donors selected to provide HLA-matched products for athymic patients who have failed prior Rethymic therapy raises feasibility concerns. Such patients may not be optimal candidates for a time-sensitive, bespoke manufacturing strategy, given their complex and unstable clinical trajectories.
- Leveraging haploidentical iPSC lines, as proposed for the off-the-shelf product, may offer greater flexibility and scalability for the initial athymic target population. This strategy could enable recruitment of partially HLA-matched patients (including patients who do not have the complex medical histories typically associated with failed Rethymic). Importantly, this would reduce the risk of generating patient-specific products that may ultimately not be utilized. Additionally, selecting donors representing common HLA haplotypes could increase the broader utility of these cell lines, which also further justifies the inclusion of two reprogramming approaches, as it may further enhance the value of these resources.
- The nonclinical plan is robust, with clearly defined and achievable milestones aligned with pre-IND requirements. The proposed studies in humanized mouse models are appropriate and informed by prior interactions with the FDA. The requested support for these activities is well justified.
- The applicants propose identifying clinical sites with relevant expertise. Given that full support for this activity is requested, it would strengthen the application to more explicitly confirm engagement with the mentioned California-based clinical sites.
- The application demonstrates proactive and appropriate engagement with the FDA; this a clear strength.
- The current personalized approach is likely to be associated with substantial cost. This may limit uptake in a rare disease population (as experience has shown for gene therapy ATMPs). A shift toward partially matched / off-the-shelf products, as discussed above, could significantly improve affordability and scalability.
- Although detailed cost assessment is challenging, the budget appears justified, and additional funding support has been secured. The timeline is ambitious but credible, supported by a multidisciplinary team.

- Manufacturing and financial risks are appropriately identified, with well-considered mitigation and contingency plans, including access to additional funding sources.The inclusion of a draft first-in-human clinical protocol is a notable strength and supports the overall readiness of the program.

Project Team and Resources

- The team is very experienced. The manufacturing sites are well versed in cGMP manufacture of cell products including iPSC derived products for clinical trials, so there are no concerns for manufacturing of the cell product.
- The team is adequately resourced, including an impressive list of external consultants providing both relevant scientific, translational and cell product development experience.
- The multidisciplinary team stands very well positioned to execute a fundable program.
- The team and its leaders are very experienced and skilled in both the manufacturing and the regulatory aspects of this field. They have recruited impressive partners for the implementation and manufacturing processes.
- The team's track record is quite impressive.
- The application presents a highly qualified and well-structured team with the expertise necessary to advance the program to IND. The principal investigator is exceptionally well positioned to lead the project, combining clinical expertise in immunodeficiency and cell therapies with a strong translational research program supporting the iTEC platform. The manufacturing operational lead is well suited to support knowledge transfer across manufacturing and testing sites. The broader team includes experienced collaborators and established manufacturing partners, with demonstrated expertise across key domains including GMP manufacturing, preclinical development, regulatory strategy, and clinical translation. Collectively, the team's leadership, expertise, and infrastructure are appropriate and represent a significant strength of the application.

Population Impact

- Congenital athymia is a very rare life-threatening condition. The applicants have wisely selected this patient population for a FIH study. They are aware of the demographics of the patient population. Because this is such a rare condition, there isn't a lot of opportunity to stratify the patient population.
- Approval of the proposed product will provide a more viable treatment option and perhaps the only treatment option for patients based on HLA type and geography.
- The applicant did a good job outlining the burden of disease to patients and families.
- The applicant described the existing data on the genetic and gender distribution of genetic athymia, which for various reasons is not particularly reliable, well. They are setting enrollment goals for their study based on the demographics of California, and they acknowledge that, given the rarity of the disease and the very limited sample size, they will enroll who they can. They do also detail the socio-economic issues that may limit the current diagnosis and treatment of infants suffering from this disorder.
- The rationale for the selected initial clinical population for this approach is strong.
- The burdens currently being placed on families and how their product would significantly lighten them are well described.
- The applicants demonstrate a strong understanding of the epidemiology and clinical characteristics of congenital athymia, including its incidence and demographic distribution in California and the United

States.The selection of this patient population for a first-in-human study is well justified, given the severity of the condition and the clear biological rationale for thymus replacement therapy.

- The application reflects meaningful engagement with patient communities and advocacy groups. The principal investigator has an established track record of involvement with relevant professional societies and patient-focused initiatives, which strengthens confidence that patient perspectives have informed and will continue to inform the development strategy.

Application #	PDEV-19725
Title (as written by the applicant)	Stem Cell-Engineered Off-The-Shelf CAR-NKT Cell Therapy for Multiple Sclerosis
Therapeutic Candidate (as written by the applicant)	Allogeneic HSPC-Engineered IL-15-Armored CD19-Targeting CAR-NKT Cell Product
Indication (as written by the applicant)	Multiple sclerosis (MS; a CNS autoimmune disease)
Unmet Medical Need (as written by the applicant)	Multiple sclerosis (MS) is a chronic inflammatory-neurodegenerative disease of the central nervous system that leads to progressive neurological disability and lifelong burden. Effective treatments are lacking, therefore there is an urgent need for novel therapies.
Major Proposed Activities (as written by the applicant)	• Completion of IND-enabling CMC and Non-Clinical studies. • Completion of IND-enabling Clinical Planning. • Preparation and submission of the IND package to FDA.
Statement of Benefit to California (as written by the applicant)	Approximately one million adults in the US are living with MS, including an estimated 90,000 individuals in California. MS imposes an extraordinary clinical and economic burden, with total annual costs estimated over $10 billion for California and $85-$110 billion nationally. The proposed stem cell–engineered off-the-shelf CAR-NKT cell therapy, if successful, can significantly improve MS patients' life quality while reducing the state's economic burden.
Funds Requested	$7,499,996
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- MS has significant long term care costs and disease progression significantly impacts patients, caregivers, and the healthcare system. An allogeneic product reduces collection risk and burden and the cost is significantly less compared to ex vivo products.
- Addresses the significant unmet need for treatments for progressive MS and aggressive relapsing-remitting MS.
- MS - unmet need, very debilitating and high morbidity with cognitive, physical loss.
- This is a first in class targeted B cell and allogeneic product.
- Potential for significant cost savings (via the treatment itself compared to costs of current lifelong treatment, plus avoiding costs of hospitalizations, medical equipment, home modifications).
- Strengths:
    - Provides a significant value proposition of patients with MS and for health care in general.
    - Strong scientific rationale and supporting preliminary work.
    - Engaged with FDA and has feedback from pre-IND meeting.
- Weakness:
    - Patient eligibility criteria for the trial are not clearly defined.
    - The choice of final drug product container may not be practical and may not fully support the value proposition.
- Recommend adding CMC and regulatory personnel when planning CMC and regulatory milestones.
- Regulatory and CMC support and leadership is a weakness. The team needs to consider the final product configuration, stability, shipping, shelf life and scalability. The team should consider the final product as a fill finish vial.
- CMC and regulatory is weak and needs to be fortified. Both areas need experienced, proactive staff to assure all issues are addressed to get into the clinic.
- Regulatory expertise is needed for the team.
- Type D response is not well considered. The mock regulatory review could help.

Value Proposition

- The proposal aims to develop a first-in-class allogeneic CAR-NKT cell therapy targeting B-cells and myeloid cells that express CD19 to potentially induce durable remission in patients with progressive multiple sclerosis.
- Anti-CD20 antibodies work by depleting B-cells but require recurrent dosing and have limited efficacy. CD20 targeting allows for targeting B-cells but not myeloid cells (macrophages).
- MS has significant long term care costs and disease progression significantly impacts patients, caregivers, and the healthcare system. An allogeneic product reduces collection risk and burden and the cost is significantly less compared to ex vivo products.
- The proposed therapy offers a significant advantage over existing standard treatments of patients with MS. In theory, it could lead to a functional curative outcome.
- The impact on the healthcare system could be enormous, since the proposed CAR-NKT therapy is low-cost with a pharmacoeconomic advantage.
- Unmet medical need that has a current costly burden to patients.
- Unmet need. Debilitating disease.
- CAR-NKT cell therapy may have more benefits than CAR-T cell therapy because CAR-NKT: 1. Can target both CD-19 expressing B-cells and myeloid cells through CD1d making it potentially more efficacious than CAR-T cells. 2. Lower risk of GvHD of CAR-NKT making it potentially safer than CAR-T. 3. Allogeneic (off-the-shelf) feasibility rather than programming each patient's own cells. This makes the treatment cheaper and more accessible.
- Alleviates the current lifetime medical treatment burden for patients.
- Good access and affordability activities planned to inform access and pricing strategies.
- It is not a remyelination approach, and the impact is likely better if you're early.
- Safety, tolerability, and efficacy profiles are critical. If patients see this as a safe and highly efficacious drug, then the therapy will have widespread adoption. Otherwise patients may depend on CD20 inhibitors such Ocrelizumab. Further, payors need to be convinced of the efficacy/safety profile.

Rationale

- The scientific rationale is sound and supported by data from the pre-IND meeting with the FDA.
- The scientific rationale is robust. Autoimmune B-cells are known to be involved in MS pathogenesis. C20 targeting monoclonal antibody Ocrelizumab is approved for MS. CD19 targeting would lead to broader B-cell population depletion. Further, allogeneic CAR-NKT cells will be off-the-shelf reducing CMC variability and cost of goods. Lastly, CAR-NKT cells will also target myeloid cells via CD1d receptor targeting and benefit MS. Overall, the proposal explains a robust dual targeting mechanism.
- Based on communication with the FDA, the completed proof-of-concept (POC) studies appear sufficient to demonstrate the biological activity of the product.
- Research studies were conducted to evaluate antigen responses of CAR19-NKT cells, efficacy of CAR-19 cells in human B-cells in vitro and in vivo (graft) and efficacy compared against CAR-T cells but not Ocrelizumab (approved therapy). Efficacy was also tested in primary MS patient blood samples against CD19+ and CD1d+ cells. CAR-NKT and not CAR-T showed knockdown of myeloid cells whereas B-cell depletion was shown by both regimens. Again, Ocrelizumab was not tested.

- Efficacy was also addressed in the widely used Myelin Oligodendrocyte Glycoprotein (MOG) antigen induced experimental autoimmune encephalitis (EAE) model. The antigen induced immune response activates B cells, CD4 T cells and macrophages that partition into CNS and cause oligodendrocyte injury to induce MS type phenotypes. Histology and function was improved in this model with CAR19-NKT vs. CAR19-T cells.
- Safety was tested in mice for immunogenicity against CAR-CD19-NKT cells and GvHD in donor-mismatched PBMCs. RNA and methylation profiling was also performed to show lower risk of allorejection vs. CAR-Ts.
- Sound rationale. The clinical approach with dose regimen could be challenging, may need more than dose.
- The research vectors and research studies are well designed. CD1d off-target studies may be better designed for IND submission.

Project Plan and Design

- The path to IND is laid out well in the agency's responses to sponsor's questions. Overall, the sponsor requires working on robust CMC, QC/analytical and non-clinical plans. Some highlights are below: 1. Type D meeting is suggested to confirm similarity of non-clinical and clinical lots. 2. The overall design of the construct is acceptable. The research/efficacy study need not be repeated but biodistribution data needs to be provided for CAR-NKT cells in NSG mice, which is missing. 3. GLP-toxicity studies need to be performed. 4. Clinical protocol needs some clarifications on inclusion/exclusion criteria, stopping rules etc. 5. Major lift on CMC/QC/analytics but feasible.
- FDA encouraged a Type D meeting to "discuss the similarities and differences between the nonclinical and clinical products." The timeline or proposal doesn't incorporate the timing of this potential meeting, just that it may happen if needed. When submitting the IND, not pursuing this meeting after recommendations by the agency will have to be justified in the Pre-IND response document submitted along with the IND. Something to consider.
- Type D response is not well considered. The mock regulatory review could help.
- GLP toxicity still needs to be completed.
- The project is well planned and designed, except for one weakness: One of the value propositions is to generate 1000+ doses of the product from 1 CBU in one manufacturing campaign for low cost (~ $5000 per dose). Because the current manufacturing process includes cryopreservation in the cryobag, this approach is not practical. Filling 1000+ cryobags simultaneously and freezing them is not feasible with current technologies. Filling and freezing about 100 cryobags may be practical, but has a risk of extended DMSO exposure and may require multiple controlled rate freezers.
- Freezing ~100 doses in 100 bags will bring the estimated cost per dose 10x (~ $50k based on applicant's calculations). I'd suggest considering validating and switching to different final drug product, such as glass vials (for example, you can robotize filling of 1000 AT-vials) or CellSeal cryovials (automated filling option).
- Scaling issues for bags are significant. Therefore, costs are likely to increase.
- Multiple subtypes of MS - will make clinical enrollment potentially an issue and the ability to demonstrate efficacy.
- We would recommend to the team that they strongly consider the correct population to enter into the clinic with. Stratify and select for success. Given the "all comers" approach and the heterogeneity of the MS population, the phase 1/2 could fail due to incorrectly matched MOA with the best homogeneous patient population.
- Inclusion/exclusion criteria were not well considered.

Project Team and Resources

- Overall, the team is composed of experts in developing CAR-NKT cell therapy. This shows strong scientific leadership.
- Clinical team/expertise is appropriate.
- The team is well qualified to perform the work and has all the necessary resources.
- The team is talented. CMC and regulatory support is weak. Need stronger leadership for regulatory.
- Strong project team and advisory board. This is clear when reviewing the package, and the confirmatory feedback received within Pre-IND communication. FDA's feedback highlighted the potential CMC knowledge gap when clarifying GMP product needs. Without key critical expertise, progress could be delayed unnecessarily.
- A clear IND-level (translational) team and leadership is missing. Overall, the group needs a CMC lead, PD, AD, Quality/QA and clinical operations roles. This is exemplified by the fact that the agency required a Type D meeting to confirm clinical representativeness of non-clinical material and that efficacy studies need not be performed with "clinical grade material". This can be mitigated by changing the hiring plan.
- Major gaps exist in CMC leadership. A CMC leader needs to be recruited to lay out a robust plan beyond the use of UCLA GMP facility. This is also highlighted in FDA's response to CMC questions. The agency did not accept the sponsor's CMC plan and suggested many improvements.
- CMC/Regulatory leadership is lacking.

Population Impact

- Good understanding of the MS patient population, and the current disparities in detection, diagnosis, access to care, and health outcomes across demographic and socioeconomic groups, especially Black people and people living in rural areas without access to MS-specific care.
- MS population analysis and potential impact are covered in the application.
- CA MS demographics need to be described.
- CA patients would benefit but could do a better job delineating the CA population epidemiology.
- Overall, the inclusivity statement is acceptable. The proposal could have done better to analyze California specific MS demographics.
- Good understanding of the financial and physical impact of lifelong use of current treatments.
- Good trial participation goals that address the current undercounting of Blacks and Latinos with MS.
- Good commitment to ongoing engagement with the larger MS community.
- The team appears to have taken FDA feedback regarding study population and indicated base case and optimal case under Patient Population accordingly. I appreciate that the FDA didn't narrow the study population within the trial, just clarified the need for separate arms of the study.

Application #	PDEV-19718
Title (as written by the applicant)	[Redacted Therapy], a one-time gene therapy for rare and common forms of fibrotic kidney disease
Therapeutic Candidate (as written by the applicant)	Adeno-associated virus mediated SGPL1 gene therapy, a potentially lifesaving treatment for sphingosine phosphate lyase insufficiency syndrome (SPLIS)
Indication (as written by the applicant)	SPLIS is a highly lethal, incurable inborn error of sphingolipid metabolism caused by inactivating SGPL1 mutations, leading to the accumulation of S1P
Unmet Medical Need (as written by the applicant)	We developed [Redacted Therapy] as a lifesaving gene therapy for sphingosine phosphate lyase insufficiency syndrome (SPLIS), a recently discovered childhood genetic disease that causes kidney fibrosis and failure and carries an 80% mortality rate in the 1st years of life with no available cure.
Major Proposed Activities (as written by the applicant)	• Completion of pre-IND enabling studies of [Redacted Therapy] dose, route of administration, durability and early safety profiling in mice and non-human primates • Completion of IND-enabling demonstrating safety and bioavailability in two species (namely mice and non-human primates) • Preparation and conduct of a pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	SPLIS is an ultra-rare genetic disease that causes kidney failure in children. By facilitating our progress toward a first-in-human clinical trial, we will derisk its development as a transformational treatment for SPLIS and broader applications including chronic kidney disease (CKD). KidneyFund.com states that in CA, over 100,000 people are living with CKD, over 16,000 new cases are diagnosed annually in the CA, over 80,000 are on dialysis, and over 30,000 are living with a kidney transplant.
Funds Requested	$12,948,726
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	86
Median	85
Standard Deviation	6
Highest	95

Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- There is a significant unmet need, and an effective treatment for severe kidney disease could be transformative for patients.
- A key concern is that the diseased kidney may not take up the AAV efficiently, raising the possibility that efficacy observed in preclinical models may not translate to patients.
- Strengths of the proposal include the potential to address an incurable and costly disease, evidence that the proposed AAV outperforms AAV9 in mouse models, the overall feasibility of the proposed work, the strength of the team, and the likelihood that the patient population, rare as it is, would strongly welcome a new therapy.
- Weaknesses include the fact that the timing of administration in the models does not align well with the clinical reality for patients, the likelihood that kidney remodeling in diseased patients will alter AAV transducibility in ways not addressed by the proposed studies, uncertainty about whether this would function as a one-time therapy, and questions regarding the future availability of the proposed AAV for clinical trials.
- The capsid intellectual property position will need to be confirmed.
- The team of subject matter experts is strong.
- Receiving Orphan Designation and Rare Pediatric Disease Designation as soon as the program is eligible will be beneficial.

Value Proposition

- There is no current therapy for this rare pediatric disease with high mortality and morbidity. The proposed product could provide an improvement for current care.
- There is high potential for the therapy to provide meaningful improvement and clinical outcomes given the high risk population. As this is an ultra-rare disease, the proposal addresses an unmet medical need and will likely have high uptake. The therapy will likely be expensive, despite having a kidney-targeting serotype given it is administered IV. The high cost therapy with low patient population will create financial viability challenges for a commercial product.
- Since SPLIS is an incurable and often fatal genetic condition causing kidney fibrosis/failure among other major health issues that typically lead to early death, it seems that the potential one-time treatment

proposed would provide remarkable improvement over current treatments. If successful with SPLIS this may also provide a treatment model for more common fibrotic conditions of the kidney,

- The endpoint (currently focused mostly on safety using mouse models) would be substantial benefits keeping children alive and relatively healthy. The burden on caregivers and families would be lifted substantially. The healthcare system would also be impacted by having lower costs in the long run (obviating the cost of symptomatic treatments).
- Kidney transplant is the only viable treatment option currently available and such treatment is not a viable alternative for most patients.
- The main roadblock to the uptake of this treatment is the substantial costs involved. The authors make a strong case using analogies from other diseases that the overall costs will in fact be lower. Moreover, they present a number of cost mitigation strategies, including global marketing.
- This qualifies as an unmet medical need, although there are concerns about the small patient population.
- This proposal could provide therapy for sphingosine phosphate lyase insufficiency syndrome, which is an ultra-rare disorder that is currently incurable with high morbidity and mortality. Current care for this condition is mostly supportive and very costly. Only ~100 cases are reported worldwide, but the applicants estimate 11,000 cases worldwide which seems like an overestimation. The applicants state that the condition is not amenable to enzyme replacement therapy (ERT) (which would also presumably be high cost) due to the protein not being a lysosomal enzyme. However, the PI lists a pilot study for ERT in the other support documents. Therefore, this statement seems contradictory. Uptake by the system (healthcare and patients) would be similar to AAV therapy for other ultra-rare diseases.
- While the cost to manufacture will be high, the overall cost of care and treatment(s) decreasing if effective will be beneficial to the patients and the treatment ecosystem. This patient population is in need of more options in general, and reducing reliance on solid organ transplant is a reduction in already constrained and high-cost resources.

Rationale

- The rationale is sound; however, the preclinical models may not translate, as the AAV may not effectively transfect fibrotic cells.
- The rationale is sound; however, it is unclear which tissues are being targeted; the application indicates this is a kidney-targeting strategy, but the proposed product uses a potentially ubiquitous promoter.
- The approach is similar to that used for Zolgensma, which establishes precedent but also raises potential safety concerns.
- From the perspective of a patient advocate, the scientific rationale, therapeutic approach, and proposed administration are compelling.
- The models presented appear compelling and impressive.
- The data demonstrating treatment with [Redacted Therapy] in mouse models of deficiency are robust, and AAV.cc47 appears to outperform AAV9 in these models.
- However, administration of [Redacted Therapy] in patients would likely not match the timing used in the mouse studies, which involved treatment in the first days of life.
- It is unclear what the disease state of the kidneys is/will be at the time of treatment. Diseased states such as fibrosis may alter AAV transduction, raising concerns about whether the therapy will work effectively in pathologically diseased human kidneys with fibrosis and sclerosis.

- Immune responses to gene delivery are likely more suppressed in newborns than in older mice or patients. It is therefore unclear what immune response will occur to the newly expressed transgene in immunocompetent animals or patients.
- The claim that [Redacted Therapy] could serve as a one-time therapy appears unlikely. Because organs grow substantially from infancy to adulthood, redosing may eventually be required, and this may not be feasible with AAV-based therapies because of immune responses.
- The data supporting [Redacted Therapy] as a therapy for kidney fibrosis more broadly, beyond sphingosine phosphate lyase knockout mice, are weak. Histopathologic quantification is not provided, and the observed effect on proteinuria is modest in a small number of animals. Because no additional studies are proposed to evaluate this question in other models, the broader potential for treating kidney fibrosis populations should not be considered a strength of the proposal. Additionally, the Adriamycin model used is an acute high-injury model and may not translate well to more common causes of kidney disease, such as diabetes or hypertension.
- AAV.cc47 has not been definitively shown to target expression in podocytes, which are an important target cell type for this disease. Prior publications have shown some transgene RNA in glomeruli, but this did not clearly correlate with transgene protein expression. As a result, the proposal may overstate the ability of AAV.cc47 to transduce podocytes.
- The normalization of transgene mRNA to muscle in Figure 4D is unusual. Normalization to a housekeeping gene, alongside comparison to AAV9 and untransduced controls, would be more appropriate.
- RNA scope studies should be performed to definitively demonstrate transgene expression in the intended tissues and cell types.
- Previous publications reported very high transduction of muscle and brain with AAV.cc47, which appears inconsistent with the data presented here. It is possible that the improved transduction associated with AAV.cc47 produces a general improvement in the mice, rather than a kidney-specific effect.
- If the AAV.cc47 capsid reduces dose requirements, this would be advantageous for both manufacturing and the pediatric patient population.

Project Plan and Design

- IND enabling data, clear budget and outcomes are appropriate
- No issues with the project plan. Sound external partners used with strong expertise to deliver upon CMC goals. The budget includes contingency and the timeline is reasonable.
- The studies proposed here are for the initial preclinical efforts so that IND approvals can be reached.
- The project proposed is a part of a long-term plan to develop a treatment for SPLIS and if I understand correctly that is the very reason that Sphinxion was founded by Dr, Saba. The timelines appear to be very carefully designed.
- The whole purpose of the first stages of this project is to ensure safety of the patients who would eventually be involved. For this purpose, they are beginning with mouse models. The plans seem reasonable.
- They have provided impressive strategies for handling the access and affordability issues.
- The proposed IND enabling studies seem clear with the exception of the limitations of some of the data as described above. The objectives seem achievable within the timeframe and budget. The immune suppression to be used in the eventual clinical trial is not described. This again points back to the issue of

timing of administration in the mice not matching human patients. Affordability in the market would be the same as for other AAVs for ultra-rare diseases, complicated by international need and market.

- The plan looks well established and thought out. Having had early communication with CBER regarding the Natural History Study in order to better support its resulting data as a comparator to the treatment studies required for BLA is a great start. It's also great to see an INTERACT already in process, as recommended by the agency to discuss CMC and preclinical studies. A Pre-IND is already planned according to the timeline. The only recommendation is to plan and submit for Orphan Drug Designation as soon as they are eligible. This can be done prior to clinical data being available. It appears this group has intentions to initiate such a designation, but it can be built into the timeline leading up to IND submission.

Project Team and Resources

- This is a strong team with expertise in the area.
- The proposal has a CMC gap - CMC expertise is needed.
- The team has strong scientific expertise but is lacking CMC internal or external strategic partner (FTE or consultant). The applicant will need to address this gap for development, CMC, and regulatory.
- The team's leadership, especially the PI, is extremely impressive. The PI has made the treatment of fibrotic kidney diseases her life's mission.
- The plans for manufacturing and so forth seem extremely well-developed for a project at this very early stage. Well thought-through.
- The team and consultants are very accomplished.
- The team has led the field in preclinical studies to date and seems appropriate. For the most part, the plan has been appropriately outlined. The structure seems to be in place.
- An important element that is lacking and not discussed is the IP regarding the use of AAV.cc47 for which the entire project hinges. The PI for the application does not control the IP for AAV.cc47. No letter of support is supplied by the owner of the IP stating that IND enabling and clinical trials are possible with this vector. At least one other company is using AAV.cc47 for kidney gene therapy and use for these studies may be restricted. Since the entirety of the proposed studies depend on the availability of AAV.cc47 for IND studies and clinical application, this needs to be addressed by the PI.
- This may be the only team to take this research on based on their early discovery research experience with sphingosine phosphate lyase insufficiency syndrome (SPLIS). The advisors for CMC and clinical development look very experienced and should provide valuable input.

Population Impact

- The PI has a very deep understanding of SPLIS and has carefully detailed the factors that will need to be addressed for successful adoption of the proposed treatment. The proposal describes the genetic factors involved in disease presentation, but notes that, because of the rarity of the condition, participants would be enrolled without regard to ethnicity or sex/gender.
- The rarity of the disease and the limited local patient population may make enrollment challenging.
- A main concern is the potentially high dose and route of administration; however, precedent exists for this strategy to work.
- The small patient population is likely to create challenges.

- The applicant company was founded to address fibrotic kidney disease, and its background knowledge in this area is impressive.
- Potential limitations include cost, which is likely to be high for an AAV therapy in the current environment, and uncertainty about whether a pharmaceutical company would ultimately support development for this ultra-rare disease.
- The PI has developed a network for identifying patients for potential therapeutic application. The PI has also built relationships with patients and families and appears to have done as much outreach and engagement as could reasonably be expected for an ultra-rare disease.
- The natural history study being conducted by the team demonstrates that they are well informed about both the patient population and the condition.
- If confirmed during INTERACT communications with CBER, the team will be better positioned to navigate the genetic, environmental, and other external factors that may affect the adoption, effectiveness, or safety of the proposed therapy.

