STANFORD UNIVERSITY

DEPARTMENT OF NEUROSURGERY
BRAIN TUMOR RESEARCH LABORATORIES

April 22, 2024

California Institute for Regenerative Medicine
601 Gateway Boulevard
South San Francisco, CA 94080

RE: Review of CLIN1-14852 "IND-enabling Studies for a 2nd Generation Vaccine Targeting Glioblastoma"

To the Application Review Subcommittee:

Thank you for this opportunity to address the recent review of our application. We have been dedicated to improving patient survival for glioblastoma, one of the most incurable human tumors. Our group discovered and pioneered a vaccine therapy against a common mutation in glioblastoma. Overall, the reviewers thought our project had significant potential:

- The project proposes a therapy which would meet an unmet medical need for the treatment of glioblastoma. Considering the previous experience from the group and direction of success, the proposed approach is likely to provide advancements from the current standards of care.
- Overall the peptide-based vaccine approach should provide a significant value proposition relative to other more complicated gene therapeutic based approaches which have potential for larger development and production costs.

Unfortunately, the project received a Tier 3 recommendation which was due to several comments that impacted a fair review of this application. In this letter and my public remarks at the ARS subcommittee meeting, I will address the problematic nature of these comments, illuminate why our work is highly meritorious and likely to provide a significant advance for the treatment of glioblastoma.

To briefly highlight the rationale underlying this project:

- A mutation of the EGF receptor that we discovered is commonly found in glioblastoma, called EGFRvIII. Others and our group have shown this to be present and essential to glioblastoma cancer stem cells (Emlet et al.[(1)]). It is now the target of several immunotherapies, including an anti-cancer vaccine we developed.
- We were funded by a Translational I award (reviews on p. 13-15) for pre-IND work to develop a more robust version of the vaccine, called Y6-pepvIII. This work was significant and published in a major scientific journal (Fidanza et al., Science Translational Medicine[(2)]) where it improved survival by 31% over the original vaccine and illuminated a new approach for improving all vaccines.

- In this CLIN1, we proposed GMP manufacture of and other work leading to IND approval, plus studies to ensure bioactivity and to develop patient monitoring assays based on our extensive experience with the original vaccine.
- We plan a Phase I trial to confirm safety and ultimately leading to a Phase II using a trial design that has already shown significant survival for recurrent glioblastoma

Nearly all of the reviewer's comments fall into 6 topics. To avoid redundancy in this discussion, we have arranged comments according to those topics and indicated the original review criteria section of that comment. (The original GWG review is on p. 12; our DEI score is strong, so it is not discussed here.)

Topic 1: EGFRvIII in Cancer Stem Cells

GWG Review:

1. (Rationale) The proposal provides evidence from previous clinical experience with the earlier generation of the peptide conjugate which supports the clinical rationale for the improved construct. However, the case for the proposed peptide to target cancer stem cells (CSCs) needs more supporting data.
2. (Rationale) No evidence for targeting of CSCs.
3. (Rationale) Animal data, including the materials used to manufacture product for nonclinical studies, does support continued evaluation of the candidate for development. Demonstration of the vaccine's impact on target cells is not clear and additional in vitro data would be helpful to support the product.

Rebuttal:
1 and 2) Substantial data was provided in the CLIN1 application (pp. 19-21) based on our publication, Emlet et al.[(1)] that EGFRvIII is an essential component of the cancer stem cell population in tumors expressing this molecule. In this paper, we also show that a bispecific antibody targeting CD133/EGFRvIII substantially eliminated the glioblastoma CSC population and decreased tumorigenesis—space limited us from presenting that data in the application. Moreover, we have a 2nd publication showing that EGFRvIII forms a stem cell hierarchy in glioblastoma and in a 3rd publication that it is a component of breast cancer stem cells, further reinforcing that EGFRvIII is a component of CSC (Del Vecchio et al.[(3)] and [(4)]).

The publication by Emlet et al has been cited at least 115 times, and at least 12 papers have confirmed and extended these findings, and that bibliography is shown on p. 16.

Another factor is that activation of the EGF receptor by EGF has been an essential component of neural stem cell media since their discovery in 1992. This is well known in the stem cell community with several hundred publications to support this fact. EGFRvIII is a constitutively active form of the EGF receptor present in glioblastoma.

