PA 14-01: ACCELERATED DEVELOPMENT PATHWAY

BACKGROUND ON REVIEW PROCESS

The objective of the Accelerated Development Pathway program is to advance development of projects with a stem cell-based therapeutic within the CIRM Disease Team and Strategic Partnership portfolio, particularly those that have the potential to reach clinical demonstration of an acceptable safety profile and proof of concept during, or before, 2017.

For this competition, CIRM grantees had the opportunity to apply for new funding beyond their parent Disease Team or Strategic Partnership awards to support new activities that would accelerate development of their therapeutic. New activities were proposed as distinct modules (e.g., manufacturing improvements, phase 2 trial) that could be considered and funded individually. Given the unique nature of this competition, the review of was conducted in two stages as described below.

First, reviewers discussed the overall merit of program and the proposed new activities against the review criteria described in the PA. Briefly, the criteria include:

- Clinical competitiveness and impact of the proposed therapy
- Relevance of the therapeutic to regenerative medicine
- Strength of the development program
- Qualifications of the development team
- Progress on the Parent Award and effective program leadership
- Appropriateness and feasibility of proposed activities to accelerate the development program to clinical proof of concept by or during 2017

Following a full discussion of the application, the scientific members of the GWG voted whether: “based upon the review criteria outlined in PA 14-01, the team has demonstrated adequate readiness and capacity to consider and integrate new proposed activities that will advance or accelerate their program toward a clinical proof of concept, potentially by or during 2017.”

A “yes” vote represents an overall score of 65 or greater.
A “no” vote represents an overall score below 65 (Tier 3).

Applications with a majority “no” or tie were placed in Tier 3, not recommended for funding. No further action was taken by the GWG on these applications. For applications with a majority “yes” vote, each of the principal new activities proposed were scored using conventional 1-100 range.

CIRM Accelerated Development Pathway: PA 14-01

TIER 1 BUDGET: $3,830,506
TIER 2 BUDGET: $15,983,676

					Range				
Application #			VOTE*	SCORE	Median	SD	Low	High	BUDGET	TIER
AP1-08039			Y						$24,999,614	
	Module 1	Ph1 Trial Additions; Device Development		91	90	2	90	95	$3,830,506	1
	Module 2	Ph2 Trial in Patient Sub-group		<65					$5,128,730	3
	Module 3	Scale up; Device Development; Bridging Studies		72	75	15	30	85	$12,772,654	2
	Module 4	Ph2 Trial in Patient Sub-group		<65					$3,313,324	3
AP1-08040			Y						$18,863,378	
	Module 1	Manufacturing Improvements		<65					$5,142,185	3
	Module 2.1	Bridging Studies Related to Manufacturing Improvements		<65					$1,557,682	3
	Module 2.2	Additional Dosing Studies		74	80	12	50	90	$3,211,022	2
	Module 3	Ph2 Trial		<65					$9,704,924	3
AP1-08043			N	<65					$11,118,419	3
AP1-08047			N	<65					$18,917,571	3
AP1-08048			N	<65					$24,885,766	3

***Following a full discussion of the application, the scientific members of the GWG voted whether:**

"based upon the review criteria outlined in PA 14-01, the team has demonstrated adequate readiness and capacity to consider and integrate new proposed activities that will advance or accelerate their program toward a clinical proof of concept, potentially by or during 2017."

M E M O R A N D U M

August 21, 2014

From: Ellen G. Feigal, MD., SVP Research and Development, and
Catherine Priest, PhD., Science Officer
To: Application Review Subcommittee, Independent Citizens Oversight Committee (ICOC)
Subject: CIRM Team Recommendation for Tier 2 applications submitted under PA 14-01, Accelerated Development Pathway Awards

CIRM Team Recommendations

In accordance with Section 7, Article V of the Bylaws of the Scientific and Medical Research Working Group and Section 6, Article VI of the Board's bylaws, both as amended on 3/19/13; the President and the CIRM scientific team, following internal review and consideration, would like the Application Review Subcommittee to consider the following:

Application: #AP1-08039
Type of Application: Accelerated Development Pathway
Tier and Average Score for Activity Modules: Module 1, Tier 1, 91; Module 3, Tier 2, 72
Title: Clinical Development of a Cell Therapy for Diabetes
Disease Target: Type 1 Diabetes Mellitus (T1DM)
Approach: Allogeneic human ESC-derived pancreatic progenitors in a retrievable immune-isolation device implanted subcutaneously that mature in vivo to insulin-secreting islet cells
Requested Funding: Module 1, Tier 1 $3,830,506; Module 3, Tier 2 $12,772,654

The review summary for the application accompanies this cover memo.

Points for Consideration:

- Reviewers described this stem cell-based product as an example of innovative science and cutting edge delivery technology, which is being applied in a clinical indication with a testable mechanism of action. If successful, this has the potential to become a platform technology for delivery of other cell-based therapeutics in a number of clinical conditions. The applicant has an approved IND for the Phase 1/2 first in human clinical trial.

- Module 1 was placed in Tier 1. Activities proposed in Module 1 were considered feasible and likely to advance the team's program toward a clinical proof of concept, potentially by, or during, 2017. Reviewers assessed the activities proposed to expand the Phase 1/2 first in human clinical trial, which is currently funded under the Parent Award, as well justified, focused and integral to achieving clinical proof of concept. The additional activities would support progress to patients, inform follow-on trials, and accelerate the overall Development Program.

- Module 3 was placed in Tier 2. Activities proposed in Module 3 would allow development and manufacture of a large capacity cell device that would be tested in preclinical models and bridged into use for future clinical trials. The activities were considered to be necessary for commercialization and for accelerating the product's path to market. Reviewers recommended that the team could initiate the proposed cell manufacturing improvements and development work for the larger capacity device along the proposed time line, but await interim results from the Phase 1/2 first in human trial before proceeding with bridging activities.

CIRM Team Recommendation for Module 1: Fund. The activities proposed in Module 1 are necessary and will effectively accelerate development of the therapeutic candidate.

CIRM Team Recommendation for Module 3: Fund. The work proposed in Module 3 is required for future development of the therapeutic product. Initiation of the activities in parallel with the Phase 1/2 first in human clinical trial will mitigate long delays to patients. To support the reviewers' proposal to stagger proposed activities, the CIRM scientific team would negotiate milestones for this work to proceed in a staged manner, with advancement through the activities dependent on achievement of milestones agreed upon with the applicant team.

Application: #AP1-08040
Type of Application: Accelerated Development Pathway
Tier and Average Score for Activity Modules: Module 2.2, Tier 2, 74
Title: Accelerated Development of Retinal Progenitor Cell Therapy
Disease Target: Retinitis Pigmentosa
Approach: Allogeneic retinal progenitor cells (RPC) administered into the vitreous cavity of the eye
Requested Funding: Module 2.2, Tier 2 $3,211,022

The review summary for the application accompanies this cover memo.

