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May 14, 2021

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

Application: TRAN1-12250
Project Title: HSC-Engineered Off-The-Shelf CAR-iNKT Cell Therapy for Multiple Myeloma
PI Name: Lili Yang, Ph.D.

Dear Members of the ICOC and Board,

We are respectfully writing to you regarding our application, that will be reviewed at the meeting of the Application Review Subcommittee (ARS) on Monday, May 17, 2021.

First we would like to thank the Grants Working Group (GWG) for their critical review of our research proposal, which received ***a median score of 84 that is only one point lower than the fundable score 85***. The GWG unanimously voted the proposal feasible (Yes/No: **14:0**), and were overwhelmingly positive about all other aspects of the proposal including necessary significance and potential for impact (Yes/No: **12:2**), sound rational (Yes/No: **12:2**), good plan and design (Yes/No: **11:3**), and importantly, the potential to serve the needs of underserved communities (Yes/No: **13:1**).

Some Highlights of GWG Review Comments

- "Multiple myeloma is a large unmet medical need."
- "Although there are many therapeutic options available for multiple myeloma, there remains a major unmet medical need for novel and potentially curative therapies."
- "Although there are multiple cell based therapies with the same target in myeloma and now an approved product, the potential advantage of the proposed solution is that it is allogeneic for HSC and may allow production of a more stable, better defined, consistent cell therapy product and will likely be cheaper."
- "The project is well planned and appears feasible. Good team and industry support. The applicants have adequately made contingency plans."
- "The iNKT cell therapy described in this proposal does not require matching between diverse polymorphic HLA haplotypes. If successful, the proposed iNKT cell adoptive cell therapy can be applied to treat all multiple myeloma patients regardless of race/HLA restrictions."
- "The inclusion of underserved communities is described and appropriate."

While we understand that our proposal is slightly below the fundable score line, we would like to take this opportunity emphasizing important aspects of our proposal and ask for the ICOC's consideration to fund this project. In particular, ***this project has several unique features making it especially suitable for CIRM's mission and its relaunched Translational Research Program (TRAN)***.

Unmet Medical Need

Our project is directly in line with the ***CIRM mission to accelerate stem cell treatments to patients with unmet medical needs; in this case, multiple myeloma (MM)***. MM is the **second most common** hematopoietic malignancy, affecting millions of people worldwide. Although novel agents such as proteasome inhibitors, immunomodulatory drugs, and autologous hematopoietic stem cell (HSC) transplantation have improved the treatment, MM remains **an incurable disease** with substantial morbidity associated with relapse including multiple bone fractures and kidney failure. In **2021** alone, it is estimated that **over 3,300 Californians** will be diagnosed with MM and **more than 1,200 Californians** will die from this disease (https://cancerstatisticscenter.cancer.org/#!/cancer-site/Myeloma). Nationwide, according to the National Cancer Institute, MM accounted for approximately **1.8% (32,000)** of all new cancer cases in the United States in 2020. Therefore, novel therapies with curative potential are urgently desired in order to address this unmet medical need.

Cell Therapy for MM- An Update

Cell therapy represents an attractive new direction for treating MM. Since after the submission of our TRAN1-12250 application in February, there has been a significant advancement in this area. On **March 27, 2021**, the U.S. Food and Drug Administration (**FDA**) approved Celgene's **Abecma**, **the first cell-based gene therapy** for the treatment of MM (https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-multiple-myeloma).

Despite its promise, the currently approved Abecma cell therapy is a personalized treatment that requires the collection and manufacturing of T cells from each individual patient, and is associated with several critical limitations:

- the therapy requires **manufacturing facilities** and cell product transportation **logistics** that **are not always available** to all MM patients in need;
- the therapy is **extremely costly**, priced at **$419,500** per patient per treatment, that is prohibitory to many MM patients;
- each cell product needs to be manufactured separately and takes time, that **delays the delivery of treatment** and may miss the time window to save patients with fast-progressing disease;
- despite the high responsive rate (70%), **the response only last on the order of months**.