The Translational I project, which was based on our 2nd generation vaccine targeting EGFRvIII glioblastoma CSC and was based on the data in Emlet et al., was highly rated by the GWG.

Thus, there is an overwhelming body of evidence and the prevailing notion is that EGFRvIII is an essential component of cancer stem cells in glioblastoma, to which the GWG concurred by approving the Translational 1 application.

3) Regarding the "vaccine's impact on target cells," this was indeed studied in our Science Translational Medicine paper[2] and this data is presented in Figure 6 in the proposal (p. 25, see below). In addition, the effect of vaccine on EGFRvIII+ cells have been studied in our previous animal study[5], and by Heimberger et al.[6] in their animal vaccination study. Three clinical trials studied the effect of vaccine on these cells as summarized in the Clinical Studies section of the proposal (pp. 33-34). Thus, the effect of the vaccine on EGFRvIII+ cells is well documented.

Screenshot from p.25 of CLIN1 application

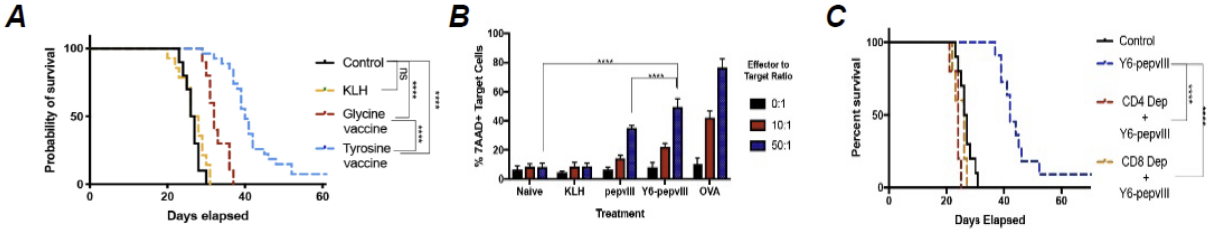


*Fig. 6. A) Overall survival of GL261/vIII tumor bearing mice after vaccination (Log-rank; n= 10 Montanide control, 14 Montanide+KLH, 10 Montanide + pepvIII, and 27 Montanide + Y6-pepvIII). B) Cytotoxic T cell killing assay assessing cytolytic capacity of T cells from KLH, pepvIII, and Y6-pepvIII vaccinated mice against GL261/vIII. See STM paper Fig. 2C for assay against GL261 cells. C) Effect of vaccination in CD4 and CD8 T cell depleted GL261/vIII tumor bearing mice (Log-rank; n= 10 KLH+Montanide, 11 Y6-pepvIII+Montanide, 5 CD4+ T cell depleted, and 5 CD8+ T cell depleted). Bars represent mean±S.D. denotes ***p<0.001, ****p<0.0001.*

Topic 2: EGFRvIII and EGF receptor are not good targets in glioblastoma

GWG Review:

1. (Rationale) Tumor peptide vaccines targeting EGFRvIII have shown equivocal clinical activity.
2. (Rationale) EGF receptor targeting has been somewhat disappointing in glioblastoma.
3. (Rationale) Unclear if targeting EGFR with immunotherapy approaches will really have benefit in the brain.

Rebuttal:

1 and 2). The vaccine targeting EGFRvIII (pepvIII/KLH, generic name Rindopepimut) has shown success in 5 clinical trials and only one trial has shown equivocal activity. Two of these successful trials are fully randomized and blinded and discussed in the application. In the ACT IV study[7], patients with residual tumor (>2 cm^3) were enrolled as a pilot but patient enthusiasm was significant resulting in ~170 patients being accrued in control or vaccine arm (163 and 175, respectively). This revealed an extremely significant HR for 2 year OS (HR=.79, p=0.029) (Fig. 1A); unfortunately, the ad hoc nature of the trial prevented this data from being used for registration with the FDA. In the ReACT Phase II trial for recurrent glioblastoma[8], there was a significant improvement in OS observed for the rindopepimut arm plus bevacizumab (Avastin) (Fig. 1B; HR=0.53; 95% CI, 0.32–0.88; P=0.01). The 24-month survival rate was 20% (95% CI, 9%–35%) for rindopepimut as compared with 3% (95% CI, 0%–12%) for control (P= 0.0179). Significantly, this trial received "Breakthrough Therapy" designation from the FDA enabling a rapid approval process. The only equivocal trial was the ACT IV trial for minimal residual disease in newly diagnosed patients.