Points for Consideration:

- This project is investigating a progenitor cell therapy approach to treat a blinding retinal disease that has no cure or approved treatment options. The program is on track to complete a regulatory filing with the FDA to allow initiation of a Phase 1 clinical trial, activities which are funded under the Parent Award.

- Reviewers agreed that process development and manufacturing improvements, such as the activities proposed in Module 1, would be essential to support advancement to later stage development. However, the proposed activities in Module 1 were viewed as lacking in focus and prioritization, and some reviewers expressed that the scope was too broad to be adequately reviewed. Module 1 was placed in Tier 3. The proposed Module 2.1 would be dependent on results from Module 1; thus, Module 2.1 was not recommended for funding.

- Activities proposed in Module 2.2 are designed to investigate the potential immune response to repeated administration of cells over time. If the initial clinical trial is successful, reviewers agreed that this will be an important question to address for later stage development. In Module 2.2, the applicant proposes to use analogous cells obtained from multiple species to investigate immune responses in different preclinical animal models.

CIRM Team Recommendation for Module 2.2: Do not fund at this time. If clinical studies suggest that a single injection is safe and offers benefit that could be enhanced by multiple injections, it will be important to understand the potential immune response to re-administration of the therapeutic candidate. Further, as the team is exploring optimization strategies to improve the manufacturing process, it is not clear how comparable the analogous cells from other species will be to the intended clinical product, or how predictive the proposed preclinical studies will be in regard to the human immunological response to repeated dosing with the intended clinical product. CIRM Team recommends that the applicant team incorporate reviewers' suggestions to improve this module and re-apply for support of the work at a later stage in the Development Program. There is sufficient time to optimize this plan for future initiation without delaying progress on the overall Development Program.

REVIEW REPORT FOR CIRM PA 14-01: ACCELERATED DEVELOPMENT PATHWAY AWARDS

AP1-08039: Clinical Development of a Cell Therapy for Diabetes

SCORES AND RECOMMENDATIONS

Module 1
Score: 91
GWG Recommendation: Recommended for funding
CIRM Recommendation: Fund

Module 2
Score: <65
GWG Recommendation: Not recommended for funding

Module 3
Score: 72
GWG Recommendation: Tier2, Moderate quality or no consensus
CIRM Recommendation: Fund

Module 4
Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
We are developing a stem cell-derived replacement cell therapy for insulin-requiring diabetes. Through a process known as directed differentiation, embryonic stem cells are turned into pancreatic cells in the laboratory. The pancreatic cells are loaded into a delivery device, which is essentially a small envelope made with a semi-permeable membrane, not unlike a flat tea bag. When the cells in the device (combination product) are implanted under the skin, they become pancreatic endocrine cells, including insulin-producing beta cells that respond to elevated blood glucose by releasing insulin in a physiologic manner. The prototype combination product has been tested in hundreds of animals, is routinely curative in a mouse model of chemically-induced diabetes, and has been shown to be safe in several animal studies. Moreover, the delivery device has been shown to protect cells from a recipient's immune system. The Team has received valuable feedback from the FDA, and we plan to launch the first clinical test of our therapeutic candidate in patients with diabetes in 2014. This first clinical trial will utilize the prototype to establish safety in humans, and determine the dosing range that might provide benefit to patients with diabetes.

The current application is to fund additional clinical research, and associated product development activity, that will (1) ensure the first trial is executed in a most informative and timely fashion, (2) accelerate the pace at which information is collected on how the product works in humans – testing various formats, and in different types of patients – and (3) substantially increase the likelihood that the most appropriate format and patient population is selected for a definitive "Phase 3" clinical trial. A Phase 3 trial serves as the basis for an application to the FDA to

obtain a license to market the product. In this way, CIRM Accelerated Development Pathway designation of the project will substantially increase the probability that, and pace at which, this product concept becomes a real treatment available to the millions of patients in need.

Statement of Benefit to California (provided by applicant)

Diabetes mellitus currently afflicts approximately 370 million people worldwide, with projections of over 550 million by the year 2030 (sources: World Health Organization; International Diabetes Federation). In the year 2000 there were approximately 2 million cases of diabetes in California (source: Diabetes Control Program, California Department of Health Services). Further, the disease disproportionately affects certain minority groups and the elderly. Despite the use of insulin and advances in its delivery, the human cost of diabetes is underscored by the financial costs to society: tens of billions of dollars each year in California alone. The primary cause of type 1 diabetes, and contributing significantly to type 2 diabetes as well, is the loss of insulin-producing pancreatic beta cells. The CIRM Diabetes Disease Team Project is developing an innovative beta cell replacement therapy for insulin-requiring diabetes. If successful, the therapy will go beyond insulin function, and will perform the full array of normal beta cell functions, including responding in a more physiological manner than manual or mechanized insulin self-administration. Because they will be more physiological, the replacement cells could reduce the long-term effects of diabetes. Moreover, the cell therapy will alleviate patients of the constant monitoring of blood glucose, painful insulin injections, and the ever-present risk of overdosing with insulin. For these reasons, it is possible that the product could transform the diabetes treatment landscape dramatically and even replace pharmaceutical insulin in the market. This product will be available in California first, through clinical testing, and if approved by the FDA for commercial production, will eventually help hundreds of thousands of Californians with diabetes. The product will substantially increase quality of life for patients and their families, while significantly reducing the health care burden in the state. The proposed project will employ Californian doctors and scientists, and success will prove highly noteworthy for the state. Lastly, once commercially marketed, the product will yield additional jobs in manufacturing, sales, and related industries, and generate revenue for California. Given the market need and the clear feasibility, the product could become the most significant stem cell-based medical treatment of the coming decade, and that will be a tremendous achievement for California, its taxpayers, and CIRM.

REVIEW SUMMARY

The therapeutic candidate under development for the Parent Award and the subject of this application is a combination product comprising an hESC-derived cell therapy delivered in a macroencapsulation device for the treatment of Type 1 Diabetes Mellitus (T1DM). The Parent Award includes the IND submission and a Phase 1/2, first in human (FIH) clinical trial. For this application, four modules of activities were proposed. Module 1 was requested to introduce additional functional studies into the Phase 1/2 FIH clinical trial funded under the Parent Award and to add a 3-year follow up period to that clinical trial. Also proposed in Module 1, is the development of an improved device that would allow more flexibility for dosing. In Module 2, the applicants requested funding for a parallel Phase 2 clinical trial in a subpopulation of T1DM patients in whom the applicants predict that effects of the therapeutic may be

rapidly detected and offer significant benefit over current therapies, which could facilitate more rapid Regulatory approval. Module 3 would fund activities to enable rapid transition to pivotal studies, including process scale-up of cell production, the development of a larger capacity device, and the bridging studies required to integrate these modifications. Module 4 would fund preclinical work and then a clinical study in another patient subgroup to address whether immunosuppressive medication could improve product efficacy.

