City of Hope
Comprehensive Cancer Center & Beckman Research Institute
Familian Science 1005
Karen S. Aboody, MD
1500 East Duarte Road, Duarte, CA 91010
Professor, Developmental and Stem Cell Biology
Tel: 626-218-8177 Fax: 626-301-8857
Scientific Leader, Neuro-Oncology Disease Team
Email: kaboody@coh.org

July 23, 2019

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 the opportunity to respond to points raised in the review of our TRAN1 application. We also thank the reviewers for recognizing the necessity, novelty, and translational potential of our stem cell-based delivery of a tumor-specific oncolytic virus for treatment of women with stage III (abdominal metastases) ovarian cancer. We appreciate their thoughtful comments, recognition of our combined expertise and track record, and their recommendation for funding.

Please note that I was the recipient of a CIRM Disease Team Award (DR1-01421), which successfully brought a first-in-human neural stem cell (NSC)-mediated gene therapy to clinical trial for brain tumor patients; this trial is currently ongoing at City of Hope. Leveraging the results obtained from CIRM funds, we were awarded a $4.7M NIH grant to support IND-enabling studies to apply this same NSC-mediated gene therapy product to children with metastatic neuroblastoma. The associated phase I trial is expected to open to accrual at City of Hope in 2019.

Cancer clinical trials administering free oncolytic virus (which self-amplifies in the context of tumor) have not demonstrated the expected efficacy. This is most likely because the virus is inactivated by the host immune system and insufficiently distributes to metastatic tumor sites. We have published multiple studies showing the significant advantage of using our tumor-homing NSCs to deliver oncolytic virus in both brain and ovarian cancer preclinical models. The NSCs 1) protect the tumor-killing virus from inactivation by host antibodies during transit to the tumor sites; 2) improve the distribution of virus to multiple metastatic tumor sites; and 3) increase tumor elimination. 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 novel therapeutic candidate, an NSC-delivered oncolytic virus product (CRAd-S-pk7 NSCs) proposed in this TRAN-1 application for treating ovarian cancer, is already in an FDA-approved clinical trial for brain tumor patients (ongoing at Northwestern University and City of Hope). Importantly, safety has been demonstrated in the first 8 brain tumor patients who have received our NSC-oncolytic virus product. Manufacturing protocols and clinical lots have already been established for use in patients. With our cumulative scientific, clinical, and manufacturing experience, my team is now ready to streamline this product toward first-in-human clinical trials for women with stage III ovarian cancer who have failed currently available treatments.

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.

In summary, there is a critical unmet need for new and more effective therapies for patients with Stage III ovarian cancer, many of whom cannot tolerate the toxic chemotherapy regimens now used. We believe our NSC-oncolytic virus therapy will significantly improve clinical outcome of these patients, while also reducing treatment-related toxicity because our tumor-tropic NSC line will localize therapy specifically to tumor sites. Because this product is already in clinical trial for brain tumor patients, has demonstrated clinical safety, and manufacturing and release protocols have already been approved by the FDA, successful completion of the proposed studies will lead quickly to approval for the conduct of clinical trials for ovarian cancer patients. Our prior experience with the FDA will expedite our production of a new clinical lot of the therapeutic candidate and facilitate the path toward a pre-IND submission for use in abdominal administration for stage III ovarian cancer.

Sincerely,

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