Application #	PDEV-19835
Title (as written by the applicant)	[REDACTED CANDIDATE]: Allogeneic, Immune-Evasive and Regenerative iPSC-Liver Organoid Therapy for Acute-on-Chronic Liver Failure.
Therapeutic Candidate (as written by the applicant)	Induced pluripotent stem cell-derived hepatocyte-like cells (iHLC) in combination with granulocyte apheresis for regenerative liver support .
Indication (as written by the applicant)	Initial indication is patients with acute-on-chronic liver failure (ACLF) with potential use in acute liver failure in adult and pediatric patients.
Unmet Medical Need (as written by the applicant)	Each year, 50,000 adult patients are diagnosed with ACLF, with 28-day mortality rates reaching 80% and ~$60,000 per hospitalization. Our goal is to reduce ACLFrelated mortality by 20%, number of days in ICU by 50% and to serve as a bridge to curative LT for patients with ACLF.
Major Proposed Activities (as written by the applicant)	• CMC: scale up and optimization of iHLC manufacturing process, analytical method development, qualification and cGMP Phase 1 manufacturing. • Nonclinical: completion of large animal feasibility and safety with IND-enabling GLP safety/toxicology studies for the [REDACTED CANDIDATE] circuit. • Regulatory: conduct of pre-IND meeting {to support activities 1 and 2), compilation and submission of IND, filing for orphan disease indication.
Statement of Benefit to California (as written by the applicant)	In California, approximately 3,000 patients with advanced liver disease are hospitalized with repeated episodes of ACLF each year with mortality rates of 50-80%; less than 30% of patients receive a life-saving transplant. By reducing ICU length of stay and the intensity of care, reducing mortality, avoiding or delaying transplantation, [REDACTED CANDIDATE] can offer large cost savings and especially benefit the significant proportion of patients currently admitted to hospitals lacking transplant programs.
Funds Requested	$11,679,420
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	85
Median	85
Standard Deviation	1
Highest	85

Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The strengths of this application are the novel concept itself of an extracorporeal dual filtration system to perform granulocyte/monocyte apheresis followed by a liver support column containing organoids composed of induced hepatocyte-like cells to support patients with liver dysfunction as a bridge to transplant, as well as the supportive data from both small and large animal models and preliminary feedback from the PDMA which the applicant addressed. The weaknesses are the complex product, the need for cryopreservation development that will be challenging yet required for success and the uncertainty about rights to use the commercially available granulocyte/monocyte apheresis device.
- CMC challenges are significant.
- Expense and scalability limit the value proposition.
- Unmet need. Strong application. It is unclear how it will benefit CA patients. Some risk with CMC as it is a combination product.
- Strengths:
    - High clinical impact addressing a critical unmet need for liver failure, which exhibits high morbidity and mortality, and for which transplant is the only curative option.
    - Potential to significantly reduce hospitalization burden and improve outcomes while patients await transplant.
    - Combination device approach could address a broad and genetically diverse patient population.
    - Novel extracorporeal, dual column, liver support system using iPSC-derived hepatocyte-like cells (iHLCs) and GMA column (already approved) to enhance metabolic function while reducing inflammatory signals.
    - Use of immune-evasive iPSCs enables allogeneic application, simplifying manufacturing and expanding accessibility.
    - Strong preclinical small animal evidence and translational relevance demonstrate efficacy. Large animal (porcine) proof-of-concept supports scalability and translational relevance.
    - Demonstrated device integrity and safety (no leakage, maintained column structure). Well-conceived manufacturing and delivery concept that employs scalable bioreactor-based

production for iHLCs, cryopreserved intermediate to enable manufacturing efficiency, quality control, and distribution, and combination device format using existing infrastructure.

- Strong regulatory responsiveness to PMDA and planning, with clear milestones and logical progression of CMC activities.
- Experienced team and strong partnerships. Highly experienced project team with relevant industry expertise. Reputable CDMO partner engaged for manufacturing support.

- Weaknesses:
  - Incomplete CMC and manufacturing detail that lacks detailed GMP-compatible Bill of Materials.
  - Insufficient detail on process development, including number and timing of engineering runs. Heavy reliance on CDMO without full visibility into the execution plan introduces risk. Cell line and differentiation risks including limited number of iPSC clones proposed for evaluation; may not be sufficient to identify optimal candidates.
  - Unclear whether GMP-compatible or "GMP-like" iPSC lines have been used to this point to generate data.
  - Uncertainty around key enabling technologies including cryopreservation, which lacks clear demonstration of feasibility, and makes it unclear if proven or theoretical. Potential need for replacement of non-GMP materials could require comparability studies, impacting cost and timeline. The overall timeline is ambitious given the extent of required process development and optimization.
  - Lack of detailed manufacturing workflow makes it difficult to fully assess feasibility. While iPSC licensing is in place, CRISPR licensing for TKO editing is unclear, posing potential freedom-to-operate risk. While scalable and broadly deployable, expected pricing may be comparable to transplant-level costs and introduces economic uncertainty.
  - Unclear whether payers will reimburse a premium therapy in addition to standard of care, creating adoption risk.

Value Proposition

- There is a compelling value proposition for a bioartificial liver support system for the treatment of Acute-on-Chronic Liver Failure (ACLF) and Acute Liver Failure (ALF).
- The goal of this application is to develop a new therapy against Acute-on-Chronic Liver Failure. Patients with advanced chronic liver failure can rapidly deteriorate and progress in a few days to full blown liver failure. In this case, the only treatment is organ transplantation which is associated with heavy immunosuppressive treatment and very limited due to the lack of organ donors. So alternative therapies are urgently needed. This program aims to develop a bridge therapy to support patients with ACLF until transplant.
- ACLF is a complex disease since the induction of acute liver failure is difficult to predict. In addition, patients with ACLF have little capacity for regeneration. Their liver is extremely damaged and a bridge therapy can only lead to transplant. So, the treatment can be life-saving but the uncertainty around duration of treatment and underlying liver disease is a challenge. Nonetheless, new therapies which could support and improve quality of life would be extremely important and welcome by many patients and clinicians.
- Liver failure has high mortality and morbidity and is only curable by liver transplant, which is severely limited by suitable donor organ availability. High hospitalization costs and poor treatment options.

Numerous therapies are being developed to address this unmet medical concern. Proposed therapy is a combination device that has high potential to treat a genetically diverse and large population.

- Therapy utilizes immune-evasive iPSCs to limit patient complications. One iPSC line enables allogeneic use and simplifies manufacturing. Affordability is likely to be similar to existing therapies (i.e. organ transplant) but widely available as it is not limited to organ availability. The question is whether premium price will be reimbursed as in addition to SOC.
- Cryopreserved combination device that can be delivered to many clinical sites. Infrastructure is available for wide adoption.
- Current therapies are limited to non-biologics or biologics that have not shown efficacy in clinical trials.
- The goal of decreasing ICU length of stay has a significant impact on quality of life and comorbidity considerations.
- This therapy can be administered in a standard ICU setting by qualified providers.
- ALF mortality and incidence rates are higher in minoritized groups who also make up a higher proportion of the population in rural and low-income areas of the state who may experience delays in access to LT – this therapy has the potential to bridge and increase access to curative LT, decreasing disparities in outcomes.
- This is an “off the shelf” therapeutic that can be available to patients on a short time frame, which is critical in the treatment of ALF. The strategy for manufacturing is based on the QbD framework to optimize costs, production, and safety.
- This is a very invasive treatment protocol requiring central line placement and extracorporeal blood circulation.
- Currently there is an unmet medical need and this would be very beneficial if a product can be produced.
- Large unmet need.
- Expense and scalability limit the value proposition.

Rationale

- The rationale of an extracorporeal dual filtration system to perform granulocyte/monocyte apheresis followed by a liver support column containing organoids composed of induced hepatocyte-like cells to support patients with liver dysfunction as a bridge to transplant is reasonable. Supportive data exists from both small and large animal models. From a CMC perspective the granulocyte/monocyte apheresis column is an existing commercial device, though there is some uncertainty about the regulatory path on including this off-the shelf column and if collaboration with the original manufacturer is required. The genetically modified iPSC-based differentiation appears sound as does the alginate encapsulation.
- Mode of action is a bit unclear and could be an issue down the road later in development. Preclinical work is strong; already doing some work on cryopreservation. The novel aspect is that these cells can be healing.
- The program aims to transfer the device/system to the clinic. The device/system consists of an extra-corporal cartridge. One is a granulocyte–monocyte/macrophage apheresis (GMA) which decreases inflammation while the other part contains hepatocytes organoids (HLOs) generated from hiPSCs encapsulated in arginate. This second part will provide hepatic function necessary for the survival of the patients.

- The mode of action of such a system is difficult to understand. Indeed, the device will only be used for a few hours (while patients might need support for days if not weeks). It is unclear how this will work. Previous data in animal models suggest that the HLOs produce factors such as AFP which promotes liver generation. It could be interesting to validate these data since recombinant AFP treatment could be more achievable.

- Extra-corporeal devices or bioartificial liver (BAL) have been tested in the clinics without success. Patients with ACLF are extremely fragile. They are prone to infection, bleeding, etc., all which are increased by extra-corporal devices. In addition, these systems can filter blood and result in negative outcomes. Based on the animal models provided, this is not the case but large animal experiments are essential.

- There is no good model for ACLF. Indeed, the rat model presented in preliminary data is interesting and the data are convincing. They have a strong effect. However, this model is not representative of the clinical profile of patients with ACLF. Indeed, BDL is only performed for 3 weeks which induces some limited fibrosis which is compatible with regeneration. Patients with ACLF present much more advanced fibrosis and scarring levels which often preclude regeneration. So, the few hours of treatment might not work and a much longer perfusion could be required.

- The HLOs are a good source of cells for such clinical application. However, these cells remain fetal in nature (AFP expression) and they do display functional activity which is below freshly isolated primary hepatocytes. This might imply that a larger quantity of cells could be required.

- The cell quantity is essential. They plan to use 500 million cells. This is already an important number but previous studies have shown that 1-2 billion cells might be necessary to support hepatic function in adults.

- The off the shelf aspect is essential for such therapy due to the rapid deterioration of patients with ACLF. Hepatocytes encapsulated in alginate beads are unlikely to survive cryopreservation.

- Strong scientific rationale. Works as an extracorporeal liver to alleviate ACLF while the patient is awaiting organ transplant. Unique approach by dual GMA-iHLC column to reduce inflammatory signal in order to preserve iHLC function. Combinatory approach improves iHLC metabolic function. The GMA column is already approved as a medical device in Japan.

- Strong small animal data demonstrates effectiveness of therapy. One porcine experiment recapitulated positive results and provided proof-of-concept for expanded large animal study. No observable leakage of alginate into blood and column integrity was maintained.

- Rodent models are appropriate for preclinical data and as a basis for large animal studies.

Project Plan and Design

- The CMC project plan seems reasonable. Appropriate focus on MCB generation, process control and scale up, analytical development & QC release. Importantly cryopreservation feasibility has been demonstrated and appropriate work on a cryopreservation/adequate shelf life strategy is included which will be critical for this type of product. Appropriate regulatory consultation both with the FDA & PDMA is planned and will be critical to success.

- The budget is a bit unclear. Good interaction with reg and clinical centers plans well described - complex product. Applicants are responsive to the PMDA comments - a good thing.

- The experiments in large animal models are essential for scalability, surgical aspect and safety. It would have been useful to include efficacy studies. There is no plan to use a large animal model for ACLF.

- It is unclear why hypo-immune hiPSC cells are needed. Applicants plan to use the GMP grade line from [REDACTED INSTITUTION]. However, it is not clear if GMP hypo-immune hiPSC cells are available. The IP around these cells is extremely complicated due to the episomal reprogramming. Applicants might

struggle to obtain all the necessary licenses. These cells have not been tested for HLOs production. This is not a simple protocol and variability between lines can be a problem.

- HLOs production is relatively complex and relies on FBS containing medium and matrigel. This will make transfer to GMP more challenging. There is no information about yield. It is not clear how many hepatocytes can be produced per hIPSC.
- The scaling could be a problem. Applicants will want to produce batches of 1 billion cells. So one batch is equal to one patient. Applicants need to target batches between 5-10 billion cells minimum; otherwise the QC and batch qualification will be a problem. The Amber 250 might not be the right approach for that since capacity is too low.
- Cryopreservation is an issue. More data on this aspect would be useful.
- Large scale alginate encapsulation will be a challenge. This is likely to delay the program.
- Responsive to PMDA comments. For example, removal of Matrigel which is a risk for human trials.
- Unclear whether any work has been performed using 'GMP-like' iPSC lines. Applicant states that 3 clones are to be evaluated, but realistically additional clones should be evaluated. Edited lines are selected for TKO and not for functionality. It is possible (and somewhat likely) that TKO lines may be inefficient at differentiating into iHLC. Recommend evaluating more clones to select an appropriate line.
- No detailed Bill of Materials is included. Applicants state materials are GMP-compatible but only general descriptions included in workflow on page 36 of application. Unclear how many of the materials require replacement of appropriate ancillary grade which would require comparability testing (cost and time considerations).
- Use of intermediate cryopreserved product is beneficial in reducing overall manufacturing time and allows for in-process testing. Cryopreservation is stated as vital to the manufacturing process but unclear whether this is theoretical or proof-of-concept has been demonstrated.
- FTO for process evaluated. Licensing in place for iPSC line, but unclear whether CRISPR-license has been obtained for the TKO process.
- Clear milestones and logical plan for CMC activities.
- The manufacturing plan relies heavily on CDMO. The timeline is tight for process development and optimization. Applicant states development and engineering runs, but unclear how many or at what timepoints. No detailed manufacturing plans are included making evaluation of the timeline difficult. Nonetheless, timelines are appropriate.
- The manufacturing plan is appropriate, with an established CDMO partner. Scalable bioreactor system used for initial iHLC production.
- Cryopreservation at the midpoint is well considered.
- Off-the-shelf is a big challenge.
- GMP iPSC sources need to be well characterized.
- The combination product regulatory path is not well considered.
- Scalability is an issue and a key challenge.

Project Team and Resources

- The team appears appropriate.
- Most work is not being done in CA.
- Unclear regulatory rights to use of products.
- The project is led by the biotech company [REDACTED]. The business expertise is extremely strong and impressive. The CEO, CTO etc. all have an impressive track record in industry. Their expertise on hiPSCs or hepatology is more limited.
- The clinical partner is very strong and there is no doubt they could develop the necessary trial. Their expertise is essential.
- The scientific lead is [REDACTED PI] who is very famous for his work on liver bud, HLOs, etc. PI has pioneered several methods to generate liver cells and his track record is impressive. All the IP and technology come from his lab based at [REDACTED INSTITUTION]. PI is also extremely busy and has at least another laboratory in [REDACTED INSTITUTION]. He is now proposing to develop a new venture in California. His expertise is essential and he needs to play a key role in this program. He will have to dedicate a serious amount of his time for this project to be successful.
- All the IP originates from Japan but seems to be owned by the applicant. However, it is not clear if this company has already raised any funding or if it will raise funding after the award from CIRM. The letter from one investor seems to suggest that it will invest if the CIRM application is successful. This is not the conventional approach. There is no information about scientific staff, research labs, etc.
- A major part of the work will take place in Japan. All the pre-clinical work on large animals and scaling, cryopreservation will be performed by [REDACTED PI] lab in Osaka. The GMP work will be done by CMO which seems to operate mainly in Japan. The letter of support is from the CMO in Japan. It seems that little work will take place in California while any resulting IP is likely to belong to Osaka. The hiPSC line will all come from Japan. The clinical trial will happen only if the technology is successful.
- Similarly, the regulatory correspondence seems to have happened in Japan, not in the US. Requirements are likely to be different.
- Strong project team with industry experience. Reputable CDMO selected.
- The study team includes the Chief of Hepatology at [REDACTED CA UNIVERSITY] who will have the clinical expertise relevant to this patient population and disease condition.

Population Impact

- Population impact is considered appropriately.
- Patients in Japan might benefit more than in California.
- Licensing for CRISPR could increase costs.
- These aspects have been considered and explained clearly by the applicants.
- Thorough understanding of the population.
- Access and Affordability planning are appropriate.
- The intended study population is appropriate for this development state given the lack of alternative treatment options and shortage of curative therapy.

- The protocol refers to a patient priority of decreasing time to treatment.
- Seems to meet or exceed CIRM expectations.

Application #	PDEV-19729
Title (as written by the applicant)	Durable Islet Transplantation to Bridge Gap in Current Type I Diabetes Therapies
Therapeutic Candidate (as written by the applicant)	[REDACTED CANDIDATE], an implantable combination therapy of iPSC-derived β-cell spheroids encapsulated in an immune-protective device to restore insulin levels.
Indication (as written by the applicant)	Treatment of insulin-dependent metabolic disease, primarily Type 1 diabetes, with potential future use in late-stage Type 2 diabetes.
Unmet Medical Need (as written by the applicant)	Current T1D treatments rely on lifelong insulin and monitoring yet fail to restore physiologic glucose level leaving patients at risk for hypoglycemia. This therapy aims to restore endogenous insulin production without immunosuppression, addressing the lack of a durable, disease-modifying treatment.
Major Proposed Activities (as written by the applicant)	• Complete IND-enabling nonclinical studies (efficacy, biodistribution, immunogenicity, tumorigenicity, GLP safety). • Advance CMC to IND readiness for iPSC-derived β cells and encapsulation device, including GMP manufacturing and release assays. • Conduct FDA regulatory interactions (Type C/INTERACT/Pre-IND) and finalize the first-in-human clinical protocol.
Statement of Benefit to California (as written by the applicant)	The proposed research benefits California by advancing a potential curative therapy for diabetes, a disease affecting millions of Californians and driving high healthcare costs. By enabling durable insulin production without lifelong immunosuppression, the project aims to reduce complications, hospitalizations, and long-term care burden, while strengthening California's leadership in stem cell innovation, GMP manufacturing, and clinical translation.
Funds Requested	$11,623,155
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCPRING 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	83
Median	85
Standard Deviation	6
Highest	87
Lowest	70
Count	15

(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The combination of an iPSC derived islet spheroid with an immune protected implantable device that had demonstrated performance in phase 1 trials was a key strength. The demonstration of 4 months without fibrosis/foreign body response and viable functional cadaveric derived islets was compelling. The strong, well defined CMC plan was also a key strength. The weakness of the application was the complicated product and risk around scale and complicated delivery for a fresh product with a 72 hour shelf life with the device loaded on site at the clinic, but still worth giving the team time to optimize the product and delivery.
- Having some clinical validation of the pouch helped this application appear to be better set up for success than previous attempts at 'cells in a pouch' in this field.
- Builds upon technology in clinical trials.
- Complex product that lacks control after implantation.
- Developing an approach for Type 1 Diabetes Mellitus (T1D), a large unmet need for replacing islet cells with iPSP cells. Unmet need and well recognized team. CMC is well planned and designed but stability/shelf life and scale up for this product may be problematic. Well laid out program plan for CMC and development.
- Lacks details on the GLP study design. What species? Design lacks details and needs more information. Do they need to implant several devices? No long-term clinical stability plan in life. Does the dosing change and would a new device be needed? Could the IM location impact efficacy, safety, and duration?
- 72 hours shelf life may be limiting.
- Fibrosis has limited prior devices, but this one may overcome it.

Value Proposition

- A iPSC derived islet replacement in an immune protected implantable device has a compelling value proposition for type 1 diabetes.
- If successful, there is a potential for high impact and high value proposition, especially by solving the issues of cell-source/quality/availability and the need for immune suppression in other approaches.
- Very complex device and approach, with unknown durability for efficacy.

- Well established work - value proposition large. Developed an approach that is based on prior well-established work. Complex encapsulated combination cell product which has some clinical data; thus, they have some data to help translate and de-risk.
- The applicant has a good knowledge of the unmet need and provides a meaningful approach to enhance the clinical outcomes in the target population. The applicant also indicates the target can be T1D as well as advanced T2D cases. The discussion includes efficacy, safety and information regarding the alleviation of patient and caregiver burden.
- A clear discussion is incorporated to argue for the feasibility of the approach in regard to availability for the patients and the practicality of the therapy in regard to the caregivers and the healthcare system.
- The proposal has addressed the therapy's ability to be accessible for patients compared to current therapies and the economics compared to the current costs of care over the lifetime of the individual.

Rationale

- The scientific rationale of the proposed product appears sound. The differentiation methodology produces spheroids with supportive in vitro and murine model performance. The delivery device has clinical data with allogeneic human islets which demonstrated safety and minimal fibrotic response and survival of islets; although efficacy was not available as patients also received standard of care intraportal islet infusion. The CMC rationale is reasonable. The manufacturing plan seems reasonable. There will be some challenges in a 72-hour shelf life from final culture steps for shipment to site and device loading/preparation at the clinical site.
- There is some clinical data already with the device component, and the nonclinical data so far are convincing, given the limitations of animal models for studying immune rejection.
- Innovative design of the device and the route of delivery for cell factories.
- Sound rationale. Not using Portal circulation delivery is a concern. IM may not be ideal. Addressed issue of fibrosis somewhat with prior clinical work with some data is encouraging. Risk is still fibrosis and inflammation which could limit efficacy in the clinic. Lack of possible inflammation is a plus.
- The proposed collaborative approach is strong - the plan is to develop an encapsulation platform between iPSC-derived β cell spheroids (Aiβ-spheroids) that is immune-protective and fibrosis-limiting novel encapsulation jointly with [REDACTED COMPANY], as a new class of living medicine delivery systems to enable durable cell therapies without systemic immunosuppression to advance a clinically relevant therapeutic product towards an IND-ready package.
- The claim is that the device uses a biocompatible, nano-porous polymer membrane engineered to permit diffusion of metabolites, oxygen, glucose, insulin etc. while blocking immune cells and antibodies. This has been a historic approach. Although this was disclosed by [REDACTED COMPANY] in Jan 2026, it is unclear how current approach is different from attempts that have not fared well especially in the context of long term sustained success.
- The applicant has considered the safety issues and has provided appropriate measures to mitigate the risks. The mouse model used is appropriate for the measures to restore glycemia. One limitation is the site of introduction. The therapeutic cells would not be regulated by the portal circulation as occurs in the native scenario.

Project Plan and Design

- The project plan seems reasonable with appropriate focus on process controls, analytical development, manufacturing scale up of both the islet replacement cells and the device. The regulatory plan seems reasonable and necessary with feedback solicited for the combination product.

- The project is pretty advanced and earlier regulatory interactions are warranted, though not clear why a Type C would be conducted first and then an INTERACT.
- The regulatory and IND-enabling plans were light on details.
- IND enabling studies are not well quoted or described.
- Durability of the effect is not well estimated or determined.
- Applicant did not address the likelihood for hypoglycemia IF cells are outside the portal system. Device CMC development work in application - could explain more about the device reg path. Interactions with Reg on a Type C. IND plan appears well developed.
- The project plan is robust and the team has considered the various modalities that are necessary to expedite and reach milestones to enable IND clearance.
- It is likely the objective will be reached within the proposed time frame. The costs for personnel, materials and reagents and the detailed framework of the budget over the proposed studies is appropriate.
- Several of the risks have been discussed and a proposed mitigation strategy has been provided. One aspect that is unclear is the assurance that this approach would be sustained over a long period of time.

Project Team and Resources

- The team seems well suited to the project needs.
- The collaboration between the primary industry partners appears adequate to support further development.
- Very good team.
- This group has done a lot of pioneering work in this field. Building on prior work.
- The leadership and the expertise of the personnel handling the components in the different areas of the proposal to insure timely progress is excellent. The important areas covered include GMP, manufacturing, analytical and regulatory components.
- There is a detailed structure for the co-ordination and execution of the project. There is ready access to various resources that are essential for the proposal to move forward and conduct the proposed activities.
- Multiple team members have a track record of supporting similar or largely similar projects that provides confidence that the proposal is in good hands.

Population Impact

- The population impact is reasonable.
- The application mentions in several places where the sponsor has considered the demographics of California as they apply to the proposed clinical development of this product.
- Seems very expensive even with scale-up production.
- This is an expensive approach but still economical for these patients.

- The applicant and the team have a good understanding of the unmet need and the impact of the approach to affect the health of the target population. The applicant is aware of the effectiveness and safety requirements of the proposed therapy.

- The proposal takes into consideration the different demographic groups that are at risk and will be part of the clinical study.

Application #	PDEV-19780
Title (as written by the applicant)	[Redacted Candidate]: Escape-Resistant Genetic Therapy for CMV Disease in Transplant Patients and Newborns
Therapeutic Candidate (as written by the applicant)	The candidate is a first-in-class precision nucleic acid therapeutic that reprograms transcriptional feedback in CMV-infected cells.
Indication (as written by the applicant)	CMV disease in transplant recipients (hematopoietic stem-cell and solid-organ transplants) and ultimately in congenital birth defects
Unmet Medical Need (as written by the applicant)	There is no approved CMV vaccine. Current CMV antivirals are toxic and cause severe side-effects. Resistance has been observed to all CMV antivirals. The proposed product is a highly tolerable oligonucleotide therapy with an exceptionally high barrier to resistance.
Major Proposed Activities (as written by the applicant)	• Early PDEV–Candidate optimization, potency assays, and non-clinical studies to inform dose selection, toxicology and CMC development. • Early PDEV–Analytical development, non-GMP manufacturing, and process optimization to generate material and data required for IND-enabling studies. • Late PDEV–IND-enabling GLP toxicology, cGMP manufacturing, release testing, and regulatory documentation to support IND submission.
Statement of Benefit to California (as written by the applicant)	Human cytomegalovirus (CMV) infects >50% of the population, disproportionally burdening Latino populations in California. CMV is a leading cause of death in transplant recipients and a leading cause of congenital birth defects (e.g., deafness, blindness). No vaccine exists and available therapies are toxic and promote antiviral resistance. There is an urgent need for new therapies. This application develops a genetic therapy for CMV that limits resistance and could be used in pregnant women.
Funds Requested	$12,887,671
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	83
Median	85
Standard Deviation	3
Highest	90

Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- Strong science, well thought out IND-enabling nonclinical plan. High unmet need.
- High unmet need and clear regulatory path.
- Scientifically this application is well-written and with robust data.
- Could be a very impactful therapy; unmet need for transplants and HIV patients. Current drugs are not great - adverse events, minimal efficacy, etc., and severe morbidity and mortality. Homeostatic control and approach well articulated; regulatory approach, preclinical and CMC path, package, and program well outlined and high likelihood of success. Complex integrated approach.
- Assessing the value proposition: The value proposition is not clearly outlined. The authors discuss standard of care and unmet needs - one of them they suggest is a CMV vaccine, which is true.
- The next unmet need the applicant states is in immunocompromised patients, but the applicant describes no patient numbers who are in need of this therapy, as well as any cost.
- The applicant then describes ganciclovir and acyclovir resistance, but no patient numbers are given. In this reviewer's experience, this resistance is actually quite rare.
- This reviewer understands the applicant's goal is to develop an additional CMV antiviral to be added to the market, though the applicant has not done a good job outlining the value proposition.
- The applicant does bring up the dose-limiting toxicity of ganciclovir and valganciclovir, which is accurate. This is the driving indicator for this application.
- The applicant discusses letermovir's retail costs, but does not give any cost of their own product.
- This reviewer has learned that the PI may no longer be in California; this is a concerning development. The PI's role on this project is essential for eventual success. If the PI were to move away from California and become unavailable to lead the project, that would seriously affect the eventual success.
- The PI has left the institution and a plan to address this should be developed as the feasibility of the project may be affected.
- Timely, impactful, and well developed proposal. There is strong preliminary data to support feasibility. The scientific detractor is the remaining concerns (although less impactful) on resistance and the limited development of alternative strategies.