As an update to the GWG recommendations, the FDA approved the IND for the Phase 1/2 FIH clinical trial in August.

Clinical Competitiveness and Impact of the Proposed Therapy
- This therapeutic candidate has the potential to significantly impact, and potentially transform, the treatment for T1DM. If the combination product proves successful, reviewers projected that it would have advantages over existing therapies and insulin delivery systems.

- The idea of pursuing administration of the therapeutic in a subset of patients, as proposed in Module 2, was viewed positively in terms of potentially advancing the product to market. However, the reviewers expressed that the proposed clinical trial in Module 2 should follow, and be informed by, the Phase 1/2 FIH trial in the general T1DM target population (the Parent Award and Module 1).

Strength of the Development Program
- The preclinical package suggests a good safety profile with promising efficacy data. However, the team is still awaiting Regulatory feedback that will determine whether the non-clinical safety and device testing are sufficient, and when they may be permitted to proceed with the clinical trial (update since the time of the GWG review, the FDA approved the IND of the phase 1/2 FIH clinical trial in August).

- Reviewers described the clinical Development Plan to the end of Phase 2 as well developed and thorough.

- Reviewers agreed that the appropriate patient population had been proposed for the Phase 1/2 FIH trial, and that the trial is designed with clear clinical endpoints and outcome measures that will broadly inform the Development Plan.

- While the team is planning for success, they acknowledge that there is a risk to the program that the therapeutic will not perform as expected from the preclinical experience. Reviewers were encouraged that the team had considered mitigation strategies (such as the activities proposed in Module 1 to allow scaling the cell dose administered) and noted that the team's plans allow them to remain flexible and responsive as clinical data become available.

- While reviewers appreciated the benefits of considering additional patient groups in the Development Plan, as was proposed in Modules 2 and 4, it was widely expressed that it was critical to first get robust clinical proof of mechanism and proof of concept information from the Phase 1/2 FIH clinical trial prior to any consideration of administration of the therapeutic to other patient subsets.

Qualifications of Development Team
- The team and their consultants are well qualified, with a strong track record in stem cell product development and bioengineering.

- Reviewers described the team as having extensive regulatory experience, strong and qualified project management, and clinical operations personnel with excellent experience in the target disease and in the cell therapy arena.

- The team has breadth of experience in academia, industry, manufacturing and clinical trials and this group has a demonstrated track record of working together.

Progress on Parent Award and Effective Program Leadership
- Development challenges have delayed progress on the Parent Award, but the team has effectively managed these delays in a timely manner and have stayed close to their original timeline in the Parent Award for IND filing.

- The team is on schedule to file their IND in Q3/2014 to support initiation of the Phase 1/2 FIH clinical trial (update since the time of the GWG review, the FDA approved the IND of the Phase 1/2 FIH clinical trial in August).

- The device testing and development activities were described as well designed and consistent with regulatory expectations.

Relevance of the Therapeutic to Regenerative Medicine
- The relevance to regenerative medicine is considered a “tremendous” strength of the project. A demonstration of success with this stem cell-based product would provide a huge leap forward for regenerative medicine.

- The project is based on innovative science that utilizes hESC-derived cells in a clinical indication with a testable mechanism of action and cutting edge delivery technology.

- The delivery component of this product could have broad implications as a platform technology for the field in that it could potentially be used to deliver other stem cell-based therapeutics for a wide range of clinical conditions.

Proposed Activities for Acceleration of the Development Program
- The expansion of the Phase 1/2 FIH trial, as proposed in Module 1, is well justified, focused and integral to achieving clinical proof of concept. Specifically, the proposed additional functional study could identify whether the product acts through multiple regulatory mechanisms important for glucose control; if so, this would present a clear advantage over standard insulin replacement therapy.

- The proposed Module 3 activities in manufacturing, process improvements and scale-up were felt to be necessary for commercialization and for accelerating the product’s path to market, with a caveat that its impact in terms of accelerating the development program will be dependent on how this activity is impacted, and informed, by results of the Phase 1/2 FIH clinical study (i.e. in determining the appropriate device size/cell dose). The proposed bridging clinical study could provide proof of concept for a commercializable product in 2017, although some

reviewers thought that timeline was optimistic. In addition, the reviewers noted the open label extension study proposed in Module 3 is appropriate.

- The proposed clinical trials in Modules 2 and 4 were viewed as non-essential and premature, due to a prerequisite for sufficient proof of concept data from the Phase 1/2 FIH trial, and a lack of preclinical data, respectively. Given the novelty of the device design and therapy, it seems likely that unexpected findings could arise from the first clinical trial that would be essential to informing the next trial(s). Therefore, activities proposed in Modules 2 and 4 were not thought to be accelerating to the Development Program at this time.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Activities proposed in Module 1 are feasible and would bolster the Phase 1/2 FIH trial funded under the Parent Award to provide information regarding clinical proof of mechanism and proof of concept in a relatively short time frame. However, some reviewers considered the timelines provided (start date and time to obtaining safety and efficacy data) for the Phase 1/2 FIH clinical trial to be overly optimistic.

- Activities proposed in Module 3 are feasible and have a high probability of success given the applicant's track record.

- The reviewers assessed the feasibility of the clinical trial proposed in Module 2 as highly dependent on the results in the Phase 1/2 FIH trial. It will likely be more difficult to enroll the patient subgroup proposed for the clinical trial proposed in Module 2 and long-term follow up of those patients could pose feasibility challenges.

Module 1
- The expansion of the clinical trial proposed in Module 1 is related to achieving the key milestone of a FIH clinical trial. Reviewers commented that the information gained by addition of the functional study and the proposed longer follow-up period to the Phase 1/2 FIH trial would both inform follow-on trials and accelerate the overall Development Program. Initiating steps to expand the dosing capability of the device in a timely manner was viewed as a valuable strategy to help mitigate future programmatic delays.

- Progressive device scale up will be critical for commercialization and initiating this work along the timeline proposed in Module 1 would accelerate the path to market, provided that it is well informed and reflects ongoing developments during the Phase 1/2 FIH clinical trial.

- Activities proposed in Module 1 were viewed as critical to support progress to patients and guide the direction of the entire clinical Development Program.

Module 3
- The activities proposed in Module 3 are to develop and manufacture a large capacity cell device that can then be tested in preclinical models and bridged into use for future clinical trials. Reviewers assessed these activities, as well as the proposed work to support scale up of cell manufacturing and incorporation of cryopreservation methods into the manufacturing process, as necessary steps to

support development for larger clinical trials and future commercialization of the product. Success in the Phase 1/2 FIH clinical trial will necessitate the activities proposed in Module 3.

- Reviewers expressed that initiating the activities proposed in Module 3 in parallel with conducting the Phase 1/2 FIH study would accelerate the overall development program and prevent possible long interruptions in clinical delivery to patients. However, some reviewers expressed that it may be prudent to approach the proposed cell manufacturing and device scale up activities in Module 3 in a staggered fashion. They proposed that cell manufacturing process improvements and development work for the larger capacity device could be initiated, but that the team await interim results from the Phase 1/2 FIH trial before proceeding with bridging activities.

