CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

Date: September 4, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05373

Enclosed is a letter from Dr. Albert Wong of Stanford University, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on September 4, 2012. As the Extraordinary Petition Policy normally refers such petitions to the ICOC meeting that first considers the application, we are forwarding the letter as correspondence to the board rather than a petition that was pursuant to the policy.

STANFORD UNIVERSITY
CANCER BIOLOGY PROGRAM
AND DEPARTMENT OF NEUROSURGERY
BRAIN TUMOR RESEARCH LABORATORIES

Re: Disease Team Application DR2A-05373: Recombinant Bispecific Antibody Targeting Cancer Stem Cells for the Therapy of Glioblastoma.

To Chairman Jonathan Thomas and the Members of the ICOC:

Glioblastoma is one of the most tragic cancers because it affects the brain and rapidly leads to a deterioration in the quality of life. Median survival is only 14.5 months and less than 10% survive 5 years making a diagnosis of glioblastoma an almost certain death sentence. It is also one of the most difficult tumors to treat—over 50 years of research has improved survival by only a few months. Yet, we firmly believe that this disease can be cured in our lifetime.

Our team thanks you for the opportunity to present this petition as we find these circumstances merit extraordinary consideration. Our approach to treat glioblastoma is based on a highly novel target that has already yielded significant results in clinical trials. This is exploited using an innovative molecule to specifically kill cancer stem cells. This science has been favorably reviewed by CIRM in the past and was on the cusp of funding. Moreover, three recent publications support our approach. We hope to show you that our project does have considerable promise and merits your full attention .

Glioblastoma arises from cancer stem cells. The basis for our optimism is the hypothesis that cancer originates from cells with stem-like properties which constitutes a major new insight into tumor formation. Like the roots of a tree, cancer stem cells are small in number but grow and divide to give rise to the full tumor. Akin to killing the roots of the tree, an important prediction is that one must kill these cancer stem cells or the tumor will always recur, but if these cells are killed then the tumor will eventually wither and die. It has been difficult to capitalize on this hypothesis as the current markers used to identify cancer stem cells, such as CD133, are also expressed on numerous normal stem cells. The EGF receptor has emerged as a promising target because it is highly expressed in a significant percentage of glioblastomas. Yet it, too, is a widely expressed normal protein, and in fact activation of this receptor is vital for growth of normal stem cells.

EGFRvIII: a tumor specific target that shows great promise as an anti-cancer vaccine. Glioblastoma tumors contain many genetic alterations that could be used as targets. One that affects the EGF receptor is called EGFR variant 3, or EGFRvIII, and is found in 30-50% of patients. As a postdoctoral fellow, I participated in its discovery and then in my own lab showed that EGFRvIII is a permanently "on" form of the EGF receptor that requires no activation. We also showed it is highly tumor specific. These properties suggested that EGFRvIII is an ideal target for therapy. We then developed an anti-cancer vaccine based on the unique portion of EGFRvIII. This drug, now known as rindopepimut, has gone through four clinical trials and is now being tested in a Phase III multi-institution clinical trial. Many other agents have failed in Phase I/II trials, but this is one of the few biologically based therapies for glioblastoma to move to a Phase III trial. Median survival in the three Phase II trials has ranged from 22-26 months. Given the history of glioblastoma, this could be a potentially important increase.

EGFRvIII is found on cancer stem cells. Why is the EGFRvIII target so promising? It contributes to cell growth and is tumor specific. Yet, a paradox is that in positive tumors it is present on less than 10% of the cells. This violated past dogma: a therapy must be directed against all cancer cells to be effective. We wondered if EGFRvIII might be present on the cancer stem cell population. Our research showed this to be the case—the EGFRvIII cells were far more tumorigenic than the more vast EGFRvIII negative cells. But not all EGFRvIII cells showed stem cell properties and we wondered if we could further refine the cancer stem cell population using a stem cell marker. Cancer stem cells in glioblastoma were originally identified using CD133 but we also found that not all CD133 cells were cancer stem cells. However, if we combined the two proteins we more precisely identified the cancer stem cells even though we now only isolated 5% of cells.

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A bispecific antibody to specifically kill cancer stem cells. We sought to use this information to improve anti-EGFRvIII therapy. Vaccines are active immunotherapy: they rely on stimulating an intact immune system to work. But some glioblastoma patients have an impaired immune system and all patients must wait nearly 2 months to start vaccine therapy while receiving radiation therapy. Monoclonal antibodies are passive immunotherapy: they do not require an intact immune system because they are directly given to the patient. If we had a monoclonal antibody that could be given to patients immediately after surgery this would avoid the treatment lag and impaired immune systems. We decided to use the tools of DNA engineering to create a monoclonal antibody based therapeutic that would simultaneously recognize EGFRvIII and CD133, thus enhancing specificity for the cancer stem cell subset. Aside from killing the most critical cells, another benefit is that this bispecific antibody (bsAb) would require less drug making it safer and saving millions of dollars in production costs.

The bispecific antibody is effective in animal studies. Our results have confirmed that this drug is indeed effective as we had hoped. We found efficient binding to cancer stem cells using 1/3 the concentration compared to an analogous molecule that only recognized EGFRvIII. Only 5% of animals treated with the bispecific developed tumors, but at the same dose 58% of the anti-EGFRvIII antibody treated and 100% of the control antibody treated animals developed tumors.

Recent publications support our approach. Since the submission of this proposal, we have published two work further supporting that EGFRvIII identifies the cancer stem cell subset[1, 2]. In addition, two other groups observed that EGFRvIII is present in cancer stem cells[3, 4] and one group is contemplating using this to target immunotherapy[4] providing important validation of our approach.