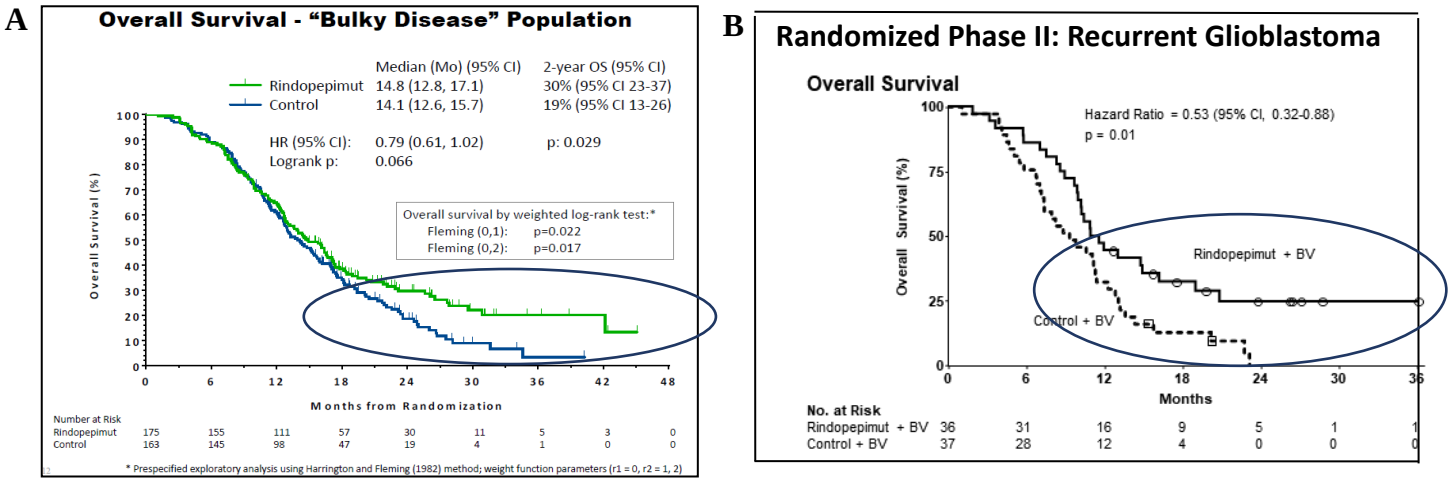
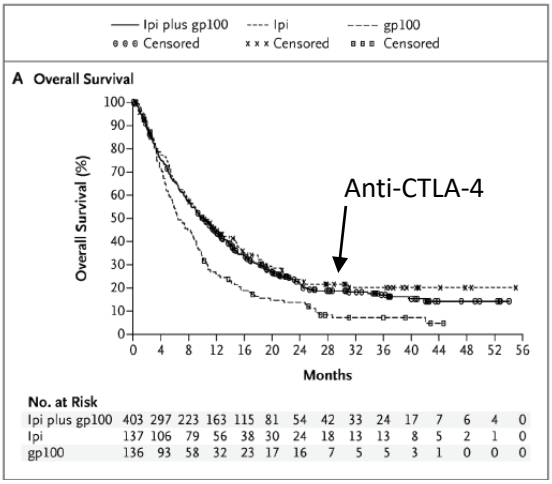


Figure 1. **A**, Kaplan-Meier curves in the bulky disease population from the ACT IV trial. **B**, Kaplan-Meier curves from the ReACT trial for recurrent glioblastoma. Both trials show increased clinical benefit for the vaccine (Rindopepimut) treated arm.

Celldex Therapeutics, the commercial sponsor, despite the clear positive signals from these two trials, had no funds remaining to pursue either the bulky disease or recurrent glioblastoma indication. Moreover, the patent on the original vaccine had expired ruling out any subsequent investment by other companies. As such, the failure to pursue pepvIII is more related to finance than science. There is a current patent on the 2nd generation vaccine which will enable future investment.