REVIEW REPORT FOR CIRM PA 14-01: ACCELERATED DEVELOPMENT PATHWAY AWARDS

AP1-08040: Accelerated Development of Retinal Progenitor Cell Therapy

SCORES AND RECOMMENDATIONS

Module 1
Score: <65
GWG Recommendation: Not recommended for funding

Module 2 (Module 2.1 excluded)
Score: 74
GWG Recommendation: Tier 2, Moderate quality or no consensus
CIRM Recommendation: Do not fund at this time

Module 3
Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
Retinitis pigmentosa (RP) refers to a group of inherited diseases, which cause retinal degeneration leading to blindness. The cardinal sign of the disease is the presence of dark pigmentary deposits in the retina, visible on ophthalmic exams. The main risk factor for developing RP is family history. It is an uncommon condition affecting roughly 100,000 Americans. There is no effective treatment for RP; once photoreceptors are lost, they are not replaced. The rate of deterioration of vision varies and most people with RP are legally blind by age 40. RP is a major cause of incurable visual loss and there is a significant medical need for innovative treatments.

The therapy being developed for the treatment of RP contains living cells called human retinal progenitor cells (hRPC's) which are injected directly into the eye in order to preserve the person's vision by protecting or restoring photoreceptor cells. In animal studies, it has been shown that when hRPC's are injected into an injured eye, the cells stayed within the eye and did not cause any detectable side effects. In some cases there was evidence that the animal's vision improved following treatment, suggesting that photoreceptors in the host eye were protected by the injected cells. The injection itself is not considered to be particularly high risk and can be done as an outpatient surgical procedure.

An initial clinical trial (I) will commence as early as late 2014. Following clinical trials (I/IIa), the proposed phase (IIb) study will include up to 70 patients, half of the participants will be treated with a single dose of hRPC's in one eye only and half will be treated with a single sham treatment in one eye only. The sham is an injection that looks and feels like the cell treatment but does not contain any cells. It is designed to provide a comparison to the participants who are treated

with the hRPC's in order to control for any effects of the procedure itself. Neither the study participants nor the physicians evaluating them will know in which group the participants were assigned. The primary goal is to demonstrate that subjects with RP who receive the hRPC's have improvement in vision in the treated eye over a 12 month period compared to the subjects who receive the sham. It is anticipated that if vision is improved by the treatment, a person's quality of life will improve as they may regain the ability to perform certain activities that they had lost. This would be a major advancement in the treatment of RP, possible saving the vision of people who might otherwise go completely blind.

The phase (IIb) clinical trials are planned to be conducted at 5 major centers in the US and will be in conformance with Good Clinical Practices under U.S. FDA IND regulations and the ICH E6 Consolidated Good Clinical Practices Guideline. No research participant will be enrolled at any site until all applicable regulatory authorizations have been obtained, including local IRB approval.

Statement of Benefit to California (provided by applicant)
The proposed project has the potential to benefit the state of California by demonstrating that California's financial commitment to regenerative medicine through CIRM has paid off and paved the way to a new dimension of treatment for diseases that would otherwise be incurable.

It is intended that the demonstrated treatment of individuals with retinitis pigmentosa (RP) will quickly lead to the treatment of other blinding diseases for which there is no cure, such as dry age related macular degeneration (AMD).

Approximately 7 million Americans live with visual impairment that affects their daily lives. Many of these individuals are unemployable and are reliant on social services and financial assistance. It is estimated that the cost to the U.S. of visual impairment exceeds $35 billion annually. As California is the most heavily populated state, it is burdened disproportionately, thereby impacting its resources, healthcare systems and public finances.

The rapid progress into the clinic for treatments to blinding disease will fuel support for the stem cell industry at large; attracting investment from big pharma that is currently lacking. This success will accelerate the development of stem cell-based therapeutics for a wide range of other conditions. In so doing, California will be the focal point for stem cell breakthroughs. This success will increase medical capabilities, strengthen the state's education system, and energize local biotechnology companies with outside investment and a payoff in jobs and tax revenues.

REVIEW SUMMARY
Based on review criteria outlined in PA 14-01, a majority of reviewers voted that the team demonstrated adequate readiness and capacity to consider and

integrate new proposed activities that will advance or accelerate their program toward a clinical proof of concept, potentially by, or during, 2017.

Retinitis pigmentosa (RP) is an inherited, degenerative eye disease that causes severe vision impairment and often blindness and for which there is currently no approved therapy. The applicant is developing a cellular therapy using human retinal progenitor cells to treat patients with RP. The goal of the parent award is to complete preclinical studies and conduct a Phase 1/2a clinical study in patients with RP.

Three modules are proposed in the current application. Module 1 is focused on improving the product manufacturing and formulation to enable scaling and commercialization of the cellular product. Module 2 comprises two preclinical components: Module 2.1 proposes to conduct preclinical studies to address comparability of therapeutic product from the current and the proposed scalable (Module 1) manufacturing processes; Module 2.2 proposes to conduct preclinical studies with analogous cells in several species to assess allogeneic immune response following repeat administration of the product. Lastly, Module 3 proposes to conduct a Phase 2b clinical trial.

Clinical Competitiveness and Impact of the Proposed Therapy
- There are no approved therapies for RP, so the disease remains a significant unmet medical need. Furthermore, the development plan, if successful, is to expand to other retinal diseases.

- There are a number of clinical trials already ongoing to treat RP using a variety of approaches including cell-based therapy.

Strength of the Development Program
- The applicant has a reasonably straightforward path to the clinic. The major challenge to this program relates to manufacturing, particularly with respect to the final formulation and in scaling up the manufacturing capacity.

- The proposed therapy has already been used to treat three patients in an uncontrolled study overseas. Data available from those patients are limited, but the human experience does provide some indication of the safety of the approach.

- The team has worked well to understand and execute on FDA recommendations and it is expected that the preclinical studies will support the clinical plan.

- Multiple batches of clinical grade material have been manufactured and tested.

- Challenges related to the manufacturing process need to be addressed before the program can advance beyond an early phase clinical trial.

Qualifications of Development Team
- The team is well qualified and includes consultants with appropriate expertise and experience necessary for the project.

Progress on Parent Award and Effective Program Leadership
- The team has made good progress in terms of meeting goals and milestones and is on track to complete a regulatory filing with the Food and Drug Administration (FDA) to begin a Phase 1 clinical trial under the parent award.

- The team responded well to feedback from the FDA on the necessary preclinical studies and incorporated that feedback into their plan in a timely and effective manner.

- The main concerns expressed were around the status of the current manufacturing process, given the lack of detail regarding methods or product release criteria. There is insufficient focus on understanding the current cell product.