Value Proposition

- Overall it is an excellent proposal and a timely one. Issues of therapeutic efficacy required additional development. The re-location of the principal investigator needs to be mentioned in the program to ensure free development of the proposal with investigators in CA.
- Excellent value and needed therapy but application lacked more detail on value and economic value novel MOA.
- An approved product would likely have immediate uptake and a valuable impact on the healthcare system.
- High unmet need.
- If successful, this product would address an unmet medical need for an underserved population with limited resources and limited treatment options; the expected impact would be high in terms of preventing sequelae of CMV infection, e.g., organ transplant failure, GVHD. This could result in a substantial improvement in clinical outcomes for this patient population.
- The applicant has presented a plan to address HEOR attributes with respect to patient uptake and impact on healthcare.
- As there are no good options for this indication an effective safe product would achieve immediate uptake by physicians and therefore patients.
- [REDACTED CANDIDATE] has the potential to be a non-drug resistant treatment for CMV infections, which would be a substantial improvement over the current standards of care.
- A global overview of what the true impact of CMV is, or unresolved CMV infection, would be much better to give a value proposition.
- The authors give seroprevalence of CMV by state, which is not a very helpful diagram as it's based on antibody levels.
- CMV is a relatively benign disease in most patients. The applicants discuss CMV seroprevalence, increasing with age and being problematic for transplant populations, but actually give no data about the size of the problem.
- In this review's experience, while it's a serious disease in HSCT, it occurs much less in the modern era than it did historically.

Rationale

- Excellent and supported by the need and impact of the targeted diseases.
- Scientifically, this seems to be a very robust proposal, the applicants are proposing an antiviral strategy utilizing DNA-duplex feedback disruptor.
- The scientific rationale appears sound as the cyclic DNA oligo is intended to act as an IE2 disruptor. Current data indicates potential future success
- Strong rationale - good early proof of mechanism data.
- The applicants have outlined a feedback circuit in Figure 4, and their target discovery was given in later figures, which is robust and very interesting.

- The applicants also tested a dose-response and a minimal effective dose in cells.
- Applicants also gave data to suggest that their technology has a high barrier to evolution of resistance.
- Applicants show their drug could protect mice from systemic CMV disease.
- Rationale very well developed; needs regulatory information, but approach and preclinical designs well developed and appear well thought out.

Project Plan and Design

- Interesting approach and design. Limited preclinical models and stagnant data recently.
- Proposed nonclinical and CMC activities are well laid out and in line with regulatory expectations.
- The activities appear appropriate.
- Risks are identified.
- The CMC project plan appears sound. The planned activities should generate sufficient materials for the nonclinical and phase 1 clinical programs.

Project Team and Resources

- Strong collective team with the concerns raised through the PI re-location cited above.
- The project team is well qualified. There was discussion of PI relocating to a hospital outside of CA. I personally don't think this is an issue. PI's frequently oversee global clinical trials, so can't be onsite at all sites.
- Significant concerns were raised during discussion about the location of the PI and their impact on successful execution of the project plan.
- Serious concern about feasibility if the PI has left California.
- Excellent team, well regarded, well respected, and published. Based on regulatory path, could have a high level of success to get through an IND into the clinic. Regulatory team and support well respected. It is unclear where the primary site and PIs are located. One of the PIs is no longer at this institution, and that raises concern on the feasibility for the project.
- Team and resources do seem to be intact to be successful.
- The budget is quite robust.
- Clear regulatory path.
- CMC manufacturing will be performed at [REDACTED CDMO], which has phase 1 manufacturing experience. All collaborators and consultants are experienced and appropriate for the milestones.

Population Impact

- Unmet need for immunocompromised patients (cancer, HIV, transplants). More information could have been developed for patients in need - transplant epi data.

- The largest impact is the avoidance of toxicity from GCV.
- There is some discrepancy between the route of administration. In the mice, it seems to be an IP injection, while the proposed clinical trial is an IV injection, the authors will test rats using an IV injection.
- The proposed clinical trial is given; the applicant does not state whether other antiviral therapies can be allowed during the testing of their novel compound.
- Overall, this reviewer agrees with the proposed patient population being adults going through HSCT, and the endpoints showing a 2-log viral reduction and looking at 100-day survival seem reasonable. Their dosing will be IV delivery of the drug every other day.
- It may be a little early to incorporate perspectives and experience from patients and individuals affected by the target indication at phase 1 in development. The product has the potential to be effective across all CMV disease populations. The program was discussed as being light on this assessment.
- Well described and appropriate.
- No concerns.

Application #	PDEV-19751
Title (as written by the applicant)	Autologous ABCD1 ex vivo gene-modified iPSC-derived microglia cell therapy for cerebral adrenoleukodystrophy (CALD).
Therapeutic Candidate (as written by the applicant)	Autologous ex vivo gene-modified iPSC-derived microglia precursor cell therapy (MGPCs) for cerebral adrenoleukodystrophy (CALD).
Indication (as written by the applicant)	Childhood cerebral adrenoleukodystrophy (CALD), the form of X-Linked Adrenoleukodystrophy (X-ALD) affecting the CNS.
Unmet Medical Need (as written by the applicant)	CALD needs safer, more accessible therapies than HSCT or SKYSONA. Our approach is available to all patients, aims to avoid toxic conditioning, enable brain repair, and includes enhanced QC for a safer product, which addresses major unmet needs that would improve patient quality of life and safety.
Major Proposed Activities (as written by the applicant)	• CMC: Test for genetic safety, refine the product, and develop the manufacturing process needed to deliver safe, consistent therapy batches. • IND-Enabling Studies: Conduct efficacy, delivery method, dose-ranging, safety, and toxicology studies required for FDA submission. • Clinical: Protocol development and finalization for IND Submission: Prepare and file IND application with the FDA to gain approval for clinical trials
Statement of Benefit to California (as written by the applicant)	This project advances a personalized therapy for CALD, a fatal disease affecting 1 in 5,000 California boys. Although the state's newborn screening enables early detection, many children lack a suitable bone marrow donor. By closing preclinical gaps, this work supports development of an autologous stem cell-based treatments option aimed to be safer for every affected child, benefiting California families and strengthening the state's biomedical innovation.
Funds Requested	$12,740,075
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	4
Highest	85
Lowest	70

Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	10

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- There are two approved therapies that cut against the value proposition.
- Key Strengths - autologous (no immunosuppression), treats loss-of-function mutation, does not require lymphodepletion/myeloablation, manufacturing process and clinical operations de-risked because applicant already has one iPSC product in clinical trials, potential route of administration may provide faster time to disease stabilization, potential for neuronal repair and remyelination.
- Key Weaknesses - not off the shelf, CMC FDA feedback response require effort, route of administration not yet defined, conditioning regimen still required, risks of off-target editing, mouse model phenotype does not test for correction despite FDA's acceptance of the model during INTERACT.
- Strengths: High clinical impact and strong unmet need that targets CALD, a severe, life-threatening disease with high morbidity and mortality. Existing treatments (HSCT, gene therapy) do exist but carry significant risks, including malignancy. Proposed therapy has potential to significantly improve or reverse disease progression, representing a meaningful advancement over current options. Compelling value proposition with strong adoption potential. Autologous, one-time treatment approach could reduce long-term treatment burden and costs and utilize existing clinical infrastructure with high likelihood of uptake due to limited effective alternatives. Supported by robust scientific rationale and data with clear mechanism of action. Strong preclinical data package with appropriate controls with positive FDA feedback for the chosen animal model and approach. Prior clinical experience in a related indication strengthens translational confidence. Well-developed automated autologous manufacturing and analytical framework. Strong focus on identity testing and off-target gene editing risk mitigation. Highly experienced team with proven track record in cell and gene therapy and active clinical programs and prior CIRM funding demonstrate execution capability. Strong financial position supports program continuity.
- Weaknesses: Animal models may not fully capture human disease biology and introduces some translational uncertainty. Incomplete CMC documentation detail that lacks updated Bill of Materials limits full assessment of GMP compliance, especially for any new or modified components. Potential scalability and cost uncertainties and long-term cost-effectiveness compared to existing high-cost therapies (e.g., gene therapy) is not fully quantified. Manufacturing and process assumptions are heavily based on the PD program, which may not fully translate to CALD-specific requirements and contains limited discussion of indication-specific process adaptations.
- Key Strengths:
    - 1) Strategy is likely to be superior to existing therapies, including making more natural CNS microglia.
    - 2) Preclinical data demonstrate the successful generation of ABCD1-corrected microglial precursors in vitro.

- 3) Strong team.
- 4) Parkinson's program in the clinic - so they know first-hand how to develop a successful program.

- Key weaknesses:
  - 1) The lack of a preclinical disease model for CALD does not allow the investigation of in vivo efficacy / longevity of therapeutic effect.
  - 2) There is some concern about the eventual need for microglial depletion in patients who clearly depend on the functioning microglia they will have at the time of pre-treatment / treatment. Also, the mouse ablation protocol, which is dependent on ablating non-native microglia, is a weakness.
  - 3) 22% success rate in making iPS clones with one or two ABCD genes - this will add time and work at the time of making the autologous precursor cells.
- Large unmet need but value proposition not clear. Therapies are available and require myeloablation and immunosuppression.
- Using iPSC to differentiate (autologous therapy) which is a plus.
- Need more FDA regulatory insight - the applicant needs to discuss the GLP toxicity plan.
- The conditioning regimen is neither well considered nor well addressed.

Value Proposition

- CALD is the severe form of X-ALD which is caused by mutations in ABCD1 that codes for the ALDP peroxisomal transporter. Loss of ADLP activity leads to accumulation of very long chain fatty acids or VLCFAs leading to microglial dysfunction, neuroinflammation and white matter loss. 40% of X-ALD patients develop CALD (4-10 years).
- CALD has near 100% mortality without treatment and standard of care is hematopoietic stem cell transplant if a donor is available with HLA matching. In case a donor is not available, SKYSONA is used which is a lentiviral gene therapy to transduce ABCD1 to autologous hematopoietic stem cells.
- The unmet need remains high as both hematopoietic stem cell therapies are slow in replacing microglia and have safety issues. These therapies also require myeloablation which has its own safety risks.
- The proposal aims to develop a direct microglial replacement therapy to replace patient's diseased microglia with gene-corrected precursors to repopulate the brain after microglial conditioning. This is an autologous therapy (taking patient's fibroblasts, correcting, and reprogramming and differentiation), therefore, the risk of graft vs host disease (GvHD) is low.
- CALD results in severe disability or death following the appearance of symptoms. Bone marrow transplants and gene therapy treatment (SKYSONA) exist, but come with side effects. Gene therapy comes with a higher chance for associated cancer. The proposed therapy has the opportunity to significantly improve or potential reverse patient disease course.
- CALD has high morbidity and mortality and is a high unmet medical need with significant burden to patients, caregivers, and the medical resources.
- The product has the benefit of not requiring immune system reset nor runs the risk of graft rejection. It is autologous gene therapy that overcomes loss of function in microglia cells (ABCD1 gene), which otherwise causes microglia cell death by accumulation of very long chain fatty acids. Skysona is an existing, FDA-approved therapy for CALD. HSCT is the current standard of care for CALD patients. Both therapies

require lymphodepletion and myeloablation before therapy can be delivered and the patient must withstand a high-risk period of recovery while their immune system reconstitutes before receiving clinical benefit. The value of the proposed approach is enhanced by de-risking that has occurred with the applicant executing its Parkinson's Disease trial (also autologous, iPSC-derived, within their own CMC facilities).

- The autologous process has been shown to be effective in the applicant's other indication which is currently in clinical trials. Costs for current treatment (HSCT or gene therapy) are considerable. Automated process of application as a one-time therapy can potentially realize significant cost savings.
- The company has developed another cell therapy being tested in the clinic and therefore there's platform potential. Further, CMC is de-risked.
- This proposed therapy, if developed, aims to target the root cause of the biology and will lead to a faster therapeutic effect while avoiding risks of GvHD, donor matching, insertional mutagenesis with lentiviral gene delivery and myeloablation. Further, underrepresented populations may have a more equitable chance of getting this treatment since donor matching may introduce the bias towards certain populations.
- There will likely not be the need for myeloablation and its associated complications with this new modality.
- Need for a safer treatment: CALD is a rapidly progressing and fatal pediatric condition for which there are currently a couple of non-ideal therapies: HSPC transplant with myeloablation if there is a matched donor (70% lack this), or SKYSONA, an autologous HSC transplant with a corrected ABCD1 gene that suffers from the effects of random genomic insertion via lentiviral transduction – with a risk of hematological malignancies. The applicant wants to develop an autologous iPSC-derived microglial precursor cell transplant method – delivered directly to the CNS. This strategy is likely to be more efficacious because there will be maturation of microglial cells, the main target in disease, directly in the CNS as opposed to the peripheral source in HSPC transplants.
- Meets the criteria for unmet medical need.
- While the authors are right to point out the barriers to treatment with the existing approved drugs for CALD, the value proposition for the proposed therapy is not clear. First, CALD is a rare disease and the fact that two approved therapies already exist is meaningful, despite their non-idealities. Furthermore, there is a possibility that improvements in the necessary pre-conditioning treatments for successful HSCT in the field broadly could be leveraged for this indication, reducing the burden on patients and increasing uptake.
- There are two approved therapies that cut against the value proposition.
- Large unmet need but value proposition not clear. Therapies available require myeloablation and immunosuppression so this program provides a value.
- Common route of administration with current infrastructure. High likelihood of adoption.
- The value proposition would be strengthened by demonstrating a clear functional benefit for direct transplantation of corrected microglial cells vs HSCT. The authors say their target is 8% microglial engraftment based on prior HSCT studies. That benchmark leaves a lot of room for increased engraftment. Is there any evidence that there could be even further functional gains with greater engraftment? If yes, that would provide a clearer value proposition for the proposed product to demonstrate "best-in-class" performance.
- Engraftment % appears low.
- The differentiated microglial precursor cells will be directly injected into the CNS but the route of administration is not completely figured out by the applicant.
- Unlikely to be more affordable than existing modalities. Depending on the eventual route of administration, this may require specialized centers for delivery.

- Overall, this is a high-reward approach but there is a significant risk of clinical translation given the early stage of the project, absence of in vivo model, preclinical studies unavailable to date that will achieve the 8% graft benchmark laid out in the proposal. Further, safety of microglial conditioning is not discussed.

Rationale

- The overall scientific rationale is solid. Microglial dysfunction due to loss of ADLP function exists in CALD. The proposal aims to replace diseased microglia with gene corrected microglial precursor cells differentiated from patient-fibroblast (autologous) derived iPSCs.
- Rationale makes sense - treats the root cause of pathology. The program seems a bit early, pilot study - GLP studies have yet to be run. Would benefit from quantifying the value over current therapies.
- Strong scientific rationale. Therapeutic modality is appropriate as it repopulates cells with the deficient gene to restore function.
- The rationale to use gene-editing to alter a defective gene and overcome a loss-of-function variant makes sense. Autologous cells eliminate the graft risks associated with allogeneic HSCT. Use of the gene-editing process proposed reduces the risk of using the Skysona lentiviral vector although off-target/mutagenesis effects must still be assessed. Both treatments are effective, but with more difficult safety profiles. The applicant's product offers a therapy with the efficiency and permanence of gene editing, coupled with a potentially improved and more manageable safety profile. Replacement of dead microglia with exogenous gene-edited microglia have the potential to halt disease and promote remyelination.
- Data available to justify approach. Animal model to evaluate in vivo testing is limited but justified as a best option.
- Extensive preclinical findings with acceptable controls. Positive FDA comments related to animal model confirm approach.
- The proposal shows ADLP expression and correct localization after gene insertion in vitro. Further reduction of VLCFAs is shown in vitro. Reduction in pro-inflammatory cytokines is also observed.
- On-target gene integration is shown and off-target effects are analyzed using long-read WGS. However, this data needs to be aligned with the regulatory agency at pre-IND.
- They have shown ability to add the correct ABCD1 gene without off target effects and make clonal iPSCs (success rate of 22%; some with one or both chromosomal insertions), differentiated to microglial precursor cells. These cells show evidence of correction in vitro (ALD protein expression, peroxisomal localization, reduction of VLCFAs, and correction of chemokine gene expression). The data in differentiated microglia like cells is not complete/impressive.
- Unfortunately, ABCD1 KO mice (or rabbits) do not have the demyelinating phenotype – so there is no animal model to test for phenotypic correction, and longevity / stability of correction. Instead, they will use the FIRE mouse, which lacks endogenous microglia to test for engraftment, differentiation, persistence of ABCD1-expressing human microglia like cells in the CNS. This is in line with their FDA INTERACT.
- Differentiation to MGPCs and engraftment of MGPCs is shown in vitro. Quantification is not provided to show the achievement of 8% engraftment as laid out in the proposal. This is a plan for the future studies which tells us that this proposal is a bit early. The mouse models used are aligned with the FDA per INTERACT feedback.
- They seem to have made the most of the FIRE mouse, however, not having the opportunity for phenotypic correction is not ideal.

- All routes of administration being evaluated are intended to have direct CNS access, facilitating microglia engraftment. Route of administration is facilitated by the goal to have a single dose, thaw and inject formulation.

- They show delivery of precursor cells via a single ICV or IT injection that microglia can engraft and differentiate and express ALD protein in the spinal cord and cortex. ICV seems to be clearly superior – however, for logistical reasons, they would like to explore IT with longer duration. They will also try the ICM route. They have estimated the need for >8% threshold for engraft chimerism – extrapolating from phenotypic improvement achieved via HSPC transplant.

- As noted above, a justification of the functional benefit of direct microglial cell transplantation over HSCT was lacking. Relatedly, the pilot engraftment studies #1 and #2 fail to quantify the % engraftment of the transplanted cells in the same way that is defined in the TPP. Without this information, it is impossible to assess whether there could be dose-dependent increases in long term engraftment that could also have functional benefit. While % engraftment is noted as a metric in Preclinical Activity 1A, the dose response is not explored.

- 8% engraftment was not met.

- The conditioning regimen is neither well considered nor well addressed.

Project Plan and Design

- The project plan seems sufficient but early.

- Non-clinical models are aligned with the FDA but GLP studies and designs are not aligned with the agency. Dose levels are not fleshed out since this proposal is a bit early on execution. It's pointed out that CIRM funds will be used to finish these studies. A pre-IND meeting should be conducted at the end of the non-clinical studies.

- FDA agreed on models and stepwise approach in performing multiple pilot safety and tumorigenicity studies. The agency asked for data from these studies to agree on definitive IND-enabling studies at pre-IND. It appears that data will be required from these pilot studies to write a pre-IND application. Pre-IND is planned for 1H 2026 which does not allow sufficient time to complete pilot nonclinical studies. It may be a typo and pre-IND meeting may be 1H 2027 since IND is expected in 2029?

- The INTERACT meeting provided actionable feedback for CMC and the applicant will be seeking a pre-IND meeting. The timing of some of the CMC activities (1F, 1B, 1F Late PDEV) compared to the timing of requesting and completing the meeting (Early PDEV) does not appear to correlate if the pre-IND meeting is intended to review output/responses to FDA feedback from the INTERACT meeting. Preparation and submission of the IND at Late PDEV is reasonable.

- Pilot study of microglial ablation and engraftment. There is some confusion in the way the protocol is written – it says ICV and it also says other routes of delivery will be tested. Either way, this is essential to test for an ablation protocol that will optimize engraftment. Will this translate to the larger animal and eventually human system?

- Primary pharmacology and toxicology: the plan seems reasonable to test for in vivo engraftment, maturation, distribution and persistence – and to evaluate proportion of non-MGPCs – followed by non-GLP and GLP studies for tumorigenicity of non-MGPCs. This is a key safety consideration.

- The main concern of the dosing strategy is the translatability of the data in mice to humans. They plan to address this issue via a pivotal route of administration and dosing large animal study in immunosuppressed animals. Microglial depletion and transplantation plus safety will be assessed. Seems like a reasonable plan. However, the route of administration, which is not decided, could be variable in mice versus large animals.

- The effect of doing microglial depletion in CALD patients cannot be assessed in the existing non-human models and is a variable that is of some concern, given that microglial dysfunction and degeneration is a key aspect of the disease phenotype.
- In preclinical activity 1A, a cleaner approach would be to characterize the microglial depletion dynamics with the drug in both the intended mouse model as well as a humanized mouse model separately. This would allow the team to make a data-driven decision on the optimal time point for microglial engraftment. In addition, any differences in kinetics between the microglial depletion kinetics in the two models would provide important translational information. This kind of small molecule study should be inexpensive and straightforward.
- Extremely little detail about the differentiation process was given. While the need to protect IP is understood, without any details on the differentiation method, yield, or purity, it is impossible to assess the feasibility of scale up and manufacturing. Given that this is proposed as an autologous therapy, meaning the process is the drug, these are critical details that must be included to be properly evaluated.
- Data demonstrating long-term ALDP expression was lacking. Gene silencing from the AAVS1 locus has been demonstrated in multiple other instances so it would be wise to confirm that is not happening here. The choice of the promoter should reduce this risk relative to other promoters, but without any other details on the sequence of the insertion construct, it is difficult to assess the risk without empirical data. I would not consider this study to be gating, but could something run in parallel to other proposed activities.
- Regarding proposed Preclinical Activity 1C, it is surprising to see no mention of their clinical stage Parkinson's product here. Presumably they had to do a very similar study for that product, the major difference being the starting iPSC clones. Are there any learnings from that can be leveraged here? Are there any bridging studies that could be done to better leverage the prior data set?
- For CMC activity 1C, is stability analysis required?
- Pre-IND timing seems early, given issues with GLP toxicity.
- Unclear mode of delivery is a risk.
- Regulatory is still a risk, the applicant needs agreement on GLP models and toxicity.
- Not clear on how to reach no-observed-adverse-effect level (NOAEL); dose ranging and clinical study weak.
- Strong manufacturing plan based on applicant’s current clinical trial. The automated autologous process generates patient specific therapy without the need for immunosuppression.
- Detailed analytical methods for product characterization. While many of the materials are likely compliant due to past clinical trial experience, the application would be strengthened with an updated Bill of Materials to ensure GMP compliance of new products, if any.
- Strong characterization for patient identity and off-target effects of gene editing.
- Applicant leverages current pipeline that has already been employed in the clinic. Application would be strengthened by specifically identifying how this plan differs from the current trial, especially since the product cell is a different lineage. A similar critique was noted by the FDA with respect to the reporter plasmid excision.
- It seems like a potency assay development activity is missing.

Project Team and Resources

- The team at the applicant institution is appropriate, and with an impressive track record. Several neurologists are experienced in the care of CALD patients.
- The past and ongoing experience with their Parkinson's disease program which is in Phase 1/2a (funded by CIRM CLN2) is a strength.
- The project team possesses the expertise to launch this clinical study. Senior management has the skills to manufacture the product, oversee the clinical trial and plan for future needs. The applicant institution has their own established CMC facility licensed by CA and is currently supporting a Parkinson's Disease clinical trial. Establishing this manufacturing process in their facility will leverage existing infrastructure and systems, improving overall economics for the applicant.
- Given the company's success in advancing their innovative Parkinson's cell therapy, they have the appropriate team to be successful in this application.
- Excellent team, CMC is de-risked but IND enabling is a risk. They are leveraging their knowledge from their Parkinson's disease project.
- Strong project team with extensive industry experience. Applicant is currently in clinical trials for Parkinson's disease.
- The team seems to be well resourced toward successful project completion.
- The company recently secured Series C funding and appears to be well-capitalized.
- Concurrent project for Parkinson's Disease funded by CIRM.
- The team seems adequate in terms of nonclinical, CMC, regulatory, clinical etc.

Population Impact

- The applicant understands their target patient population and is developing a therapy that addresses the root cause of the disease, along with a process and drug product configuration that simplifies clinical logistics, enabling reach to patients who are not co-located to major medical centers.
- This modality will be applicable to CALD patients with any type of loss of function ABCD1 variants.
- The proposed therapy should work across all the mutations of ABCD1. Use of autologous cells removes donor matching necessity. Non-White populations generally have lower donor-matching rates as addressed in the proposal.
- Thorough understanding of the population. Minority populations are over-represented in trial due to less HLA matching and opportunity for HSCT (most common treatment).
- The proposed product would have a positive population impact by addressing the lack of HLA-matched HSCT products for certain demographics.
- Relationship with patient advocacy groups is appropriate and will be useful.
- The proposal does plan for advocacy engagement, broad access, and travel support. However, there's limited discussion of socioeconomic status even though autologous cell therapies are expensive.
- Since this is an x-linked gene, CALD is observed in mostly boys. CALD occurs across all ethnic groups.

- Clinical trial plan does address reducing family burden to improve participation by using travel support vendors and experienced clinical sites.

- Advocacy, patient and key opinion leader engagement is addressed.

Application #	PDEV-19728
Title (as written by the applicant)	AAV gene therapy for brain metastases
Therapeutic Candidate (as written by the applicant)	A locally delivered AAV immuno-gene therapy
Indication (as written by the applicant)	Adults with brain metastases arising from solid tumors, regardless of primary tumor origin
Unmet Medical Need (as written by the applicant)	Brain metastases are common, life-limiting, and poorly served by current therapies. Existing treatments rely on surgery and radiation with limited durability and cumulative neurotoxicity. No approved gene therapies or locally delivered biologics exist, leaving patients with few effective options.
Major Proposed Activities (as written by the applicant)	• Define [redacted product name] biological activity across brain metastases using organoid and in vivo models. • Advance scalable producer cell line manufacturing of [redacted product name] and demonstrate GMP feasibility. • Prepare regulatory and clinical infrastructure for a tumor-agnostic basket IND.
Statement of Benefit to California (as written by the applicant)	Brain metastases affect a large and growing population of adult cancer patients in California and contribute substantially to morbidity, healthcare utilization, and cost. This project advances a scalable, locally delivered therapy designed to address intracranial disease directly, reducing reliance on repeat surgery and radiation. It positions California as a leader in CNS gene therapy innovation, supports high-skilled biotech jobs, and accelerates California patient access to novel treatments.
Funds Requested	$12,999,999
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	81
Median	84
Standard Deviation	8

Highest	88
Lowest	-
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- A highly translatable approach that could lead to significant learnings in the clinic.
- A tumor-agnostic approach that builds upon the FDA plausible mechanism pathway.
- Huge unmet need - but unclear outcomes that are being measured.
- Approach could have a huge impact and proof of mechanism and plausible pathway. The team could translate this.
- This application is focused on developing a therapy for metastatic brain tumors by delivering an AAV gene therapy designed to induce sustained intratumoral expression of [redacted].
- Overall, this was a well thought out proposal with a team with AAV and CMC depth. The proposal is expensive and contains unnecessary costs but this was not a deterrent. The differentiating approach for manufacturing to ultimately bring down costs is appreciated. Key issues were the validity of the approach and the lack of CMO and clinical oncology depth. With this said, I support recommending for funding to test the concept given the medical need.
- Brain metastasis is a significant clinical problem.
- Substantial refining of the development plan to streamline and accelerate by leveraging learnings from the adult program (to be done in collaboration with CIRM personnel) is needed; as currently proposed, it is unclear if all proposed activities are necessary to translate and expand patient population.
- If the claim of the proposal that this therapy would work with a single injection into the tumor mass, then this might be an achievable outcome. There are substantial concerns regarding the viability of that claim.
- On a general level, the absence of any in vivo data on metastatic brain tumors suggests that this application falls in a much earlier stage of development than is appropriate for the proposal that was submitted. While it may be that the approach would lead to an IND application, and even agreement for a phase 1 trial, there is no evidence presented that the proposed approach will yield any therapeutic benefits.
- Achievable outcomes have a high degree of uncertainty, with no in vivo support on metastatic brain tumors from preliminary observations.