Not mentioned anywhere in the review is the fact that Y6-pepvIII is an improved, more robust version of Rindopepimut. Fig. 6A of the application (screenshot on p. 3) shows the greatly improved survival by this 2nd generation vaccine.

There is no question that anti-CTLA-4 antibodies have catalyzed the tremendous enthusiasm for cancer immunotherapy. It is worth noting that two of the four initial Phase III trials for this drug failed, illustrating that the correct indication is vital. However, the company sponsor (Medarex/BMS) had the resources to run multiple trials resulting in the approval of this drug and ushering in the era of immunotherapy. One wonders if a smaller company had run a single initial trial and failed where the field of immunotherapy would stand today.



It is worth noting that in the original report of the success of anti-CTLA-4 therapy in the New England Journal of Medicine[9], there is a similarity in the improvement in OS and long term survival to the ReACT trial (Fig. 2). As we mention in the application, we hope to combine Y6-pepvIII-pepvIII with bevacizumab in a Phase II trial.

Figure 2. Effect of anti-CTLA-4 (ipi) treatment on melanoma patients. Data is from the registration trial for approval of ipilimumab

3) With respect to whether targeting EGF receptor has been of benefit in glioblastoma, recently there have been two reports of EGFRvIII and EGF receptor targeting in immunotherapy for glioblastoma. Using simultaneous targeting of EGFRvIII and EGF receptor, there is heretofore unseen dramatic regression of tumor within 1-5 days by MRI in the 3 patients presented which merited publication in the New England Journal[(10)]. The second report in Nature Medicine[(11)], another highly cited journal, also showed unexpected regression in the first 6 patients treated. It should be noted that both modalities were CAR T cells, which had been thought to be not amenable to solid tumors, and these are the 2nd generation therapies where the first clinical trials were equivocal. Thus, a previously unsuccessful approach and target was enabled by further research, much as we are doing with our 2nd generation vaccine.

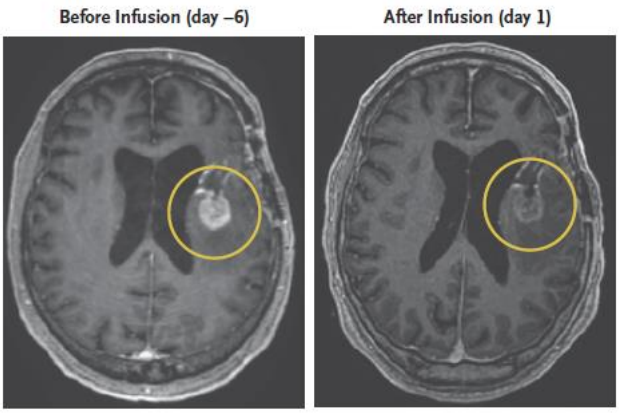


Figure 3. Dramatic regression in one day of glioblastoma in 74 y.o. man with EGFRvIII+ recurrent glioblastoma using EGFR/EGFRvIII targeted CAR T cells.

Topic 3: Toxicology

GWG Review:

1. (Rationale) The justification for single dose in toxicological study is unclear.
2. (Plan/Design) The rationale for the proposed tox study design was not provided, including dose and regimen to support proposed clinical protocol.
3. (Plan/Design) The FDA denied a pre-IND based on previous pre-IND for a similar product. No information was provided regarding recommendations from the previous program.
4. (Plan/Design) It is unclear what material is intended for use in the toxicology study; importantly if similar process will be used compared to the clinical process.
5. (Plan/Design) The proposed toxicology study is not sufficiently justified nor does the protocol that was provided make sense. Sacrifice is proposed for Groups 1and 4 at day 11 (but there is no Group 4), a control only group is proposed for sacrifice on Day 39. Toxicokinetic studies are mentioned but no animals are included for this purpose. Pretest serum for antibodies not generally collected in mice. Days of scheduled sacrifice are not generally on the day of the last dose.

Rebuttal:

1 and 2). There are multiple misstatements regarding toxicology. Our toxicology plan is clearly stated in the proposal and involves a single animal species at various doses. It is based on our extensive experience with this product as Dr. Wong is a co-holder of the first IND for the pepvIII vaccine. We state the current plan is modeled directly after the toxicology studies that Celldex performed in consultation with the FDA.