- Another major concern was insufficient data on the proposed mechanism of action.

Relevance of the Therapeutic to Regenerative Medicine
- The project is highly relevant to regenerative medicine as it is using a progenitor cell therapy approach to treat a blinding retinal disease that has no cure or approved treatment options.

Proposed Activities for Acceleration of the Development Program
- Only some of the proposed activities were viewed as essential for accelerating the development program.

-It was noted that the activities proposed within Module 2.1 are dependent upon the activities within Module 1 and would not be relevant in the absence of Module 1.

- Module 3, the proposed follow-on clinical trial, was viewed as premature based on the current status of the project.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Many of the proposed activities in Module 1 lacked sufficient detail to be able to fully assess feasibility and reviewers did not think the timeline for the proposed manufacturing improvements was realistic.

- Reviewers did not see a clear, focused plan for prioritizing the many activities proposed.

- The proposed Phase 2b clinical trial as described in the timeline will not meet the target timeline of the RFA. Moreover, some reviewers did not believe that patients would be enrolled as quickly as the applicant estimates, further questioning the feasibility of the trial as proposed.

Module 1
- Although improving the manufacturing process is important and essential to the development of the therapeutic, a major concern was that each component will take a long time to conduct and the lack of detail in the proposal reduced confidence that the applicant understands the complexity of what will be required or how to do it.

- Reviewers considered Module 1 to be insufficiently developed. Many aspects of the manufacturing process were identified that could be examined and/or changed but a detailed plan was not provided as to how those studies would be executed or how they would be prioritized.

Module 2.2
- Module 2 proposes two activities: 2.1) preclinical studies to examine comparability of therapeutic product from different manufacturing processes and 2.2) preclinical studies to assess the immune response following repeat administration of analogous retinal progenitor cells in animal models. Since Module 2.1 is dependent on activities that would be conducted in Module 1, and Module 1 was not recommended for funding, a motion was passed to consider only Module 2.2. The score of this module, therefore, reflects Module 2.2 alone.

- Reviewers agreed that repeat treatment administrations may be necessary, making the potential immune response an important question to study and one likely to be required by the FDA.

- Some reviewers did not agree with the large animal species identified by the applicant for the proposed allogeneic preclinical studies and pointed out that differences in the anatomy of the eye, and particularly the structure of the retina, should be considered in the selection of an appropriate animal species. It was also noted that some expenses in the proposed budget for the large animal study seemed excessive.

- If an immune response were observed upon repeat dosing, it was unclear to reviewers how the particular immunosuppressant drugs to be examined were selected and why others were excluded.

Module 3
- It is premature to consider funding a Phase 2b trial based on the current status of the project which has not yet begun enrolling the initial clinical trial.

- The Phase 2b clinical study as proposed would not be completed within the 2017 timeframe; in addition, the reviewers did not think that the planned timeline to enroll patients was realistic.

- Some concern was expressed over the proposal to move into a larger study using patients with more moderate visual impairment since that could unfavorably impact the considerations of risks of the treatment versus the potential benefit to the patients.

- Additional endpoints should be included to ensure that signals of efficacy won't be missed.

REVIEW REPORT FOR CIRM PA 14-01: ACCELERATED DEVELOPMENT PATHWAY AWARDS

AP1-08043: The Accelerated Development of Monoclonal Antibody UC-961 For Eradication of Cancer Stem Cells

SCORES AND RECOMMENDATIONS

Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
This application is for supplemental funding to accelerate clinical development of UC-961 (cirmtuzumab), a fully-humanized monoclonal antibody that binds to the extracellular domain of ROR1, which is a surface protein expressed on embryonic cells and cancer cells. ROR1 is not expressed on normal adult tissues. However, ROR1 is highly expressed on the surface of chronic lymphocytic leukemia (CLL) cells and on cancer stem cells (CSC), which account for the drug-resistance, relapse, and metastasis of many cancers. Because UC-961 is highly specific for ROR1, it does not bind normal adult tissues, but instead binds tightly to CLL cells and to CSC. Treatment of CLL cells or CSC with UC-961 inhibits the proliferation, migration, survival, and metastatic/engraftment potential of CSC. Moreover, UC-961 may eradicate CSC while sparing stem cells of normal tissues, potentially providing for a revolutionary, highly-specific, and effective anti-cancer therapy.

Under the auspices of a CIRM Disease-Team 3 Award, we will conduct a phase I/II study to determine the safety, tolerability, and activity of UC-961 in patients with CLL. Supplemental funding will allow for assays on leukemia cells of patients before, during, and after therapy with UC-961 to examine for treatment-induced effects that may correlate with clinical outcome. Also, these assays may define new biomarkers that can identify patients who most likely will benefit from UC-961 anti-CSC therapy. Finally, supplemental funding will allow another clinical site to activate this trial to accelerate patient accrual.

Supplemental funding also will allow us to initiate follow-on phase I clinical trials for patients with pancreatic adenocarcinoma or ovarian cancer with protocols cross-filed under our IND for UC-961. These studies will determine the safety, tolerability, and potential activity of UC-961 in patients with ROR1+ CSC-driven, solid-tissue cancers. These studies will incorporate biomarker studies and imaging assessments to define a clinical proof of concept and to inform decisions for subsequent pivotal clinical testing on a registration pathway. In addition, these studies will incorporate correlative studies on primary-cancer-derived xenografts, primary cancer cells, or blood samples of treated patients, testing the activity of UC-961 alone or in combination with other active anti-cancer drugs (e.g. gemcitabine in pancreatic cancer, platinum and taxane in ovarian cancer). These studies may identify treatment effects that correlate with clinical outcome and identify subsets of patients who most benefit from treatment with UC-961 for further examination.

Statement of Benefit to California (provided by applicant)
Cancer is a leading cause of death for Californians. Thousands of adults and children in

California succumb to cancer relapse following treatment with surgery, radiation, and/or conventional chemotherapy. Although gains have been made in the treatment of some cancers, over 50% of adults diagnosed with leukemia will die of their disease. The outlook for patients with many solid-tumor cancers is even worse, particularly for those patients with tumors having poorly differentiated, high-grade malignancies, which have an increased propensity for metastases and/or early relapse after therapy. Nonetheless, current therapies can cost several tens of thousands of dollars per patient per year, factor in cancer-related depression, and do not cure the disease. For the physical, mental, and financial health of the citizens of California, we need to find curative treatments for patients with cancer.

What has held up progress toward a cure? Compelling evidence indicates that the leukemias and many solid tumors are not curable because most treatments do not destroy small numbers of multi-drug resistant cancer stem cells (CSC); dormant cancer stem cells (CSC) provide for the drug-resistance, relapse, and metastasis of many cancers. Required are agents that can eradicate CSC while sparing the vital stem cells of normal tissues.

