CALIFORNIA'S STEM CELL AGENCY

MEMORANDUM

TO: APPLICATION REVIEW SUBCOMMITTEE OF THE GOVERNING BOARD
FROM: CIRM LEADERSHIP
SUBJECT: CIRM Team recommendations regarding TRAN applications
DATE: JULY 2019

The GWG recommended seven TRAN1 applications for this cycle requesting a total amount of $30.7M. There are currently $20M available in the budget approved by the ICOC for the TRAN program in 2019. CIRM has recovered about $19.3M in funds that are currently unallocated but which the ICOC will have an opportunity to allocate as deemed appropriate at the September ICOC meeting.

The CIRM Team recommends that the Application Review Subcommittee approve funding of four recommended applications, which will use the available $20M and leave consideration for the remaining 3 applications open for possible allocation of funds in September. We suggest the following:

The CIRM Team recommends approval of the following 2 applications (highest scores):

TRAN1-11536
TRAN1-11532

The CIRM Team recommends approval of any 2 of the following, with remaining 1 held open for possible future allocation of funds (all very similar scores and all in neurobiology field):

TRAN1-11579
TRAN1-11548
TRAN1-11628

The CIRM Team recommends holding open the following applications for possible future allocation of funds:

TRAN1-11555
TRAN1-11544

We are providing additional portfolio information (appended) regarding these applications for your consideration during programmatic review.

Portfolio Information for TRAN Applications Recommended by GWG

Application #: TRAN1-11536
Type application: Pre-clinical development of therapeutic candidate
Median Score: 92 (mean=92)
Title: Ex Vivo Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-linked Hyper-IgM Syndrome
Requested Funding: $ 4,896,628
Indication: Treatment of X-linked Hyper-IgM Syndrome, an ultra-rare immune deficiency disease
Therapeutic Approach: ex vivo correction by CRISPR/Cas9 of the defective CD40L gene in the patient's own hematopoietic stem/progenitor cells prior to transplantation back into the patient
Candidate: Autologous human hematopoietic stem cells (HSCs) that have been gene corrected at the CD40L gene locus

Portfolio Consideration:

- CIRM currently funds 1 discovery-stage project in this disease area, which elucidated the actual therapeutic candidate to be further developed in this TRAN1 proposal.

- CIRM currently funds 23 awards pursuing autologous, gene-modified HSCs as a therapeutic platform for treating blood/immune diseases
    - 5 grants (4 projects) utilizing CRISPR/Cas9 for gene correction (2 DISC2, 1 TRAN1 closing/progressing into CLIN1; 1 CLIN1)
    - 16 utilizing lentiviral vectors to deliver therapeutic gene modification (9 clinical trials, 2 CLIN1, 2 TRAN1, 3 DISC2)
    - 2 utilizing zinc finger nuclease strategies for gene editing (clinical trials stage)

- Category of CIRM technology focus and interest: Gene modified cell therapy

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Application #: TRAN1-11532
Type application: Pre-clinical development of therapeutic candidate
Median Score: 88 (mean=86)
Title: PRPE-SF, Polarized hESC-derived RPE Soluble Factors, as a Therapy for Early Stage Dry Age-related Macular Degeneration
Requested Funding: $ 3,733,556
Indication: dry Age-related Macular Degeneration
Therapeutic Approach: Biologic that does not target one specific mechanism but rather its multitude of factors may work through a combined paracrine mechanism
Candidate: Preparation of soluble factors from cultured polarized retinal pigmented epithelial cells (RPE) derived from hESC.

Portfolio Considerations:

- CIRM currently funds 9 active awards addressing vision loss, 8 focused on retinal diseases and 1 on corneal injury

    - 5 development stage cell therapies (2 CLIN2/DR3A, 3 TRAN) to treat AMD and/or retinitis pigmentosa; 2 discovery-stage projects using PSC are deriving retinal tissues for modeling retinal disease and/or exploring retinal cell replacement strategies; 1 discovery stage award is pursuing a small molecule therapy for gene-specific photoreceptor disease
    - The therapeutic candidate differs from other candidates in the CIRM portfolio of blinding eye diseases in that it develops a biologic rather than a cell-based or small molecule approach

- This approach leverages preclinical and manufacturing experience developed through prior CIRM-funded awards

- Category of CIRM technology focus and interest: Soluble factor preparation is manufactured from polarized hESC-derived RPE (Uniquely fundable by CIRM)

Application #: TRAN1-11579
Type application: Pre-clinical development of therapeutic candidate
Median Score: 85 (mean=85)
Title: Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Cord Injury (SCI)
Requested Funding: $ 6,235,897
Indication: Spinal cord injury
Therapeutic Approach: Combination product focuses on restoration of the connectivity of the population of axons severed by the injury
Candidate: A combination product composed of allogeneic human ESC-derived neural stem cells with a spinal cord identity in a gel-like matrix containing growth factors.