Screen shot from p. 36 of the CLIN1 application indicating our experience with the FDA for the peptide vaccine

The drug itself is the peptide LEEKKYNYVVTDHC conjugated 1:1 with KLH. This represents the 13 a.a. peptide derived from the EGFRvIII junction with novel glycine substituted by tyrosine and a C-terminal cysteine for conjugation purposes. Because it is a vaccine, this molecule is considered a biologic by the FDA and its review will be handled by the Center for Biologics Evaluation Research (CBER) division. CBER has extensive experience with peptide vaccines for INDs related to cancer therapy. We also have experience from our work on filing an IND for the first Phase I clinical trial to test the original anti-EGFRvIII vaccine. Peptide vaccines have significant advantages over other biologics such as cell products or cellular derived products, and even small molecules.

The production of the peptide can take place on standard peptide synthesizers involving standard amino acids. Because the goal of the vaccine is to be taken up locally by dendritic and other immune cells, it is given intradermally and does not reach the blood stream. Thus, there has been no need for ADME studies. Multiple dosing studies are not required because it has been found that one dose (500 µg) given monthly is sufficient to trigger an immune response in many trials; more peptide conjugate does not elicit a stronger response. In general, peptide vaccines have an excellent safety profile and one species for toxicology studies has been sufficient.

Screen shot from p. 38 which indicates our plan for toxicology and the rationale for single dose and regimen based on Celldex's experience with their most recent IND filing.

Toxicology
Specific objective: The toxicologic effect of high doses of the vaccine with repeated dosing will be assessed on rats (30ug for rats, compared to 500ug for humans; ~66.7ug/kg for rats compared to 6.7ug/kg for humans). Our study design is nearly identical to that used for the IND filing for pepvIII by Celldex, the company sponsor (who called the drug CDX-110) in their phase II/III studies. This showed almost no adverse effects except for local lymphocytic infiltration (see Appendix). Our pre-clinical work on Y6-pepvIII used even higher doses in mice (up to 3mg) and did not show any significant adverse effects.
Dates of Project: Q5-Q6
Backward and Forward Dependent Studies: This will be performed on vialed product provided it passes sterility studies.
Need for CIRM Funds: Funds requested to support all of the activity.
Location: CRO within California

3). We submitted our request for a pre-IND meeting to the FDA along with our pre-IND package (this was included in the original CLIN1 proposal). This request was turned down citing our prior experience (note: critique states our pre-IND was denied, it was the meeting that was turned down) and thus the FDA is confirming our plans for toxicology. One remark concerns the recommendations from the previous program, which was not included since the CLIN1 application requests current FDA comments. It also did not seem relevant given we are corresponding with the FDA regarding the present program.

Screen shots from pages 42 and 43:

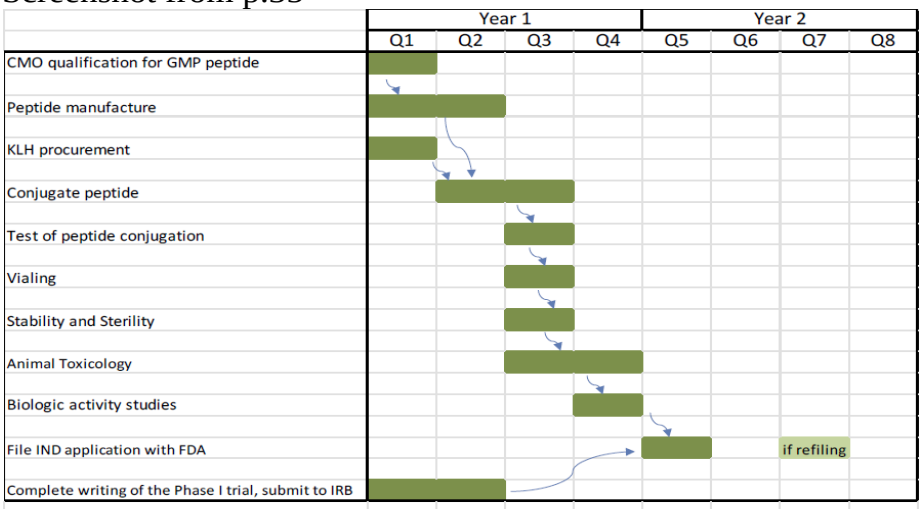
Three different IND applications based on pepvIII have been submitted and successfully approved. The PI of this proposal was co-investigator on one application, the other two were industry sponsored. Celldex Therapeutics had submitted the most recent IND application to the FDA. From our work in commercializing pepvIII, we transferred our experience to the clinical and scientific team at Celldex. Thus the Y6-pepvIII peptide was synthesized under similar cGMP conditions and we obtained KLH from the same source and performed similar SMCC conjugation. Based on previous experience with the low incidence of side effects from other INDs related to peptide vaccines, the FDA recommended similar animal toxicology studies for these three previous applications. In further consultation with Dr. Lawence Thomas of Celldex, who was primarily responsible for the animal studies in the latest Celldex IND submission for Rindopepimut, we performed animal toxicology studies and biologic activity studies that mirrored what was performed by Celldex.