- There are substantial concerns with the research design and over-representation of the relatively meager preliminary data.
- Lack of data from the trial in adults leaves critical questions unanswered.
- While it is understood that it is the aspiration of the applicants to provide tumor-agnostic therapy that will work in everybody, such aspirations are frequent and associated successes are nonexistent.
- Recommend a gate for funding of establishing clinical proof-of-concept from the adult program.
- The leadership team is also missing key elements.

Value Proposition

- Brain metastasis is a devastating complication associated with some of the most prevalent solid tumors (i.e., breast, lung, melanoma, colorectal, renal).
- The intended patient population is clinically important: adults with recurrent or progressive brain metastases after standard local therapy, where additional durable local treatment options are limited.
- Effective therapies are extremely limited and minimally effective.
- Very high unmet need.
- Huge unmet need but no clear outcomes and no measures discussed in the proposal.
- Unmet medical need but seems to be a moonshot application.
- A locally delivered, single-administration therapy could be attractive if it truly provided durable local control while reducing repeat radiation, hospitalization burden, or neurologic decline.
- The application correctly recognizes that surgery, stereotactic radiosurgery, and whole-brain radiotherapy remain the current standard, and the most plausible niche for the product is as a salvage or complementary local therapy rather than a replacement for established local modalities.
- The approach will minimize safety concerns typically associated with AAVs. Clear unmet medical need. However, it is treating a diverse population with different treatment strategies. Sound approach to make it more affordable. Unclear about potential uptake.
- The application overstates how practice-changing this could be for brain metastases. For many patients, surgery and radiosurgery already provide effective local treatment. The more realistic use case here is a narrower, highly selected salvage population, which materially lowers the breadth of the value proposition.
- As the options for treatment of metastatic brain tumors are insufficiently effective, a successful approach would be expected to have a high uptake. That said, any speculations regarding uptake are wholly dependent upon the efficacy of the approach.
- Whether this program can be more accessible than existing therapeutic approaches is not made clear in this proposal. If the claim of the proposal that this therapy would work with a single injection into the tumor mass, then this might be an achievable outcome. Given the questions discussed later regarding the viability of that claim, that this might be an achievable outcome has a high degree of uncertainty.
- The unmet need is real, but the claimed differentiation is presently too broad relative to the evidence. This appears more like an early, hypothesis-generating metastasis program than a near-IND, tumor-agnostic opportunity with a compellingly defined clinical value proposition.

- The proposal does not yet establish that the product meaningfully improves upon current care in metastases. That remains hypothetical because there are no treated brain-metastasis patients and no completed metastasis-specific in vivo efficacy data.
- The tumor-agnostic positioning is especially ambitious. Demonstrating activity in organoids from several histologies is interesting, but it is not sufficient on its own to support a broad basket strategy in a clinically heterogeneous metastasis population.
- The proposal lacks estimates of overall prevalence rates for brain metastasis across the various solid tumors. Albeit limited, these data are available.
- The proposal lacks estimates of the percentage of brain metastasis that are unifocal versus multifocal. Albeit limited, these data are available.
- Significant questions regarding rationale for this proposal relative to a prior CIRM-funded program.

Rationale

- The platform itself is credible. The product has an established mechanism, a coherent local-delivery strategy, and extensive prior work in CNS oncology. The large-animal pig data are a genuine strength and support feasibility of MRI-guided convection-enhanced delivery, localized biodistribution, and a generally manageable safety profile for intracranial delivery. The program also benefits from an active adult recurrent high-grade glioma IND, which substantially de-risks the delivery platform and some aspects of safety monitoring.
- Comprehensive data are available to support the use of the product to treat brain metastases, primarily through data generated in their similar program using the product to treat glioma (which utilizes the same construct, capsid, formulation, and route of administration).
- The nonclinical work is well aligned with the FDA feedback and the agency's guidance on plausible mechanisms.
- The translational path is highly de-risked due to the open IND for adult high-grade glioma.
- Sound approach in using AAV to deliver cargo intracranially with evidence to support safety profile of vector. Unclear how well the vector will be distributed within the tumor but data presented shows promise.
- Some limited preliminary evidence suggests that the product is effective across brain metastasis regardless of primary tumor (i.e., tumor agnostic).
- The central scientific problem is that the brain-metastasis-specific efficacy case is not yet mature enough. The proposal's own scientific rationale states that activity across breast, lung, and melanoma brain metastasis organoids supports evaluation of a tumor-agnostic intracranial strategy, while the orthotopic in vivo efficacy foundation is drawn from adult CNS tumor models, some explicitly glioma-based. The application acknowledges this limitation and proposes to mitigate it during the award by performing targeted orthotopic CDX brain-metastasis studies. That means the critical efficacy bridge for this indication is prospective, not already established.
- Metastasis-specific evidence is mostly organoid-based at present. That is not enough to justify a high-confidence tumor-agnostic development plan for multiple metastatic histologies.
- The completed in vivo efficacy studies are not in brain metastasis models. Glioma data may support delivery feasibility and a general intracranial biologic effect, but they do not adequately substitute for efficacy evidence in metastatic lesions of diverse origins. There are no human efficacy data and no dosed patients in the related glioma program yet, so even cross-indication clinical translatability remains untested.

- The proposal is asking to fund the generation of the decisive metastasis efficacy dataset. For a late-stage preclinical award, that weakens the argument that the application is already sufficiently de-risked for this indication.

- No information is provided on effectiveness in different tumors in vivo. Indeed, the bulk of the in vivo experiments so far have been conducted using a single glioblastoma cell line.

- There are multiple concerns with the scientific rationale of the therapeutic approach, the planned route of administration, the availability of compelling evidence of disease modifying activity and relevant pre-clinical modeling. There were also significant limitations in the data presented.

- The proposed scientific rationale is that injection of the product will cause direct tumor lysis, release of inflammatory cytokines, activation of the innate immune response and generation of an adaptive immune response. No data are provided indicating that this actually occurs. Moreover, the proposal includes use of peri-operative corticosteroids, which would suppress the immune response. This is not discussed as a potential concern.

- Too much of the experimentation provided relies on organoid models, which lack an immune response and lack vascularization, key elements of tumors in vivo. Figure 4 refers to activity across different tumor types examined in an organoid model. In this experimental system, which is the major experimental system proposed for use in this application, organoid size is decreased by 40 to 50%, and the dead cells are increased by 20 to 50% compared to the control virus. No information is provided on the number of different cell lines tested, on the importance of the local effects of the protein, or on the durability of treatment effects (which seem to end at 6 days). There are no publications available.

- In respect to orthotopic tumor models, the information presented is solely on a single cell line that is a glioblastoma cell line. The bioluminescent imaging is interesting in that none of the mice show tumors, which is interesting in regard to this one particular cell line. It is impossible to extrapolate further beyond this cell line, a point of particular importance as this is a proposed trial on metastatic brain tumors.

- Studies in the large animal pig model appear to be confined to biodistribution.

- Studies by this team have focused entirely on production of the product and establishing workflow, with little attention to establishing biological properties of the material.

- The applicants refer to a robust intracranial in vivo foundation informing dose and delivery, but there is little on efficacy. While the claim is made that the glioma data are highly informative in respect to moving forward, that is a statement of belief rather than being supported by data.

- Their summary of completed data stated that in the second dose ranging model, the treatment did not significantly impact group mean tumor volume and median survival across a broad range of doses that represent the lower range of dosing. As they propose to include patients with antibodies to the virus of interest, this could effectively reduce dosage.

- Organoids do not make sense for immune recruitment studies.

- As previous studies suggest [redacted] is sufficient to eliminate tumor forming cells, the limited efficacy in organoids is disturbing. While it could be that there would be better responsiveness in a host with an intact immune system, that is speculative.

- The subject of targeting cancer stem cells is not even considered as an important study (nor analyzed in any way), something surprising in any proposal hoping to treat metastatic tumors.

- The rationale is sound but the clinical inclusion criteria may not be reasonable for participant selection and enrollment (too high functioning).

- Unclear rationale for the applicants' switch to a producer cell line (PCL) based upstream manufacturing strategy; the applicant states that this is to support scalability, supply reliability, and future clinical and

commercial readiness. As evidence of this, the applicant is proposing to engage with Dark Horse, others to map out the value proposition of this change.

- Any change in manufacturing should be considered in context of additional required development work to support that change; the applicant recently opened an IND for the same product in a very similar indication, which was supported by a prior CIRM award and a comprehensive nonclinical development program; under this proposal, the applicant is proposing to repeat much of this nonclinical work (at great time and expense); additional information is required on value of CMC change in this context of development program. Additional discussion on how previous data could be leveraged to shorten and/or accelerate development program if CMC change(s) are implemented. For example, is there a role for analytical bridging studies or must the nonclinical toxicology studies be repeated.

Project Plan and Design

- The work plan is detailed, internally consistent, and professionally constructed across nonclinical, CMC, clinical-readiness, regulatory, and access workstreams. The CMC plan is unusually mature for this space, with existing GMP experience, a clear producer cell line (PCL) scale-up strategy, and a rational comparability path. The regulatory strategy is thoughtful and appropriately staged, using prior FDA interactions in glioma as a partial foundation.
- Budget and milestones require strong coordination and guidance from the CIRM team to ensure value proposition.
- The project needs to be streamlined and the approach more direct. Need clinical input into trial design.
- It is not clear how data from the preclinical studies will inform the dosing of the product in the clinical trial.
- The plan is expensive for a program whose key metastasis efficacy rationale is not yet established. A substantial fraction of the budget supports platform expansion, manufacturing scale-up, and basket-trial readiness before the indication-specific biologic case is fully proven. The proposal bundles together multiple ambitious goals: cross-histology efficacy mapping, basket-trial positioning, major manufacturing evolution, large-animal bridging toxicology, and extensive clinical-readiness work. That breadth may be premature for a metastasis program still anchored largely by organoids.
- Due to the insufficient pre-clinical data on cancer, the project risks seem high.
- Novel approach in attempting to establish a producer cell line this early in development to supply a phase 1/2 trial. Limited data in comparability of products from triple transfection compared to PCL but will drive down product costs. Potential to improve safety using a PCL to mitigate unintended DNA delivery. Realistic timeline presented. Risks in establishing a PCL with high upfront cost. Scale is also high to implement a new technology.
- The patient population chosen for the trial are individuals who have a single intracranial metastatic lesion. No information is provided on the frequency of such a population in people with brain metastases, both in respect to the brain and in respect to frequency of metastases in other parts of the body in such patients.
- Moreover, no consideration is given to the fact that these are people with metastatic cancers who may have tumors spread in other regions of the body, something that itself would have likely effects on survival. Thus, even if there were a local effect on the single tumor site infected, a failure in respect to survival could be for many different reasons and uninterpretable in respect to how responsiveness could be improved.
- Even if the hypothesis is correct that this is a harnessing of the immune response, there are no studies on the immune response nor are any proposed in the patients.
- While this approach might get to IND, the design beyond that is poor and the pre-clinical data warranting enthusiasm for this approach are lacking.

Project Team and Resources

- Experienced team with a great set of consultants/contractors. High CMC depth that is not often observed. Definitely sufficient resources to support the program and position for success. Potential costs seem high at this stage of development. Clear plan, well thought out.
- The cost of goods are being considered, thinking about the end product and could be transformative. Great team, experienced.
- The team appears good and has had success on a highly similar CIRM-funded program.
- This is a strong and credible group with relevant experience in development, neuro-oncology, intracranial delivery, CMC, and regulatory execution. The institutional and partner environment is also strong, including experienced CROs, manufacturing partners, and high-volume academic centers capable of future clinical execution. This strength supports confidence that negative conclusions here reflect concerns about the indication-specific evidence base, not concerns about the competence of the team.
- The leadership team has excellent AAV expertise, comparable expertise on cancer is lacking. This is reflected in the lack of attention to tumor biology throughout this proposal.
- The project team would benefit from having clinicians who provide supportive or palliative care to patients with brain metastasis involved in this project.
- The clinical team needs to be expanded to work with these end-stage patients.

Population Impact

- A tumor-agnostic approach is likely to increase accessibility.
- Enrollment targets by ethnicity and age are supported by the data provided in the proposal.
- Single dose administration will decrease burden on patients and family caregivers.
- Plans are in place to reimburse patients for transportation, lodging and care coordination.
- An independent board-certified neuro-oncologist will serve as a medical monitor.
- A data safety monitoring board will be convened to oversee the clinical trial.
- Epidemiology is not discussed in enough detail in the proposal - no mention of what the impact is on various different types of cancer metastases.
- The proposal argues for large population impact by pursuing a tumor-agnostic basket strategy across common metastatic histologies. The projected impact is somewhat overstated at present. The likely near-term clinical role is narrower, including recurrent or progressive intracranial disease after standard local therapy, in specialized centers capable of MRI-guided convection-enhanced delivery. That still may be meaningful for some patients, but it is not yet a broad population-level solution. Population impact could become substantial later if metastasis-specific efficacy and trial feasibility are convincingly demonstrated, but that has not yet been shown.
- There appears to be very little experience with affected individuals in the leadership team.

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

Overall, reviewers in the minority thought the unmet need in metastatic brain cancer is large and the proposed approach could have a huge impact. They thought the approach was highly translatable and would lead to significant learnings in the clinic. In addition, the project has an established team and had success with a similar program with prior CIRM funding. Reviewers acknowledged the project was high risk and high cost, but thought the award could be modified to leverage learnings from adult clinical studies, and funding gated to proof of concept data from the clinical program in a different indication.

Application #	PDEV-19710
Title (as written by the applicant)	Small non-coding RNA drug for Duchenne muscular dystrophy
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate, is a synthetic chemically modified non-coding RNA oligonucleotide
Indication (as written by the applicant)	Duchenne muscular dystrophy (DMD), the most common and lethal form of muscular dystrophy
Unmet Medical Need (as written by the applicant)	DMD is the most common and lethal form of muscular dystrophy, affecting 1 in 3,500 to 1 in 5,000 live born males worldwide, making DMD rare. Patients die in their third decade of life due to heart failure. No current therapy has been proven to slow the progression of heart disease in DMD.
Major Proposed Activities (as written by the applicant)	• Prepare and conduct of a pre-IND meeting with the FDA • Completion of IND-enabling studies • Prepare and submit IND for the first-in-human studies of oral [REDACTED CANDIDATE] in healthy subjects, clinical trial planning, and trial start-up
Statement of Benefit to California (as written by the applicant)	Even with standard-of-care, DMD patients die in their third decade of life due to heart failure. No current therapy has been proven to slow or halt development of heart disease in DMD. Our work seeks to develop a new, orally-active drug that will halt or even reverse the progression of DMD, improving quality of life to affected Californians. The California-based drug development efforts will also provide jobs, strengthen our economy and further establish our state as the leader in biotechnology.
Funds Requested	$6,484,315
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	8
Highest	84
Lowest	-
Count	14

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The strength of this application is in its novel approach to a therapy for Duchenne muscular dystrophy (DMD). The CMC manufacturing plan for the sncRNA drug substance is well described and with a robust process development and process control plan. The weakness is the lack of detail around the final formulation and particularly how the drug product would be manufactured and classified. From the application and responses to CMC questions, it appears that the final product is meant to be a compounded product prepared on-site by the hospital pharmacy. The regulatory path for a compounded drug product is unclear, as CDER would expect a classical drug formulation with stability, container closure, and traditional release testing.

- The regulatory references and clinical plan appear inconsistent with the agency feedback being referenced. Under Clinical Planning within the proposal, it states, "In reviewing the clinical trial protocol for a Phase 1 safety trial, CDER endorsed the concept of beginning with a first-in-human safety study in normal volunteers." This is not consistent with the FDA written response provided within the application. The FDA Introductory Comments stated, "it is premature to agree with the proposed study population, dose/dosing regimen, safety monitoring and other specific features of the design of your first-in-human (FIH) study."

- Borderline false statements made in the regulatory section.

- Key Strengths:

    - Unmet need in DMD, tackled with targeting a novel pathway ([REDACTED PRODUCT] adds confidence to the candidate's success).

    - Strong team with successful track record.

    - Strong preclinical data - benefiting heart and skeletal muscle.

    - Applicable to all DMD patients, irrespective of dystrophin pathogenic variant.

    - Oral delivery.

    - Additive/synergistic with other drugs.

- Key weaknesses:

    - It is unclear if peripheral monocytes have the same phenotype as bone marrow derived macrophages - for the development of exposure biomarker.

    - It is unclear whether the C2 (minus lipid) formulation will provide enough biodistribution via oral delivery in large animal models/humans.

- There was some discussion regarding the need for adding regulatory expertise to the team (for CDER/small RNA development).

- Strong demand for a therapy in this patient population. Current gene and ASO approaches have not provided definitive solutions. Cost effective approaches are needed. Simple delivery is a bonus for patient uptake of any ultimate therapy. Strong biology and suite of data to support, the lack of clear dose response is difficult to understand. Transition to human parts of the regulatory information are based on a different molecule and lack of clarity on DP handling is hard to understand at this point.
- All DMD patients could benefit.
- The regulatory plan is not well formulated.
- Key Strengths:
  - Strong need.
- Key Weaknesses:
  - Clinical regulatory input and poor representation for regulatory path.
  - CMC is confusing.
  - No discussion that the final drug product can be used with concurrent meds and adjunct therapies.
- This reviewer's view is that this is a novel approach to treat a disease that has challenges with its current treatment options, in that this could use a different approach to drive meaningful change and at a relatively lower cost. The primary concern was oral delivery; however, this was addressed by the scientific panel. The secondary concern was the weakness in CMC expertise that clearly translated in the proposed strategy. While gaps exist, this reviewer believes this could be overcome and hence recommended for approval. It is unclear what the DP strategy is.
- Would meet an urgent unmet need, via a therapy that is significantly easier for patients to take.

Value Proposition

- There is a need for new therapeutic options for Duchenne Muscular Dystrophy and the applicant's proposed sncRNA drug is a novel approach that if effective would have a compelling value proposition.
- Unmet need and novel modality: This therapy for DMD is based on a novel targeting of macrophage dysregulation to achieve beneficial immunomodulation and antifibrotic actions to improve cardiac and skeletal muscle function. While there are new disease-modifying drugs approved for DMD (gene therapy, and exon-skipping oligos which work for specific mutations) there is still an unmet medical need. This modality is more specific than corticosteroids.
- Promising molecule, oral delivery: candidate is a phosphorothioate version of a small ncRNA RNA molecule, in a custom micelle that allows oral administration. Preclinical data are promising in terms of improving cardiac and skeletal muscle function in animal models (even reversing dystrophic cardiomyopathy). The RNA molecule is made by standard solid phase synthesis, and the oral route of administration will be more acceptable and easier to administer.
- Wide applicability: It is mutation agnostic (unlike exon-skipping oligos) and will be usable by all patients.
- May even be additive/synergistic with other modalities.

- The value if successful for patients with DMD is substantial as there are no current therapeutics and existing therapies in development may not provide the necessary step change in disease management. The therapy would, if successful, be given orally thus offering good accessibility. Uptake therefore would be high given the burden of disease. It would be imagined that a dose 2 x week would be used, if the current design were successful.
- All DMD patients could benefit.
- Large value proposition.
- High potential to provide a safer alternative to current lines of treatment and at a substantially lower cost; treatment will lower the burden on the healthcare system and would stand out as a primary treatment option; high competition in the space however products are not all alike or target disease subpopulations.
- Positive impact on cost to health care system and patients: The therapy, though likely ongoing, would reduce costs of hospital visits, durable medical equipment and home modifications.
- Broad potential impact and uptake: All patients with DMD could benefit from the proposed therapy – there are no exclusions because of type, age, or stage of disease.
- Definitely an unmet need but unsure if the applicant proposed a compelling case for funding.
- Mechanism of action could be extremely important and helpful to this population, and the idea that this could become a monotherapy option or the possibility of being used with other therapies, including gene therapy, could be a significant improvement for this patient population.
- Being an oral medication is beneficial for patients, caregivers, and the health system. It could drastically reduce patient burden and cost associated with treating DMD.

Rationale

- The scientific rationale for the proposed drug mechanism of action appears reasonable.
- From a CMC perspective the manufacturing plan for the sncRNA is well described. The formulation of the final drug product at a high level seems appropriate with an oral formulation using materials generally known to be safe. However, the manufacturing plan for the final drug product, its packaging, release testing and stability is not well described. It appears that the applicant plans to have the final drug compounded at the hospital pharmacy rather than developed as a final drug product, which would not be appropriate for a traditional CDER IND process. This reviewer would strongly recommend CMC regulatory consultation and if this is the proposed path to describe in detail and request feedback during an INTERACT or pre-IND meeting.
- Novel mechanism: The mechanism of action is by preventing cytosolic dsDNA-mediated proinflammatory dysregulation of macrophages, which is triggered by chronic tissue damage.
- Solid rationale: Target is the bioactive cargo of EVs from cardiosphere-derived cells (CDCs; cardiac progenitors), which are currently in a Phase 3 trial; an allogeneic cell therapy (IV) to confirm muscle and cardiac benefit in DMD, which is pending BLA, and is also being developed by the same group. However, the current PDEV project is for a different candidate to be developed as a bioactive ncRNA for oral administration.
- Strong preclinical data: The candidate is more bioactive (anti-inflammatory gene expression) and stable (RNase resistance) than target. Its cardioprotective effect is macrophage-specific (i.e., not seen when macrophages are depleted in mice). It effectively reduces cytosolic dsDNA aggregates in mouse and human macrophages. It shows effective cardiac [LVEF, fibrosis] and skeletal muscle [treadmill, torque, fibrosis] protection in the mouse model [which is cardio-selective, with benefits seen] given twice weekly for 4 weeks via oral gavage.

- Initial safety profile in preclinical model: Serum chemistry showed no difference in mice model with vehicle versus candidate.
- Efficacy demonstrated only in mouse model, and in in vitro human macrophages – although applicant did get IND approval for their cell-based therapy solely on this preclinical data. Will also have to see how oral PK/PD in larger animals/humans will work – especially the oral formulation which required higher doses for skeletal muscle efficacy in the mouse model.
- The rationale is that macrophages are dysfunctional in DMD; this has been shown and is relevant to disease burden, according to the application. This has an impact on both cardiac and skeletal muscle, which are severely impacted in DMD. The work involves the development of [REDACTED PRODUCT] - bioinspired from cardiosphere EV transcriptomics and developed into a single ncRNA therapeutic that is also formulated for oral delivery and within FDA RNA therapeutic guidance. The pilot data are supportive of the development. The supporting data leads from the cardiospheres to the EVs to the RNA to the bioinspired therapeutic. The pilot data are generally very supportive of the transition to the current PDEV application. There are some questions regarding the statistical analysis and the conclusions drawn, but otherwise the data are supportive of a novel RNA therapeutic, simple delivery, safety, and efficacy in relevant models of DMD.
- Oral delivery is not well addressed.
- The route of administration poses the largest question as RNAs tend to be highly susceptible to degradation and it is unclear if an oral route is viable.
- Application references many preclinical and nonclinical activities to be complete based on future contracting.

Project Plan and Design

- The CMC plan for sncRNA DS is well described and well planned. The final drug product is planned to be a compounded mixture with generally considered to be safe, food grade excipients. The drug product manufacturing and release criteria are planned to be further developed during the grant period. There is some regulatory risk in treating this as a compounded final drug product rather than standard manufacturing and drug product release.
- Available guidance and experience: This genetic therapy will be evaluated by CDER (not CBER). The applicants already have correspondence from FDA regarding pre-IND workup for another related ncRNA oligo therapeutic on which the preclinical plan is modeled. The plan is also informed by the applicants' previous preclinical development of [REDACTED PRODUCT] in a mouse model.
- Reasonable preclinical development plan: long-term efficacy in mouse model; PK in mouse; safety and tox in mouse and large animal model (per CDER recommendation, including genotoxicity studies and development of a biomarker assay that correlates with exposure); CMC; clinical planning; and initial market access planning.
- Slight risk in key request by CDER: Development of serum biomarker(s) that correlates with [REDACTED PRODUCT] exposure is planned by isolating circulating monocytes to confirm reduction in cytosolic DNA (mechanism of [REDACTED PRODUCT]). It is unclear if circulating monocytes have the same phenotype plus phenotypic correction as bone marrow-derived macrophages.
- The project planning involved a logical series of pivotal preclinical studies to evaluate long term efficacy and safety, regulatory, CMC and clinical. The clinic is a first in human healthy volunteer study aligned to current FDA guidance on healthy subjects first (4 dose cohorts). The plan looks well managed, risk mitigated. Discussions on the DP regulatory aspect are needed.
- The regulatory plan is not well formulated.

- Clinical plan and correspondence with CIRM and FDA. The project is not set up for success there are CMC and dosing concerns.
- Limited scope and detail shared as applicants are primarily outsourcing activities to well established contract organizations with depth of experience. Significant jump in manufacturing scales however this is not concerning if process technologies are consistent and contingency exists (called out in contract).
- Multiple contract organizations and consultants appear to be referenced as regulatory support.

Project Team and Resources

- The team could benefit from a CMC expert/consultant and CMC regulatory expert to guide the planning, particularly with regards to regulatory feedback and IND submission.
- Strong team. PI is relatively junior but is independently well-funded, and has been a key team player in the development of mechanism and rationale for target. The rest of the team members are strong, with appropriate leadership and experience in DMD and cell & genetic therapies.
- Dr. [REDACTED]: senior leadership; 4 INDs as sponsor (including [REDACTED]); 2 pre-INDs for RNA-based drugs. Dr. [REDACTED] – also at [REDACTED], previously at [REDACTED], found EVs/small RNA as the basis for CDC-based therapy.
- The team has a leading DMD physician and clinical trialist.
- The applicant may benefit from adding regulatory and CMC expertise for small RNA drug.
- The team is led by a PI who has been developing much of the cardiosphere technology and is now leading this; the PI is an associate professor and has a proven track record. The others are also experienced and led by the group of [REDACTED PI] and co-workers experienced in all aspects of such grants and transition to trials. The host is well versed in provision and management of such complex grants.
- There is a gap in regulatory expertise in the team.
- Excellent team needs CMC and reg team. Applicants' need a clear path forward for clinical phase 1/2.
- CMC primarily outsourced but with a reputable provider; limited third-party or internal resources to establish and validate the CMC pathway (outside of the reputable provider listed).
- FDA recommended a preclinical consultant, and although a consultant was mentioned with extensive CDER experience, it's not clear why the regulatory references throughout the application are not consistent.

Population Impact

- This section appears reasonable.
- This is a mutation agnostic therapy so will have wide applicability irrespective of dystrophin gene variant.
- Oral formulation will be a plus for the DMD population.
- This is a strong aspect of the proposal. The PDEV would lead to next-funding DMD patient assessment following a successful first-in-human healthy volunteer study within-PDEV.
- Could have a large impact.

- Potential for high population impact as treatment can be relatively simple and safe with broad application. The key question is the effectiveness of delivery.
- Good understanding of current DMD patient population, and the disparities in detection, diagnosis, access to care, and health outcomes across demographic and socioeconomic groups.
- Good engagement with the DMD community to understand patient needs.
- The study population intended for this study appears less restrictive than other studies or approved therapies looking to treat DMD. This could help more DMD patients, and if successful, could be implemented early in development and potentially reducing muscle and heart development and health. If these patients could live more independently and for longer, it would be a significant success.