This project will fund clinical development UC-961 (cirmtuzumab), a fully-humanized monoclonal antibody that binds an extracellular epitope of ROR1, which is an onco-embryonic antigen. While ROR1 is not expressed on normal post-partum tissues, it is highly expressed on the surface of chronic lymphocytic leukemia (CLL) cells and on cancer stem cells (CSC). Because UC-961 is highly specific for ROR1, it does not bind normal adult tissues, but instead binds tightly to CLL cells and to CSC. Treatment of CLL cells or CSC with UC-961 inhibits the proliferation, migration, survival, and metastatic/engraftment potential of CSC. As such, UC-961 may eradicate CSC while sparing stem cells of normal tissues. Such studies may lead to the potential commercialization of UC-961, which could provide a revolutionary new form of anti-cancer therapy for Californians with intractable malignancies.

In summary, the benefits to the citizens of California from the CIRM disease specific grant in cancer are:
(1) direct benefit to the thousands of leukemia and solid-tumor cancer patients
(2) financial savings due to effective treatments that may eradicate CSC and obviate current therapies that are less clinically active and/or cost-effective

REVIEW SUMMARY

The applicant is developing a therapeutic antibody candidate that can kill cancer cells and cancer stem cells that express a specific cell surface protein. While typically absent on healthy adult cells, activation of this protein promotes survival, proliferation and migration of cancer cells. The cellular pathway activated by the protein is stimulated in over 90% of people with chronic lymphocytic lymphoma (CLL). In the Parent Award, the applicant has proposed a Phase 1a/b clinical trial in patients with CLL to identify a safe and efficacious dose of the therapeutic antibody. In June 2014, the applicant's IND was approved by the FDA to begin the first in human clinical trial in CLL. In this application, additional funds were requested to add 1) new bioassays and an additional trial site to the funded Phase 1a/b clinical trial in CLL, and a Phase 1b re-treatment trial in CLL; 2) a Phase 1 clinical trial in pancreatic cancer; and 3) a Phase 1 clinical trial in ovarian cancer

Clinical Competitiveness and Impact of the Proposed Therapy
- Although CLL is a highly competitive area, reviewers were very enthusiastic about the candidate therapeutic, describing it as a highly novel target with the potential to be a first in class antibody therapy for CLL.

- Pancreatic and ovarian cancers have great unmet medical need, but reviewers were less convinced by the data provided that the therapeutic candidate under development could have significant benefit in these cancers.

Strength of the Development Program
- Reviewers commented that reasonable contingency plans have been made to address potential clinical challenges in the CLL Phase 1a and, if needed, Phase 1b trials.

- Reviewers noted that the development/regulatory path for a monoclonal antibody therapeutic is well-defined, which will benefit the team's program progress.

- A major strength of the project is the growing pharmaceutical/industry interest in the candidate therapeutic, and the team was encouraged to continue seeking discussions with potential partnering groups (update since the GWG review, the applicant finalized a collaborative agreement with an industry partner in August).

Qualifications of Development Team
- Reviewers described the team as highly qualified to complete the proposed studies. The PI is a recognized leader in the field of CLL and other members of the team have experience in hematological malignancies and solid tumor oncology.

Progress on Parent Award and Effective Program Leadership
- The Parent Award is focused on CLL as a first clinical indication and has a high probability for success. The team is making timely progress and has effectively incorporated changes to reflect regulatory input.

- Reviewers were encouraged by the team's progress on establishing correlative biomarker assays, which may be highly relevant for future development of the therapeutic candidate and selection of the most appropriate patient populations for treatment.

Relevance of the Therapeutic to Regenerative Medicine
- The therapeutic candidate antibody recognizes a cell surface protein that is expressed on cancer cells and cancer stem cells.

- If initial clinical studies demonstrate significant cytotoxic effects of the candidate therapeutic on cancer stem cells, reviewers agreed that it could help prevent drug resistance, metastasis and relapse in a number of cancers.

Proposed Activities for Acceleration of the Development Program
- Reviewers described the follow-on clinical activities proposed for the CLL trial as "logical," but unlikely to accelerate the overall development time line toward demonstration of clinical proof of concept for CLL.

- While the reviewers appreciated the value of extending the Development Program to additional clinical indications, they did not think that adding additional Phase 1 trials at this time would sufficiently advance the team's progress to demonstration of clinical utility for the therapeutic candidate.

Feasibility of Proposed Activities for Acceleration of the Development Program
- The Phase 1b retreatment trial for CLL that was proposed would provide valuable long-term safety and efficacy data at the targeted Phase 2 dose. While reviewers felt the study was important and appropriate , they did not think it could be initiated until quite late in the activities conducted under the Parent Award, given the lengthy time proposed to complete the Phase 1a component, and would be unlikely to accelerate overall progress. The reviewers strongly encouraged the applicant to consider ways to accelerate the completion of the Phase 1a component e.g., adding more clinical sites.

- The team noted that the therapeutic candidate could be more potent in some tumor types than in others; reviewers questioned how informative the dosing information gained from the CLL trials would be for expansion of the therapeutic to other clinical indications. Overall, the reviewers thought the highest probability of success would be in CLL, and thought CLL should remain their primary focus to establish proof of concept.

- Reviewers encouraged the team to reconsider the clinical endpoints proposed for the pancreatic and ovarian cancer trials to maximize the functional information that could be gained from these studies.

- Reviewers questioned whether proposed studies that would require comparison of solid tumor samples collected pre-treatment to post-treatment samples would be limiting for patient recruitment and selection.

REVIEW REPORT FOR CIRM PA 14-01: ACCELERATED DEVELOPMENT PATHWAY AWARDS

AP1-08047: Accelerated development of a combined gene and stem cell therapy to treat amyotrophic lateral sclerosis (ALS)

SCORES AND RECOMMENDATIONS

Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
Therapeutic candidate: This project will use a powerful combined neural progenitor cell and growth factor approach to treat patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease). Human neural progenitor cells can be isolated and expanded in culture to large banks of billions of cells. When transplanted into animal models of ALS they have been shown to mature into support cells for dying motor neurons called astrocytes. In other studies, growth factors such as glial cell line-derived growth factor (or GDNF) have been shown to protect motor neurons from damage in a number of different animal models including ALS. However, delivering GDNF to the spinal cord has been almost impossible as it does not cross from the blood to the tissue of the spinal cord. By directly transplanting the modified stem cells in the spinal cord, they will be located in the vicinity of sick motor neurons. A number of advances in stem cell biology along with new surgical devices have allowed us to develop this approach for the treatment of ALS.

The disease: There are approximately 5,600 new cases of ALS in the USA each year and as many as 30,000 Americans may currently be affected by ALS. The initial features of the disease include muscle twitching, cramping, stiffness, muscle weakness affecting an arm or a leg, slurred and nasal speech, and difficulty chewing or swallowing. This quickly progresses to full paralysis. Most patients are likely to die of respiratory failure, ALS amenable to cell/gene therapy approaches as it is an incurable and terminal disease, with a very high cost/risk benefit ratio.

