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Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
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Application Number: CLIN1-10967
Title: *Ex Vivo* Gene Engineering of Blood Stem Cells for Enhanced Chemotherapy Efficacy in Glioblastoma Patients
Principal Investigator: J. A. Zaia

We are pleased with the recommendation from the Grants Working Group (GWG) that reviewed our proposal [CLIN1-10967] to treat glioblastoma. The reviewers recognized that our approach "*will allow for a more aggressive chemotherapy regimen while limiting the major side effect of hematopoietic stem cell toxicity*," and thought that "*the proposed treatment will offer significant value to glioblastoma patients if it is shown to improve overall survival and quality of life over standard of care*." The GWG raised a few minor concerns which we address below.

Some reviewers believe our timeline is too aggressive. Our timeline is ambitious but realistic, and is based on our extensive experience, having worked with vector-modified stem cells in past clinical trials. There are three main reasons that justify our accelerated timeline:

1) The new vector is manufactured by Lentigen Technology Inc., a leader in the field of vector manufacturing that produced the previous vector used in the pilot clinical trial NCT01269424. Our new (and improved) vector is optimized based on our experience with the previous vector, and Lentigen has already provided us with sufficient new vector to complete the first Task of the proposed project. Importantly, Lentigen has reserved and scheduled manufacturing slots for production of additional vector to accommodate our timeline.
2) To accelerate the project, we have already developed with the manufacturer of the cell processing equipment (Miltenyi Biotec) a program specifically intended for our production of the gene-modified stem cells for this trial.
3) Our team comprises seasoned experts in process development, manufacturing, and clinical development of cell product for numerous diseases. Some of them led the two previous clinical trials that used a similar approach (NCT00669669 and NCT01269424) in glioblastoma patients.

In summary, we have planned this project thoroughly and are confident that we can meet our proposed timeline.

A second comment expressed concern over the lack of preclinical data with patient derived glioblastoma cells. The increased sensitivity of glioblastoma cells to our proposed combination chemotherapy was previously shown in published *in vitro* studies (*1*), in animal models (*2, 3*) and in two early phase clinical trials (*4, 5*).

A third concern was the lack of preclinical data supporting the improved vector design compared to the previous vector used in pilot clinical trials. As mentioned in the proposal, our preliminary studies and data from our collaborators show a significant increase in the transduction efficiency of the new and improved vector: 55-71% for the new vector compared to 8-18% with the previous vector. One reviewer, in fact, noted that *"the proposed preclinical experiments are adequate and will verify whether the modified vector design will improve expression of the construct and the overall safety profile of the engineered HSC."*

A final point was whether higher doses of temozolomide (TMZ) chemotherapy would be clinically effective, not toxic, and improve the patient's quality of life. Two pilot clinical trials (NCT00669669 and NCT01269424) using a similar therapeutic approach support the safety and efficacy of our proposed strategy and show a preserved quality of life in glioblastoma patients (*6, 7*). Our optimized vector should allow us to reach better outcomes.

Finally, glioblastoma is incurable; patients' survival remains approximately 15 months, and chemotherapy is currently limited by its toxicity on bone marrow and blood stem cells. We are eager to move our therapy to the clinic and achieve a better outcome by aggressively sensitizing tumor cells to chemotherapy while simultaneously protecting the patient's blood stem cells. Based on our experience with two previous FDA-approved pilot trials, we foresee no major hurdles to completing an IND, recruiting patients, manufacturing the therapeutic cell product, and eventually conducting the clinical trial.

Yours sincerely,

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References:

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