Application #	PDEV-19746
Title (as written by the applicant)	A Regenerative Small Molecule Therapy for Vision Restoration in Glaucoma
Therapeutic Candidate (as written by the applicant)	The therapy consists of a defined cocktail of pharmacologically active small molecules designed to restore vision.
Indication (as written by the applicant)	The target indication for this therapeutic candidate is irreversible vision loss caused by glaucoma.
Unmet Medical Need (as written by the applicant)	Glaucoma is among the leading causes of permanent blindness due to loss of retinal ganglion cells in the retina, collectively affecting millions of individuals worldwide. There is no treatment to restore vision in these patients.
Major Proposed Activities (as written by the applicant)	• Determine dose–response relationships, in vivo efficacy, toxicity, biodistribution of candidate small-molecule cocktail in rodent models. • Determine dose–response relationships, in vivo efficacy, toxicity, biodistribution of candidate small-molecule cocktail in non human primates. • IND enabling documentations
Statement of Benefit to California (as written by the applicant)	Vision loss imposes a substantial economic and societal burden in California, with an estimated per-person incremental cost of approximately $16,000 per year and total direct and indirect costs exceeding $13 billion statewide, driven by medical care, long-term support services, lost productivity, and caregiver burden. This therapy could significantly reduce long-term healthcare expenditures, disability-related costs and supports broad patient access across California's diverse population.
Funds Requested	$9,495,876
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	3
Highest	83
Lowest	70
Count	15

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The strength of this program is its novel approach to in vivo reprogramming and simplicity of the proposed drug product. The weakness is the final drug product CMC. The application stops at describing externally sourced drug substance; there is no description of the CMC plan for formulation, packaging/container closure, stability, or release testing for the final drug product. The formulation itself could have a large impact on delivery and efficacy, while a proposed approach to drug product CMC will be critical for a successful regulatory strategy.
- Key Strengths: Potentially restores vision; small-molecule formulation should be manufacturable; cost-effectiveness should be better than cell and gene therapy approaches; stable formulation should allow global reach for treatment.
- Key Weaknesses: The CMC section is lacking detail and does not adequately describe materials being used for formulation, what the final formulation is, what stability exists for drug product, what the manufacturing process is, or what steps are required to get from a non-GMP preclinical formulation to a first-in-human, aseptic drug product for clinical trial.
- Major deficiency in CMC and CMC/regulatory capabilities within the team.
- Strong rationale and meets an unmet need. Tremendous unmet need; strong preclinical data, model, and strong rationale. The application includes the structural and functional endpoints. Very weak CMC; no information on drug substance and drug product. No information on formulation, stability, solution versus suspension. It is unclear whether intellectual property exists on the formulation, the method of use, and/or composition of matter.
- Weaknesses include the fact that there is no mention nor consideration of delivery device, injector, and/or syringe. Stability considerations in final fill-finish are needed. It is unclear how this will be mixed and administered in the office and/or clinical trials. It is unclear whether repeat dosing will be needed. Timelines seem unrealistic. Longer safety studies and repeat dosing may need to be studied.
- Unclear manufacturing plan.

Value Proposition

- There is a high unmet need in glaucoma and the proposal is a novel approach to reprogramming endogenous Müller glia into retinal neurons in vivo to restore vision.
- Glaucoma is a debilitating disease and would benefit from a vision-restorative treatment (which is not currently available today). Afflicted individuals are older and reliant on caregivers and services at increasing levels of need as the disease renders them blind. Current therapies treat symptoms and only manage to slow (not prevent) vision loss. Use of a small-molecule chemical cocktail to reprogram Muller glia cells into retinal ganglion cells is appealing if such a process is not off-target, not tumor-inducing, can restore RGCs with sufficient neuronal capacity to interact with the optic nerve and actually restore vision.

The treatment would need to be durable (although repeat dosing would likely not be as cost prohibitive as cell/gene-editing treatments).

- The durability of the effect and efficacy are unknown.
- Strong rationale; sound preclinical proof of concept. Unmet need and strong interest in Neuroprotective approaches by VCs and strategics. Demonstrated functional endpoints as well. ERGs and perimetry could be approvable functional endpoints and clinically meaningful.
- This study aims to address a critical unmet need in vision restoration to the aging community improving quality of life to what is currently a permanent condition with no market treatment.
- This reviewer would have concerns about treatment in one eye as the other will receive a placebo and the effects on mental and physical health with monocular vision in the event there is some success and potentially waiting for years not knowing if the other eye will ever receive such treatment. If there is success after the study is concluded on individuals, it would be beneficial to know the other eye would receive such treatment as well.

Rationale

- From a CMC perspective the rationale is only partially described. The application stops at describing externally sourced drug substance, there is no description of the CMC plan for formulation, packaging/container closure, stability or release testing for the final drug product. The formulation itself could have a large impact on delivery and efficacy while a proposed approach to drug product CMC will be critical for a successful regulatory strategy.
- There is preclinical evidence that the cocktail is able to reprogram Muller glia cells into RGC-like neurons (CiGNs) although these cells are not characterized as replacement RGCs per se.
- Transient exposure to the cocktail initiates the regenerative cascade to create CiGN and functional vision restoration lasts for months in mouse models.
- pERG and pVEP show clear measurements of electrical activity and electrical response to the brain, hallmarks of cells sending data/signals to the brain along the optic nerve.
- Testing of reprogrammed human cells (immunofluorescence, qPCR, scRNAseq) indicate expression of RGC-specific markers demonstrating RGC-like reprogramming in Muller cells.
- Large animal studies are needed to demonstrate feasibility and durability.
- Sound rationale. Translatability is a risk from rodents to large animal models to humans. Glaucoma needs these types of approaches.

Project Plan and Design

- The manufacturing plan is incomplete. The final drug product consists of two mixtures that contain six and two small molecules/peptides respectively. These compounds are commercially available at GMP grade. However, the application does not detail any plans for formulating these molecules into the final drug substance or drug product. It is unclear where this manufacturing would occur, assuming the final formulation is liquid, what the solvent would be nor what the release criteria would be.
- Description of CMC starting materials appears inaccurate and incomplete. "GMP-grade" does not exist; grade is USP, NF, EP, ACS, etc., and knowledge of grade will be required for first-in-human regulatory filing. This suggests a lack of CMC knowledge amongst the applicant team members.

- It is unclear how a process can take from 2 - 25 weeks. No manufacturing process is described in the proposal.
- No final formulation or preliminary stability is described or plans to finalize such are described in the proposal.
- It is unclear how raw material quality will be assured from an overseas supplier. The proposal talks about approved qualified suppliers and passing quality testing, without describing how the applicant will confirm that the vendor will supply material of consistent, acceptable quality.
- The INTERACT meeting timing is logical however the Pre-IND meeting at 15 to 18 months from T0 appears too early, particularly if IND ready is 54 months - consider having this meeting ~6-9 months before IND filing.
- If the regulatory strategy is serious about following a 505(b)(2) pathway, this should be identified to regulators not later than the Pre-IND meeting.
- Consistency with DS and DP formulation needs quite a bit of work.
- CMC lacking; formulation is not defined. Regulatory information and CMC expertise lacking; no mention and consideration of stability, formulation pH, device containers, needles, and viscosity of the formulation. Risk for translating to older patients with more liquid vitreous and ILM could still be a go/no-go factor. ILM degradation is not a possibility in the clinic. No mention of need for repeat dosing nor duration of effect. No consideration nor mention of potential enzymatic effect from aging and/or disease state vitreous on peptides after injection.

Project Team and Resources

- The team would benefit from the addition of a CMC specialist and a regulatory specialist.
- The Project Team is scientifically sound. They have a seasoned consulting clinical lead.
- It is unclear how CMC and Regulatory leadership/management will be performed.
- It is unclear that *[redacted company name]* will perform sufficient due diligence to completely understand raw material quality and the manufacturing process for FIH administration.
- CMC/Regulatory expertise is needed.
- Excellent team and strong previous research - leaders in the field. NHP vendor well established need CMC and reg experts.

Population Impact

- This appears adequate.
- The ability to restore vision would positively impact patient ADLs, caregiver support needs and burden on the healthcare provider/payor system. The ability to deliver this therapy in a decentralized way would positively impact underserved populations. If the formulation can be made stable in various storage conditions (ambient or 2-8C or short-term elevated), it can be useful on a global basis, in disparate regions.
- Large unmet need. Consideration for travel and recruitment discussed. Little to no mention of patient engagement and or non-profit collaborations.

- After rodent trials are completed, actual human trials are expected in 2030, the plan is to move to patients primarily 20-84 years of age prioritizing older adults with a blend of 50/50 male to female, the target population race and ethnicity is consistent with California's population numbers.
- Applicant has categorized cases by race and ethnicities with higher instance in the hispanic population.
- There are outreach plans in place for patients from underserved communities, working with patient advocacy groups, community clinics and local providers. There will be a wide range of resources for recruitment with community engagement.
- *[Redacted university name]* has a Race and Equity Center that will function as a DEI resource for staff, patients and recruitment.
- *[Redacted university name]* has a strong track record in the space of recruitment of underserved populations.
- There will be a budget that will assist with costs such as transportation, lodging and meals, patient navigators, child, care, lost wages and more
- Finally, to summarize from a non-scientific patient advocate perspective and unaware of current research into improving or curing glaucoma, this reviewer is enthusiastic about this application. The applicant touched on most hallmarks in relation pertaining to patients that CIRM has come to expect.
- Stability concerns.

Application #	PDEV-19715
Title (as written by the applicant)	Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia
Therapeutic Candidate (as written by the applicant)	Human induced pluripotent stem cells derived enriched progenitor cells (hiPSC-GEPs)
Indication (as written by the applicant)	White matter stroke and vascular dementia
Unmet Medical Need (as written by the applicant)	There is no therapy for vascular dementia. The brain responds to this disease, and initiates a reparative response, but is blocked from fully engaging this response. This therapy addresses this condition by delivering a stem cell-derived product that enables recovery in vascular dementia.
Major Proposed Activities (as written by the applicant)	• cGMP manufacturing • GLP in vivo toxicology and efficacy studies • IND submission
Statement of Benefit to California (as written by the applicant)	This research will develop a therapy for a disease with no treatment, vascular dementia, that is common and devastating in its consequences. The intellectual property for this therapy is held by a State of California public university and commercialization will directly benefit the State of California.
Funds Requested	$7,499,999
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	2
Highest	78
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0

(1-84): Not recommended for funding	15

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- White matter stroke (WMS) and vascular dementia represent an unmet medical need with no treatment options that address the root cause of the problem. The focus on this patient population and the development of immature glial progenitor cells from pluripotent stem cells by the applicant is a strength.
- The weaknesses involve the manufacturing plan. The applicants need to address the manufacturing problems outlined below. The applicants should avail themselves of a consultant well versed in pluripotent stem cell isolation, expansion, cell banking and differentiation before they start any work in the future.
- There is a lack of clarity regarding immune suppression. While immune suppression is proposed for the clinical trial, the nonclinical data do not address how much immune suppression is needed (dose/duration) and how immune suppression (or stopping immune suppression) might affect the duration of the therapeutic effect.
- Adequate CMC and nonclinical planning was lacking for this stage of a program headed to an IND.
- Key Weakness - There was a clear discussion and concern about the manufacturing process being suboptimal regarding technology choice, materials, scalability and overall capability to meet clinical needs and demand.
- Corticosteroids and immunosuppression could make the disease worse - a serious safety issue.
- Allogenic cells hence patients will need immunosuppression in a cognitively depressed patient population. High risk to have elderly patients on immunosuppressant. CMC, cell line expansion appears to need help (no need for high dose antibiotics).
- Strengths: Strong scientific merit and high unmet medical need. Good preclinical proof of concept. Weaknesses: Lots of work to do on the manufacturing. Very open and manual with up to 80x 6 well plates, testing specifications (karyotype, STR, etc.) should be re-evaluated.
- This proposal builds on prior CIRM-funded preclinical work by PI on using hiPSC-derived glial enriched progenitor (GEP) cells as a regenerative therapy for stroke, particularly targeting white matter injury and vascular dementia. The project aims to transition this therapy from lab to clinic through seven key activities, including manufacturing, potency testing, preclinical safety/efficacy studies, clinical protocol development, regulatory approval (IND), and access/affordability planning.
- The proposal addresses a major unmet need, as current stroke treatments benefit fewer than 10% of patients. Unlike time-limited neuroprotective therapies, this stem cell–based approach offers a broader treatment window and potential to improve recovery and quality of life. Delivery is planned via intracerebral transplantation.
- Strengths include strong preclinical evidence, a comprehensive translational plan, consideration of safety and affordability, and a highly qualified, multi-institutional team.

- Several weaknesses, however, are noted, including missing or unclear scientific rationale (e.g., dosing, timing, patient selection, target brain regions, and outcome measures), limited recent supporting publications, unclear timelines for several activities, administrative concerns (e.g., subcontracting issues with collaborating university), limited demonstrated collaboration among some team members, and writing quality issues (numerous typographical errors).

- Overall, the proposal is scientifically promising and clinically relevant, with a solid path toward clinical trials, but requires clarification in key areas and stronger justification of certain design choices.

Value Proposition

- The applicants aim to produce a glial enriched progenitor cell (GEP) population from hIPSCs. These cells will be used to treat white matter stroke and vascular dementia.

- WMS accounts for up to 30% of all strokes. WMS stroke leads to progressive loss of white matter over time and leads to vascular dementia.

- GEPs are immature glial progenitor cells that promote white matter repair by maturing into astrocytes and support neural repair.

- Stroke is a huge unmet medical need and the applicants intend to target specific stroke types where white matter is impacted.

- There appears to be a significant unmet need and not many treatment options for WMS. However, if this product is not intended for patients over 75 years old, the value proposition becomes unclear.

- Significant unmet need exists for patients not over 70 years old; however, the value proposition remains unclear.

- It is not clear how 8 weeks of immune suppression in these patients may affect the overall duration of the treatment effect.

- The safety issue is a concern that relates to value.

- Stroke is the leading cause of long-term adult disability and subcortical white matter stroke accounts for 30% of all stroke subtypes (240k annually in the U.S.). Currently no disease modifying therapies exist and standard of care is largely supportive. There is potential to meaningfully improve cognitive and motor function in these patients.

- Could preserve quality of life and independence, reduce reliance on caregivers, and decrease long-term healthcare utilization associated with chronic disability.

- Given that this is an allogeneic therapy it could improve accessibility. As a one-time treatment the cost could be high up-front but off-set the cost of long-term medical/supportive care. Uptake could be high given these considerations.

- This proposal is a logical continuation of an earlier CIRM funded preclinical grant by the PI, and her research team, examining the therapeutic potential of allogeneic human induced pluripotent stem cell (hiPSC)–derived Glial Enriched Progenitor (GEP) for stroke, in particular those patients with white matter injury and vascular dementia (VaD).

- As this proposal transitions from the laboratory to the clinic, seven key enabling deliverables are proposed to guide the safety and efficacy of hiPSC-GED for its clinical application, namely CMC Activity 1A: Clinical-grade hiPSC-GEP Manufacturing (Activity 1), CMC Activity 2A: Potency assay development (Activity 2), Nonclinical/Preclinical Activities 1A and 2A: Pivotal GLP studies (Toxicology and efficacy) (Activity 3), Clinical Activities 1A and 2A: Clinical protocol draft and Community engagement (Activity 4), Regulatory Activity 1A: IND submission (Activity 5), Access and Affordability Activity 1A: Automation and Comparability

study (Activity 6), and Regulatory Feedback (Activity 7). These are all necessary steps for initiating the clinical trials of hiPSC-GEP in stroke.

- Because stroke remains a significant unmet clinical need with therapeutic options limited to largely "neuroprotective" strategies, such as tPA and mechanical thrombectomy, which benefit only less than 10% of ischemic stroke patients, the introduction of "neuroregenerative" treatments, in this case stem cell therapy, will likely impact on uplifting the quality of life of stroke survivors who are not able to avail of the currently available therapies.
- With neuroprotective treatments requiring intervention within a few hours or at most a few days, the wider therapeutic window with the neurogenerative stem cell therapy will clearly increase the targeted ischemic stroke patient population, which may enhance accessibility while lowering treatment costs for the general stroke community.
- The cell delivery approach is via intracerebral transplantation, a feasible and practical regimen considering the intended localized brain deposition into the white matter, with neurosurgeons Dr. [REDACTED] taking the lead supported by the experienced stem cell pioneer Dr. [REDACTED].

Rationale

- The supporting data shows significant impact in animal models of white matter stroke.
- Major concerns are with manufacturing - where the applicants need to do quite a bit of work.
- The program appears late stage and much of the IND-enabling work appears to be complete.
- Corticosteroids and immunosuppression could make the disease worse - a serious safety issue.
- Strong preclinical data, strong rationale.
- White matter stroke triggers limited neural repair by inducing new connections to form. However, compared to cortical stroke, white matter stroke does not have as robust of a repair process. Lesion expansion is common due to a lack of differentiation of OPCs in the adjacent tissue. Astrocytes guide axons and promote new connections in the developing brain, suggesting that astrocytes could help with disconnection that occurs in WMS. This approach replaces lost cells and promotes repair of damaged axons, different from other approaches that are focused on neuron repair.
- Differentiation protocol leverages hypoxia pathway to force cells down the astrocyte lineage leading to a more astrocyte-enriched population and an overall shorter process (4x faster). Scalable and clinically compatible differentiation protocol.
- Efficacy has been demonstrated in 21 preclinical studies, some of which used cells produced with a representative mfg process. Significant improvements, claim more substantial and complete than other PSC-derived cell types.
- GLP-Like tumorigenicity/toxicity has been completed. No off-target cell outgrowth or tumor formation.
- Based on the previously funded CIRM grant by PI, there is solid evidence that hiPSC-GEP modifies the stroke outcomes characterized by improved histopathological and behavioral recovery in clinically relevant animal models of ischemic stroke.
- While generally supported by the PI's past reported studies, there are some missing rationale that will require clarifications, namely the justification to use the proposed cell doses and timing, brain target locations (which white matter structures), targeted patients (since chronic white matter injury results in VaD, unclear if only patients with VaD are enrolled here), the choice of primary outcome using 10% improvement in motor Fugl Myer scale with sensory subscale as opposed to higher percentages and other stroke scales, using Seahorse mitochondria as a major biological activity assay (PI's expertise on this is

lacking - scarce data and no publication), and the choice for "impurities are not greater than 0.1% for OCT4 and Nanog".

- As noted, the two publications by the PI on this topic appeared in 2021, begging the question why recent papers have not been produced over the last 5 years to support the missing rationale and justifications detailed above.

Project Plan and Design

- This reviewer's comments pertain to manufacturing. Firstly, not all the donor screening tests have been completed and it may be that they cannot be done. While it is possible to apply for an exemption, it would be much more desirable to start with a donor where all the consents are in place.
- The manufacturing program is based on expansion of iPSCs in 6 well plates - this is not appropriate. The RCB has been made with over 100x 6 well plates. That is a huge amount of manipulations where the lid of a vessel has to be removed for media replacement over the course of cell growth - this greatly increases the chances of contamination being introduced during cell growth.
- There are many different ways to expand iPSCs using large vessels like T flasks and cell stacks. Using these vessels will decrease the chance of contamination and allow increased expansion of the cells to produce robust large cell banks.
- The use of antibiotics is not desirable in cell culture. While allowed it is much preferable to use antibiotic free medium. The exception is when isolating cells from a tissue sample where contamination might be present. Would suspect the prolonged use of antibiotics by the applicants is necessary because of the large number of manipulations needed when expanding in 6 well trays.
- The applicants make a point of sourcing xeno-free components for growth of cells but they grow their cells on matrigel which is made from a rodent cell line. While matrigel is perfectly fine for research work there are a number of defined or at least human alternatives to matrigel and when making important cell banks one of those should be used. Laminin 521 is one of multiple examples that have been used extensively.
- When the RCB was karyotyped only 17/20 cells were normal. That is not acceptable in this reviewer's opinion. In the majority of cases once aneuploidies start to arise in pluripotent cell culture, they quickly take over the culture until the aneuploid cells represent the majority of cells in the culture. That is because these cells often have a selective advantage (grow more quickly, survive cell splitting and plating more efficiently etc).
- This reviewer would want the starting material to be pristine with a normal karyotype. It is not a very high bar as traditionally only 20 metaphase spreads are analyzed for karyotype so would want the analysis to show 20/20 cells have a normal karyotype.
- This reviewer thinks new cell banks need to be made using technology that is appropriate for expanding pluripotent stem cells. Would have to make sure all the donor criteria are met or use a starting cell line from a donor that meets all requirements.
- The 2 proposed preclinical studies did not appear necessary, and the applicant proposed at their pre-IND meeting that no further nonclinical studies are needed. So Preclinical Activity 1 and Preclinical Activity 2 should NOT be funded as proposed. The FDA did request an additional nonclinical study in a large animal model so perhaps CIRM funds could be used for that.
- There are challenges on the manufacturing side: manual picking on rosettes, and cell bank karyotyping. The STR profile should match the initial donor.
- CMC needs help and support. Cell banks need testing and analytical work. Testing reagents concern exists with clinical immunosuppression in these patients. Age, duration, amount, and type of immunosuppression

are unclear. Budget assignment for preclinical studies is unclear and not aligned with FDA recommendations (may need large species).

- CMC
    - Very open and manual process up to 80 6-well plates and picking of neural rosettes is high risk for contamination and operator error.
    - Three GMP lots for IND submission should not be necessary
    - Switching from RUO to GMP materials at such a late stage presents risk.
    - Need to ensure appropriate analytics are in place.
    - A validated potency assay is not required for phase 1. Starting on this early makes sense but should be characterization and not on lot release.
- Nonclinical
    - Studies appear to be appropriate and can be adjusted based on Pre-IND feedback.
    - It is unclear what is rate limiting to the start of the GLP Tox study (critical path).
    - Risks captured and contingency plans make sense.
- The lab-to-clinic transitional studies proposed here are logical IND-enabling steps to bring hiPSC-GEP toward initiating clinical trials. The proposed seven translational activities are within the thematic focus of ensuring the efficacy of intracerebral transplantation of hiPSC-GEP for stroke indication.
- All the preclinical development objectives will be achieved within the proposed budget (spread across the three institutions) but the timelines appear unclear (proposed as 18 months for Activity 1, but was difficult to decipher for Activities 2-7).
- Potential project risks with mitigation and contingency strategies are generally acknowledged.
- Access and affordability are thoughtfully considered in each stage of the project.

Project Team and Resources

- The team appears qualified and the staffing appropriate for this project.
- This reviewer thinks they need some guidance, perhaps in the form of a consultant, to help them devise a robust plan for obtaining a cell line and expanding it in culture.
- Several CMC and nonclinical gaps were identified which gave concern that the team may not be sufficiently experienced to achieve an IND with this program.
- Engineering runs and GMP need more explanation and planning. The team may lack preclinical and CMC expertise and insight.
- It would be helpful to get more input on CMC perhaps from a consultant.
- PI who started the early preclinical studies of this project has relocated. The collaborative teams between the two universities highlight the contributions of expert stroke neurologist and seasoned stroke

neurosurgeon, with younger breed of stroke experts coupled with IND/regulatory expert, altogether creating a strong and cohesive research team who are definitely capable of bringing hiPSC-GEP to the clinic.

- There is generally a robust plan for the coordination and execution of the project among collaborating institutions. The only caveat here is the acknowledgment that [REDACTED INSTITUTION] only allows one subcontract but there are two [REDACTED INSTITUTION] subcontracts here (Dr. [REDACTED PI] and Dr. [REDACTED PI], with the former, $137k listed as "TBD" and the latter for $2.2 million cleared). How this TBD will move forward is not explained, which may be critical since Dr. [REDACTED PI] is listed as a Co-I for the product potency testing.

- While PI's in this proposal have a proven record of collaboration (albeit until 2021), the PI and the [REDACTED INSTITUTION] team have yet to demonstrate collaborative efforts with [REDACTED PI].

Population Impact

- White Matter Stroke affects people in all demographic groups. Concern is getting the applicants to the starting line with robust cell banks and culture technology appropriate for today's best practice technology.

- The trial population rationale appears to have considered increasing trial participation (above their population share in CA) in groups known to be at a disproportionately higher risk of stroke and/or vascular dementia.

- No access and affordability.

- Clinical study population appears to be appropriate.

- The PI has listed appropriate safety assays to mitigate general risks associated with hiPSC-GEP ectopic tissue formation or tumorigenic potential.

- Genetic profiling of hiPSC-GEP up to 120 days in culture is provided, showing "pro-repair" properties. Additional GLP toxicology assays are proposed to further ensure safety of transplanted hiPSC-GEP.

- There is a general discussion on the demographic populations in California at risk for the target indication.

- A thoughtful discussion is welcomed on how PI's past research activities segway to the proposed studies and how they may directly impact on the targeted patient population.

- As noted for this PI's previous CIRM grant application, more diligent and rigorous grantsmanship needs to be carefully incorporated - there are just so many typographical errors in this application.

Application #	PDEV-19832
Title (as written by the applicant)	A Novel Peptide-MHC Adaptor CAR-T Cell Therapy for Targeted Elimination of Autoreactive T Cells in Type 1 Diabetes.
Therapeutic Candidate (as written by the applicant)	ctLNP-saRNA (anti-biotin CAR induction) + CAL (biotinylated peptide-HLA multimer); optional half-life–extended CAL
Indication (as written by the applicant)	Stage 2 type 1 diabetes (autoantibody+ dysglycemia) to delay/prevent progression to Stage 3 disease
Unmet Medical Need (as written by the applicant)	Stage 2 T1D patients face near-term progression to insulin-dependent diabetes, and current immune therapies are non-specific, transient, or burdensome. A scalable, antigen-specific, prevention-ready approach that can generalize across epitopes is needed.
Major Proposed Activities (as written by the applicant)	• CMC: finalize processes, analytics, and GMP manufacture/release of ctLNP-saRNA and CAL (with qualified alternate LNP supplier plan). • Nonclinical: dose/PK-PD optimization and IND-enabling GLP tox/biodistribution for both components plus combination strategy. • IND: regulatory interactions (pre-IND), integrated control strategy, and clinical trial start-up planning to enable IND activation.
Statement of Benefit to California (as written by the applicant)	California has one of the largest pediatric and adult T1D populations and a growing burden of chronic disease complications. This project advances a California-led, scalable immunotherapy platform with potential to reduce lifetime insulin dependence and downstream healthcare costs, strengthen CA biomanufacturing/clinical trial infrastructure, and support high-skill jobs and training.
Funds Requested	$12,996,187
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	73
Median	75
Standard Deviation	5
Highest	80

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The applicant has acknowledged the necessity of developing an uncomplicated "care pathway" that minimizes patient burden as well as compatibility with a wide-range of health-system workflows.
- The applicant has carefully considered the proposed clinical population including development of companion diagnostic which should better identify not only eligible participants and allow stratification but also can be used for PD monitoring to facilitate study design and evaluation. However there is regulatory risk in initiation of FIH trial in this asymptomatic population.
- Costing for pre-IND and IND preparation appears much higher than current industry standards, especially pre-IND.
- Very innovative approach.
- HLA-restriction lowers the impact.
- Specific peptide binding CAR-T - nice concept. Adaptable for other autoimmune conditions. Concern for tolerization and rationale for Type 1 Diabetes Mellitus (T1D). The concept is valid and well studied preclinically. Construct could be a platform.
- Off target effects not addressed and approach may not work in clinic and translate from mouse.
- Unclear if the approach can be expanded to widespread use.
- Strengths: Strong value proposition; Sound scientific rationale; Supporting preliminary data; Strong manufacturing (CMC) data.
- Weaknesses: Specific HLA-restricted, unclear population impact.

