

To: ICOC members
From: Catriona Jamieson, MD PhD, Director, UC San Diego Sanford Stem Cell Institute and Alpha Stem Cell Clinic
Date: October 23, 2022
Re: **Response to GWG UCSD Alpha Stem Cell Clinic Review**

Dear CIRM ICOC members,

We would like to thank you for providing this opportunity to highlight the decades of experience in stem cell and gene therapy clinical trials development and administration that our team brings to the ASCC network as well as to clarify three key aspects of our proposal as outlined below.

I. Training Programs

One third of the new gift from T. Denny Sanford will be dedicated for funding faculty and fellows working in the stem cell and gene therapy research arena.

- **Clinical fellows/early career investigators:**
 - **CIRM Clinical Fellowship:** CIRM clinical trainees participate in translational clinical research and experience with **Division of Regenerative Medicine (DRM)** faculty mentorship.
 - The UCSD ASCC dedicated CIRM Clinical Fellowship Training Program will commence in 2023 as a stand-alone one-year elective program that will accept 4 eligible fellows a year to train for 3 months on the inpatient Cell and Regenerative Medicine, 3 months at the ASCC outpatient clinic in the Koman Outpatient Pavilion (KOP), 3 months in the advanced cell therapy lab (ACTL) and 3 months in the Sanford Stem Cell Innovation Center or laboratory at SCRM. Participation in the UCSD CIRM Scientific Training Program, Sanford Symposia and DRM lecture series will be required.
 - **Fellows represent California demographics and are selected partly based on their contribution to diversity, equity, inclusion, and accessibility programmatic goals.**
 - Demonstrating ASCC Network collaboration: UCSD ASCC will consult UCSF ASCC for their expertise to build a complementary Cell/Gene Therapy physician-scientist training program.
 - The **Translational Regenerative Medicine (TRM) course** within the Master of Applied Studies CREST will be provided for all clinical fellows and may be expanded with other electives to obtain a Master of Advanced Studies degree. Notably, DRM faculty receive support for teaching from the Sanford Stem Cell Institute. The TRM course focuses on patient-based research within stringent ethical and regulatory guidelines in academia and industry. (Also available to junior faculty, PharmDs, and research associates.)
 - **Advanced Cell Therapy Center training** will be provided for fellows.
 - **Sanford Stem Cell Innovation Center training** will be provided as part of the fellowship program to understand therapeutics development platforms.
 - **Sanford Stem Cell Center basic and translational laboratory training** opportunities will be provided for physician scientists.
 - **Regulatory and clinical trials** training will be provided for clinician

scientists.

- **Staff/Nurses/Research coordinators:**
 - UCSD ASCC nursing staff medical education will be supplemented with City of Hope CIRM Cellular Therapies Clinical Nursing Education Curriculum.
 - Recruitment of future research coordinators will be strengthened by supporting staff to participate in the UCI Certificate Training Programs for Medical Professionals and Clinical Research Coordinators.
- **Investigators:**
 - **Sanford Surgical Training Center:** Training in neural stem cell implantation procedures using state-of-the-art surgical techniques, equipment, stabilization platforms, and porcine models. Includes: a) Stem Cell Training Center, b) Intraoperative Imaging Capabilities, c) Neurosurgical Training and device development program, and d) Analytical Assay Capabilities.
 - **Preclinical FDA Regulatory Compliance Training for Regenerative Medicine Therapies:** A) Regulatory Process and Terminology; B) Regulatory Process and Regulatory Issues for Cellular Therapies; C) Good Documentation Practices.

II. Value Add to the Alpha Stem Cell Clinic Network/Cell and Gene Therapy

- **ASCC UCSD demonstrates a track record of accelerated clinical trial development with 30 clinical trials launched in seven years since inception.**
- World class genomics, imaging technologies and stem cell science at UCSD have accelerated design and implementation of innovative clinical trials by UCSD ASCC faculty members together with CIRM and local industry partners, including three FDA approved therapies by the PD and many first-in-human regenerative medicine trials that have expanded to the ASCC network.
- Cell and gene therapy studies represent the majority of UCSD ASCC trials because of growing partnerships within the San Diego biotech and pharma hub, which consists of over **600 companies**, and will expand with Sanford START pre-IND and IND enabling program support.
- **Highlights/Demonstrated ASCC network collaborations and value to the network:**
 - **Enhancing HSC engraftment with engineered human endothelial cells (E-CEL cells)**
 - Phase 1 study of AB-205 (E-CELERATE) in Hodgkin or non-Hodgkin lymphoma following autologous stem cell transplantation (Angiocrine, NCT03925935; COH reliant site). This is CIRM funded through a CLIN2-11371.
 - **Switchable CAR-T cell trial**
 - Phase 1 study which was initiated at UCSD ASCC reveals that seven of nine patients showed a response (78%), with six of nine showing a complete response (67%) (Calibr/AbbVie, NCT04450069).
 - **iPSC-derived NK cells**
 - FT500 as Monotherapy and in Combination with Immune Checkpoint Inhibitors in Subjects with Advanced Solid Tumors (Fate Therapeutics, NCT03841110).
 - **CAR-T cells targeting Stem cell properties in Cancer**
 - A Phase 1b/2, open label, multi-center, clinical study of CAR-T targeting Claudin 18.2 in patients with advanced gastric, pancreatic, or other specified digestive system cancers (CARsgen Therapeutics, NCT04404595). Recruiting at

Hematopoietic Stem Cell Gene Therapy for Cystinosis

- Phase 1/2 study of stem cell gene therapy for cystinosis (NCT03897361; UCSD ASCC). This is a CIRM funded grant, CLKN2-11478. Enrollment target met.

