CALIFORNIA'S STEM CELL AGENCY

MEMORANDUM

TO: CIRM GOVERNING BOARD
FROM: CIRM LEADERSHIP
SUBJECT: CLIN2-11431 Applicant Response to Subcommittee Questions
DATE: FEBRUARY 2019

At the January 30, 2019 meeting of the Application Review Subcommittee, the Subcommittee deferred consideration of application CLIN2-11431 to allow the applicant and CIRM to provide additional background information. Specifically, the Subcommittee was interested in understanding the scope of work, progress-to-date, and use of funds for the active Disease Team Award, which has funded preclinical and clinical activities that the CLIN2-11431 proposal intends to complete. Additional clarification was also requested regarding the alignment of the two projects, number of patients to be treated, the contribution of co-funds by the applicant, and the contingency plan described in the application.

Appended to this memo is the response from the applicant to the following questions posed by CIRM:

1. Describe how remaining funds from the Disease Team Award and required co-funding will be utilized. Describe whether co-funds have been secured and source of co-funds.
2. Describe how the already expended funds for the Disease Team Award were utilized and how they align with the budget and activities that were originally proposed, particularly for the phase 1 trial. Describe any delays, including the cause and impact on the progress of the project to achieve completion of the trial.
3. Provide a high-level, activity-based justification for the additional funds requested in the CLIN2-11431 application to complete the phase 1 clinical trial.
4. Justify the intended total number of patients to be enrolled for the phase 1 trial, including how many are covered by the Disease Team Award versus the new proposal.
5. Provide a plan for advancing the therapeutic candidate through the phase 1 clinical trial and steps anticipated to ultimately commercialize the product

The applicant has also submitted several letters in support of the proposed project.

CIRM Disease Team DR2-05365

1. *Describe how remaining funds from the Disease Team Award and required co-funding will be utilized. Describe how remaining funds from the Disease Team Award and required co-funding will be utilized. Describe whether co-funds have been secured and source of co-funds.*

A total of $19,068,382 was awarded to the Disease Team in June 2013. The funds were used to translate promising studies shown in mice to a clinical trial for patients with the bubble boy disease (severe combined immunodeficiency [SCID]) in order to replace chemotherapy with a non-toxic protein (antibody) that targets the molecule called CD117. The Team successfully achieved the goal of translation from mouse studies, and has treated the first six (6) patients on the clinical trial. The results in these patients look very promising and they show marked clinical benefit from the treatment.

$500,000 of CIRM funds remain. These remaining funds will be used to follow the health of the treated patients and monitor laboratory studies. As stipulated by CIRM, the Team agreed to raise an additional $2.3M from co-funding sources in order to continue treatment of patients on this trial. The team successfully raised $550,000 which has been used to support the ongoing clinical trial activities. Further co-funding of $ 1.75 M will be used to continue to enroll more patients onto the study so that an optimal dose of the antibody for achieving engraftment is determined. Co-funding will also be used to offset the cost of maintaining the therapeutic antibody on a stability program and support the opening of other treating centers to accelerate the accrual of patients to the study. Co-funds have not yet been secured. However, potential sources include the NIH where grants by the Principal Investigator (PI) are currently under review, other funding agencies and philanthropic support. Moreover, to ensure the continued advancement of the development of this anti-CD117 antibody as conditioning regimen in combination with blood stem cell transplantation, the PI is in the process of commercializing the program. Active advanced negotiations are ongoing with investors, one of whom has submitted a letter of support regarding an intention to co-fund pending completion of due-diligence.

2. *Describe how the already expended funds for the Disease Team Award were utilized and how they align with the budget and activities that were originally proposed, particularly for the phase 1 trial. Describe any delays, including the cause and impact on the progress of the project to achieve completion of the trial.*