EGFRvIII and the bispecific antibody could catalyze further breakthroughs in glioblastoma therapy. While the furthest along in research and therapy, EGFRvIII is not the only tumor specific target. There are potentially other molecules that could also be targets. Our approach, if given the chance to succeed, could spur others to develop cancer stem cell specific antibodies.

This work was very favorably reviewed by other CIRM review panels. We are excited to bring this therapy to clinical trials and applied for a Disease Team Award. We were extremely disappointed with the score that we received because it did not reflect the underlying science and our significant efforts in putting together an outstanding team that would rapidly bring this drug to trial. This is not our isolated opinion: our Planning Award was reviewed very favorably. After consulting with CIRM staff, we also submitted a very similar application to the recent Early Translation III Awards where it received a score of 63. ***Indeed, the application above ours and several below were selected for funding.*** Had we known more about the extraordinary petition process at the time, we would have made an appeal for our ET3 application.

Scientific Rebuttal. We will briefly discuss the major points made in our Disease Team critique. An extensive point-by-point analysis has been made and submitted to the CIRM staff. We are able to refute nearly every negative comment made either through referencing available scientific information or our application.

1***. The blood brain barrier is an impediment to delivering our bispecific antibody.*** For normal brain, the BBB is a formidable challenge to delivering antibodies and small molecules. However, it is now known for glioblastoma that the tumor is highly hemorrhagic and the endothelia is defective allowing penetration of antibodies. Over 25 clinical trials using systemic (IV) administration of monoclonal antibodies for glioblastoma without any methods to enhance delivery have been approved by the FDA. Twelve of these trials have used an anti-EGFR antibody. We were well aware of this potential criticism and discussed our plans in the application but this was not acknowledged. In any case, we did not view the delivery issue as significant because we could also deliver the bispecific directly to the tumor cavity after surgery.

2. Is this agent specific for cancer stem cells and will it be safe in humans? We presented an abundance of flow cytometry, self-renewal, and marker analysis data to show that EGFRvIII /CD133 defined the cancer stem cell population. The fact that we could prevent tumor formation with the bispecific by targeting only 5% of cells and the 4 recent publications are also compelling evidence. We also demonstrated that, at the concentrations used in anti-tumor experiments, there was little binding and lysis of normal neural stem cells. The concentration used is 1/3 that approved for anti-EGFR monoclonal antibody therapy in humans, which has proven to be safe. Whether there is binding to other CD133 positive cells that causes a safety issue is not presently known. This can

only be determined through toxicology experiments in cynomolgus monkeys, and this was proposed in the application as it is otherwise prohibitively expensive.

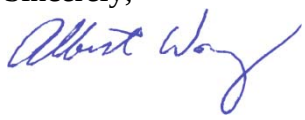
3. Project is not yet ready for a Disease Team Award. Our project was vetted by the Planning Award process and selected for full submission. According to our timeline, all of the necessary preclinical work to submit the IND would be complete by month 41 which further reflected our readiness. We did also plan to simultaneously further develop the anti-EGFRvIII agent, but this was a contingency in case there was any toxicity from the bispecific antibody. This did not reflect any uncertainty on our part, but was meant to ensure that an IND was filed by the end of the 4th year.

4. Mechanism of Action (MOA) work is not justified. As was mentioned in the application, many of the anti-receptor antibodies approved by the FDA have different mechanisms of action. While we designed this reagent to enhance antibody dependent cellular cytotoxicity, there may be other means by which this agent inhibits cancer cells and such knowledge is an essential part of the target product profile (TPP). While the reviewers thought that we devoted substantial time and effort to MOA studies, in reality this was less than 20% of the budget. Another comment mentioned that we did not have the right environment. Aside from three other Disease Team Awards being given to Stanford, we feel that we have the right mix of performance sites where MOA work is done in our laboratories, but all GMP and GLP work is done at the CROs and CMOs.

5. The team lacked experience and overlooked developing key product attributes. We found these comments surprising in light of the background of the people recruited for this project. A condition for submitting the full DT application was to present a revised development plan. To meet this condition, we sought biotech industry professionals specifically versed in the development of monoclonal antibodies. Due to their industry perspective, all of the consultants, CMOs, and CROs who contributed to this application were well aware of the mandate to meet deadlines and provide deliverables. Clearly, this dominated all of our discussions as we knew from other Stanford Disease Team awardees that milestones must be met in order to obtain further funding. My own expertise in developing the vaccine candidate for Phase I clinical trials was also overlooked.

Recently, I received a call from a vaccine treated patient thanking us for enabling her to see her son's high school graduation. It is stories like this that energize us to move this project forward. We strongly believe this approach will be an extremely effective and innovative next step in curing glioblastoma. This bispecific antibody could illuminate a new paradigm for the specific targeting of other cancer stem cells. Using traditional funding mechanisms to develop new drugs is a notoriously slow and incremental process. Funding from CIRM would dramatically accelerate the pace of this project and bring this potentially lifesaving therapy to patients in the shortest time possible.

Sincerely,



Albert J. Wong, M.D.
Professor
Stanford University Medical Center

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3. Schulte A, Gunther HS, Phillips HS et al. A distinct subset of glioma cell lines with stem cell-like properties reflects the transcriptional phenotype of glioblastomas and overexpresses CXCR4 as therapeutic target. Glia 2011;59(4):590-602.
4. Morgan RA, Johnson LA, Davis J et al. Recognition of glioma stem cells by genetically modified T cells targeting EGFRvIII and development of adoptive cell therapy for glioma. Hum Gene Ther, in press (available online), 2012.