Rationale for proposed therapy: (i) astrocytes surrounding dying motor neurons are also affected by ALS, and thus lose their nurturing capacity for the sick motor neurons and (ii) powerful growth factors such as glial cell line-derived neurotrophic factor (GDNF) can protect motor neurons in animal models.

Our new accelerated development award: The focus of this new proposal will be to perform essential preclinical studies in both small and large animals that will establish optimal doses and safe procedures for continuing the administration of cells to other segments of the cord. Expanding on the clinical data to be gained in our original award where cells will be transplanted into one side of the lumbar spinal cord (that supplies the legs with neural impulses), we propose to in parallel

advance the development to a second clinical study delivering the cells to the cervical region of the spinal cord where potential impact on breathing can be measured. The additional information gained by this second study will allow for us to determine if, in addition to establishing that this approach in safe in both regions of the spinal cord, to determine whether a higher dose or more injection can lead to greater clinical effect, and whether a series of functional measures are predictive of slowing progression of this devastating disease.

Statement of Benefit to California (provided by applicant)
ALS is a devastating disease, and also puts a large burden on state resources through the need of full time caregivers and hospital equipment. It is estimated that the cost of caring for an ALS patient in the late stage of disease while on a respirator is $200,00-300,000 per year. While primarily a humanitarian effort to avoid suffering, this project will also ease the cost of caring for ALS patients in California if ultimately successful. As the first trial in the world to combine stem cell and gene transfer of a growth factor, California will also take the lead as a center of excellence for these types of therapeutic strategies. This in turn will attract scientists, clinicians, and industry interested in this area of medicine to the state of California, thus increasing state revenue and state prestige in the rapidly growing field of Regenerative Medicine.

REVIEW SUMMARY
This application focuses on the development of a genetically modified neural progenitor cell therapy for amyotrophic lateral sclerosis (ALS). ALS is a degenerative motor neuron disease characterized by muscle wasting for which there is currently no cure and only modestly effective treatment. Under the CIRM-funded Parent Award, the applicant is performing activities required to support the filing of an Investigational New Drug (IND) application with the FDA. The Parent Award also supports a Phase 1 clinical trial of unilateral transplantation of the therapeutic candidate into the lumbar spinal cord of patients with ALS. Activities proposed in the current application can be grouped into three areas: 1) manufacturing optimization and scale-up; 2) additional preclinical animal studies to support cell transplantation into the cervical spinal cord; and 3) a second Phase 1 clinical trial of bilateral lumbar and cervical transplantation to be run in parallel to the trial funded by the Parent Award.

Clinical Competitiveness and Impact of the Proposed Therapy
- There are competing cell therapy programs for ALS that are further along in clinical development but none have demonstrated efficacy. The applicant's approach is unique in its combination of cell and gene therapies.

Strength of the Development Program
- Reviewers described the development plan as superficial. It is not clear what outcomes of the Phase 1 trial would compel a Phase 2. The favored efficacy endpoint and desired margin of improvement are not specified.

- The argument for moving from unilateral lumbar injections to bilateral and then cervical is strong. Cervical injections may offer the best chance to impact quality of life and survival.

Qualifications of Development Team
- The team is very strong scientifically, both in the areas of neural stem cell biology and ALS.

- A reviewer recommended using the NEALS consortium as a source of ALS natural history data and to inform aspects of clinical trial design and statistical powering.

Progress on Parent Award and Effective Program Leadership
- The Parent Award has suffered some setbacks and delays related to manufacturing. Reviewers described these as critical issues that need to be addressed and resolved before accelerating activities should be considered. They noted that these issues could further impact the timeline of the Parent Award and delay proposed activities.

- Reviewers agreed that the team is generally making good progress under the Parent Award, despite some significant setbacks.

Relevance of the Therapeutic to Regenerative Medicine
- The therapeutic candidate is clearly relevant to regenerative medicine.

Proposed Activities for Acceleration of the Development Program
- Reviewers agreed that the proposed manufacturing optimization and scale-up activities are worthwhile but that their request for additional funding is premature given the status of manufacturing under the Parent Award.

- Reviewers supported the goal of testing bilateral and cervical injections in a clinical trial but questioned the proposed plan and timeline. Some reviewers suggested waiting for clinical data from the unilateral lumbar trial before designing the next clinical study. Other reviewers felt that the development program, as a whole, could be accelerated by delaying the timeline of the Parent Award and doing preclinical studies with cervical injections. These studies could support both lumbar and cervical injections in the same Phase 1 clinical trial.

- Reviewers would have appreciated a more detailed response to the most recent FDA letter. They noted several FDA comments that could affect the design of preclinical studies.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Reviewers were concerned about the feasibility of the proposed preclinical timeline, given manufacturing delays and the need to lock down the design of the delivery device.

- Reviewers also questioned the feasibility of the clinical timeline, specifically whether the FDA would allow bilateral and cervical injections prior to the availability of safety data from unilateral lumbar injections.

REVIEW REPORT FOR CIRM PA 14-01: ACCELERATED DEVELOPMENT PATHWAY AWARDS

AP1-08048: Development of a Phase II Study of Stem Cell Gene Therapy for Sickle Cell Disease

SCORES AND RECOMMENDATIONS

Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)

Sickle cell disease (SCD) results from an inherited mutation in the hemoglobin gene that causes red blood cells to "sickle" under conditions of low oxygen and block small blood vessels in vital organs. It occurs with a frequency of 1/500 African-Americans, and is also common in Hispanic-Americans, who comprise up to 5% of SCD patients in California. The median survival based on 1991 national data was 42 years for males and 48 years for females. More recent data indicate that the median survival for Southern California patients with SCD is only 36 years, suggesting that serious problems exist regarding access to optimal medical care in this community. By 20 years of age, 15% of children with SCD suffer major strokes and by 40 years of age, almost half have had central nervous system damage leading to significant cognitive dysfunction. These patients suffer recurrent damage to lungs and kidneys as well as severe chronic pain that impacts on quality of life.

While current medical therapies for SCD can make an important difference in short-term effects, the progressive deterioration in organ function results in compromised quality of life and early deaths in populations who are generally adversely affected by health care disparity. Transplantation of bone marrow from a healthy donor as a source of new adult blood-forming ("hematopoietic") stem cells can benefit patients with SCD, by providing a source for life-long production of normal red blood cells. However, hematopoietic stem cell transplantation is limited by the availability of well-matched donors and by the immune reactions that may occur between the cells of the donor and the patient. Thus, despite major improvements in clinical care of SCD patients, SCD continues to be a major cause of illness and early death.