Utilization of Funds

The aim of our Disease Team Award was to develop a protein, an antibody, that binds a molecule called CD117, to replace toxic chemotherapy and radiation for the purpose of permitting donor blood stem cells to permanently engraft in children with the lethal bubble boy disease called severe combined immunodeficiency (SCID). In addition to its capacity to bring safer curative therapy to children with SCID, this antibody has the potential to positively impact the treatment of many other disorders including but not limited to diabetes, sickle cell disease, cancers of the blood, and AIDS/HIV. The team launched its program based on promising studies in mice that showed that targeting CD117 with an anti-mouse CD117 antibody, together with transplantation of purified donor blood stem cells, resulted in a safe and effective cure of the mouse form of SCID. The Team's focus was to translate this discovery to a human clinical trial, which it accomplished. We are very happy to report that the early data from the clinical trial show both safety and effectiveness of the antibody in allowing donor stem cells to engraft in SCID patients. These results are being presented at international scientific meetings and have been met with high enthusiasm from world-renowned experts. We include with our responses, letters we have received from such experts affirming the importance of this trial, particularly in light of the emerging clinical data. Table 1 shows the notable achieves achievements accomplished by the Team during the period of funding.

In order to translate the mouse studies to a human trial several phases of development were required and were divided into 4 major activities as shown in Table 2. Table 2 shows activity type, detail of what was performed, and original budget and actual dollars spent to date. We note that subsequent CIRM awards now divide these phases into distinct awards, i.e., Tran 1, Clin1, and Clin2. We wish to emphasize that our Team accomplished all of these phases under a single award.

Table 1: Disease Team DR2-05365 – Achievements

- **Translated from mouse studies to human clinical trial a first-of-its kind anti-CD117 therapeutic antibody to replace toxic chemo/radiation for blood stem cell transplantation**
- **Clinical trial results to date show safety and efficacy in children with the bubble boy disease (severe combined immunodeficiency [SCID]). These results will apply to the 3 other CIRM funded gene therapy trials for SCID as non-toxic anti-CD117 conditioning will improve the safety of those therapies as well**
  - Trial provides proof-of-concept this anti-CD117 antibody is a platform therapy that will lead to new treatments for many other conditions including: diabetes, kidney transplantation, myelodysplastic syndrome (MDS)* and acute leukemias, sickle cell disease, and HIV/AIDS
- Preclinical studies led to discoveries:
  - Potency of anti-CD117 antibody increased when combined with other antibodies – a strategy being pursued by commercial entity Forty-Seven. Forty-Seven originated from CIRM funding
  - Antibody is active against leukemia causing stem cells – an IND has been approved for our team to test if the anti-CD117 antibody can improve cure of patients with MDS* and acute leukemia
- Developed two GMP-clinical grade antibodies that permit purification of blood stem cells. Applications extend to other conditions, including gene therapy, cancers, autoimmune disorders

*MDS is a group of disorders in which diseased stem cells result in failure to make healthy blood and/or transform to leukemia. >10,000 new cases/year in US. MDS primarily affects elderly (>65 yrs). Blood stem cell transplantation is the only cure.

Table 2: Disease Team Activities, Project and Actual Costs

Activity	Description of Activities Achieved	Budget	Actual
Chemistry, Manufacturing and Controls (CMC)	Tech transfer, pilot batch production, ongoing stability testing of anti-CD117 therapeutic antibody. Cell line development, production, ongoing stability testing of 2 GMP-grade antibodies for sorting purified stem cells. Milestones reached on time.	$ 3,100,000	$ 4,200,000
Research/ Pharmacology	*In vitro* and *in vivo* studies, PK, PD, dose finding, safety, MOA, IND enabling and discovery studies Milestone reached on time.	$ 4,160,000	$ 2,900,000
Safety and Clinical Pre-IND	IND enabling human studies including PK assay, stem cell isolation validation), pre-IND and IND filing Milestone reached on time per Amended NOA. IND approved.	$ 3,000,000	$ 3,100,000
Clinical trial:	Patient recruitment, screening, enrollment. Patient treatment, monitoring, laboratory studies, travel, data analysis and data management. Clinical operations including site initiation, site management and monitoring, safety management, reporting. Delays encountered in Clinical Trial Phase.	$ 5,200,000 (Stanford - $3.8M/UCSF - $1.4M)	$ 5,500,000 (Stanford - $4.1M/UCSF - $1.4M)
Facilities and Indirect costs	Institutional operational costs	$ 3,600,000	$ 2,850,000
	Subtotals	$ 19,060,000	$ 18,550,000

CIRM Disease Team DR2-05365

Delays and Impact on progression to complete study

Delay at the pre-IND/IND stage:

Prior to clinical trial approval, progress on the pre-IND/IND submission was delayed by CIRM for 8 months through holding of funds based on concerns raised by the Clinical Development Advisory Panel (June 2014). The panel noted the following:

- concerns the IND would not be approved by the FDA given the complexities of the clinical trial of incorporating a conditioning anti-CD117 antibody plus purified CD34+CD90+ stem cells
- lack of utility for an CD117 antibody for transplant given "newer approaches", specifically low dose Busulfan and newer related chemotherapy agent, Treosulfan
- the use of anti-CD117 antibody alone may be limited to immune incompetent individuals. The Team was directed to consider refocusing trial design efforts and discussions with the FDA on a combination antibody conditioning approach of anti-CD117 with the novel anti-CD47 antibody which the PI had demonstrated looked promising in mice

A compromise position resulted in a two stage design for the ultimate FDA approval with anti-CD117 antibody initially being tested as a dose escalation with standard-of-care CD34+ grafts for the first group of patients, with a crossover to a second sub-cohort using the optimal dose of CD117 antibody with grafts of purified CD34+CD90+ that have minimal T cell contamination. This delay, which required justification to CIRM for use of the anti-CD117 as a single agent, trial redesign including consideration of CD117 plus CD47, FDA consultations, and renegotiation of milestones, resulted in an 8 month delay. The Award was amended in June 2015 with new milestones after the Pre-IND meeting in which the FDA agreed with the planned strategy of anti-CD117 antibody with CD34+CD90+ grafts. The Team met the milestone of IND approval in accordance with the Amended Award.

Delay at the clinical trial stage:

Progress was delayed at the clinical trial stage for three major reasons.

(1) The Institution Review Board (IRB) enforced an age restriction on our protocol, requiring that the first two patients treated be >18 years and undergo a 100 day waiting time for each before treatment of children <18 were allowed, as approved by the FDA. Because of SCID is a rare disease, and SCID patients >18 years in need of a re-transplant are extremely rare, this rule made it prohibitively difficult to enroll a first patient. After months of attempting to recruit in this age range the team appealed to the IRB who agreed to allow patients >12 years. Because most SCID patients in need of re-transplant are <12 years, the team subsequently worked with the FDA and lRB to reduce the age range cut-off for the first Group to >2 years. The first patient was enrolled and treated a month after the age restriction was reduced. This delay time was approximately 9 months.

(2) Significant delay was the result of 3 competing trials for patients with SCID which opened during the same time period as our study. Because SCID is a rare disease these competitive trials lengthened the time of recruitment. Two of the competing trials are funded by CIRM, and our co-investigator is PI of one of the studies and co-Investigator on another. Although all three trials use the chemotherapy Busulfan, a stem cell niche clearing agent with resulting health risks for pediatric patients, the anti-CD117 trial had not yet proven its safety or efficacy. Hence, during the initial stages of our trial physicians and patient families directed many patients to these competitive trials. With the promising medical safety and efficacy data on the anti-CD117 trial, our trial is now clearly competitive and may even be preferred because of the avoidance of Busulfan to patients. The time impact on patient recruitment is estimated at 12 months.

(3) Reticence on the part of parents and physicians to enroll pediatric patients onto a safety study **and to be the first child to receive the antibody** factored into the delays. Candidate patients and parents held back their participation, until safety and efficacy were demonstrated. As noted, enrollment has accelerated as news of safety and efficacy has reached the transplant community. Currently 2 subjects are waiting to enroll in next dose cohort pending DSMC review. 2 more are undergoing screening.

3. *Provide a high-level, activity-based justification for the additional funds requested in the CLIN2-11431 application to complete the phase 1 clinical trial.*

Budget total: $5,999,982

Funds will be used to continue follow up care and monitoring of the 6 patients treated on study to date and to enroll, treat, provide follow up care and monitoring of an additional 18 patients. The team will provide safety oversight, data generation and analysis, and data management. The 18 patients will be enrolled and treated through Year 2. All patients will be monitored for two years after their treatment. There are 7 major activities:

Activity	Description	Budget
Clinical Trial Site: Patient study related activities	Pre-transplant and Transplant: Screening assessments, antibody infusion and cell transplant, PK (measure antibody in blood), shipping patient samples, hospitalization, patient travel and lodging Post-transplant follow up: physical exam, laboratories and special tests, patient travel and lodging	$1,771,746
Medical and Scientific Services	Clinical site management and monitoring, safety CRO, clinical data processing and data management, biostatistical services	$547,000
Study Management	Study oversight of patient safety, treatment and monitoring, research laboratory tests including processing, data analysis and interpretation. Implement changes in study design. Oversee opening and training of personnel on clinical sites.	$1,376,200
Regulatory	Oversee and implement interactions with FDA and IRB. Communications include but not limited to annual IND updates and investigator brochure, implementation of protocol amendments,	$360,000
Clinical Trial Meetings, Travel and Publications	Data Safety Management Committee meetings; meetings of clinical and research teams to assess trial results; staff travel to meetings to present trial results; advertisement and outreach; publication costs	$38,000
CMC: Antibody Stability and Storage	Storage and stability testing to ensure integrity of study drug (therapeutic antibody) and two GMP antibodies for sorting of blood stem cells.	$440,000
Facilities and Indirect costs	Facilities operational costs	$ 1,457,036

4. *Justify the intended total number of patients to be enrolled for the phase 1 trial, including how many are covered by the Disease Team Award versus the new proposal.*

The intended total number of patients to be enrolled on this Phase 1 trial is 24. The goal of the study is to determine if the anti-CD117 antibody can replace chemotherapy and safely and effectively allow engraftment of purified donor stem cells in children and babies with SCID. There are two patient groups which are divided based on age and prior transplant history. The first group to enroll is comprised of children >2 yrs of age and who were previously diagnosed and underwent a transplant as infants. The second group is comprised of babies who are newly diagnosed with SCID. The reason for the two groups is based on safety concerns: The first group is older and considered more clinically stable than the newborns. Patients in this first group previously had donor stem cell infusions but because their donors' stem cells did not permanently engraft, their immunity is poor and they require life-long infusions of immunoglobulin. In order to boost their immunity they are given a re-transplant on this study.

The study is designed as a "3+3" dose escalation with a "Crossover " arm. There are 3 increasing doses of the antibody and 3 patients in each dose cohort. This trial design of 3 patients starting at relatively low antibody dose is to test that the antibody is safe in at least 3 patients before increasing to the next dose level. The study aims to determine among 3 doses which dose is the best in terms of safety and giving therapeutic benefit. Patients receive "standard" donor stem cell grafts following antibody treatment. The older children are enrolled first. If the antibody is safe at the first dose level then treatment of the newborns is allowed to commence. Hence, 18 patients will be tested in this part of the study. Patients are also monitored for success in achieving donor cell engraftment as the antibody dose increases. An optimal dose of the antibody is chosen based on the safety of the dose and the level of donor engraftment achieved. The study then crosses over to use the optimal antibody dose with transplantation of grafts of purified donor stem cells. The goal of the crossover is to determine if the purified stem cells engraft equally or better than standards grafts and have fewer side effects compared to standard grafts. For this part, in the older patient group, it is estimated that 3 patients will undergo re-transplant and that 3 patients in the newborn group will undergo transplantation.

Under funding of the original Disease Team award, 6 patients in the first re-transplant group have been treated to date. We propose to treat 18 patients under the new proposal to complete the study. In the first 6 patients the antibody has been shown to be safe at the first two doses and the next and final dose will be tested in the next re-transplant cohort. The Team has been excited to report that we are seeing evidence of successful engraftment in these patients and that health of these first patients has improved with the treatment. Our results have been reported at international scientific meetings. Global medical and scientific experts on SCID transplantation are aware of our early results and their letters of support (attached) attest to the importance of this study for these patients and many others because the anti-CD117 antibody has the potential to eliminate the organ damage caused by chemotherapy.

5. *Provide a plan for advancing the therapeutic candidate through the phase 1 clinical trial and steps anticipated to ultimately commercialize the product.*

Commercialization Plan

The first step in the commercialization of anti-CD117 antibody is the continuation of this CIRM funded phase 1 trial for severe combined immunodeficiency as well as to initiate additional trials for additional oncology and gene therapy indications. The PI and colleagues have founded a company to commercialize the anti-CD117 antibody. We are in active discussions with investors and industry experienced advisors to refine the clinical development plan as well as actively pursuing discussions with the FDA to define the most appropriate accelerated path to regulatory approval.