On August 16, 2019 we submitted our pre-IND meeting request along with the pre-IND package including data justifying scientific rationale for Y6-pepvIII and animal toxicology studies showing no significant reactions to Y6-pepvIII. On August 29, 2019 the FDA informed us that the pre-IND meeting request was unnecessary due to our "antecedent experience with the similar product." Thus, there were no regulatory concerns regarding our package.

Our plan will be to synthesize Y6-pepvIII and conjugate to KLH under GMP conditions, perform necessary sterility, toxicology and biologic activity assays and then submit the IND package to the FDA.

4) Concerning the remark regarding what "material is intended for use in the toxicology study; importantly if similar process will be used compared to the clinical process." Our flow chart and project narrative states that there will be only one product, the Y6-pepvIII/KLH conjugate that will be used for toxicology and is the subject of the IND.

Screenshot from p.35



5). The final comment is extremely problematic: "The proposed toxicology study is not sufficiently justified nor does the protocol that was provided make sense. Sacrifice is proposed for Groups 1 and 4 at day 11 (but there is no Group 4), a control only group is proposed for sacrifice on Day 39. Toxicokinetic studies are mentioned but no animals are included for this purpose. Pretest serum for antibodies not generally collected in mice. Days of scheduled sacrifice are not generally on the day of the last dose." We do not propose 3 or 4 groups nor is there a day 11 or day 39 in our toxicology studies. We do not propose any toxicokinetic studies. Pretest serum (baseline) will be collected and animals are sacrificed following the last dose as it was in the pre-IND package. These comments have no bearing at all to our proposed work.

Topic 4: Feasibility

GWG Review:

1. (Feasibility) There is a concern that relevant assays to measure activity will not be available for Phase I, which may make it difficult to justify advancing expeditiously with an active dose to Phase II.
2. (Feasibility) There is concern regarding stability of product based on experience with the previous product.
3. (Plan/Design) The project is well planned overall with suitable timelines proposed for development and qualification of test methods and production of clinical grade animal toxicology material.
4. (Feasibility) The project timelines are feasible to achieve the projected year 2 filing of the IND application with the FDA.
5. (Feasibility) There is some concern with achieving timelines.

Rebuttal:

1). The assays which we propose to measure activity are the antibody titer assay, the proteasome digest assay and the intracranial tumor assay. The antibody titer assay was demonstrated in our pre-IND package. The proteasome and intracranial tumor assay have already been developed and described in our STM paper. As such, all assays are already available.

2)The concerns we raised regarding the stability of the Celldex product was for a period of ~6-8 years. We anticipate that we will conclude any Phase I trial within 3 years of manufacture. We have an excellent plan in place to monitor the biologic activity and we will manufacture new drug for the Phase II trial if there is a diminution in activity.

3-5). Comment 5 is at variance with 3 and 4. Considering the relatively straightforward synthesis and toxicology, the clear endpoints of the Phase I trial, we do believe that we will readily meet the timelines of the proposal.