Value Proposition

- The applicant proposes a novel approach (depletion of pathogenic T-cells and induction of tolerance) to intervene during the presymptomatic phase of T1D to not only delay disease progression but also provide durable antigen-specific immune tolerance.
- The applicant has acknowledged the necessity of developing an uncomplicated "care pathway" that minimizes patient burden as well as compatibility with a wide-range of health-system workflows.

- Once validated in the proposed indication, there is potential for expansion of the technology platform to other organ-specific autoimmune diseases.
- Unmet need, rare population.
- Did not address the challenges with protein scale-up.
- The therapeutic modality has the potential to target antigen specific cells for depletion and then hyporesponsiveness in a unique manner. This specificity would be an improvement over current broader immunosuppression.
- There is an unmet need for safer, more streamlined and tailored therapies for T1D. If safe and then efficacious, then this proposal would introduce a new drug in class for antigen specific tolerance.
- This proposal does not improve upon accessibility or affordability, as the treatment is restricted by HLA and costs of repeated anti-Biotin CAR and MHC-peptide multimer may add up, but it is scalable and modifiable, which makes it more affordable/accessible than other antigen-specific therapies.
- As a new in vivo CAR with lnRNA and then MHC-peptide multimer engagers, feasibility is likely there, but practicality will only come when clinics adjust to these new technologies and use of more sophisticated biomarkers as PK/PD measures. So, with time.
- This proposal addresses an urgent and unmet need in the treatment of T1D. It provides a meaningful improvement to limit progression from Stage 2 to 3.
- The proposal would provide a substantial advance in approaches to prevent progression of the disease and significantly impact the patient, caregivers, and the health care system.
- The applicant is aware of the disease burden and health care outcomes of the affected population.
- The proposal includes discussions on affordability and describes the competition from other approaches.
- The value proposition is clearly outlined in the application and includes (i) prevention of progression T1D from stage 2 to stage 3, (ii) off-the-shelf scalable product with low-cost (per dose) manufacturing, (iii) broad accessibility through outpatient clinics, and (iv) long-term control of the disease through multi-dosing.
- It is not clear what fraction of T1D patients may benefit from this preventative therapy, since initially it will be restricted to HLA-A*02:01 population.

Rationale

- Initial preclinical data supporting plausibility of mechanism of action.
- Clear appreciation of potential and considerations of rational mitigation strategies.
- Potential regulatory risk for FIH studies in this asymptomatic population.
- Very innovative approach.
- Rationale makes sense but very early. Novel approach and early proof of concept.
- The fundamental scientific rationale and background data are strong for the actual drug, but also the route of administration.

- There is concern about the single specificity chosen since the specified CD8 T cells may also play a monitoring role, as they are found throughout the pancreas tissue and may not all be inflammatory (PMID33067232).
- There is concern about testing safety in stage 2 T1D. It is unclear why the applicant would not test in longer-standing T1D where less beta cells are present that could be lost.
- There is compelling preclinical data for the dual treatment approach of debulking and then tolerizing. However, TR1 and other forms of tolerance differ greatly in mouse and human, and the tolerance angle is far less supported than the depletional CAR-T modality. In addition, TR1 are difficult to measure in humans, so it is unclear what success looks like. It is unclear whether some in vitro beta-cell/T-cell cultures would help define both the depletional and modulating mechanisms of this treatment and development of robust biomarkers.
- The focus is on Stage 2 T1D when the autoimmune cells are beginning to expand and a consequent significant impact on the killing of beta cells. It may be tricky to confirm the window when each patient can be precisely targeted.
- The approach is scientifically sound and is based on the stage of T1D. The aim is to preserve endogenous beta cell function and delay progression to stage 3 by addressing heterogeneity of the disease but not specifically curative.
- The 2-component immune reprogramming strategy is designed to be specificity guided depletion of pathogenic T cells combined with antigen-specific immune tolerance.
- The applicant provides preliminary data and provides references from previous studies that support the scientific approach.
- Key limitations acknowledged by the applicant are the extent of coverage of antigens and HLA and off-target effects coupled with safety of induction associated with cytokine release.
- The scientific rationale is sound. The authors provide a great scientific rationale, based on (i) a review of the literature and (ii) experimental data in vivo.

Project Plan and Design

- Well thought out questions to address in proposed preclinical development plan. However proposed studies do not completely align with online application costing.
- Costing for pre-IND and IND preparation appears much higher than current industry standards especially pre-IND.
- Mouse-to-human immunological differences are not well accounted for.
- Antigen coverage is limited by their approach.
- Drug product not identified. Low preclinical data with their proposed approach.
- Translation from mouse to humans is risky. CMC and GMP are well laid out; however, challenges are not well addressed and discussed in enough detail. Contingencies not addressed. It is unclear what success looks like. Proposal disconnect with budget and funding for IND-enabling steps. CMC well outlined and no red flags.
- The manufacturing and safety studies are essential and well designed.
- The timeline and budget seem optimistic given the novelty of the proposed therapy.

- Validity of risks and mitigations are clear and appropriate, although there is the rare, unlikely risk that debulking results in removing some protective cells and then doing harm.
- Stage-appropriate access and affordability planning are limited, but more so due to the treatment itself. The effort is being made as is reasonable.
- The applicant describes the risks associated with the approach such as acute infection during induction and off-target immune effects and provides mitigation strategies.
- The objective as proposed will likely be achieved within the time frame. The budget details are appropriate for the described Aims.
- The project appears well planned and designed.
- Strong CMC package and supporting data.
- Very early stages of T1D may not be the best to assess the safety of in vivo CAR-Ts, due to potential risks of toxicity. More advanced symptomatic stages of T1D could be better to test in vivo CAR-Ts in first-in-human/Phase 1 trial.

Project Team and Resources

- Internal and external resources appear adequate.
- Good and solid team. Pulled in team members to help.
- The team is well qualified and resources are in place to implement the plan to navigate to IND submission with a clear plan.
- Consultants are used as appropriate.
- The team has the leadership, the expertise and skills in relevant functional areas required to undertake and execute the studies.
- There is a substantial plan that integrates the various components with co-ordination and execution components.
- The team has access to the resources and equipment and facilities to successfully conduct the proposed activities.
- The team as described has a track record in a similar area.
- The team is qualified to perform the work. Major manufacturing activities will be outsourced to industry CDMOs.

Population Impact

- The applicant has carefully considered the proposed clinical population including development of companion diagnostic which should better identify not only eligible participants and allow stratification but also can be used for PD monitoring to facilitate study design and evaluation.
- HLA-restriction lowers the impact.
- Large unmet need but may be difficult to identify the specific patient population.

- Population effect is considered, although Stage 2 T1D may bring on more risk for initial safety trials that may be better run in later disease individuals. Also, adults in stage 2 will be harder to recruit, whereas stage 3 could more easily encompass a range of populations represented in CA while also testing safety.
- The applicants do not have a strong track record in T1D trials, but are connecting with the right communities for support.
- The description covers aspects that are relevant for genetic environmental and associated factors that can influence the effectiveness of the proposed therapy.
- The intended clinical study is appropriate. However, precisely assessing and labeling the target population also has limitations.
- The proposed therapy will be limited to the patient population with HLA-A*02:01 restricted insulin epitope. It is not clear how large this T1D patient population is.

Application #	PDEV-19734
Title (as written by the applicant)	A Safe and Effective Genome Editor for Definitive Therapy of Fibrodysplasia Ossificans Progressiva
Therapeutic Candidate (as written by the applicant)	A base editor capable of correcting the most common FOP ACVR1 617 G>A mutation back to the wild type G
Indication (as written by the applicant)	For the treatment of patients with the classical form of fibrodysplasia ossificans progressiva (FOP)
Unmet Medical Need (as written by the applicant)	FOP is a severe, progressive disease where permanent heterotopic ossification (bone formation in soft tissues) fuse joints & cause immobility. No definitive therapies exist. Our potential therapy allows surgical release of a locked joint to restore mobility, and supports future systemic therapy.
Major Proposed Activities (as written by the applicant)	• Prepare, submit, and conduct INTERACT, pre-IND, and IND-enabling meetings with the FDA to obtain IND clearance • Complete IND-enabling community engagement, safety, and efficacy studies with the investigational product • Complete GMP manufacturing and first-in-human clinical protocol development
Statement of Benefit to California (as written by the applicant)	Patients with FOP and their families suffer severe medical, social, and economic hardships from this progressive and lifelong disease. Our approach benefits Californians with FOP by providing opportunities to restore basic mobility to help with activities of daily living. It may allow some patients more independence to eat and care for themselves. This also benefits families by reducing care burden. Our findings regarding the biology and delivery methods may also be applicable to other diseases.
Funds Requested	$12,022,344
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	72
Median	75
Standard Deviation	7
Highest	80
Lowest	-

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- Fibrodysplasia Ossificans Progressiva is a debilitating disease that has a very expensive drug available. Unmet need exists.
- Preliminary data are interesting, but additional data and work are needed to support preclinical proof-of-concept and the specific proposed therapeutic approach; further recommend conduct INTERACT meeting immediately / as soon as feasible to refine plan and proposed approach.
- Would benefit from a more developed preclinical approach with a LNP identified. Redosing not discussed and addressed. Could there be an adaptive immune response? Lacks data for translating to in vivo efficacy.
- The local injections are good preliminary approaches, but systemic delivery should be tested.
- Strengths - A clear patient population with an unmet need and the target is known and amenable to therapeutic approach.
- Weaknesses - A lot of logical leaps need to be true for this strategy to pan out. This project is very early and there's not enough data to support this as a product concept worth pushing towards the clinic yet.
- Strengths:
    - value proposition
    - devastating disease with no meaningful treatment
    - very strong team of expert clinicians
    - comprehensive mouse and large animal testing strategy
- Weaknesses:
    - no product defined
    - screening of LNPs not completed
    - no in vivo evidence for effective base editor delivery
    - no strategy to address the challenge of systemic treatment beyond liver

- unclear CMC strategy
- INTERACT meeting to inform applicant's preclinical development strategy would have been helpful

- The CMC plan is underdeveloped. Vague clinical development plan with local injection however a systemic delivery and exposure is what is needed. AAV strategy makes sense but they focus on LNPs as their approach and it is not clear why. Lacks underlying approach and rationale for the process with LNPs. CDMOs information is weak.
- Although there is a significant unmet need, the overall impact to Californians is low given the status as an ultra-rare disease.
- Excellent plan to support patients and their caregivers during the trial, and to engage with the FOP community during the development journey.

Value Proposition

- Area of significant unmet medical need, with fibrodysplasia ossificans progressiva (FOP) characterized by progressive and permanent abnormal bone formation in soft tissues; existing therapy has severe side effects (and is expensive) and many patients accumulate permanent mobility loss.
- The value proposition of a therapy for FOP that could prevent heterotopic ossification (HO) is very high for patients and caregivers; FOP is an ultra-rare disease with significant morbidity and life expectancy is to the 40s; unmet need is highest in young children where there is no existing standard of care.
- Major unmet medical need: anti-Activin A, Alk 2, and MMP9 inhibitors are under development, and could potentially be treatments to alleviate signs/symptoms, but would not cure the disease. The U.S. marketed drug--Palovarotene, an RAR-gamma agonist--has only modest efficacy and a substantive risk profile, i.e. narrow benefit-risk ratio, and was rejected for approval by the European Union.
- Significant unmet need for patients.
- The proposed therapy addresses a significant unmet need in a devastating indication. I commend the team for broadening the scope to include the family and community impact of a single patient.
- There is an unmet need. However, there is detail lacking that would enhance the translatability. It is perhaps too early with a lot of unknowns to identify the ideal candidate that translates.
- Potential remediation of local "fusion" through gene editing (base editing). The authors highlight the devastating nature of joint ankylosis which can inhibit routine activities. Ultimately, life-span is shortened because of bone overgrowth of the chest wall due to multiple episodes of traumatic injury.
- If successful, proposed therapy would offer significant value to patients with FOP.
- The proposed therapeutic strategy, base editing of disease-causing mutation, could offer relief to patients affected by this devastating disease.
- Proposed therapy is an LNP containing a base editor that will repair the predominant (95% of FOP patients) mutation; proposed initial study is patients with FOP, with ankylosed joints that undergo surgical resection (which is notably, NOT recommended for FOP patients) following by administration of the drug product with intent to prevent formation of new HO.
- Feasible if evidence for prevention of ossifications can be obtained.

- Patients would probably want to assume the significant risks associated with taking the proposed therapy, given the lack of alternative treatment.
- Uptake is highly questionable as surgical resection is not recommended and therefore would be at risk, there's no existing data in the application to infer this strategy would have any success; kids do not even get vaccinated b/c of risk of HO formation at the injection site so seems like high barrier to entry to do both an exploratory surgery and a novel drug with limited supporting data.
- Limited impact due to ultra-rare prevalence.
- It is uncertain as to the local (muscle) success of gene editing and one time therapy which would be a very high one-time expense, plus there is uncertainty about the overall benefit-risk profile for this new intervention which would very likely require multiple editing interventions depending the location of the muscle trauma/ joint ankylosis.

Rationale

- Strong scientific rationale. Adenine base editing, given the G->A mutation in FOP, and opportunity for addressing major signs of this devastating disease. It seems like the probability of having an impact outside of the local improvement in bony formation is very low.
- This proposal was extremely well written and presented. The rationale and supporting evidence were very clear. The base editor therapy directly addresses the causative mutation in nearly all FOP cases.
- Target clearly defined - ACVR1 c.617 G>A.
- The supporting data showing iterative optimization of the base editor and guide RNA to precisely target the mutation was clear. Although the optimized editing components have reduced the bystander edit at position 620 to below the LLOD, it may be important for the team to determine if that would result in a synonymous or non-synonymous change in the protein and whether the variant protein is predicted to be functional, as an additional safety consideration.
- The proposed project is very early with limited data to support scientific approach.
- Rationale makes sense but this is a very early program. No data is presented in this application that suggests that the LNPs can actually work. Local delivery is not the ideal way to treat this disease and full base editor info is lacking. No in vivo evidence for efficiency of gene editing.
- Preliminary data on AAV delivery and LNP delivery of luciferase - no evidence for meaningful base editing after local or systemic administration.
- In vivo editing proof of concept needs to be demonstrated.
- There are no base editors approved for current therapies, so this is a novel approach is untested in clinical practice, with questions related to: (a) degree and duration of efficacy; (b) efficiency of the editing itself; (c) specificity of the base editing, which could cause off-target toxicities; it seems like at least in the preclinical in vitro setting, the investigative team has identified the right ABE-sgRNA; and (d) toxicity (-ies) related to the LNP (carrier), though the available data on this new class of LNP seem positive.
- LNP toxicity needs to be considered - LNP formulation not defined.
- Interestingly, a large part of the application highlights data for a different strategy using an AAV to express the correct ACVR1 gene with a miRNA to knockdown expression of the mutant copy. This data is impressive. If this application were for the AAV approach, I would be much more favorable. A large argument for the LNP base editing mRNA approach is the potential for an inflammatory response following AAV treatment. Was this seen in the mice? The mouse data presented showed promising efficacy, were

there safety signals not presented? Why would we think an intramuscular (IM) injection would not cause inflammation? Does a novel LNP not cause inflammation?

- The ACVR1 c.617G>A mutation is autosomal dominant and mutant cells have a growth advantage, so it is expected that the mutant cells would outcompete the corrected cells.
- For the data purporting inflammation response or lack thereof, there are not appropriate controls, for example in the iPSC cultures, a HD iPSC control would be beneficial to understand if the reduction in ALP is to a "normal" level.
- The logic of the LNP choice is confusing. E7 LNP was used to conclude 80% BE efficiency in iPSCs, but E3 is the LNP selected for future investigation. E3 LNP was selected based on transduction of iMSCs with a very high dose; E3 LNP has sig lower transduction efficiency on iPSCs compared to E7, so what would the BE efficiency be with E3? The data suggesting the novel LNP could be "safer" than "traditional" LNPs is lacking. Doses used are not disclosed. It would be useful to understand what the doses used translated to in terms of transfection efficiencies, otherwise not relevant at all. The novel LNP is now "E20", the LNPs keep changing and yet the authors are making generalized conclusions about the novel (singular) LNP. It's bold to assume that they would behave comparably in this model when they clearly do not in others (like iPSC transfection).
- The only in vivo data presented with the novel LNP is luciferase delivery IM with IVIS measurement, not really telling anything about potential relevant biodistribution of an editor.
- While the novel LNP is promising, one must evaluate the discovery work with preclinical in vivo models which are not yet done.
- No interaction with FDA yet.

Project Plan and Design

- Comprehensive application that steps through their proposed approach to development
- The in vitro work on editing efficiency and off-target toxicity (or editing specificity) seems solid. LNP toxicity is always an uncertainty and the team, while optimistic, will be assessing such. The pending preclinical in vivo work will be critical and is planned.
- Future market access is difficult to predict. However, the deep engagement of the PI to the FOP community is very important and gives this investigative team a deep understanding of the burden of illness and the impact on joint ankylosis/disability on QoL. Given the paucity of effective systemic therapies at this time, at least, the team's plan seems very reasonable.
- The budget seems reasonable and the letter of support offered additional support if necessary.
- Appreciate the applicant planning to conduct an INTERACT meeting as one of the first activities, with future pre-IND gating later stage preclinical development; outlined plan appears reasonable it's just very early to comment on ability to operationalize or translate technology on path to IND.
- 200 LNP to be tested to inform the choice of LNP for the proposed product.
- Comprehensive non-clinical testing strategy in mice and large animals.
- The project plan is overall very solid. Perhaps the team should consider focusing on local delivery first and consider expanding to systemic delivery if local delivery is successful. There are many proposed large animal studies, at significant cost, for such a small patient population. Focusing on local delivery could help improve this cost benefit analysis.

- Planned non-clinical (NC) activity 1A has a goal to correct >20% of muscle tissue within 1 cm of IM injection, interesting considering anticipated spread in large animals was millimeters, unclear that this low bar would be ameliorative considering the growth advantage of mutant cells.

- Specificity shows up as both a non-clinical and CMC activity. Specificity is not a CMC activity, it's a safety (NC) activity. There needs to be an understanding of gRNA purity and potential impact to specificity, which is not appropriately covered anywhere. Planned NC activity 1B is premature. Understanding planned doses and pharmacology should be completed first. Off-targets will increase with increased exposure, but exposure ex vivo should target some fold above the expected effective dose based on other NC studies. There is a reference to off-targets at homologous loci, written as if that might be a known list already. What are those, are they genes of concern?

- In preclinical activity 1B, could the off-target analysis be conducted in PDGFR+ cells? Differences in the chromatin accessibility between the undifferentiated iPSCs and differentiated progeny could very well affect the off-target profile.

- Planned non-clinical activity 2A, I find it hard this is needed at all. Is there an established link to translate in vitro iPSC inflammatory response to anything in vivo?

- Planned NC 2B, why would this be tested in WT mice rather than diseased mice? It's established that the FOP mice have a hyper inflammatory response, or that seems to be the theme throughout, so how are WT mice the appropriate model here? Seems like a missing study to test the underlying thesis is to treat a FOP mouse that has HO with the AAV strategy, then resect and see if new HO forms; higher probability of affirming the underlying concept; we're doing a lot of basic science still to force this LNP BE strategy to work when we don't know if the concept is sound.

- Large animal studies, 5C should be taken out and go straight to 5D. GFP is not relevant, you can do IHC against your effector.

- Is preclinical activity 5D strictly necessary? It is a thoughtful control experiment, but may be nice given the high costs.

- An alternative off target strategy to what is proposed in preclinical activity 6 is recommended. Off target analysis needs to be conducted in human cells. A common strategy is to use a tissue distribution study, like in preclinical study 5B, to prioritize tissues for further analysis. In vitro human primary cells should be used to examine off target editing effects.

- Regarding preclinical activities 5A and 6: How best to model the elevated immune response seen in patients? If possible, in vitro studies that capture the difference in the immune response to the LNP and editor in patient cells vs WT cells could be informative to interpret immune responses in animals.

- A major conundrum is how to balance the strength of the scientific proposal with the very small patient population, which likely presents challenges to obtaining additional funding for the clinical plan. I would encourage the team to identify any potential platform aspects of their work, such as using the same LNP, base editor and route of administration for other indications. Identifying and de-risking these additional opportunities early could make the investment in developing this therapy more broadly impactful.

- LNP development is risky because no lead has been identified.

- Durability of effect and toxicity of the drug product need to be accounted for in their development plans.

- Adaptive response to LNP or editor needs to be addressed.

- No interaction with FDA yet, appears a bit late for this application. Have not tested the LNPs yet so it is a risk. Large animal studies and possible off target aspects need to be better delineated. Is there a way to get to a go/no go faster?

- CMC strategy not developed.

- The clinical section, seems like a lot of this we should know now to support the underlying thesis of why this strategy could work. Seems like we don't know the outcomes of surgical resection generally as it's not recommended and the team needs to do an extensive literature review; would not start in kids, 70% of planned enrollment is <15 yo.

Project Team and Resources

- The team has a systematic plan of moving from in vitro work, to a FOP murine model, then to large animals. The work to assess (and hopefully confirm) the low/no pro-inflammatory response to the IP seems systematic and clear. Including a better developed "control" experiment with the adenine base editor is an important project.
- The project plan seems clear and achievable.
- The applicant institution as an academic/ research institution is outstanding (facilities, experienced personnel, et.al) and the manufacturing capabilities seem available.
- Clinical experts in FOP on board and required to recruit a sufficient number of patients affected by this ultra-rare disease.
- The PI is an acknowledged expert in FOP, and their collaborators are world-class. The novel LNP offers the potential of a higher delivery to the target.
- Yes, it appears they have assembled the necessary team to be successful.
- The team is strong on preclinical work with mouse models. PI is an FOP expert and they acknowledge their limitations.
- The team has expertise in this disease indication, largely from a basic science perspective and clinical care, which notably doesn't include a lot of resections as that's not recommended and clinical plan step 1 is to do a literature review.
- I didn't see any estimate of how long it might take to recruit enough patients for the Phase 1 trial, given the extremely small patient community.
- LNP expertise is needed.

Population Impact

- The team is at a major FOP center, and as such, likely has strong relationships with the FOP community.
- Strong commitment to the FOP community in terms of engagement with trial design and outcomes, and support for patients.
- Patient perspective as to study participation motivation is included.
- Outstanding expertise in FOP has been shown by the applicant.
- Applicants demonstrate a strong commitment to understanding patient concerns: They have leveraged patient experience data from the International FOP Association as well as direct discussions with patients to better understand patient experiences with the disease and their priorities for treatments.
- The intended clinical study population is appropriate.
- The applicant and collaborators are well-connected to the FOP Advocacy Group, and have carefully assessed the burden of illness, and the specific intervention which could dramatically improve an affected

patient's QoL, via their registry. Thus, if positive, the trial outcomes which would be important, clinically relevant ones to affected patients.

- Direct community/potential patient engagement--this has and is an important feature advanced significantly by the Clinical and Translational Science grant (CTSA centers), and the *[organization]* center is outstanding. This is planned for this project and should provide important insights re: proposed target goals, safety, etc.
- There is an unmet need however it is an ultra rare population - funding would not even cover the clinical costs.
- Adoption is going to be highly questionable given patients are discouraged from surgical intervention.
- Limited.

Application #	PDEV-19732
Title (as written by the applicant)	In Vivo Generation of TRAC Locus-Specific CD19 CAR T Cell Therapy for B Cell Malignancies
Therapeutic Candidate (as written by the applicant)	A first-in-class in vivo CAR-T cell therapy that generates site-specific TRAC-integrated CAR-T cells directly in the patient after a single dose.
Indication (as written by the applicant)	Relapsed or refractory CD19-positive B-cell malignancies, including B-cell non-Hodgkin lymphomas and CLL/Richter's transformation.
Unmet Medical Need (as written by the applicant)	CAR-T therapy can be life-saving for B-cell cancers, but many patients never receive it due to manufacturing delays, limited access to specialized centers, or rapid disease progression. This project aims to remove these barriers by enabling fast, scalable, in vivo CAR-T generation.
Major Proposed Activities (as written by the applicant)	• Conduct nonclinical pharmacology and dose-finding studies in humanized mice and non-human primates to define effective and safe dosing. • Complete IND-enabling biodistribution, toxicology, and immunogenicity studies informed by FDA interactions. • Advance manufacturing, analytical assays, and clinical planning to support IND submission and trial readiness.
Statement of Benefit to California (as written by the applicant)	B-cell cancers cause thousands of deaths annually in California, and access to CAR-T therapy is limited to a small number of specialized centers. By eliminating leukapheresis and complex manufacturing, this project aims to reduce time-to-treatment and enable broader access across California's diverse and geographically distributed population. The approach has the potential to lower costs, expand eligibility, and improve equity in advanced cancer care statewide.
Funds Requested	$12,231,968
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	73
Median	70
Standard Deviation	4
Highest	84
Lowest	70

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The applicant has considered the need to improve the current treatment barriers including access, eligibility and time to treatment in the development of the proposed therapy.
- There appears to be sufficient information to prepare a pre-IND which should favorably impact the timeline. The costing of pre-IND and IND has not been adequately considered.
- The outline of proposed preclinical studies do not align with associated costs. More importantly it is expected that the duration of the large animal study will need to be longer and rodent study may not be needed.
- There are several key persons listed all with only 10% effort assigned. A project manager has been budgeted but will need to be hired.
- This is a proposal with a CAR-T Cell Therapy for B Cell Malignancies. This approach towards CD19 is used for refractory B cell cancers. Concern for this approach still has the issue for safety and efficacy with in vivo genetic alterations versus ex vivo CAR-T genetic engineering. Unclear if this is better than what we have.
- The major strength of the application is the novel approach and use of cutting edge technology.
- The major weaknesses include the crowded nature of the in vivo CAR-T field, with some products already entering clinical trials. In addition, there are many CD19 targeting approaches, and the ability to carry out a clinical trial may be limited. The plans for further product development are of inconsistent quality, and it is not clear whether these are adequate to secure an IND.
- Strengths:
    - Sound scientific rationale.
    - Supporting preliminary data.
    - Novel, interesting technology.
- Weaknesses:
    - Information on a subset of B cell lymphoma/CLL patients who will be enrolled in the proposed trial is not detailed enough.
    - No information on how AAV-T specificity to T-cells is engineered.

