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Application and Review Subcommittee (ARS)/
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine

Re: DISC2-14083
"Development of novel small molecules against cancer stem cells in solid cancers"

Dear members of ARS/ICOC,

In our DISC2 application we propose the development of novel compounds against glioblastoma, the deadliest form of adult brain cancer. Our compounds have specifically been designed to cross the blood-brain-barrier (BBB), prevent the radiation-induced conversion of non-stem tumor cells into cancer stem cells and target existing cancer stem cells, all without increasing the toxicity of radiation. Importantly, we have demonstrated that the lead compound targets glioma stem cells *in vitro* and *in vivo.* In combination with radiation, it significantly prolongs the median survival of mice bearing patient-derived orthotopic xenografts (PDOXs). The compounds are all patentable and a provisional patent has been filed by UCLA.

The scientific reviewers were uniformly enthusiastic about our proposal, emphasizing

• that the small molecular drug development will likely result in a candidate that could improve therapeutic efficacy of radiation therapy in GBM patients, a major unmet medical need;
• that the proposed project is uniquely enabling for the advancement of a cancer stem cell-targeting therapy;
• that the candidates selected in the preliminary screen show a promising activity profiles against GBM both in vitro and in vivo without significant toxicity;
• the strong preliminary data and the feasibility of the research.

I would like to address concerns raised by some reviewers including the comparison and relation of our compounds to dopamine receptor antagonist, additional targets, and the potential toxicity of our compounds on the immune system.

"Actions other than kinase inhibition should be appropriately considered or discussed."

- Our novel compounds -while structurally related to each other- have no structural relationship with dopamine receptor antagonist. While they are superior in BBB-penetration and inhibition of radiation induced phenotype conversion they also lack the sedative effects of dopamine receptor antagonist, making them more favorable drug candidates especially for patients with GBM who are usually treated in an out-patient setting. Ongoing studies have used click-chemistry using MXC017 as a bait to identify

potential additional targets by mass spectrometry. These studies will be finished before the potential funding start of this proposal.

"Study of Delayed Adverse Effects."

- At present we are testing our lead compound in immune-competent mice bearing syngeneic glioma cells (Gl261 in C57Bl/6 mice). The is part of our standard approach to test efficacy of our compounds in the presence of an intact immune system and this approach will allow for monitoring any toxicity on the immune system.
- In immune-compromised animals we did not see any toxicity in the spleen as a major lymphatic organ.
- Toxicity on the immune system is usually toxicity against the entire hematopoietic system. Our NSG mice have been treated continuously with 5 weekly injections for >10 weeks. In none of the mice - including long term survivors- did we observe clinical signs of anemia that would point to hematologic toxicity of our compound.

"Project plan and timeline does not fully demonstrate an urgency that is commensurate with CIRM's mission"

We would like to point out that our DISC2 application is based on years of discovery and the development of novel compounds. A funded DISC2 application will enable us to accelerate treatments against cancer stem cells in patients suffering from glioblastoma, a population with urgent unmet medical needs, in line with CIRM's mission. The projected timeline has been modified from 2 to 3 years in response to the previous review. It takes all necessary steps into consideration to safely translate our findings into the clinic.

In summary, our DISC2 proposal is a direct response to the CIRM Strategic Plan calling for the full use of stem cell technology to establish novel research platforms that may be high risk but will have high impact in the field of regenerative medicine.

We appreciate the consideration of the CIRM ARS/ICOC for funding our DISC2 application.

Sincerely,

Frank Pajonk, MD/PhD
Professor
Departments of Radiation Oncology and Neuro-Surgery

This letter is original with the undersigned author.