Topic 5: Mass Spectrometry

GWG Review:

1. (Plan/Design) With the institution's mass spectrometry facility described as impractical for research or informing decisions, the applicant requests the purchase of a LC MS/MS as it would significantly accelerate studies. It is not clear from the proposal that the level of internal expertise available to operate and maintain the proposed equipment will support accelerated studies.
2. (Plan/Design) A detailed implementation plan for the installation and qualification of the mass spec would benefit the proposal. The personnel dedicated or expected to provide support for the equipment should be included.
3. (Plan/Design) The equipment purchase rationale is not adequately justified.
4. (Feasibility) The team is staffed appropriately to support the clinical aspects and the virtual manufacturing aspects of the product. The use of product testing vendors for analysis by mass spec provides expertise to support testing. However, due to the criticality of the test method for release and stability testing and prolonged turn-around time for test articles, the proposal's request for supporting equipment is understandable. It is not clear if expertise to support the equipment is available. The timelines for equipment implementation are also unclear, and the applicant does not indicate whether there will be cross-qualification of the equipment with the institutional facility.

Rebuttal:

1-4) We do agree that our plan for the LC tandem mass spectrometry instrument was not adequately developed and that there should be plans for training for our staff, installation and qualification of the device. Due to the turnaround times at the Mass Spec facility at Stanford (now exceeding 3-4 weeks per sample), we do believe that having such an instrument will greatly facilitate our discovery methods and hence identifying parameters for monitoring future clinical trials. Nevertheless, the costs associated with the LC MS/MS can be reduced. First, the vendor has recently informed us that the device has a price reduction of ~$250K (now $750K). We also inquired about leasing options and for 2 years with no residual payment this would be $656K. Finally, if it enables the funding of the application, this request could be deleted altogether resulting in a total project cost of $3,386,974 (inclusive of IDC).

Topic 6: Impact

GWG Review:

1. (Impact) The applicant admits that is likely that the product may need to be combined with other therapeutic modalities to be effective.
2. (Impact) Glioblastoma remains an unmet medical need. There are, however, currently programs in development that are showing promise.
3. (Impact) Unclear if clinical response will be strong enough to have impact.

Rebuttal:

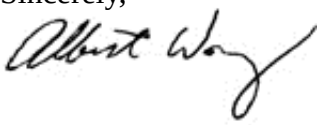
1). It is now very much appreciated that therapies must be tried in combination to achieve any meaningful cure for glioblastoma. It is unlikely that any modality currently in development will work as a single agent. We look forward to manufacturing Y6-pepvIII and obtaining the IND as this will enable us to perform our own studies and seek collaborators. In the application, we state that our plan is to combine Y6-pepvIII with bevacizumab to replicate the ReACT trial for recurrent glioblastoma. This is likely to have a high degree of impact on survival and attract commercial development. From the Phase I trial, we will learn what inhibitors of checkpoint molecules can also be combined. Indeed, there is a wide variety of agents that would be compatible and synergistic with this vaccine.

2). While there are programs in Phase I/II that look promising, the anti-EGFRvIII vaccine is one of the furthest in development and has already shown extremely promising results in randomized Phase II and III trials. The limitation in further development has been the expired patent on Rindopepimut. The Y6-pepvIII/KLH drug overcomes that limitation.

3). The data that we have presented thus far demonstrates that Rindopepimut already has an impact on glioblastoma given the proper indication. In combination with an even more robust version in Y6-pepvIII, we are confident that we will have an impact on survival in glioblastoma.

We have presented evidence that our application was strong in all aspects required for the CLIN1 program. It is based on a well-validated target for glioblastoma that has already shown success in clinical trials. Our product is more robust and will build upon what has been learned in previous studies to ensure that the clinical trials will be successful. We are confident that our program will extend survival in this difficult disease.

Sincerely,



Albert J. Wong, MD
Professor
Dept. of Neurosurgery/Cancer Biology Program
Stanford School of Medicine

On behalf of the Stanford Neurosurgery and Neuro-oncology co-Investigators:
Stephen Skirboll, M.D.
Gordon Li, M.D.
Melanie Gephardt, M.D., Ph.D.
Lawrence Recht, M.D.
Michael Lim, M.D.
Steven Chang, M.D.