Value Proposition

- The proposed novel approach to an in vivo CAR-T cell therapy should improve not only patient treatment experience but also facilitate time and access to treatment for advanced cancer patients.
- Advantage for this approach: cheaper, faster and perhaps improved access. Improving time to treatment and access given location and geography of patients. Product viral shell with gene editing materials and CAR specific to T cells only? Benefit if this can be redosed.
- The proposal seeks to develop novel reagents to produce in vivo CD19 targeting CAR-T cells for B cell malignancies. All B cell malignancies have multiple treatment options, including ex vivo autologous CAR-T cells and allogeneic BMT. Therefore, there is no clear unmet need. It is not clear whether the agent will be more effective than these approaches.
- There are issues with all approaches, but the investigators propose that this would decrease time to treatment and decrease the number of patients who progress during ex vivo manufacturing. This approach may also be cheaper and may allow redosing, although most B cell ALL (model that will be tested) patients who fail CD19 CAR-T do so due to antigen loss, so redosing would not be ideal. This approach may also improve access, though it is unlikely to be provided in a community setting, as the major issue is addressing toxicities, such as ICANS and CRS. Therefore, this approach is likely to incrementally improve B cell ALL treatment compared with current approaches.
- Data exists for the efficacy of in vivo CAR for small numbers of patients. There are several other CD19 in vivo CAR-T products, including those in clinical trials. However, these are not done through gene editing. Several lucrative acquisitions of in vivo CAR-T biotech have occurred. Therefore, although novel, the product is behind, and other strategies are likely to reach the clinic more quickly with ample funding. Although the gene editing approach is novel, it is not clear that this will be significantly more effective or safe than the other approaches that are being developed.
- This disease continues to show disparate outcomes and mortality in minority groups, even after adjusting for income, creating a need for therapies that overcome some of the barriers to treatment, including geographic location and time to treatment, that this product may address.
- There is a decreased patient burden by eliminating the need for leukapheresis.
- There is no need for redosing given the observations from preclinical studies showing long term genetic modifications.
- IV administration has minimal patient burden and can be implemented across settings including those without quaternary care facilities.
- This team has collected data about provider perspectives on CAR-T uptake, which is expected to continue to increase and become standard of care.
- The proposal offers significant value over the current standard of care treatments in B cell NHL, including approved B cell directed MAbs and CAR-Ts. The proposed therapy addresses current bottlenecks associated with approved marketed autologous anti-CD19 CAR-T, namely (i) manufacturing delays and slots availability, (ii) long manufacturing/turnaround time, (iii) rapid progression of disease, and (iv) leukapheresis collection.

Rationale

- The rationale is sound and supported by the data obtained in well-designed proof of concept studies in relevant animal models including dose and regimen exploration.

- The proposed construct should reduce off-target effects and genomic risk which will need to be confirmed with supporting data.
- Going from an ex vivo to an in vivo approach. This approach is of interest as the next step for CAR-T therapies.
- Gene-editing approaches to CAR-T cell production have been limited to ex vivo and allogeneic production thus far. The gene-editing approach also differs from insertional approaches and mRNA approaches. The relative efficacy and safety of each of these approaches is debatable.
- The preliminary data support the approach. In humanized mice, the proposed combination results in up to 31% CAR expression in human T cells and B cell aplasia. Data are also provided that EDV production can be produced by cells in suspension, and the effects on CAR-T production are dose-dependent. Preliminary studies also demonstrate a tumor reduction and increased survival of mice harboring a human B cell ALL cell line. Studies in large animal models demonstrate transient CAR-T cell production and B cell aplasia.
- There are a few details regarding the EDVs, including the targeting of T cells and composition.
- The scientific rationale sounds.
- Preliminary data support the rationale.
- It is not clear from the application how AAV-T specificity to T-cells is engineered.

Project Plan and Design

- The proposal proposes INTERACT and pre-IND meetings. There appears to be sufficient information to prepare a Pre-IND which should favorably impact the timeline. The costing of Pre-IND and IND has not been adequately considered.
- The outline of proposed preclinical studies is not clearly aligned with the associated costs.
- It is expected that the proposed rat study too may not be required for the evaluation of potential vector and excipient based toxicity.
- It is expected that the duration of the definitive GLP large animal model study will have to be at least 3 months in duration instead of the proposed one month.
- Reasonable approach and plan. Preclinical a bit weak, duration of GLP studies limited. Lacking a translatable plan into the clinic.
- The project will continue tasks towards an IND application. These include dose-finding in the humanized mouse B cell ALL model, comparing IV and SC formulations in large animal model, examining biodistribution and editing in cells other than T cells, examining the potential for off-target editing in T cells, and assessing immunogenicity in large animal model. At a high level these are reasonable for further investigation of the product, but it is not clear whether they are adequate for the IND application.
- Given the current very dense therapeutic landscape for B cell lymphoma, it is unclear which subset of patients would be eligible for the proposed in vivo CAR-T therapy. Patients who have failed the standard of care CAR-Ts and MAbs may be good candidates, but previous anti-CD19 therapy was listed as an exclusion criterion.

Project Team and Resources

- The team is qualified to perform the work and has all the necessary resources.

- Perhaps they are a bit behind larger pharma and other companies putting emphasis and money behind this. Small team.
- The team is experienced in the specific technologies, manufacturing, and drug development.
- All manufacturing activities will be outsourced to CDMOs.

Population Impact

- The applicant has considered the need to improve the current treatment barriers including access, eligibility and time to treatment in the development of the proposed therapy.
- Does this fulfill an unmet need and can this improve the care and access to these therapies - unclear.
- The proposal describes a plan for patient and community engagement and ongoing engagement with patient advocacy groups, but this seems very general and underdeveloped and lacks detail.
- There is a plan for adequate representation of all race and ethnic groups that are prevalent in the state of California.
- Overall, the proposal did not read as compelling about the significance of this technology for an investment of this size. The commitment to the patient population felt superficial and some of the data about disparities seemed to be based on national statistics and cancer overall rather than this specific set of diagnoses.
- Patients who are eligible for standard CAR-Ts and MAbs but cannot get them are another category, which could be enrolled in the proposed trial. It would be good to provide more details about this category of patients, such as: autologous CAR-Ts therapy is too risky due to the rapid progression of disease, no manufacturing slots available for autologous CAR-T, insurance denial, contraindications for MAbs.

Application #	PDEV-19744
Title (as written by the applicant)	IND-Enabling Development of a Human iPSC-Derived Cardiomyocyte/Mesenchymal Stromal Cell Organoid Patch for Ischemic Cardiomyopathy
Therapeutic Candidate (as written by the applicant)	Human iPSC-derived Cardiomyocyte/Mesenchymal Stromal Cell Organoid Patch
Indication (as written by the applicant)	The initial target indication for this therapeutic candidate is ischemic cardiomyopathy leading to heart failure.
Unmet Medical Need (as written by the applicant)	Heart failure caused by ischemic cardiomyopathy remains a major unmet medical need, as current therapies do not repair damaged heart tissue. Many patients worsen despite treatment. This proposal addresses this gap by developing a regenerative cell-based approach.
Major Proposed Activities (as written by the applicant)	• Conduct preclinical studies to evaluate efficacy, safety, and feasibility of the cardiomyocyte/MSC organoid patch in relevant heart failure models. • Develop and refine manufacturing, quality, and characterization data to support consistency, safety, and future IND-enabling activities. • Define a regulatory strategy, including data requirements and milestones, to support progression toward IND readiness.
Statement of Benefit to California (as written by the applicant)	This project puts California patients first by advancing a regenerative therapy for heart failure, a condition that remains inadequately treated. By supporting translational stem cell research, this work aims to create new options for patients who do not benefit from current therapies. The project strengthens California's leadership in regenerative medicine and supports long-term healthcare sustainability for its citizens.
Funds Requested	$5,504,460
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 70

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

Mean	72
Median	70
Standard Deviation	2
Highest	75

Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The applicant's more detailed information on how to implement FDA's CMC feedback and how to translate into the clinic are strengths. This is a very strong team with a lot of experiences from which to draw.
- Strong background and experience of the team in the ex US trials with a pure iPS-CM population.
- Rationale makes sense, but it lacks evidence of MSC benefit specifically. The applicants state the approach instills paracrine effects, but there are no experimental data to support this MOA.
- Many aspects of the vision are unclear, including the MOA, the delivery, the ultimate trial (which lacks details) and attention to detail.
- Pilot data on this particular population is not expansive.
- Strengths: - Pioneers in clinical translation of the cell sheet technology - Conditional ex-US approval (but it's unclear this is for the same product proposed in the application) - solid safety profile.
- Weaknesses: - The product and its manufacturing process are not well described (and perhaps different from the one for which conditional approval was obtained) - No mention of immune rejection / immune suppression - A bypass only control group is needed - Limited preclinical data, especially if applicants plan to introduce a new product - The advance over previously tested cell products with paracrine activity is not clear.
- Limited value proposition with limited efficacy.
- CMC issues are concerning.
- Patients with advanced heart disease are not the group being treated. Unmet need addressed by an experienced team. Scientific rationale and CMC are weak.
- Strengths include a strong clinical relevance and unmet need, compelling scientific rationale and therapeutic approach. Clear biological justification due to cardiomyocytes' limited regenerative capacity. Co-implantation of MSCs is to enhance engraftment and function. Robust preclinical evidence. High potential adoption given the lack of alternatives, and uptake by clinicians and patients is expected to be strong if efficacy is demonstrated. Foundational elements for manufacturing are in place, including the selection of a GMP line with established DMF and licensing.
- Weaknesses: Significant gaps in CMC and manufacturing strategy include: missing details on Bill of Materials, bioreactor system, media exchange, sampling plan, hypoxia conditions, cryopreservation, and analytical methods. Lack of clarity on whether GMP-compatible reagents are used throughout the process.

No defined potency assays presented for cardiomyocyte and MSC components. There are regulatory readiness concerns identified by the FDA, and the proposal lacks a clear plan to address them. It's unclear how the current process will be modified to meet IND requirements. Scale-up and tech transfer risks include an unclear scale-up strategy. As a CDMO has not been identified, the Tech Transfer timeline and cost are uncertain. Given the extent of outstanding CMC and regulatory work, achieving an IND-ready process within 24 months appears unlikely. Affordability and manufacturability uncertainty due to a complex manufacturing process with unclear scalability raises concerns about cost of goods and commercial viability.

Value Proposition

- Scientifically interesting and valued approach to improve outcomes post MI and prevent advancement to heart failure. The therapy is a mix of CMs and MSC cells. The MSC component also offers value for paracrine effects and immune modulation. An invasive, but doable treatment with high value for populations, including those underrepresented. There is, however, very little detail on the cost analysis. This is a surprise based on the fact that a related product is already tested in humans ex US.
- If successful, this approach would be positive for patients; even modest gains in heart function could be clinically meaningful. The proposed therapy, however, incorporates extremely complex manufacturing. This may be challenging to scale or to produce at low enough cost.
- Clear unmet medical need for novel therapies in chronic heart failure.
- The target patient population with hibernating myocardium will most and foremost benefit from the bypass surgery.
- Limited value proposition with limited efficacy.
- The application left a reviewer skeptical.
- Limited therapies for late-stage heart failure exist. This therapy has potential to have significant clinical benefit.
- Application of a patch over the infarcted area is an appropriate approach.
- The ability to treat heart failure will reduce medical burden and cost, if the approach is successfully developed. Heart failure remains an unmet medical need that affects a large number of patients.
- Unclear affordability due to the long and unclear manufacturing strategy.
- Uptake would likely be high due to lack of effective treatments.
- Unmet medical need with no viable treatment.

Rationale

- This "organoid", defined by a mix of cardiomyocytes and MSC, acts via immunomodulatory/paracrine conditioning of the environment. The data herein shows that the MSCs add the value via paracrine effects to the organoid which will help support the recovery of the heart. It is not really stated if there is functional involvement from the CMs, presumably so. The rodent data looks ok - but the reviewer does not find animal numbers, power calculations and so on. The pivotal relevant preclinical model data is really not presented completely and is difficult to judge.
- Rationale is supported by literature describing similar regenerative medicine approaches. The applicant has some pharmacology in a relevant model of ischemic cardiomyopathy that shows modest gains in ejection fraction following administration. They appear to see dose response effects which helps reinforce

biological plausibility. The applicant shows some data on increased secretion of different growth factors, cytokines/chemokines, etc. in vitro.

- There have been many investigational agents in this field which have not progressed. It's unclear if/how the applicant will succeed where so many others have failed.
- Is the referenced clinical data from a similar or the same product?
- There's limited data to support a novel product.
- Very little preclinical data to support the clinical program.
- Scientific rationale is sound; cardiomyocytes do not renew after death. Co-implantation with MSCs is a viable strategy. Delineating whether improved contractility or paracrine support is the primary MOA would strengthen application.
- Strong demonstration of pre-clinical efficacy in supporting publications.
- Preliminary preclinical and manufacturing data are provided in the proposal.
- On page 24 of the proposal, the investigators indicate that approximately ten patients were treated with the cardiac patch. It appears from the information provided that the Phase I/IIa study was done outside the US. However, the summarized data are for only one patient. What are the results for the other implanted patients?

Project Plan and Design

- Nicely laid out development program with a productive preIND meeting; applicant appears to have incorporated nonclinical and clinical FDA feedback into plans (this reviewer defers to CMC experts upon how well the FDA CMC feedback was incorporated). PreIND feedback provides a roadmap to what needs to be accomplished to open the IND.
- The design is for the stage products stage of readiness. CMC, pivotal relevant preclinical model data (following FDA's feedback to focus on this specific model). Quite a limited level of detail is provided for much of the work. In addition, the ultimate clinical trial synopsis is weakly developed. Contingency plans are represented and appear valid.
- Are the IND enabling relevant preclinical model study and rodent study, per the FDA critiques, completed?
- It's unclear how FDA's CMC critiques will be addressed and by whom.
- The proposed clinical trial needs more detail. How many patients are to be treated in the dose finding portion? What is the proposed immune suppression plan?
- CMC issues are concerning.
- The clinical synopsis is weak.
- The manufacturing process begins with a GMP line with a DMF. The applicant has secured licenses to use the line.
- The manufacturing process lacks many details. Specific missing information is the Bill of Materials, the bioreactor identity, media exchange process, sampling plan, hypoxia conditions, and cryopreservation process. Assay methods and equipment are also missing to evaluate if the chosen methods will be GMP compliant. Missing details were mentioned in the IND response from the FDA and the sponsor states that

they will address the points raised. No plan for how the team will do so is included in the Proposal (which states that additional studies are underway but provides no details).

- Unclear if GMP-compatible reagents are used throughout the manufacturing process. Comparability studies would be required for any reagents not compatible, are required before CMC lock and would put the timeline at risk.
- Missing details make it difficult to determine that the current manufacturing process can be modified to address previous FDA comments.
- Representative potency assays need to be developed for both CM and MSC products.
- Based on the number of points brought up in the FDA review, development of an IND-ready process is likely to take significant time, and it is unclear whether the allotted 24-month timeline is feasible.
- Applicant confirms selection of an experienced CMO but did not name that entity, suggesting this has not yet been completed. Since the scale-up process is not established, the technology transfer process timeline and budget are unclear.
- Ischemic cardiomyopathy has a significant impact on patients' functional status and quality of life.
- It is not clear how the dosing of the patch will be determined from the preclinical studies in the relevant preclinical model.

Project Team and Resources

- The team seems well positioned with expertise of the PI in the area of translational science and some clinical trial experience. The wider group covers most bases, but the cost analysis/price of goods and so on seems weakly developed.
- Strong team experienced in translation of technology into clinical testing and obtaining conditional approval.
- Experienced group with clinical data safety data without risk of arrhythmia.
- Unclear dosing regimen.
- The clinical protocol is appropriate.
- Strong team and industry support strengthens the proposal.
- The team and resources appear to be adequate to carry out the proposed investigation.
- These appear sufficient.

Population Impact

- If successful, population impact would be of high value. There are competing interests and approaches, but this project (due to the ex-US trial) is well advanced. The data supporting this product is not well presented, and therefore it's slightly lacking to convince this reviewer to support the application.
- Population impact is considered.
- Large impact.

- Enrollment targets are representative of diverse populations.
- Investigators describe variations in the prevalence of ischemic cardiomyopathy by ethnicity and age. Projected enrollments for the clinical study reflect these disparities.
- Plans are in place to assess the workflow implications for this therapy at each clinical site.
- Patients will receive assistance with transportation and housing.
- An independent medical monitor and data and safety monitoring board will oversee the activities of the clinical trial.
- This appears sufficient.

Application #	PDEV-19722
Title (as written by the applicant)	Regenerative iPSC-Derived Liver Graft for Functional Hepatic Replacement
Therapeutic Candidate (as written by the applicant)	An allogeneic hypoimmunogenic iPSC-derived multicellular liver organoid graft delivered in a MAP scaffold w/in a retrievable macroencapsulation device
Indication (as written by the applicant)	Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) as a bridge-to-transplant or bridge-to-recovery therapy.
Unmet Medical Need (as written by the applicant)	ALF and ACLF have mortality rates exceeding 60% without transplant, and no approved bridge therapy exists. Donor organ shortages leave many patients without timely options. This therapy addresses the critical gap by providing temporary, biologic liver support during the transplant waiting period.
Major Proposed Activities (as written by the applicant)	• Establish GMP manufacturing of hypoimmune iPSC-derived liver organoids and MAP-in-pouch drug product. • Complete IND-enabling efficacy, biodistribution, immunogenicity, and tumorigenicity studies in rodent and large-animal models. • Conduct FDA INTERACT and Pre-IND meetings and prepare IND submission and Phase 1/2a clinical protocol.
Statement of Benefit to California (as written by the applicant)	This project will support development of a regenerative therapy for acute liver failure, a life-threatening condition with limited treatment options affecting patients across California. By advancing an off-the-shelf liver graft to bridge patients to transplant or recovery, the research aims to reduce waitlist mortality and improve outcomes. The work will be conducted at California institutions and may reduce the clinical and economic burden of liver failure on the state's healthcare system.
Funds Requested	$12,999,998
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	71
Median	70
Standard Deviation	3
Highest	80
Lowest	70

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

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- The complexity of cell types in the product may not be required.
- The supporting preclinical work is lacking.
- Overall product concept, complex cells and device clear clinical need are strengths.
- Strengths: The concept of bridge to transplant or bridge to regeneration is innovative. Weaknesses: Product concept is overly complex and others' encapsulation devices have led to fibrotic response with other products.

Value Proposition

- The value proposition is high given the large unmet need for liver transplant in the ALF setting. The concept of an engineered tissue as a bridge to transplant is innovative.
- There is no doubt that such therapy will be life saving, risk is limited and will require minimal surgery. Thus, acceptance will not be a problem.
- Given the large unmet need in acute liver failure, the value proposition for this innovative approach is high.
- Large unmet medical need, as less than 40% of those eligible for liver transplant receive a donor organ. There is no approved temporary liver support therapy. Extracorporeal systems have shown limited success.
- This therapy appears to present a remarkable improvement in the life chances of those suffering from end stage liver disease both from ALF and ACLF. By producing an off-the-shelf liver graft to bridge patients to recovery or transplant, the project hopes to reduce the substantial waitlist mortality. There are about 25,000 on the transplant waitlist with fewer than 40% receiving an organ annually. The applicants show that their product would be superior both to those products currently available to patients and others currently in the developmental process. They clearly show this in terms of the efficacy and safety, but most impressively in terms of the patient, caregiver and health system burdens.
- The impact of this would be remarkable since ALF and ACLF affect about 1 in 10,000 persons in the US with mortality rates approaching 60%. Current treatment relies on expensive and intensive supportive care during the wait for transplant. No current therapy provides the combination of support needed to provide hepatic assistance while patients await organ availability. What happens to patients, caregivers and the health system as patients wait is devastating. This included sudden hepatic function loss, extreme emergency hospital costs, and death.

- This implant is a one-time procedure, after which it provides support with only routine postoperative care. Any hospital with normal bedside capacity could use this graft without specialized teams currently available at only a few centers. This radically democratizes access to make this care available throughout California.
- The plans presented and the partners enlisted make the feasibility and practicality of this care very favorable in my view.
- This proposal aims to develop a cell-based therapy against acute liver failure (ALF) and acute on chronic liver failure (ACLF). These diseases have different etiology and patient populations. The extreme situation for both diseases requires liver transplantation for which the lack of organ donors, immunosuppression requirements and surgical risk are major problems. So, a therapy that could replace or delay liver transplantation would be welcome.
- In both extreme cases of ALF and ACLF, multi-organ failure occurs in a matter of days, and the only treatment available is liver transplantation. Thus, a bridge therapy could help either to avoid transplantation by allowing the endogenous regeneration to occur, or it could help to procure an appropriate organ. However, it is important to underline that for ALF (and to a lesser degree for ACLF), most patients can recover as their liver can regenerate using standard of care. In some centers, success rates can be extremely high. ACLF is more complex since even if patients can recover, this is only temporary as the underlying chronic disease is still present. So, in this case transplantation will still be needed. Those points underline the difficulty to measure the efficacy of bridge therapy, the challenge in patient selection and the limited impact on extreme cases.
- Affordability will be a key aspect due to the number of cells necessary for such therapy. The dose will be on the order of a billion cells. This is probably an underestimation; the usual estimation is 2-5% of liver mass or around 2-5 billion cells. Thus, cost optimization of large-scale production is essential. Otherwise, the cell product will only be available to a small number of patients.
- Patients will need to be transplanted very rapidly in a matter of 2-3 days, so the therapy must be off the shelf and ready to administer extremely fast for clinical feasibility. How this important aspect of the complex proposed therapy can be achieved is never explained.
- This therapy offers a potential bridge option for those eligible to receive a liver transplant. It would be interesting to better understand if this is an initial proof of concept study leading to a possible curative therapy in the future.
- The therapy, although allogeneic, is likely to be expensive. However, given that there is no other option for these patients, there would be demand for available off the shelf cryopreserved, ready to use grafts.
- A very complex product with bioprinting and macroencapsulation.
- Qualifies as an unmet need, but overall, the application does not appear to meet the funding threshold.

Rationale

- The rationale for the overall approach is solid. The approach combines an allogeneic multicellular liver organoid within a pouch to serve as an additional physical immune barrier. The ability to both activate a kill switch and retrieve the implanted pouch provide multiple safety mechanisms.
- The main goal is to transplant liver cells into patients with ACL or ACLF to provide enough hepatic functions to avoid multi-organ failure until endogenous regeneration or liver transplantation. This is a good rationale supported by previous clinical work showing that encapsulated primary hepatocytes can rescue a paediatric patient with acute liver failure.
- The supporting preclinical work is lacking. Very little detail about nonclinical study 4 was shared, specifically around characterization of the liver organoids that led to the functional outcomes reported.

Understanding what fraction of each cell type was in the grafts would provide helpful benchmarks for the proposed scale up work.

- The preliminary data provided are limited and not convincing. The characterization of the organoids are limited. The experiment in an animal model only shows that transplanted cells can survive and produce limited amounts of AAT (Albumin would be a better readout for these studies. AAT can be expressed at high levels in cells with low functional maturation). The selected mice model is not relevant for ALF or ACLF. The injury is relatively slow since it is not induced by a toxin. This model is used to monitor engraftment of hepatocytes and to produce humanized mice; it's not a disease model. A more appropriate model would be mice with acetaminophen overdose.
- Solid overall rationale, but supportive preclinical data are lacking. A panelist wondered why the product is so complex, felt it can be simplified, and they noted no preclinical model can predict the fibrosis in humans.
- Very little information about the differentiation process was provided. For example, the yield and efficiency at the current research scale with the current (presumably non engineered iPSC line) would be helpful to inform the scale up manufacturing plan and the path to achieving a process capable of sustaining the estimated therapeutic dose of 1e9 cells per patient.
- The complexity of cell types in the product may not be required.
- There is no information about the protocol used to produce liver organoids. A reviewer wondered about the fraction of hepatocytes in the organoids and their level of function compared to primary hepatocytes. This metric is essential since, if low, it could further increase the number of cells needed to achieve therapeutic benefit.
- The entire construct is too complex. It will rely on multiple iPSC derived cell types, for which the existing clinical trial experience is unclear to this reviewer. Fibrosis and vascularization are problematic. Endothelial cells might not be useful since vascularization might take time while the therapeutic effect needs to be immediate. Fibroblasts will rapidly proliferate in vivo and create a fibrotic environment. The encapsulation in collagen beads will be incredibly difficult to scale up and significantly increases the volume of the organoids. Several macroencapsulation devices will be likely needed for one patient. The unsuccessful Theracyte device experience with pancreatic islets left a reviewer hesitant about macro-encapsulation approaches.
- Preliminary data showing secretion of human AAT seems extremely slow and can only be detected after 25 days. This is simply not compatible with ALC/ACLF.
- Cryopreservation of liver organoids will be extremely challenging if not impossible. This aspect is almost never mentioned, and it is not clear how one can develop an off the shelf product without this aspect.
- The use of hypo immune cells with both an HSV-TK safety switch and a macro-encapsulation device needs to be better justified. It is not clear if the GMP grade version of the iPSC line to be used is already available. This is likely very difficult and costly to achieve.
- Hypoimmune iPSCs present an opportunity to eliminate the need for immunosuppression. It's unclear why a macro-encapsulation device is needed if the cells are hypoimmune. These iPSCs efficiently and consistently differentiate into liver organoids with multiple cell types. A safety switch is also integrated into the iPSCs.
- The technology enables rapid onset of action (within a week or so) in preclinical models.
- iPSC-derived hepatocytes produce albumin and A1AT, cytochrome P450 enzymes in vivo. Preclinical studies show rescue of liver function and improved survival.
- The peritoneal route of administration has precedent with hepatocyte infusions in ALF where it was demonstrated to be a safe and a well-vascularized transplant site. A fibrotic immune response to the macro-encapsulation device may prove a limitation.

- The data presented are very persuasive. The background data including the limitations of current and future proposed therapeutic devices is very strong.

Project Plan and Design

- Their off-the -shelf and allogeneic strategy enables ready-to-use grafts which could be stocked by transplant centers across California ensuring market access.
- Additional functional studies should be included in the early PDEV work proposed in section A. In particular, an in vivo study with the proposed cell line must be included to derisk any differences in differentiation and function of this cell line compared to the un-engineered cell line used in nonclinical study 4. These should be added as part of activity A1.
- The supporting preclinical work is lacking.
- The rationale behind the preclinical studies towards IND clearance is difficult to follow. Testing the encapsulation device's immunogenicity in an immune deficient model does not make sense. There is animal work for safety. They are testing different versions of their approach, but never for efficacy. There is no information on dose in cell numbers/volume to be used in animal models. They need to focus on this first and define a cell product specification. Moving immediately into relevant preclinical models without efficacy data does not make sense. The use of the proposed relevant preclinical model does not make sense in the context of ALF/ACLF.
- The investigators could consider use of the humanized liver FRG mouse from Yecuris as a means to demonstrate both function and potentially immunogenicity. This model may better capture the intended integration of the graft with the human liver.
- Preclinical efficacy and GLP toxicology studies seem appropriate. It's unclear if the proposed models are sufficient to judge potential for a fibrotic response.
- The HLA engineering approach may not be sufficient to fully block activation of diverse NK cell repertoires. The humanized mouse model described in activity A3 may not sufficiently explore human NK cell diversity. Additional in vitro experiments incubating the liver organoids with primary NK cells from 3-5 donors and measuring cytokine responses could be considered.
- The strategy for the FDA Interact meeting was lacking. The timing for this meeting should be dictated by project milestones. It was unclear what data the team thought they needed to request the meeting and what feedback they hoped to get. It seems that the meeting should not be initiated before completing at least activities 1-4, including the expanded in vivo work suggested above. At the same time, it would be unwise to initiate activity 7 before receiving feedback. Likewise, the team would benefit from getting feedback on the process in activity B2, so ideally there would be progress made on process scale up before the meeting.
- Differentiation is more challenging than the team expects.
- Timelines are not ideal, regulatory interactions put the program at risk, and scale up is not detailed. How can this be scaled up from a CMC perspective? Expansion needs to be de-risked.
- The GMP work is nicely described and rational. Key aspects could be better detailed. For example, it is not clear if the master hIPSC cell bank is cGMP or GMP. Three months to generate a characterized WCB seems extremely short. How many vials will they generate?
- There is no indication that any differentiation protocol can be easily transferred to GMP. The tech transfer might be very complex. There is no information about bioreactors, number or cell to be produced per run/batch, and potency assays are too limited. Can they easily transfer the encapsulation method to the GMP suite?

