12/6/17

To: CIRM ICOC Board Members
Re: Application DISC2-10599, Translational Imaging Tools for Human Regenerative Therapies
PI: Alice F. Tarantal, PhD, UC Davis

Our team respectfully requests the consideration of our Quest application at the December 2017 ICOC meeting. This application addresses transformative total-body positron emission tomography (PET) imaging technology, which currently is only available in California, demonstrating unprecedented sensitivity for quantifying radiolabeled human stem/progenitor cell distribution in the context of cell transplant and tracking across age groups.

A crucial gap for effective *in vivo* imaging technologies in clinical applications of human stem cell research is the need for cell detection sensitivity, and to ensure that images can accurately quantify the number of engrafted cells at any given anatomical site. Nuclear medicine techniques, especially PET, have higher sensitivity than magnetic resonance imaging and can provide three-dimensional (3D) quantitative images deep inside the human body. However, imaging techniques with improved sensitivity to detect small quantities of cells are needed to evaluate the safety and efficiency of regenerative approaches for a spectrum of human diseases across the lifespan. The Precision Medicine Initiative is an effort to tailor disease treatment and prevention to the individual, and more effective quantitative imaging tools are needed to address personalized care.

PET is the most sensitive method for imaging and assessing molecular interactions in the human body. Current PET systems scan only a small anatomical area (Figure 1). Through NIH and other supported activities, including an NIH Transformative R01 ($15.5 million) and collaborations with industry partners, Dr. Cherry and team are near completion of EXPLORER, the world's first total-body PET scanner for humans that allows all tissues and organs to be imaged simultaneously.

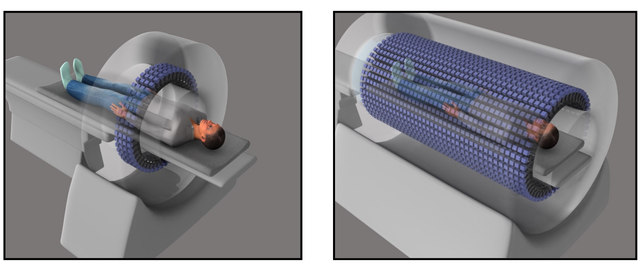

Figure 1. Image on left shows conventional PET scanner with limited coverage of the human body. EXPLORER total-body imaging shown on right covers the entire patient with all of the tissues and organs imaged at the same time. EXPLORER also significantly reduces radiation dose and scan time [Science Translational Medicine 2017 Mar 15;9(381)].

The goal of this Quest application is to demonstrate new PET applications for stem cell therapeutics using the currently available miniEXPLORER system, an established preclinical model, and tools and technologies that are in place and poised for use. This proposal will address transformative technology that is currently only available in California and will be used worldwide in the near future for patients in need. California will be a leader in developing and applying this technology for stem cell/regenerative medicine for a spectrum of human diseases that impact a range of organ systems and age groups (pediatrics to geriatrics). The EXPLORER scanner will be able to perform total-body studies *at 1/40th the current radiation dose*, allowing PET scans at fractions of the annual radiation dose individuals receive from natural background sources (e.g., round-trip flight from San Francisco to London). *A scaled version of the EXPLORER scanner is available for immediate use for the studies proposed.* The first scanner in a human clinical setting will be operational at the UC Davis Medical Center in 2018. EXPLORER systems will be in place globally by 2020, with approximately 30-50 scanners anticipated by 2024. ***The studies proposed set the stage for stem cell applications and the transformative tools developed, tested, and successfully applied in California*** (Figure 2).

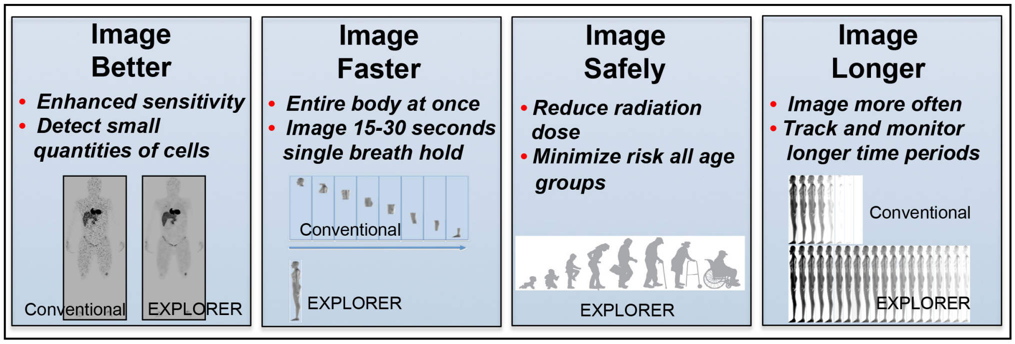

Figure 2. EXPLORER will fill a gap and a current medical need providing a stem cell imaging technology that will significantly improve patient care across the lifespan, from pediatric to geriatric applications.

This proposal includes a highly accomplished multidisciplinary team with extensive expertise in designing, building, and optimizing PET scanners for commercialization; in the design, synthesis, and *in vivo* evaluation of PET probes, biomarkers, and quantitative tools; and in the development of stem cell and gene-based therapies in preclinical primate models for translation to address human disease. Studies proposed in this Quest application will initiate and ***establish a new field of total-body PET imaging in regenerative medicine***, developing necessary methodologies and obtaining essential data in innovative ways to support translation to humans, and as new regenerative/stem cell approaches are developed and applied in human clinical trials. In the studies proposed we will compare the new EXPLORER total-body scanner to a commercial human PET/CT imaging system using sophisticated simulation tools – organoids and phantoms – to develop quantitative imaging methods with 3D constructs and defined quantities of cells to simulate tissues *in vivo*. We will also develop algorithms to suppress background in the scanner to enhance detection sensitivity for small numbers of radiolabeled cells. Cell dose selection for *in vivo* imaging will be based on these *in vitro* studies. The ability to perform total-body PET preclinically in a highly relevant primate model has immense scientific and translational value.

We were pleased that the reviewers expressed enthusiasm for the significance, potential, and rationale of the proposed studies. Reviewer comments included: **"*….outstanding technology….plenty of data to demonstrate feasibility…..wide breadth of stem cells and progenitors measured…*"** and **"*…an outstanding PI and team*"**. Some methodological concerns were raised which are primarily clarifications of data presented in the application.

With the human scanner currently under construction, **protocols that have been fully optimized and validated are needed to ensure we do not delay human applications**, including for the youngest patients in need. CIRM is in a unique position to set the stage for use of this new, transformative technology, and while California maintains a leadership position.

We hope that our application will be considered.

Respectfully submitted,

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