CALIFORNIA'S STEM CELL AGENCY

MEMORANDUM

TO: CIRM GOVERNING BOARD
FROM: CIRM LEADERSHIP
SUBJECT: Proposal to expand project eligibility to gene therapy
DATE: NOVEMBER 15, 2018

BACKGROUND

On October 11, 2018, the Science Subcommittee of the Governing Board discussed changes to the eligibility of projects applying to the CIRM translational and clinical funding opportunities. The Subcommittee recommended removing eligibility of small molecules and biologics to the TRAN and CLIN1 programs as proposed by the CIRM team, but also raised the possibility of expanding eligibility to gene therapy projects.

On October 18, 2018, the Governing Board discussed expanding eligibility of CIRM translational and clinical projects to gene therapy. The Board recommended that the CIRM team clearly define the scope of eligible gene therapy projects, with a request to include only those with a regenerative medicine aim, and provide examples of projects that would or would not be eligible under the proposed change.

On November 8, 2018, the Science Subcommittee of the Governing Board considered this revised proposal to expand eligibility to gene therapy approaches for the CIRM translational and clinical funding opportunities. The Subcommittee recommended that the proposed changes be considered by the full Governing Board. In addition, they recommended that the process for determining that a project represents a "vital research opportunity" be conducted on a project by project basis at the GWG rather than have the GWG make this an a priori declaration for all eligible gene therapy projects.

RATIONALE FOR ADDING GENE THERAPY PROJECTS

CIRM consistently seeks to maximize opportunities that can accelerate treatments to patients with unmet medical needs. CIRM was founded on the promise that stem cell research and related technologies would help deliver regenerative medicine therapies that are not just palliative, but durable and curative. Since 2005, CIRM has contributed to

a significant advancement of regenerative medicine through its stem cell-based programs and the field as a whole has now seen the first FDA approvals for cell and gene therapy with CAR T cell technology. Reflecting on this milestone, the FDA Director, Scott Gottlieb, remarked in a statement given in September 2017 that "we've now reached a momentous inflection point in science". Enactment of the 21st Century Cures Act was, in part, an acknowledgement of an incoming wave of innovative products poised to pursue market approval. The Act specifically carved out a new expedited program, akin to existing fast-track and breakthrough therapy designations, where regenerative medicine products intended to treat a serious or life-threatening condition can receive a regenerative medicine advanced therapy (RMAT) designation. As of October 2018, the FDA has granted 27 RMAT designations for cell and/or gene therapy products.

Clearly, there is a growing wave of regenerative medicine treatments that are a culmination of efforts in both cell therapy, where improved cell production, differentiation, and delivery methods have developed; and gene therapy, where more rapid, safe, and precise approaches to manipulating genes have emerged. CIRM has supported projects that combine stem cell and gene therapy technologies, such as the gene-corrected stem cell transplants at UCLA that essentially cured 5-year old Evangelina Padilla Vaccaro and several CAR-T cell approaches using stem memory T cells that aim to tackle various cancers. The support of stem cell research that contributes to these treatments is and will continue to be the core of CIRM funding. However, treatment opportunities in regenerative medicine that utilize gene therapy technologies but not necessarily stem cells are also valuable and worthy of pursuit.

Examples of gene therapy that are regenerative and potentially curative that would not obviously involve stem/progenitor cells include the targeted *in vivo* delivery of genes to the liver to produce critical factors missing in hemophilia B or other blood clotting disorders; the targeted correction of mutated dystrophin gene in muscle cells for muscular dystrophy; and genetically engineered T cells that specifically target cancer cells. Similarly, fundamental stem cell research on lineage fate determination has led to "direct lineage reprogramming" which is accomplished through manipulation of gene expression in one differentiated cell type resulting in the conversion to another. Examples include the conversion of fibroblasts into cardiomyocytes or hepatocytes to replace damaged or diseased heart or liver cells, respectively. In instances, where stem/progenitor cells are not clearly utilized or targeted, these approaches would not be eligible for CIRM funding.

The field of regenerative medicine brings together technologies that include stem cells, gene therapy, and tissue engineering that in many cases combine to produce a therapeutic product. In some cases, one technology leads the way. For CIRM and the patients it aims to serve, it is vital to support technologies which prove to be highly complementary and augmenting to stem cells, such as gene therapy. Therefore, CIRM is seeking to expand eligibility to projects that propose a gene therapy approach intended as a regenerative medicine therapy for a rare or unmet medical need.

REQUESTED ACTION

To address previous concerns related to the scope and definition of gene therapy, CIRM recommends that project eligibility in the CIRM translational and clinical programs include a therapeutic candidate that is:

*A gene therapy approach (**i**) that targets a stem cell for its therapeutic effect, OR any other somatic cell if deemed a "vital research opportunity" by the CIRM Grants Working Group; AND (**ii**) is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs; AND (**iii**) is being developed for a rare or unmet medical need unlikely to receive funding from other sources.*

Additionally, CIRM recommends that we define "gene therapy" for the purpose of these solicitations as follows:

CIRM considers gene therapy to mean a human therapeutic intervention intended to: 1) alter the genomic sequence of cells or 2) alter the cellular lineage via gene delivery (i.e., direct lineage reprogramming). The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, introduce new or modified genes that augment the therapeutic potential of the target cells.

CIRM requests the Science Subcommittee's approval to modify the concept documents and related Program Announcements with the changes proposed above.