Overall, the approval of Abecma marks a new era of cell therapy for MM, but calls for the development of more advanced forms of cell therapy that can address the current limitations, many particularly affect serving the needs of underserved communities.

An "Off-The-Shelf" Cell Therapy to Serve the Needs of Underserved Communities

Allogeneic cell therapies that can be manufactured at large scale with low cost, can be distributed readily to treat a broad base of MM patients, and can be curative have the potential to address the current cell therapy limitations, especially those serving the needs of underserved communities. Our **TRAN1-12250 proposal** aims to develop such an allogenic "off-the-shelf" cell therapy for MM. The recent FDA approval of Abecma encourages the development in this area. Meanwhile, although there are other lines of allogeneic cell therapy for

MM under development, they are all at quite early stage. Therefore it should be **a good timing** for CIRM to consider investing in this project.

Several aspects of our proposed **TRAN1-12250** project are particularly fit to **address the needs of underserved communities**, as highlighted below:

- Racial and ethnic disparities and the impact of socioeconomic status in cancer outcomes are well described. Based on data from the California Cancer Registry, Black patients experience inferior outcomes compared to other racial/ethnic groups across the major cancer types studied. Blacks have an increased incidence of multiple myeloma compared to Whites, younger age at diagnosis, and the mortality rate is higher for Black patients compared to White patients. Despite these figures, the majority of epidemiological studies and clinical trials underrepresent Black patients and predominantly include White patients.
- The field of cellular therapy can further the already present disparities as the likelihood of finding an HLA-matched hematopoietic stem cell (HSC) or cord blood donor among whites of European descent is 75%, whereas among Hispanics of South of Central American and blacks of South or Central American descent the probability of finding a donor was 34% and 16%, respectively. Therefore, HLA restricted cellular therapies (TCRs) or cellular therapies that require HLA-matched donors limit access to care in our diverse California population. ***Importantly, iNKT cell therapy described in this proposal does not require matching between diverse polymorphic HLA haplotypes. Thus, our iNKT cell adoptive cell therapy can be universally applied to all populations regardless of race or ethnicity.***
- The FDA approved BMCA directed therapy, Abecma®, costs **over $400,000** for the infusion which is exclusive of all other costs related to the therapy. This limits the centers available to provide the therapy and difficulty with approval and authorization from non-private insurers. The proposed "off-the-shelf" CAR-iNKT cell therapy, once developed, has an estimated cost of **~$5,000** per dose, making the therapy much more affordable.
- ***The proposed therapy uniquely addresses the underserved communities in California because it would be equally available to all patients in California without preference for race, ethnicity, sex, gender or socioeconomic status, which will overcome an unmet medical need for patients that may not have access to an alternate cell therapy due to HLA matching or cost.***

Feasibility & Deliverable

- **A Strong Research Team & Previous Successes:** This TRAN1-12250 proposal gathers **a strong research team at UCLA** comprised of scientists and physicians who are experts on immunotherapy and who are active in translational medicine, aiming to develop innovative allogeneic iNKT-based cell therapies. The research team has previously completed a CIRM supported **TRAN1-08533** project on developing an autologous HSC-engineered iNKT cell therapy that led to **a successful pre-IND meeting with the FDA**, ready the therapy for clinical trials. The research team has also successfully completed another CIRM supported **DISC2-11157** project that led to a novel *Ex Vivo* HSC-Derived CAR-iNKT Cell Culture Method enabling the proposed new TRAN1-12250 project. This new project will benefit from our pre-established strong translational team assembled under CIRM support, our pre-existing clinical platform at UCLA for developing gene-engineered HSC therapies, and our translational and clinical experiences acquired from the previous CIRM projects. ***With TRAN1 grant support,***

this promising stem cell-based off-the-shelf CAR-iNKT cell therapy will be able to enter clinics through an accelerated translational path envisioned and enabled by CIRM.

