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Dear Dr Bonneville,

Thank you for considering our appeal for our revised CIRM TRAN1-13996 (Overcoming Resistance to Standard CD19-Targeted CAR T Using a Novel Triple Antigen-Targeted Vector) which received a score of 83 which was the same as the score in the original submission. We are very encouraged by the consistent and uniformly high enthusiasm displayed by the panel in their comments on the novelty, potential impact, and thoroughness of our proposed studies. Comments that the proposal was “novel” and “unique” and “had the potential to improve patient care significantly” were brought up along with being “commended for the expertise of the PI and team”. There was also a significant component of the panel (6 out of 13) who wrote a minority opinion and felt the proposal was of exceptional merit and should be funded. After carefully going over the reviewer’s critiques, it was evident that some of points raised in the original reviews were brought up again, and perhaps we did not sufficiently explain them in the revision. This was particularly regarding the need to re-derive the vectors and perform in vivo efficacy studies. We wish to clarify this and explain this was due to key personnel changes that occurred when the primary data were obtained and published versus now moving forward towards clinical translation. Please see our point-by-point responses below which we hope will clarify the issue regarding this and mitigate such concerns which we would hope would then make the proposal a clear case for moving forward and funding. In response to specific comments raised by the reviewers:

1. “am confused - much of the proposed work seems already completed as part of that publication. Why does so much work need to be done or repeated? Indeed, several reagents to be created in the Project Plan, such as engineered target cells, are already available and used in publications by the team”

We again apologize for the ambiguity as we can see where it may have been confusing as to why such studies are proposed and in fact needed. In the revision, we pointed out in several places that the development of the vectors and preclinical efficacy work that was published had been performed when the Caring Cross collaborators who developed them on our team were at another company. Therefore, access to the primary animal efficacy data and certain reagents was no longer possible. Furthermore, the vector used for this application now involve optimization of the backbone plasmid affecting CAR production along with use of an improved producer cell line for the vector. The “payload” or CAR sequences used, are identical though, so it is expected that similar but possibly even greater efficacy can be achieved. Nonetheless, these differences then mandate rederivation from information in the public domain of both the vector and the antigen-loss cell lines used, with the current formulations in this proposal to evaluate them preclinically in order to generate primary for pre-IND studies acceptable to the FDA. This hopefully explains why we still need to perform the preclinical studies using the actual vector being generated by us for scale up. We need to have primary data on all aspects (efficacy and potential toxicities) to demonstrate to the FDA on the product to move forward for clinical translation. Fortunately, we already are in the process of starting to replicate the models and findings with the help of Caring Cross and preliminary data from the PI’s laboratory at UC Davis indicate even more robust anti-tumor effects result.

2. “The preliminary data did not compare the in vivo efficacy of the product to the tandem CD19/CD22 CAR product that failed in the clinic (even though it was compared in vitro). A resubmission should include this comparison and a discussion of its relevance to a future clinic trial.”

This is a valid point. Fortunately, we feel the primary issue has been resolved based on both the published studies on the tandem CAR issues combined with data from our group as well as other laboratories using a bi-cistronic configuration. The clinical experience at Stanford documenting that the CD22 is not as effective in a tandem format has been published and shown to be mediated signaling defects inherent to the tandem configuration (Spiegel JY et

al., ***CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial****, 2021,* Nature Medicine, PMID: 34312556). Similarly, we have published data that the bi-cistronic format precludes this defect and allows for robust CD22-mediated signaling and anti-tumor effects. Therefore, only increased efficacy is predicted, negating the need for more comparison studies involving this and other vectors. Importantly, other investigators, including investigators at NIH (Nirali Shah et al, ClinicalTrials.gov Identifier: NCT05442515) have come to the same conclusion and new protocols using a bi-cistronic CD19/CD22 bispecific approach are being evaluated clinically. Therefore, in the interests of expediency, it is likely not necessary to further confirm the signaling and functional issues associated with tandem CD22 approaches and how they can be circumvented with bi-cistronic approaches. Furthermore, what also makes our vector unique is the CD19/CD20/CD22 tri-specific targeting which adds yet another obvious advantage for tumor antigen access. This alone makes the approach unique over existing and clinically used single and double antigen-targeting constructs and allowing application for multiple B lymphoma/leukemias which can differentially express these antigens to various degrees. That being said, the in-depth studies being proposed comparing the effects of different antigen-loss tumor lines and our long-term in vivo studies should yield more revealing data on the efficacy of our product under different conditions mirroring the clinical scenario. This is important as relapse is being increasingly recognized as a growing problem with CAR therapies as longer follow-up clinical monitoring data is being generated.

3. "Much of the planned work appears to be already published"

As mentioned earlier, it is true that the basic tenets and robust data indicate that the DUO CAR is ready for clinical assessment. However, as also pointed out, this work is not industry sponsored, and key personnel involved with the generation/evaluation of the vector now are with Caring Cross, who is willing to partner with UCD to develop this clinically and to make these therapies affordable and accessible to all who need them. This means that the current vector and assessment need to be redone to meet FDA criteria since technically these are different reagents, and we cannot access primary in vivo data necessary for pre-IND studies.

Furthermore, the joint efforts between an academic medical center (UC Davis) and a non-profit organization (Caring Cross) on this project is also aimed at developing an optimal and cost-efficient CAR T cell clinical development and application approach to address efficacy, accessibility and affordability to all citizens of California. The innovations being developed on manufacturing steps as well as point of care manufacturing of this product could dramatically change the way CAR T and cell engineered products are produced in California to be more accessible and cost-effective. We want to establish a UC-centered CAR T development and clinical application program that can be emulated throughout California with partnering with private and industry to expedite clinical translation.

Finally, one of the major critiques of the initial application concerned the DEI section. This was significantly improved in our resubmission, as reflected by the scores and comments, and we hope the panel will also consider this in their overall scoring.

Thank you for your consideration of the appeal and we hope this clarifies some of the issues raised and given the very high enthusiasm among the panel and scores along with likelihood for rapid clinical translation, can be considered worthy of moving forward.

Sincerely,

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