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Chairman Jonathan Thomas, PhD, JD
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, California 94612

RE: TRAN1-12258, *CAR-Tnm cell therapy for melanoma targeting TYRP-1*

Dear Chairman Thomas and ICOC

As the principal investigator of the group that submitted the above referenced application, I want to thank the Grants Working Group (GWG) for recommending it for funding. The goal of our project is to address an unmet clinical need by developing the proposed cutting-edge technology and bringing it to clinical trial. The GWG recognized the importance of our proposal and I would like to address some of their specific concerns below.

Does the proposal have the necessary significance and potential for impact? (Yes:13 / No:1)

Overall, **the GWG agrees that metastatic melanoma refractory to immune checkpoint blockade (ICB) therapy and other drug combinations has no effective and approved treatment**. ***Our product candidate will directly impact this unmet medical need***. However, there are some concerns regarding the market size. Reviewers raise questions regarding the impact of checkpoint inhibitors (first-line therapy for melanoma patients) and TIL therapy on the TYRP-1 expression profile. We have assessed the expression of TYRP-1 in pre-treatment and post-treatment lesions from patients treated with ICB (anti-PD1, anti-CTLA-4, or a combination of both therapies) and shown that TYRP-1 expression does not present statistically significant changes in patients that do not respond to treatment (Figure 1).

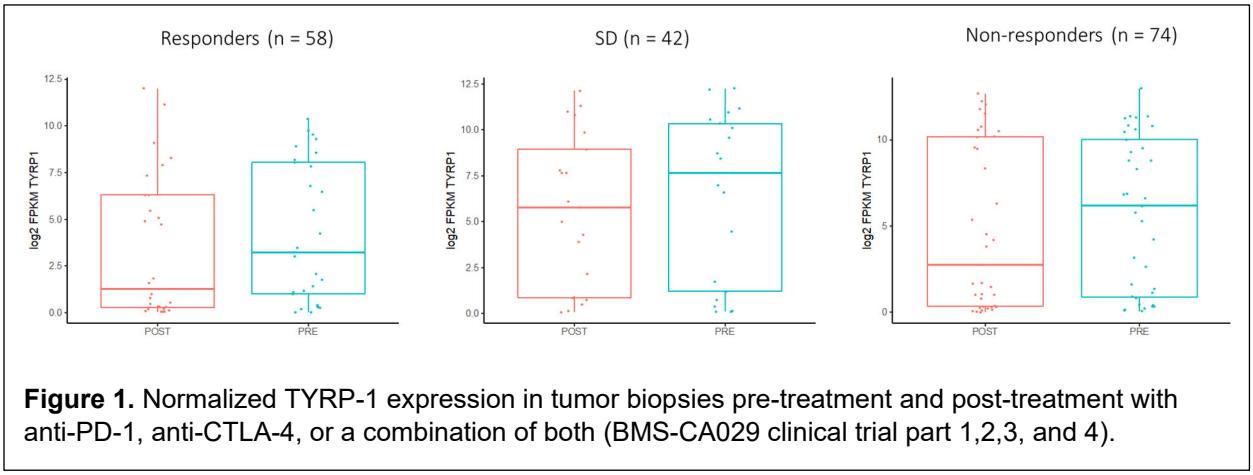

Figure 1. Normalized TYRP-1 expression in tumor biopsies pre-treatment and post-treatment with anti-PD-1, anti-CTLA-4, or a combination of both (BMS-CA029 clinical trial part 1,2,3, and 4).

The reviewers also mention that TIL therapy could also be used for the same patient population and potentially be approved for clinical use sooner. We agree with the reviewers on the encouraging results obtained to date with TIL therapy. However, ***TIL therapy requires that patients have tumor lesions that can be resected to grow the TILs and reinfuse them to the patient later and pre-existing antitumor T cells in the tumors that can be expanded. Despite pre-existing tumor-reactive T cells being present in a fraction of patients with melanoma, there are still many patients that lack them. Therefore, only a subset of patients is eligible for TIL therapy***. The experience of our team is that TILs can be grown at a small scale from 49.7% of the patients attempted (for research use only, a total of 167 biopsies processed). These limitations are especially relevant for patients with acral, mucosal, and uveal melanoma that present lower mutation rates, and as a result, are less immunogenic and show less T cell infiltration. ***Our therapeutic candidate overcomes both limitations since we engineer the autologous naïve/memory progenitor T cells with a synthetic receptor that will redirect the effector activity of these T cells against tumors with high TYRP-1 expression***.

Is the rationale sound? (Yes:15 / No:0)

Overall, the reviewers agree that the therapeutic target, the application, and the therapeutic strategy are sound and well-chosen. One concern is the cost/benefit of selecting naïve/memory subpopulation of T cells.