- **A Translation & Commercialization Path:** We have established industrial partnership to promote the translation and commercialization of the proposed "off-the-shelf" CAR-iNKT cell therapy for MM. In particular, **Appia Bio** is a biotechnology company committed to developing allogeneic off-the-shelf cell therapies for patients. Appia has licensed the Yang Lab's HSC-engineered off-the-shelf NKT and T cell therapy patent estate from UCLA, and is currently developing several lead allogeneic cell products; the first IND filing is expected in early 2023. While the proposed ^{Allo}BCAR-iNKT cell product is not in the company's current pipeline, Appia has offered to support the proposed TRAN1-12250 project by sharing their company experience in developing their current pipeline products. In particular, Appia can provide consultation on the CMC, IND, and clinical development of the ^{Allo}BCAR-iNKT cell product. Meanwhile, the company remains interested in the possibility to collaborate or participate in our product development at a later stage (see **Support Letter**). Notably, earlier this week Appia just announced its $52 million Series A financing (https://www.appiabio.com/appia-bio-launches-with-52-million-series-a-financing-and-establishes-scientific-advisory-board).

Potential to Address MM and Beyond

If successful, our proposed TRAN1-12250 project may lead to ***an off-the-shelf BCAR-iNKT cell therapy for MM, that is potent, economic, and ready to deliver to all MM patients in need without gender/age/genetic restricts, and can particularly serve the needs of underserved communities.*** Because iNKT cells are powerful innate immune cells equipped with multiple weapons to attack MM (i.e., through CD1d marker recognition as well as natural killer T cell killing function), such a "multi-targeting" capacity may allow the BCAR-iNKT cell therapy to counter-react tumor antigen escape and prevent MM relapse, and ***may eventually provide a cure*** for this challenging disease. Moreover, because the same "off-the-shelf" CAR-iNKT cell therapy platform can be extended to target other cancers through engineering the cells to express the corresponding CAR target molecules, the TRAN1-12250 project has the potential to develop ***a potent off-the-shelf cell therapy platform for treating a broad range of cancers and a large population of patients, and thereby has a significant impact on modern medicine and human health.***

Regarding some specific concerns from the GWG review:

- ***Data sharing plan***: We plan to abide by the principles for sharing research resources as delineated by the NIH Data Sharing Policy, as well as follow the additional data sharing requirements specified by CIRM.
- ***Preliminary data:*** Since after the submission of this TRAN1-12250 application in February, we have continued developing the project and have generated additional large set of preliminary data. In particular, we have generated preliminary data demonstrating the "triple-targeting" mechanisms that the ^{Allo}BCAR-iNKT cells can deploy to attack MM tumor cells; we also have studied primary MM patient tumor samples and validated tumor cell killing. These additional preliminary data should significantly address the related comments raised by the GWG.

We are happy to discuss this further and will present at the ARS meeting on May 17th, 2021.

Sincerely yours,

Lili Yang, Ph.D.
Associate Professor of Microbiology, Immunology & Molecular Genetics, UCLA

Together with the Advisory Board:
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RE: Dr. Lili Yang, CIRM TRAN1 (Therapeutic) Application

Dear Dr. Yang:

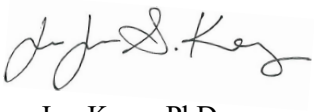
This letter serves as an attestation that Appia Bio is happy to support your CIRM TRAN1 grant application and subsequent cell therapy development.

Appia Bio is a biotechnology company committed to developing allogeneic off-the-shelf cell therapies for patients. Appia has licensed the Yang Lab's HSC-engineered off-the-shelf NKT and T cell therapy patent estate from UCLA. We are developing several lead allogeneic cell products at the preclinical stage and into IND-enabling studies. We expect to accomplish the first IND filing in 2023 with the recent Series A fundraise of $52 million.

While your proposed allogeneic BCMA-targeting CAR-engineered iNKT (^{Allo}BCAR-iNKT) cell product is not in our current pipeline, we are happy to support your project by sharing with you our experience in developing our current pipeline products. In particular, we can provide consultation on the CMC, IND, and clinical development of your ^{Allo}BCAR-iNKT cell product. Meanwhile, we remain interested in the possibility to collaborate or participate in your product development at a later stage.

Best of luck in your application!

Sincerely,



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