- This treatment will be very costly due to the number of cells necessary but also due to the different IP aspects. Freedom to operate with the hiPSC cell line is probably complex and will require important fees and royalties. This will further increase the cost of therapy. The macroencapsulation device will bring similar limitations. It is difficult to understand how they can achieve an affordable therapy with such a complex system.
- Scalability must be addressed sooner. A 1L bioreactor might provide only enough cells for 1 patient.
- The GMP production plans for cryopreservation of individual cell types but not for the organoid encapusulation device.
- Proof of concept for scale up to bioreactors plan seems reasonable with appropriate release testing, timeline and criteria for tech transfer. However, the approach adds complexity with bioprinter and macroencapsulation device use. Residual iPSC assay sensitivity is less than 0.1%; applicants should provide rationale for this limit.
- The budget seems appropriate for such an ambitious program.
- Pre-IND feedback prior to starting IND-enabling preclinical studies will be helpful to inform study design.
- Later PDEV activities include final GMP manufacturing validation through thorough examination runs, toxicity and other safety studies, a model to show surgical feasibility, then the IND process. The partners in this process include multiple universities to create a viable 5-year plan.
- The applicants did a clear job of examining the various risks and providing appropriate contingency plans.

Project Team and Resources

- No information on the licensing or contracting with producer of the engineered iPSC line was given. If the cell line already has a drug master file with the FDA, it was unclear if a MCB already existed. It was also unclear if the line's producer would have future access to the MCB and WCB generated with the proposed CIRM funds. It seems that a cost-sharing approach could be more appropriate for activity B1.
- This team would benefit from CMC and timeline planning. The existence of a master cell bank is unclear.
- The team combines an impressive track record in bioengineering and clinical hepatology. This team also has a lot of experience and brings essential clinical knowledge.
- The involvement of the expert on hiPSC differentiation is essential. They seem to be the only expert on hiPSCs differentiation and production of liver / endothelial cells on the team. Their presence is crucial and reassuring. However, their involvement needs to be better described, and they should have a more central role. Important tech transfer will be necessary from their lab.
- The GMP facility expertise seems convincing. However, questions remain around the transfer of key equipment.
- The clinical trial could be achievable, and a reviewer would have found it useful to know the number of patients who could fulfill the inclusion criteria.
- Overall, this is an experienced team in the liver space, biology and clinical translation. Their CMC experience is less clear. Project management and organization/communication plans are established.
- A fibrotic response to the macro-encapsulation device is a big risk. Are there ideas about how to mitigate this?

- The PI and their team are very accomplished scientists, engineers and researchers. Their publication and previous roles are very impressive. The reviewer is impressed by the proposal's selected partners and collaborating institutions.
- The experience in working with stem-cells is very impressive.

Population Impact

- A reviewer found the understanding and discussion of the genetics and environmental factors that are involved with alcoholism and end stage hepatic diseases to be one of the strongest parts of the proposal. This reviewer highlights that co-occurring substance use problems are a very frequent complication and cause of death for those with mental illness. This product might have served as a bridge to a longer life for loved ones lost to liver failure. The applicants' discussion of both etiology and ethnic risks was very sound and useful.
- The discussion of both the risks that develop and the current barriers and obstacles to proper care was insightful. The discussion of the varying impacts in occurrence, mortality and stigmas in Hispanic, Black, Native American, Asian and White communities was clear and insightful. It matched observations from a panelist's previous work.
- The knowledge derived from patient and family experience with liver failure, waiting lists and care burdens is substantial.
- The allogenic nature of this cell therapy allows it to be used in any patient with ALF, with a significant impact for the Hispanic community in California, who have a high rate of death due to liver failure.
- The allogeneic approach should enable more applicability across the CA population.
- All these aspects are well described and considered in the proposal.
- Population impact is described and sufficient. The population for the intended clinical study is straightforward.

Application #	PDEV-19720
Title (as written by the applicant)	[redacted] gene therapy for the treatment of congenital lipodystrophy
Therapeutic Candidate (as written by the applicant)	[redacted] is a redosable gene therapy using the Fusogenix PLV platform to restore endogenous leptin for treating congenital generalized lipodystrophy.
Indication (as written by the applicant)	[redacted] treats congenital generalized lipodystrophy, a rare genetic disease marked by leptin deficiency and early-onset metabolic complications.
Unmet Medical Need (as written by the applicant)	[redacted] addresses the unmet need in CGL by enabling durable, redosable endogenous leptin production, improving metabolic outcomes, and reducing treatment burden where daily injections and current therapies are insufficient, leveraging a validated Fusogenix PLV platform.
Major Proposed Activities (as written by the applicant)	• Conduct a pre-IND meeting with the FDA • Completion of IND-enabling studies, including GLP tox and integrated large animal assessment • Submit an IND application to the US FDA for PLV-based therapeutics to enable initiation of clinical studies using the gene therapy
Statement of Benefit to California (as written by the applicant)	[Redacted] benefits California by addressing a rare, early-onset metabolic disease that contributes to diabetes, liver disease, and cardiovascular complications, among the state's highest healthcare burdens. Developing and manufacturing both drug substance and product in-state strengthens local biotech capacity, supports high-skilled jobs, ensures reliable supply, and builds a redosable gene therapy platform for future therapies.
Funds Requested	$8,971,749
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	84
Lowest	-
Count	15

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- Target is a very rare disease that has an existing therapy that reduces the value proposition.
- Nicely laid out plan, some gaps regarding value proposition.
- Strong mouse data; however, the mechanism of action and science is unclear. It is unclear how this plasmid is working.
- Is there truly an unmet need? Rationale for development is weak, and does not back up true need. Did they speak to patients and advocacy groups? This could help inform clinical study design. The why is lacking.
- Comprehensive submission overall but gaps in development, science and rationale (science and unmet need). Recommend establishing a more positive value proposition and impact on the population.
- There's an issue with what the cargo is that's being delivered. No plasmid map could be found, which is very unusual for an application proposing a genetic correction of disease. We have no idea what the integration looks like for this plasmid. The authors need to recognize that then there's an inherent cancer risk, of course, when medicines integrate into the genome, which is not brought up.
- There also was a comment from the FDA about adipocyte-specific promoter controlling expression with and without rapamycin activation, though this was also not present in the application and is not clear to the reviewer why it is mentioned.
- No rationale is given for the route of injection.
- Very good to remarkable phenotype data in ob/ob mouse and diet induced models. Would also test CGL mouse model.
- Good attempts at measuring antibodies and whether repeat injection is feasible.

Value Proposition

- Applicant is developing the product for Congenital Generalized Lipodystrophy (CGL); CGL is a severe disease and patients exhibit a debilitating metabolic syndrome characterized by severe diabetes, insulin resistance, hypertriglyceridemia, and hepatic stenosis.
- Congenital lipodystrophy (CGL) is rare with 500-600 cases worldwide and current treatment consists of daily injections. From this study the end result is not a cure but an attempt to reduce injections from daily to annually.
- A very rare disease that has an existing therapy.

- There are therapies available for patients with CGL via leptin replacement therapy which has been available for 10+ years; therapy requires daily dosing however, and the applicant cites challenges with patient compliance, injection-site reactions, and that it doesn't treat all manifestations of disease as evidence of urgent unmet need; additional information on support for these statements would be helpful - for example, patient advisory boards where patients are asked about burden or daily injections or summary of worse outcomes for patients due to non-compliance, other. These data were not provided, which may limit the value proposition of new therapy.

- Not sure if an unmet need - drug available but requires a daily treatment. Could help with patient uptake and fulfill an unmet need - what is the value proposition for a less frequent treatment given there is a current treatment that is not a cure.

- In terms of value proposition, the therapy could provide meaningful and substantial improvement to patients with this disease. Whether it'll be superior to metreleptin is unknown. Certainly, the route of administration is going to be different, where one is subcutaneous, like insulin, and the other is intrathecal. In this reviewer's experience, many patients are willing to undergo subcutaneous injections and are more averse to intrathecal injections.

- In trying to understand the entirety of the unmet need, it's an extremely rare disease with very few cases worldwide and an unclear impact on the healthcare system. There is a drug available on the market which is seemingly fairly effective in treating the lipid dystrophy, and improves the metabolic disease, the weight loss, and allows for significant hemoglobin A1c reduction. Although it is not a complete cure, it is fairly effective. This diminishes the value proposition of the new drug.

- Being rare and the aim is not a cure coupled with the limited number of actual Californians impacted (this number is undefined but can be estimated) with CGL I don't see how this is funding well spent. We would be lucky to see an actual benefit to California tax payers who would be funding this study.

- CGL is a rare disease, though the applicant's approach is part of a platform technology. Success here may translate to success in other indications.

- Whether this new drug will be more accessible or affordable is unknown. Given that it's a genetic medicine, typically these end up being high-cost drugs.

- Not cited in this proposal but the current cost to treat patients annually is $1 million + with usual cost to patients being low to zero dollars through various means. No indication for "market" cost of per dose for this treatment.

- Regarding feasibility and practicality for use in patients, again, this is addressed in the fact that many diabetic patients are able to monitor and give themselves subcutaneous insulin once or even multiple times during the day. While it's possible that an intrathecal injection, even if it's one to two times per year, may be met with more adversity. Assessment of the patient community would be useful to answer this.

- In the context of a rare disease with existing therapy, the applicant should provide additional information, including supporting data, on the value proposition of their proposed approach and ensure that preclinical and clinical studies are designed to evaluate whether the product can meet that value proposition.

Rationale

- Applicant has conducted numerous preclinical platform studies which provide support for therapeutic approach.

- Applicant has also generated preliminary pharmacology data in numerous biologically relevant mouse models; data provide compelling evidence and justify further development. Sufficient evidence that the product may be disease modifying and holds potential for the treatment of CGL.

- The current data indicates that the efficacy of the administered drug product could last months. The product is a proteolipid vehicle to deliver the plasmid payload for human leptin.
- The integration risk of the plasmid is not evaluated.
- No rationale for mechanism of delivery - why intrathecal? Lack of scientific rationale.
- Much of the applicant's initial data is intramuscular and intravenous injection. While in one of their efficacy platforms, they did move to intrathecal injection in mice, which, of course, is nearly impossible given the small spaces in mice to inject, it is unlikely that the injection was purely IT. In fact, there's no detailed procedure on how this was done in mice, whether it was true intrathecal or intracisternal. That should be spelled out.
- There's an issue with what the cargo is that's being delivered. No plasmid map could be found, which is very unusual for an application proposing a genetic correction of disease. We have no idea what the integration looks like for this plasmid. The authors need to recognize that then there's an inherent cancer risk, of course, when medicines integrate into the genome, which is not brought up. If the authors are worried about intellectual property, I'm sure the system has been patented, so there's no reason to not explain to the reader what the plasmid and FAST protein are that they're injecting into animals and people. Despite these unknowns, their pilot data in the ob/ob animal are quite good and have significant corrections in weight loss as well as leptin restoration. There are mouse models for CGL that exist, and it would behoove the authors to actually test their drug in one of the mouse models. For instance, the BSCL2 mouse model might be a reasonable animal given it shows fatty liver, hypertriglyceridemia, and insulin resistance. It is interesting that these mouse models were avoided in the preclinical testing of this drug.

Project Plan and Design

- The overall plan for IND-enabling studies does seem reasonable. Overall, it seems like the team has good expertise in what they're proposing as far as the lipid nanoparticle. They have a robust plan for execution of the project with appropriate experiments designed. They plan to use a CRO for much of this research.
- Looking at the potential impact, this assumes that the therapy is adopted and works appropriately. I can see the rationale for a once every 6-month or every 12-month intrathecal therapy to control this disease.
- It does seem to be a therapy in line with the current standard of care that is addressing a leptin deficiency in an otherwise very complicated genetic disorder. Again, there are many aspects of this genetic disorder in people, even though the current standard of care is restoring leptin which is what this drug is doing. It's an appropriate pathway to choose or improve upon.
- CMC: Master cell bank already generated from previous TRAN grant, method development, drug substance and drug product stability studies, FAST protein and plasmid manufacturing, drug product formulation development and scale-up. Lacking a GMP drug product batch to support Phase 1 clinical program; no batch numbers provided for supporting the clinical trial.
- Scale and batch size details are needed.
- Mechanism of delivery for subcutaneous versus intrathecal is unclear as to design and rationale.
- The applicant presented a comprehensive plan to achieve IND (and beyond). The program is at a very early stage of development with very little regulatory guidance received. I appreciate the long-term planning of potential animal studies (and study design), but it is quite premature to map this out with confidence. It is critically important that the applicant conduct a pre-IND at the right stage, and certainly before their later-stage studies, IND-enabling studies, or any large animal work.
- The gates and triggers for different activities - primarily regulatory interactions - are unclear from the time timeline GANTT provided; strong recommendation for CIRM to work with the applicant on appropriate gates.

Project Team and Resources

- The team has a strong, successful track record. CMC, prior work strong.
- The team has successfully manufactured and tested materials for other clinical phase products. The team is resourced to successfully conduct the proposed CMC activities.
- In reviewing some of the budget supplemental information, I find the budget numbers to be very high.
    - For instance, a biodistribution study in ob/ob mice, with 60 animals taking six months is going to cost upwards of $600,000. This seems to be exceptionally high for such a limited number of mouse studies. (a realistic cost is $60,000).
    - This is the same cost for the multi-dosing and single-dosing mice as well.
    - My comments extend from my expertise in maintaining large numbers of mice with rare disease and doing similar studies, but at much less the cost than what's stated.
    - A budgetary cost of $5 million over their time frame might be achievable, yet would put a lot of stress on the system, in the reviewer's opinion.
- Regarding regulatory correspondence, there's a question from the FDA about potency, which should be addressed by the applicant. There is also commentary about the use of rapamycin after injection of the drug product, though this is not clear in the application. There was also concern by the FDA about FAST proteins being adopted and expressed on cellular host cell membranes, which could be immunogenic or cause cells to fuse into syncytia. FDA did recommend to assess for anti-drug antibodies after FAST protein and after repeat injection.
- There also was a comment from the FDA about adipocyte-specific promoter controlling expression with and without rapamycin activation, though this was also not present in the application and is not clear to the reviewer why it is mentioned.
- Disease advocacy groups need to be engaged.

Population Impact

- They need to confirm their base assumptions of the population that would want this therapy.
- This is a novel therapy and could better address needs and therapy. Current drug on market is daily - a potential benefit.
- It is not clear if they interviewed patients to understand: (1) greatest disease burden, (2) is an IT route acceptable?
- It is noted that CGL affects all racial and ethnic groups without gender bias, not much is mentioned beyond this that is significant to the CGL population.
- I would have concerns of "future" trial participants that are on current daily treatment being given placebo treatments that could worsen their condition, assuming they may need to potentially stop their daily injections that mitigate their current condition for this study.
- There could be a great benefit to the limited patients if lifetime treatment doses can be reduced.
- Although this is an early-stage application for a very rare condition it was near void of any meaningful information to support patients. Also, with constraints on funding and the fact we are stewards of ever

shrinking tax payer funds I don't see the return on investment to serve the broader population of California.

Application #	PDEV-19712
Title (as written by the applicant)	A novel epigenetic gene therapy delivered using lipid nanoparticles to treat advanced HPV-associated cancer
Therapeutic Candidate (as written by the applicant)	A lipid nanoparticle formulated with a BE2K mRNA, which is a generalized epigenetic repressor to treat HPV-associated malignancies.
Indication (as written by the applicant)	For this study the target indications are locally advanced and/or recurrent HPV-associated cervical and oropharyngeal cancers.
Unmet Medical Need (as written by the applicant)	Conventional treatments have high toxicity and poor outcomes for locally advanced and recurrent HPV-associated cancers. [Redacted Therapy] represents a novel generalizable treatment targeted to the HPV's cancer drivers to improve safety and outcomes in advanced malignancies with limited treatment options.
Major Proposed Activities (as written by the applicant)	• LNP optimization and dose/regimen studies. • Efficacy studies in syngeneic and PDX models. • In vitro safety and GLP toxicity studies. • Process development of the [Redacted Therapy]. • Manufacture of the cGMP [Redacted Therapy] drug product. • Assay development for BE2K mRNA detection. • Submit a Pre-IND packet and hold a meeting with the FDA. • Submit an IND. • Perform affordability and accessibility analyses.
Statement of Benefit to California (as written by the applicant)	HPV-associated cancers remain a growing public health burden in California, with poor outcomes in advanced disease and disproportionate impact on vulnerable populations (largest numbers in the USA), including people with HIV, immunocompromised individuals, and veterans. The proposed BE2K gene therapy represents a broadly applicable treatment for HPV-driven cancers, with potential to improve outcomes, reduce recurrence, and lower long-term healthcare costs across California.
Funds Requested	$12,720,367
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 67

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	68
Median	67
Standard Deviation	8
Highest	84
Lowest	-
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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.

Key Strengths and Weaknesses

- It is unclear how much need there is for this product when there is an HPV vaccine and several other products in development that target E6/E7-driven cancer.
- The preliminary data are weak - 10 doses are required in mice just to see a small difference in tumor growth. This data do not give confidence that the product can be effectively translated to a once/weekly dosing regimen in people.
- Treatment for lipid nanoparticle for gene treatment for HPV cancers (mRNA), some standard treatments do exist. Some local, i.e., pap smears, hence is there a need.
- Advanced diseases - there is an unmet need so this product may help that specific population.
- CMC was well designed and approached in a thoughtful and stepwise process. Although they claim they are genotypic agnostic, they are targeting specific genes.
- Mouse model preclinical tumor data appears underwhelming. Dosing is extreme for such a small possible benefit.
- The strength of the proposal is the intent to develop therapies for advanced HPV-associated cancers in which current strategies are not uniformly effective or safe. Another strength is the CMC program, which is well described.

- Major weaknesses include limited preliminary data that the product can induce tumor regression, the limited evidence of long-term epigenetic silencing, limited analysis (largely phenotypic) of the immune-competent systems, and the lack of experience regarding the molecular biology of the approach and early drug clinical development.
- HPV vaccine already exists.
- Therapy may be short-lived in advanced disease.
- The numerous injections do not correlate to the proposed clinical injection that are less numerous and farther apart.
- Strengths - Target makes sense, strategy of silencing viruses makes sense. Weaknesses - Data not convincing (in vivo in particular) especially when comparing the treatment regimen in mice to anticipated regimen in humans.

Value Proposition

- Unclear value proposition. There are many other products in development in this space, and there is an HPV vaccine.
- There is an unmet need for treating advanced HPV-related cancers. Other potential products do exist. They have not cited the history and expertise on the original construct.
- The product is an RNA-containing LNP intended to treat HPV+ cancers. HPV+ cancers are common, and while early-stage disease can be cured with local treatment, patients with advanced disease continue to have poor outcomes. Current treatments for advanced disease include chemotherapy and immunotherapy, but these are effective in only a subset of patients. Therefore, new and effective strategies for advanced HPV+ cancers represent an unmet medical need.
- The intended delivery method for this therapy is local injection, which may not provide meaningful long-term effects, especially in patients with metastatic disease.
- It is not clear whether this approach would be more or less expensive than current therapies. If available, it is unclear who would administer the therapy and how that might affect overall treatment costs.
- The value proposition is questionable given the vaccine.
- There are potentially additional indications (earlier treatment, anal cancer) for this therapy if it is successful for the currently intended patient population.
- There are numerous competing products in development; the one described in this proposal seems to have some advantages in terms of the patient population that can be treated and patient burden.
- The delivery method of intratumoral injection is feasible across a wide range of settings and can increase accessibility, but it is associated with some risks and, in preliminary stages, will require imaging to guide administration, with an associated burden on the health care system.
- In terms of treating people who are not vaccinated, from a societal level, addressing the financial barriers of the vaccine would be substantially less costly than development of this technology.
- The data about prevalence and incidence across groups are not presented in a clear and scientific way.
- While there is the potential for this technology to improve accessibility for some populations, there is no content on how this would be accomplished, so this feels underdeveloped and not of importance.

- [Redacted Therapy] has the potential to address unmet medical needs for patients with advanced HPV+ head and neck and cervical cancers. [Redacted Therapy] provides a proven gene therapy approach that could be used to treat these aggressive cancers once they have progressed after administering the current standards of care.

Rationale

- The MOA is somewhat novel; targeting BE2K could be more broadly applicable than other therapies that might be HPV genotype–restricted.
- The in vitro data look promising, but the in vivo data are concerning: there was only a small effect on tumor growth when the product was administered 10 times.
- Advanced cancers are more metastatic, and their product may be better suited for local disease, given that their delivery is intratumoral.
- The product includes an mRNA encoding a chimeric protein consisting of the E2 DNA-binding domain with the KRAB repressor domain. This is intended to bind to the E2 binding sites within the LCR enhancer to promote E2-mediated repression of the E6 and E7 viral oncogenes, as E2 expression can be lost in these tumors. Interestingly, this E2-KRAB repressor domain fusion approach was first described in 2011, yet the investigators do not cite it.
- Several groups have demonstrated that E6/E7 silencing has anti-tumor effects, providing a rationale for this approach. A portion of HPV tumors (low) will have additional mutations (i.e., TP53) that allow them to become E6-independent, which may not be impacted by the fusion protein.
- The KRAB domain is also intended to induce epigenetic silencing through chromatin and DNA methylation changes. It is unclear whether these changes will be transient or permanent.
- This approach may be more effective in cancers with integrated HPV viral genomes that tend to have higher expression levels of E6/E7. However, some portion of these cancers may have episomal HPV with low E6/E7 that appear to be dependent on alternative oncogenic pathways, and it is not as clear that this approach would work in these tumors.
- Preliminary data indicate that BE2K can decrease LCR promoter activity and E7 expression, with a reciprocal increase in p53 and p21 expression. This leads to decreased proliferation and increased apoptosis. There is evidence of H3K9me3 at the LCR. It is not clear if silencing is maintained over time.
- Data are also provided that LNPs can deliver RNA to cancer cells in vitro and in vivo. Intratumoral injection limits the growth of cell line xenografts, demonstrating a moderate effect on tumor growth but no regression, which limits enthusiasm for this approach. PDX models have also been examined, but no growth curves are provided, raising questions about anti-tumor efficacy in these models. Furthermore, this is important, as tumor size is an endpoint in the proposed studies. In addition, this approach may be adequate in localized tumors but is unlikely to be effective in metastatic disease.
- The proposal seeks to understand the impact of BE2K on the development of anti-tumor immunity, which could be advantageous in advanced disease; however, no preliminary data are provided in this regard.
- The rationale is logical, but the data are not convincing. In vivo data in xenograft studies suggest that 10 intratumoral injections over a period of approximately one month can slow, but not stop or cause regression of the tumor; the study did not look at long-term effects (i.e., survival benefit).
- [Redacted Therapy] provides a genotype-agnostic approach to treating HPV+ cancers, which could make it universally applicable. LNP-mRNA approaches have been successfully utilized for other indications.
- [Redacted Therapy] is intended to be administered intratumorally, which may provide a more efficacious route of administration for these cancers (rather than systemic).

Project Plan and Design

- It is unclear why the C3.C4 model was not part of the preliminary data, as it could have been tried right away and would be most relevant.
- The INTERACT meeting was denied, but the regulatory strategy is not well described (e.g., the applicant is not sure if they need certain large animal, IND-enabling studies).
- It is unlikely that nonclinical activities 2–5 are needed for nonclinical activity 6 (tox study) and for a successful IND.
- The nonclinical approach appears more appropriate for generating data for a publication, rather than focusing on the most critical work needed to advance into a clinical trial.
- There is not likely to be much value in exploring PDX models.
- Their product may not be best matched to the unmet need, which is more advanced disease. CMC was strong and well designed. The CDMO is a proven vendor, and their stepwise process was well presented. Not having a large animal study may hurt them and may create regulatory hurdles from a dosing translation aspect.
- The proposed studies are straightforward and will contribute to the preclinical development of this product. These include optimizing the LNP, but it is unclear whether this is necessary.
- Dosing will also be investigated, but it is not clear that the models chosen are relevant for future human studies.
- Two different animal models will be used to study the impact of [Redacted Therapy] on host immune responses. These studies are primarily descriptive, and further functional immune studies would help validate the findings.
- Molecular studies, including ChIP-seq, RNA-seq, bisulfite sequencing, and ATAC-seq, may be important in validating the potential long-term effects. This is especially important as this is an mRNA approach and the effect will be limited to the half-life of the mRNA and fusion protein. Studies to determine whether there are genomic off-target effects may not provide the resolution needed to understand long-term effects.
- Many of the tasks will be carried out by CROs, which provides some reassurance for the technical quality of the proposed studies.
- Some of the planned activities should be informed by prior studies, which is not how the plan is written. For example, Nonclin 2B proposes a study that tests 5 µg; the highest dose to be tested in Nonclin 2A is 6 µg. It is unclear why the applicant would not test a dose in 2B based on outcomes of 2A. Specificity needs to be rethought. It is recommended to think in terms of testing a dose that is a pre-specified fold greater than the EC90. Transfection will result in greater exposure than LNP; the applicant should try to mimic exposure in vivo. ChIP-seq is likely overkill. It is unclear how the applicant will do dose translation for the clinic if large animals are not being used. A basket trial design might lead to challenging data interpretation here; there is no evidence of comparable biodistribution.
- The CMC project plan appears appropriate, with the first phase including the transfer of materials to the CDMO, process development, ENG batch manufacturing, and analytical assay qualification. For phase 2, the CDMO will scale up and produce a cGMP batch of the final drug product and initiate stability studies. Only one batch is required for the entirety of the planned Phase 1 clinical study.

Project Team and Resources

- The identified subcontractors appear experienced, but it also appears that quotes have been obtained for studies that the applicant is not sure are needed. The application would have been stronger if the team had incorporated more of a regulatory strategy.
- The PI is a fairly junior academician. It is not clear if the team has the necessary expertise and experience.
- The investigative team is led by a junior faculty member with limited experience in many of the biological or technical aspects of the proposed studies, as indicated by the CV provided. Additional experts will be enlisted for the proposal, but it is not clear whether these individuals have the experience to adequately complete the proposed studies.
- Two clinicians are enlisted for the clinical trial, but they are also junior, and it is unclear whether they have early-stage drug development experience.
- The study will be conducted within a strong research institution with resources and expertise to support this type of research.
- The applicant has enlisted a proven CDMO with expertise in LNP-mRNA products. The team is also appropriately staffed to support the successful execution of this program.

Population Impact

- The applicant has considered the genetic background of the potential patient population and attempted to incorporate these considerations into the different types of models to be used in the nonclinical studies.
- There is an unmet need for advanced cancers driven by HPV. HPV vaccines do exist.
- This treatment would provide benefit to vulnerable individuals, including immunocompromised individuals, people with HIV (PWH), and those who are not receiving the vaccine for various reasons.
- My primary concern about this proposal is the lack of attention to representation of the diverse population of California. The expected enrollment includes ~75% White, which is based on COH's prior data on solid tumor trial enrollment, but this is not a sound justification for overrepresentation of this demographic group. There is some content on differences in prevalence, incidence, and strain of HPV across demographic groups, but this is confusing and reads as incomplete and not well thought through in terms of population implications.
- There is no evidence to suggest that this team is partnered with stakeholders, including patients, providers, and patient advocacy groups.
- The sponsor has a firm understanding of all factors that could impact the success of the proposed therapy. All proposed activities are appropriate to enable development through to a successful IND application.