CALIFORNIA'S STEM CELL AGENCY

TO: Members of the ICOC

FROM: Gil Sambrano, Ph.D., Director Portfolio Development and Review

DATE: May 9, 2016

RE: CIRM recommendation on application TRAN1-08522

BACKGROUND

Following the GWG review of Translational Program Applications on February 11-12, 2016, CIRM learned of circumstances that could materially impact on the potential success or failure of the product proposed under application TRAN1-08522, which was recommended for funding by the GWG with a score of 87. On March 7, 2016, the company sponsor of a Phase 3 clinical trial published a press release indicating that its clinical trial in newly diagnosed glioblastoma patients had been discontinued because interim analysis revealed it unlikely to meet the primary endpoint of overall survival. The product under investigation in the Phase 3 trial is the first generation version of the product proposed for development in application TRAN1-08522. The proposed second generation product is presented by the applicant as a better optimized and more robust vaccine based on survival in an animal model of cancer.

PROCESS

CIRM contacted the applicant and the applicant agreed to postpone ICOC consideration of the application to allow CIRM to obtain input from the GWG to inform CIRM's recommendation to the Board. CIRM provided the applicant an opportunity to prepare a written response to the GWG regarding the impact of the press release on the potential development of the proposed product. The press release and the applicant's response along with letters of support from company sponsors were provided to the GWG panel that participated in the February 11-12 review. The same panel convened by teleconference on April 26 to discuss and advise CIRM about the impact of the press release on the project.

TRANSLATIONAL

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08522
Title (as written by the applicant)	2nd Generation Vaccine for the Treatment of Glioblastoma
Translational Candidate (as written by the applicant)	It is a peptide conjugated to KLH and used as an anti-cancer vaccine.
Area of Impact (as written by the applicant)	This is a better optimized, more robust vaccine that aspires to greatly improve glioblastoma patient survival over the current vaccine.
Mechanism of Action (as written by the applicant)	The vaccine stimulates B cell and T cells. We have found this may be mediated through more extensive processing of our candidate by the proteasome. Once these immune system cells are stimulated, they will attack tumors expressing EGFRvIII.
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common and deadly brain tumors: median survival is only 14-16 months and five-year survival of 9%. Therapies are desperately needed to significantly prolong survival. Our 2nd generation vaccine shows a 2-fold increase in survival over a vaccine that has already shown promise.
Project Objective (as written by the applicant)	Pre-IND meeting and readiness for GMP manufacture.
Major Proposed Activities (as written by the applicant)	• Synthesis of the peptide under GMP-like conditions and conjugation of the peptide to KLH under GMP-like conditions. • Confirming structure and biologic activity of the conjugate, and confirming it has an excellent safety profile in toxicology tests. • Planning meetings with the FDA and then preparing the Phase I trial protocol in anticipation of filing IND
Statement of Benefit to California (as written by the applicant)	Californians will benefit from this research project in several significant ways. The research will take place in California and directly benefit the economy through hiring of employees and purchase of supplies and reagents. If the therapeutic is successful, it will extend the long-term survival rates for Californians with glioblastoma. If it is commercialized, profits derived from the vaccine will further improve the California economy and lower costs to uninsured patients.
Funds Requested	$2,929,889
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

TRANSLATIONAL

Final Score: 87

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

Median	90
Standard Deviation	7
Highest	90
Lowest	65
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	12
Tier 2 (1-84): Not recommended for funding.	2

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	0	5
Is the rationale sound?	9	0	5
Is the proposal well planned and designed?	10	0	4
Is the proposal feasible?	10	0	4

Reviewer Comments

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

Strengths

- Glioblastoma represents an important and unmet medical need.
- This approach could also be relevant to other tumors, thereby increasing its potential for impact.
- There is a very well thought out plan. A strong scientific rationale supports the proposal.
- The proposal included excellent preliminary data.
- This is a great team that has achieved significant accomplishments.

Concerns

- KLH- peptide approach may not work in the immune privileged environment of the brain. Peptide based vaccine will not work for a glioblastoma vaccine. Previous studies with different cocktail of peptides failed.

Additional Comments

- No relevant comments were made by the GWG.

CALIFORNIA'S STEM CELL AGENCY

GWG ADVICE

Overall GWG reviewers agreed that the report of the failure of the Phase 3 trial using the first generation product does not affect their review and recommendation to fund the project. Reviewers reiterated that this is a risky proposal and the reported termination of the Phase 3 trial on the first generation product confirms the high-risk nature of an immunotherapy approach. However, reviewers also felt that it is important to support the continued development of better optimized products since the drug target still holds promise and there is a great unmet medical need for patients with glioblastoma. It was also pointed out the the control arm of the study performed much better than in most trials and therefore it is difficult to interpret outcomes from the Phase 3 trial at this time. The applicant has proposed development of a second generation product that reviewers believe to be a significant improvement over the first generation product and therefore, worth pursuing.

CIRM RECOMMENDATION

CIRM recommends funding this application.