Pipeline

- Compassionate-Use IND. UCSD supported UCLA in a compassionate use IND filing that cross-referenced UCSD IND# 117975 for cirmtuzumab, which was developed at UC San Diego with CIRM funding (PI Carson; Co-PI Jamieson, CIRM DR1-01430) in patients with relapsed or refractory chronic lymphocytic leukemia (NCT02222688). The close relationship between respective ASCC sites facilitated rapid document transfer for IRB approval of cirmtuzumab. This is now progressing to a Phase 3 Study sponsored by Oncternal that will open at UC San Diego and other ASCC sites.

- **Lead Offerings to Network Partners:**

- **CIRM Clinical Fellowship Program:** Opportunity for CIRM clinical fellows to utilize the robust the Sanford Stem Cell Institute and UCSD ASCC regenerative medicine infrastructure for cellular therapy and other advanced regenerative medicine therapies.
- **Sanford Molecular Imaging Facility:** Access to in vivo monitoring studies of engrafted stem cells/other cellular therapies in clinical trials and preclinical models for faculty and fellows through our CIRM funded training grant and the Sanford Stem Cell Institute.
- **Advanced Cell Therapy Laboratory (ACTL):** Provides GMP manufacturing and training services to investigators and clinical fellows as they transition cell therapies through IND-enabling and Phase 1/2 clinical studies.
- **Stem Cell Genomics and Bioinformatics Core:** A) Identification of stem and progenitor DNA somatic mutations; B) Sample mutational burden and mutational signatures; C) Stem and progenitor cell transcriptomics; D) Comparative analysis of stem cell genomics and transcriptomics data.
- **Sanford Surgical Training Center:** Porcine-model training for ASCC site PIs and CIRM clinical fellows to develop core competencies in neural stem cell and other stem cell implantation techniques. Training for other surgical interventions with stem cells and devices that enhance endogenous repair and regeneration.
- **Strategic Research Advising Team (START):** Advising services including FDA regulatory path and strategy guidance as well as training for CIRM clinical fellows within the ASCC network.
- **Biostatistics and Data Management Services:** FDA-compliant database and training.

III. Diversity, Equity, Inclusion, and Accessibility (DEIA)

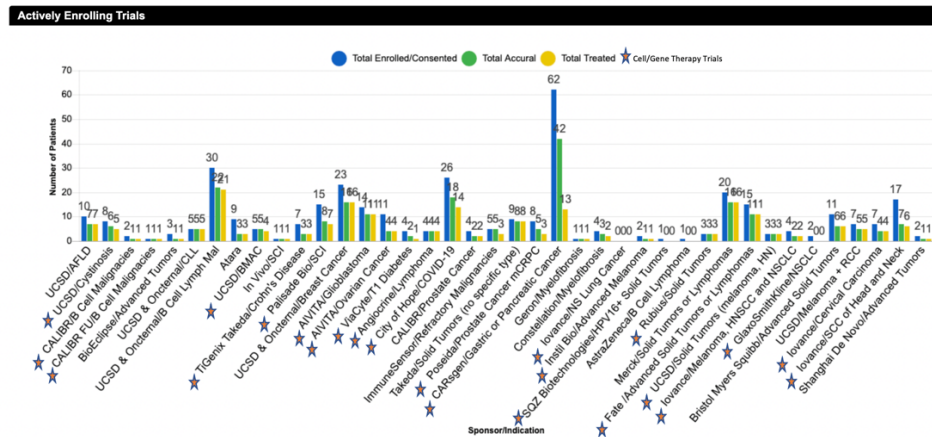
To ensure greater DEIA in our Sanford Stem Cell Institute ASCC, we have hired Mary Bass, former Executive Director from the Americans for Cures Foundation to strategically coordinate community outreach, ASCC collaborations with CIRM Community Care Centers, faculty engagement and workforce training.