Appendix

Original Review from the GWG for CLIN1-14852

Key Questions and Comments

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

Impact

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes:4 **No:**8	• The project proposes a therapy which would meet an unmet medical need for the treatment of glioblastoma. Considering the previous experience from the group and direction of success, the proposed approach is likely to provide advancements from the current standards of care. • Overall the peptide-based vaccine approach should provide a significant value proposition relative to other more complicated gene therapeutic based approaches which have potential for larger development and production costs. • Glioblastoma remains an unmet medical need. There are, however, currently programs in development that are showing promise. • The applicant admits that is likely that the product may need to be combined with other therapeutic modalities to be effective. • Unclear if clinical response will be strong enough to have impact.

Rationale

GWG Votes	Is the rationale sound?
Yes:0 **No:**12	• The proposal provides evidence from previous clinical experience with the earlier generation of the peptide conjugate which supports the clinical rationale for the improved construct. However, the case for the proposed peptide to target cancer stem cells (CSCs) needs more supporting data. • Animal data, including the materials used to manufacture product for nonclinical studies, does support continued evaluation of the candidate for development. Demonstration of the vaccine's impact on target cells is not clear and additional in vitro data would be helpful to support the product. • Tumor peptide vaccines targeting EGFRvIII have shown equivocal clinical activity. • EGF receptor targeting has been somewhat disappointing in glioblastoma. • Unclear if targeting EGFR with immunotherapy approaches will really have benefit in the brain. • The justification for single dose in toxicological study is unclear. • No evidence for targeting of CSCs.

Plan/Design

GWG Votes	Is the project well planned and designed?
Yes:2 **No:**10	• The project is well planned overall with suitable timelines proposed for development and qualification of test methods and production of clinical grade animal toxicology material. • The FDA denied a pre-IND based on previous pre-IND for a similar product. No information was provided regarding recommendations from the previous program. • It is unclear what material is intended for use in the toxicology study; importantly if similar process will be used compared to the clinical process. • The rationale for the proposed tox study design was not provided, including dose and regimen to support proposed clinical protocol. • The proposed toxicology study is not sufficiently justified nor does the protocol that was provided make sense. Sacrifice is proposed for Groups 1 and 4 at day 11 (but there is no Group 4), a control only group is proposed for sacrifice on Day 39. Toxicokinetic studies are mentioned but no animals are included for this purpose. Pretest serum for antibodies not generally collected in mice. Days of scheduled sacrifice are not generally on the day of the last dose. • With the institution's mass spectrometry facility described as impractical for research or informing decisions, the applicant requests the purchase of a LC MS/MS as it would significantly accelerate studies. It is not clear from the proposal that the level of internal expertise available to operate and maintain the proposed equipment will support accelerated studies. • A detailed implementation plan for the installation and qualification of the mass spec would benefit the proposal. The personnel dedicated or expected to provide support for the equipment should be included. • The equipment purchase rationale is not adequately justified.

Feasibility

GWG Votes	Is the project feasible?
Yes:8 **No:**3	• The project timelines are feasible to achieve the projected year 2 filing of the IND application with the FDA. • The team is staffed appropriately to support the clinical aspects and the virtual manufacturing aspects of the product. The use of product testing vendors for analysis by mass spec provides expertise to support testing. However, due to the criticality of the test method for release and stability testing and prolonged turn-around time for test articles, the proposal's request for supporting equipment is understandable. It is not clear if expertise to support the equipment is available. The timelines for equipment implementation are also unclear, and the applicant does not indicate whether there will be cross-qualification of the equipment with the institutional facility. • There is a concern that relevant assays to measure activity will not be available for Phase I, which may make it difficult to justify advancing expeditiously with an active dose to Phase II. • There is concern regarding stability of product based on experience with the previous product. • There is some concern with achieving timelines.

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes:11 **No:**1	• The applicant is relying on host institution catchment area, experience, and resources. • The applicant has developed specific goals to achieve inclusive distribution for their future clinical trial product by enhancing enrollment for the Black and Latino population to at least match the distribution observed in the region. • The proposal includes outreach and engagement by various approaches, one of which includes creating information portals for the prognosis and treatment community by building a website and mobile app that will inform patients about various options and facets of glioblastoma.

Diversity, Equity, and Inclusion in Research

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8.0

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.***

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.

References that confirm and extend our finding of EGFRvIII in glioblastoma cancer stem cells

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