Portfolio Considerations:
- Unique approach reletive to other SCI grants in CIRM portfolio.

- CIRM currently funds 6 projects developing therapies for spinal cord injury including 1 clinical trial stage (CLIN2) and 2 discovery stage projects; 2 additional discovery stage awards are developing tools for use in understanding and developing SCI treatments

- Award would advance previously funded project into preclinical development. The candidate was identified under prior and current CIRM grants

- Category of CIRM technology focus and interest: PSC-derived differentiated derivatives (hESC-derived NSC), cell therapy (Uniquely fundable by CIRM)

Application #: TRAN1-11548
Type application: Pre-clinical development of therapeutic candidate

Median Score: 85 (mean=84)
Title: An Optimized Human Neural Stem Cell Line (hNSC) for the Treatment of Traumatic Brain Injury (TBI)
Requested Funding: $ 4,833,271
Indication: Traumatic brain injury
Therapeutic Approach: Transplanted cells in the injured CNS result in integration, neuro-protection, and anti-inflammation
Candidate: hESC-derived neural stem cells enriched for CD133, a neural stem cell marker

Portfolio Considerations
- CIRM currently funds 1 discovery-stage project in this disease area

- Award would advance previously funded project into preclinical development. The candidate was identified under prior and current CIRM grants

- Category of CIRM technology focus and interest: PSC-derived differentiated derivatives (hESC-derived NSC), cell therapy (Uniquely fundable by CIRM)

Application #: TRAN1-11628
Type application: Pre-clinical development of therapeutic candidate
Median Score: 85 (mean=84)
Title: Human Neural Stem Cells (hNSCs) for Neuroprotection in Perinatal Hypoxic-Ischemic Brain Injury (HII)-Pre-IND-Enabling Studies
Requested Funding: $ 4,963,684
Indication: Perinatal hypoxic ischemic brain injury, a common cause of cerebral palsy and cognitive disability
Therapeutic Approach: Transplanted cells exert a neuroprotective effect against hypoxic-ischemic brain injury
Candidate: Established stable human neural stem cell line

Portfolio Considerations:
- The targeted indication is unique in the CIRM portfolio

- Category of CIRM technology focus and interest: Cell therapy

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Application #: TRAN1-11555
Type application: Pre-clinical development of therapeutic candidate
Median Score: 85 (mean=83)
Title: BCMA/CS1 Bispecific CAR-T Cell Therapy to Prevent Antigen Escape in Multiple Myeloma
Requested Funding: $ 3,176,805
Indication: Multiple Myeloma
Therapeutic Approach: Bi-specific CAR T targeting tumor specific antigens

Candidate: Autologous T-cell therapy enriched in stem-cell memory phenotype engineered ex vivo to express a single-chain bispecific chimeric antigen receptor (CAR) targeting BCMA and CS1

Portfolio Considerations:

- CIRM currently funds 2 projects targeting multiple myeloma: a clinical trial award (CLIN2) using an autologous CAR T cell strategy that targets the BCMA antigen, and a Translational stage project with an immunotherapy approach

- CIRM currently funds 5 additional projects employing autologous CAR-T technologies for various cancers including ovarian (DISC2), glioma (DISC2, CLIN2), B cell malignancy (CLIN2) and prostate cancer (CLIN1)

- The therapeutic candidate differs from other CAR-T candidates in the CIRM portfolio in terms of its bispecific targeting strategy, although one of the targeted antigens (BCMA) is the target of a currently CIRM funded CAR CLIN2 award (referenced above)

- Category of CIRM technology focus and interest: Gene-modified cell therapy

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Application #: TRAN1-11544
Type application: Pre-clinical development of therapeutic candidate
Median Score: 85 (mean=83)
Title: Neural Stem Cell-mediated Oncolytic Immunotherapy for Ovarian Cancer
Requested Funding: $ 2,873,262
Indication: Ovarian cancer metastases
Therapeutic Approach: Elimination of tumor cells via cell based delivery of an oncolytic virus
Candidate: Allogeneic tumor-tropic neural stem cell for delivery of oncolytic virotherapy

Points for Consideration:

- May have an accelerated path toward the clinic as leverages technology, protocols and expertise gained in prior and ongoing clinical trials (with related and actual candidate)

- CIRM currently funds 17 projects addressing solid tumors, 3 of which target ovarian cancer; the 3 ovarian cancer projects are all discovery stage (one hypothesis testing project (DISC1), two candidate discovery projects (DISC2); the DISC2 projects are developing an iPSC-derived immunotherapy and a CAR T cell approach

- The therapeutic candidate employs an approach and technology (oncolytic virotherapy) that is unique within the CIRM portfolio

- Category of CIRM technology focus and interest: Gene-modified cell therapy