- Because the UCSD Health System provides care for a large under-served population (>\$599 million in charity care in 2021) in San Diego, Palm Springs and El Centro, the

- UCSD ASCC Cell and Regenerative Medicine (ASCC CRM) service has enrolled **533** racially and socioeconomically diverse patients (**1.4:1 male to female; 28% non-white patients** including **15% Hispanic/Latinx patients**) to **59 clinical trials** with **53% of enrollees** recruited to cell and gene therapy trials.
- By increasing to four dedication clinical coordinators at our downtown Hillcrest hospital that serves the underserved communities and regulatory staff, Telehealth and EPIC EMR patient eligibility evaluation as well as genomic stratification for patients at UCSD and partner health centers, the aim is to enroll **6% Black/African American, and 30% Hispanic/Latinx patients.**
 - Coordinate these activities with UC San Diego Health Community Advisory Board, Office for DEI, access to Trial Experts' networks of patients and patient advocacy groups, community liaison, and programs delineated in the full proposal.
 - **Community Trial Education** will include expansion to health care providers at community health centers, development of multilingual content and accessible communication methods via digital, phone, and email.
 - A **Regenerative Medicine Education platform** will feature video content targeting the lay public with content on stem cells, ASCC facilities, trial education, current clinical trials, and screening services.
 - **Social media engagement** will provide education regarding clinical trials in stem cell and gene therapies and enhance adherence to clinical trials thereby leading to increased rates of trial completion. **Social media analytics will be implemented as metrics for website usage and circulation. Danielle Lewis is our dedicated communication director who will be leading this effort.**
 - **Community Accessible Regenerative Medicine Acceleration (CARMA)** bus program will be initiated to enhance trial accrual and completion by providing clinical trial laboratory follow up closer to home, as well as educational seminars for surrounding hospitals with our Nurse Practitioner, Athena Mohebbi, PhD, FNP-BC, BC-ADM.
 - **Sanford Stem Cell Clinical Center:** Funds will support clinical trial participants in need of transportation, lodging, and childcare to access trials. Clinical trial budgets will also be negotiated to help support and cover expenses to support patients from priority populations.
 - **Hillcrest Medical Center Trial Site:** Partner with the UCSD Moores Cancer Center and UCSD Health System to open a new Hillcrest trial site.
 - **Eisenhower Medical Center:** Expand access to cancer stem cell targeting and cellular therapy clinical trials at the Eisenhower Medical Center in Rancho Mirage, which has a **58% non-white** service area population.
 - **Innecare:** Develop recruitment partnerships with Innecare, a federally qualified health center that provides healthcare services to over 50,000 people to increase awareness of trials in underserved communities.
 - **UCI ASCC AI/Machine learning approaches for patient recruitment:** Partner with UCI to analyze electronic health records to help identify clinical trial eligibility.
 - **UCI ASCC Real-world Laboratory for Developing a Micro-Network, Quality Design Studios, and Interoperability Assessment:** Complement in-house efforts to implement DEI principles into clinical trial protocols by participating in UCI ASCC's Quality Design Studios program.

- **Data platform for monitoring accrual:** The Data team will track trial metrics, including trial launch, enrollment, and treatment, in real time and share weekly reports with the Alpha Clinic and Research team. Research PIs and experts will be engaged in Alpha Clinic meetings once quarterly to review if trial milestones are being met and to review safety profiles of investigational products (Figure 1 and Table 1 below).

Figure 1. Active UCSD ASCC CRM Clinical Trials

**Table 1.**

Network Value of UCSD ASCC Cell and Regenerative Medicine (SSC CRM):

Active Clinical Trials: 41	Total consented/enrolled: 366	Total accrued: 243
Industry Trials: 31	Total consented/enrolled: 249	Total treated: 199
Investigator initiated trials: 10	Total consented/enrolled: 117	
Cellular and gene therapy active trials: 22 (54%)		
Cellular and gene therapy active enrolled: 201 (56%)		

Total trials ever: 59 Cell/Gene therapy: 57%

Total trial enrollment ever: 541 Cell/Gene therapy: 53%

Pipeline trials: 9/16 (56%) are Cell/Gene therapy

CIRM UCSD ASCC Fellowship Training Program:

A CIRM UCSD Fellowship Training Program will be established for 4 fellows annually in 2023 as a 12-month clinical fellowship, consisting of 3 months on the Cell and Regenerative Medicine (CRM) Service and 3 months in the outpatient stem cell clinic in KOP, as well as 6 months of clinical or translational research with a dedicated mentor with the Division of Regenerative Medicine (DRM) and Sanford Stem Cell Institute. Additional training will be provided through the Translational Regenerative Medicine course; Sanford Regulatory training for TPPs, Pre-INDs and INDs; the Sanford Surgical Training Center; and the existing CIRM Scientific Training Program and DRM Seminar Series.

The Division of Regenerative Medicine provides faculty support to train fellows. While DRM faculty receive FTE support, fellows will be eligible for additional research funding through the Sanford Cell Institute.

DEIA Recruitment and Retention Plans:

Current demographics: Male to female ratio 1.4:1. Participants of non-White race 28%. Hispanic/Latinx 15%.

Goal for DEI in the future will be 6% or more Black/African American and 30% or more Hispanic/Latinx.

Within first year UCSD ASCC will establish an independent community advisory board and DEI program to bolster existing community engagement and DEI programs.