City of Hope

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The Independent Citizen's Oversight Committee (ICOC)
The California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application: **TRAN1-11544**
Title: **Neural Stem Cell-mediated oncolytic immunotherapy for ovarian cancer**
Principal Investigator: **Karen S. Aboody, M.D.**

Dear Members of the Board,

Thank you for your generous consideration to reallocate funds for TRAN-1 applications recommended for funding but carried over from the July 2019 ICOC/Application Review Subcommittee meeting, and for this opportunity to respond to the meeting. We also thank the Grants Working Group (GWG) for their constructive review and for recognizing the necessity, novelty, and translational potential of our proposed use of a **fetal tissue-derived neural stem cell (NSC) line** to deliver an oncolytic virus to tumor sites in women with stage III (abdominal metastases) ovarian cancer. Here, we would like to highlight important features of our project.

Our project will meet a **critical unmet need** for new, more effective therapies for patients with stage III ovarian cancer, many of whom cannot tolerate the toxic chemotherapy regimens now used. Ovarian cancer is the most lethal gynecologic malignancy, afflicting approximately 22,000 women per year in the U.S. Once ovarian cancer has metastasized to the abdominal cavity (stage III), patients have a median survival of only three years after standard treatment with surgical debulking and combination chemotherapy. Patient quality of life is greatly compromised by toxic side effects that prevent most patients from completing their full course of chemotherapy due to severe abdominal pain, nausea, and vomiting. By using tumor-tropic NSCs to localize oncolytic virus therapy specifically to ovarian tumor sites, our approach has potential to **significantly improve clinical outcome** of these patients, while also reducing treatment-related toxicity. Furthermore, this therapy can kill tumor cells that are both chemo-resistant and radio-resistant, and stimulate a secondary immune response for enhanced tumor killing.

Our project will also **bring novelty to the CIRM portfolio**. The current CIRM portfolio includes only three projects targeting ovarian cancer, none of which have yet reached the TRAN stage. This would be the only TRAN project aiming to treat ovarian cancer, and, as described below, it is on a fast track to clinical translation. Furthermore, our study would bring novel technology to the CIRM portfolio through our use of an oncolytic virus delivered by NSCs. In addition, and important in light of recent federal restrictions on fetal tissue research, our study aligns with CIRM's interests in funding research involving embryonic stem cell and fetal tissue. **Thus, our project furthers CIRM's mission and has potential for substantially broadening the scope of CIRM funding.**

We also note that the NSC-delivered oncolytic virus therapeutic candidate is on a **streamlined path to approval** for conduct of clinical trials for ovarian cancer patients. It is already in an FDA-approved clinical trial for brain tumor patients (ongoing at Northwestern University and City of Hope), has demonstrated safety in the first 8 brain tumor patients who have received it, and manufacturing and release protocols have already been approved by the FDA. Our team's cumulative scientific, clinical, and manufacturing experience, and past experience with the FDA regarding the NSC line, will expedite our production of a new clinical lot of the therapeutic candidate and submission of a pre-IND application within three years. We anticipate then rapidly advancing this therapy toward first-in-human clinical trials for women with stage III ovarian cancer who have failed currently available treatments.

In summary, this project has tremendous potential to greatly improve survival and quality of life of patients with stage III ovarian cancer, a group of patients who urgently need better treatment options. Furthermore, we anticipate that successful development of this approach in ovarian cancer could ultimately be translated to many other solid tumors, including lung and breast cancer.

Again, I am very grateful for the possibility that funds will be reallocated to support projects that were carried over from the July 24 ICOC meeting and ask for consideration to fund this application at the October meeting of the ICOC and

Application Review Subcommittee. I will be attending the meeting and will be happy to answer any questions regarding my application.

Kind regards,

Karen Aboody, M.D.
Professor, Developmental and Stem Cell Biology

P.S. Response to reviewers comments was addressed in my letter of July 23, 2019, and repeated here for your convenience.

The reviewers raised two minor concerns that we have endeavored to address below:

1. **Rejection of NSCs by the host**

   Two of 15 reviewers noted that, "*it is unclear if these modified cells will be rejected in humans*"; and "*It is unclear whether the cells will be invisible to the immune system.*"

Response: We do not expect natural killer (NK) or T-cell mediated rejection of the NSCs to be a limiting factor while they are en route to the tumor. When administered into the abdomen of immunocompetent mice with ovarian tumors, 60–80% of these NSCs delivered their viral payload to 98% of ovarian tumor sites within 3 hours after administration. This is much faster than the NSCs can be cleared by the immune system. Additionally, immune correlative data from our first 2 completed and 1 ongoing NSC-mediated gene therapy brain tumor trials demonstrate a lack of T cell and NK-mediated immune responses in patients who received multiple treatment rounds. These gene therapy trials used the same NSC line used in our oncolytic virus studies. Additional preclinical and clinical correlative investigations will further examine the interplay between oncolytic virus and host immune responses within the body and tumor environment.

2. **Efficacy and survival data**

   Two of 15 reviewers noted that "*There is an absence of any efficacy data in the proposal which is a critical flaw*"; and "*Extended survival has not been demonstrated in any animal model*."

Response: Because it is known that total tumor weight and volume of ascites (intra-abdominal fluid resulting from tumors) directly correlate with long-term survival, we used these measurements as a more objective and rigorous read-out of post-treatment efficacy. In our 2019 publication (Mooney, et al., *Mol Ther Oncolytics*, 2019), we demonstrated both a significant decrease in total tumor weight and reduced volume of ascites in mice treated with our NSC-oncolytic virus product versus control animals in both immunocompetent and immunodeficient models of intra-abdominal ovarian cancer. Our recent studies have further shown a significant survival benefit in mice with cisplatin-resistant ovarian cancer treated with our NSC-oncolytic virus product.