Our team recently demonstrated in preclinical and clinical studies using other CAR-T cell constructs that selection of this subset of T-stem cells allows high expansion of the CAR-T cells, persistence, and very relevant clinical activity in phase I clinical trials (unpublished). Given these results, we firmly believe that the cost of the selection of naïve/memory progenitor T cells is warranted. Additionally, it allows the administration of lower doses of T cells with improved in vivo functionality, which compensates partially for the cost of population selection. Therefore, ***selecting T cells with stem cell memory phenotype provides the benefit of using their in vivo regenerative properties to provide more functional antitumor activity and long-term memory against cancer***.

Is the proposal well planned and designed? (Yes:12 / No:3)

Overall, reviewers agree that the project is well designed. However, several concerns were raised. Reviewers think that we should plan to address the expression of TYRP-1 in normal tissues earlier in the timeline. We agree with the reviewers that this is a very relevant issue to examine, and if funded, we will move this milestone forward in the proposed timeline. Additionally, there are concerns regarding the potential ocular toxicity that this therapy might cause. The epitope targeted by the TYRP-1 CAR is conserved between humans and mice. As a result, immunocompetent C57BL/6 mice are an ideal model to conduct the complete toxicology study. This study includes a full histopathology analysis. We plan to analyze tissues from multiple organs and focus, on the organs that are known to have pigmented cells that may express TYRP-1, in particular the retina, inner ear, and skin. Of note, in our studies thus far in C57BL/6 mice, we have noted local fur depigmentation over the sites of B16 melanoma implantation when the TYRP-1 CAR T mouse cells are inducing complete antitumor responses. Importantly, no evidence of vestibular problems or loss of eyesight in the mice that survive long term after B16 melanoma eradication by the TYRP-1 CAR T mouse cells.

It is relevant to mention the recent results from a phase III clinical trial studying the activity of Tebentafusp, the first therapy to ever demonstrate an improvement in overall survival in patients with uveal (eye) melanoma (AACR annual meeting 2021, Clinical Trials Plenary Session – Phase III Clinical Trials – CT002). Tebentafusp is a T cell engager targeting the human histocompatibility complex HLA-A2*01 presenting a gp100 peptide, and the clinical benefit was achieved without any evidence of toxicities on

tissues with pigmented cells. TYRP-1 and gp100 are both proteins involved with pigment biosynthesis and are co-expressed in the same tissues. Consequently, we expect similar safety profiles, with the added benefit that our approach is not HLA-restricted. HLA restriction limits the use of tebentafusp in only 40% of the general population with uveal melanoma. ***Since the great majority of patients with uveal melanoma have highly pigmented cancers that, unfortunately, do not respond to existing targeted therapies and immunotherapies, we anticipate that the majority of patients will be eligible for our TYRP-1 CAR approach***.

Several reviewers raised concerns regarding the manufacturing plan. In the proposal, we show data on small-scale manufacturing and in vitro antitumor activity for naïve/memory progenitor T cells from two different donors (figure 5C). Additionally***, for large-scale manufacturing, we will extensively benefit from the protocols and expertise of Dr. Yvonne Chen (co-PI). Her team is currently conducting a phase I clinical trial using naïve/memory progenitor T cells genetically modified with an epHIV7-derived lentiviral vector. Our clinical candidate will use the same subset of T cells and the same lentiviral vector backbone***. As a result, we anticipate that our final manufacturing protocol will be very similar. To date, seven patients have been treated in the clinical trial conducted by Dr. Chen's team. All patients have shown a lack of severe toxicities (only grade I-II adverse events) related or potentially related to CAR-T cells and presented impressive clinical responses (AACR annual meeting 2021, Clinical Trials Plenary Session – Immuno-oncology and Cell Therapy Trials – CT003).

Is the proposal feasible? (Yes:15 / No: 0)

Overall, all reviewers stated that the proposal is feasible and the timeline reasonable. Additionally, they agree that the team is qualified and has previous experience with multiple similar translational projects and clinical trials.

Does the project serve the needs of underserved communities? (Yes:15 / No: 0)

Reviewers agree that the proposed project addressed the needs of underserved communities and nicely identifies the underserved population and incidence that the future clinical trials will target. Of note, given the highly diverse population of patients in Southern California, likely the most diverse in the world, at UCLA, we take care of a large proportion of patients that are Latinx, Black, Asian, and Pacific Islanders and have different subtypes of melanoma. In particular, acral and mucosal melanomas are highly pigmented (TYRP-1 positive) and have a higher frequency in Latinx and Asians. Additionally, uveal (eye) melanomas are seen in all racial and ethnic subgroups and have very limited current treatment options. Finally, the project will be supported by the UCLA-UCI Alpha Stem Cell Clinic (ASCC), a first-of-its-kind, cross-institutional "Center of Excellence" to conduct stem cell clinical trials, including support for pipeline research including pre-IND and IND applications to the FDA. The ASCC attracts a diverse patient base in Los Angeles and Orange counties that together constitute about 34% of the total California population and 12% of the total U.S. population.

I will be attending the May 17, 2021 ICOC meeting and I am happy to answer any questions.

Sincerely,

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