The stem cell therapy approach to be developed by this group will be used to treat patients with SCD by transplanting them with their own bone marrow adult hematopoietic stem cells that are genetically corrected by adding a designed hemoglobin gene that blocks sickling of the red blood cells. This approach has the potential to permanently cure this debilitating illness with significantly less toxicity than with a bone marrow transplant from another person. A Phase I clinical trial using stem cell gene therapy for patients with SCD is being performed by this multi-disciplinary Disease Team, combining world-leading experts in stem cell gene therapy, clinical bone marrow transplantation and the

care of patients with SCD. The goal of this Accelerated Development Pathway proposal is to extend the studies to more patients to further assess the potential benefits. New approaches to produce the gene delivery vector and for stem cell processing will be developed and used to support a Phase II clinical trial. Successful use of stem cell gene therapy for SCD has the potential to provide a more effective and safe treatment for a larger proportion of affected patients.

Statement of Benefit to California (provided by applicant)
Development of methods for regenerative medicine using genetically-corrected human stem cells will result in novel, effective therapies that improve the health for millions of Californians and tens of millions of people world-wide. Sickle cell disease (SCD) is an inherited disease of the red blood cells that results from a specific hemoglobin gene mutation. SCD disproportionately afflicts poor minority patients in the State of California, causing severe morbidity, early mortality and high medical costs. We will develop and perform a Phase II clinical trial to evaluate the efficacy of a novel treatment for patients with SCD, using their own adult blood-forming stem cells, after correcting the hemoglobin gene defect. Successful treatment of SCD using adult blood forming “hematopoietic” stem cells corrected with gene therapy may provide a clinically beneficial way to treat SCD with greater safety and wider availability than current options. The clinical trial to be performed will treat SCD patients from across the state of California at Southern and Northern California clinical sites. All scientific findings and biomedical materials produced from the studies will be publicly available to non-profit and academic organizations in California, and any intellectual property developed by this Project will be developed under the guidelines of CIRM to benefit the State of California.

REVIEW SUMMARY
The therapeutic candidate for the Parent Award, and the subject of this application, is an autologous stem cell gene therapy for the treatment of sickle cell disease (SCD). The IND for the Phase 1 clinical trial funded under the Parent Award is approved by the FDA and is on schedule to open enrollment of adult patients with SCD. The production process for the candidate therapy to be used for the Phase 1 clinical trial results in a level of gene transfer to stem cells which is likely to be therapeutic and may decrease disease severity. However, more effective production of genetically modified hematopoietic stem cells (HSC) will be required for the larger, later clinical trials. For this application, three modules of activity were proposed. Module 1 describes activities to improve vector production quality for higher titer and gene transfer activity. In Module 2, the applicant proposes to improve cell processing by enriching HSC to greater purity prior to gene transfer, which could decrease the amount of vector needed. In Module 3, the applicant proposes to combine the results of activities proposed in Modules 1 and 2 to translate the most effective methods for production of genetically modified HSC into a Phase 2 clinical trial for SCD.

Clinical Competitiveness and Impact of the Proposed Therapy
- There is a large unmet medical need for a less toxic, lower risk therapy for SCD.

- If successful, the impact of the stem cell gene therapy could be considerable, as the approach is potentially curative and would allow treatment of patients not eligible for allogeneic HSC transplant.

- Several other competing technologies for SCD are also in early development, some of which may have clear logistical and technical benefits over the proposed approach to treating SCD.

Strength of the Development Program
- The reviewers commended the team for successful filing and clearance of the IND for a first in human stem cell gene therapy Phase 1 clinical trial for SCD. The team has a clear path for evaluating the therapeutic candidate. However, the reviewers thought that the activities proposed in this application would not accelerate the team's overall development program.

- Process development changes are proposed in Module 2 that would select an enriched HSC population for gene modification and subsequent administration in the Phase 2 clinical trial proposed in Module 3. Thus, it is unclear whether the approved Phase 1 clinical trial, which will use the originally characterized stem cell gene therapy, would significantly inform or accelerate a successful Phase 2 trial utilizing a different gene-modified cell product.

- The reviewers raised concerns about the current manufacturing process for the product, which could limit commercial viability of this program.

Qualifications of Development Team
- The team, along with their clinical investigators, is exceptionally qualified and has a strong track record in stem cell gene therapy.

Progress on Parent Award and Effective Program Leadership
- Reviewers agreed that the team has made admirable progress on the activities funded under the Parent Award and have achieved IND approval.

Relevance of the Therapeutic to Regenerative Medicine
- The relevance of the candidate to regenerative medicine is considered to be very high. The proposed gene modified stem cell has proven antecedents and a clear therapeutic rationale for this disease indication. A successful therapeutic could have impact for a variety of related diseases.

Proposed Activities for Acceleration of the Development Program
- Reviewers saw that incorporation of the proposed activities in Modules 1 and 2 could pose major regulatory challenges for the development program. As the

proposed changes in the manufacturing process would result in a different final product than that for which an IND has been approved in the Parent Award, equivalency and safety of the new product would need to be confirmed in preclinical studies, which could have major impact on timelines and progress to clinic.

- Reviewers agreed with the need for improved vector production to achieve higher titer and gene transfer activity. However, there was concern that the approach proposed in Module 1, may not address the underlying limitations of the globin gene vectors. The applicant did not provide sufficient evidence that the proposed scale up process would result in a higher titer vector with increased transduction efficiency and low toxicity.

- Reviewers agreed that improvement in the transduction efficiency of HSC would add value, and were intrigued by the preliminary data presented in support of the work proposed in Module 2. However, reviewers did not see sufficient evidence of a possible mechanism of action for the increased transduction efficiency, which lowered their enthusiasm for the proposal.

- In Module 3, the applicant proposed to expand administration of the candidate therapeutic in a Phase 2 clinical trial to a wider age range of patients. Reviewers commented that this would require further justification and Regulatory review, and they were concerned that the FDA may not agree with the expansion, given that a different level of risk assessment could be appropriate for the additional patient population.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Reviewers did not think that the activities proposed in Modules 1-3 would accelerate progress toward more rapid demonstration of clinical proof of concept for the stem cell gene therapy in SCD.

- Reviewers expressed that the activities proposed in Module 1 were not presented with sufficient clarity and quantifiable success criteria to allow assessment of their feasibility. The lack of a detailed, milestone-based development plan with the external vector production organization was considered a weakness of the proposal.

- Reviewers felt that the applicant has given insufficient consideration to the significant loss and potential damage of HSC that would occur during the extra isolation steps proposed in Module 2. Moreover, some of the reagents and equipment that would be used for the isolation and purification of the HSC are currently unavailable and the success of the project is dependent on the availability of these components. Any delay in their availability would impact the proposed timelines, which reviewers described as already unrealistically aggressive.

- The Phase 2 clinical trial proposed in Module 3 would incorporate the process modifications identified in Modules 1 and 2 and could not begin until after their completion. Under the proposed timeline, the Phase 2 trial is not scheduled to initiate until late 2017 and the planned clinical efficacy data would be collected at 6 months after treatment. Thus, it would not be possible to evaluate the impact of the proposed improvements to accelerate demonstration of clinical proof of concept by 2017, which is a stated goal of this RFA.