CIRM Hemoglobinopathy Programs

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ICOC Meeting

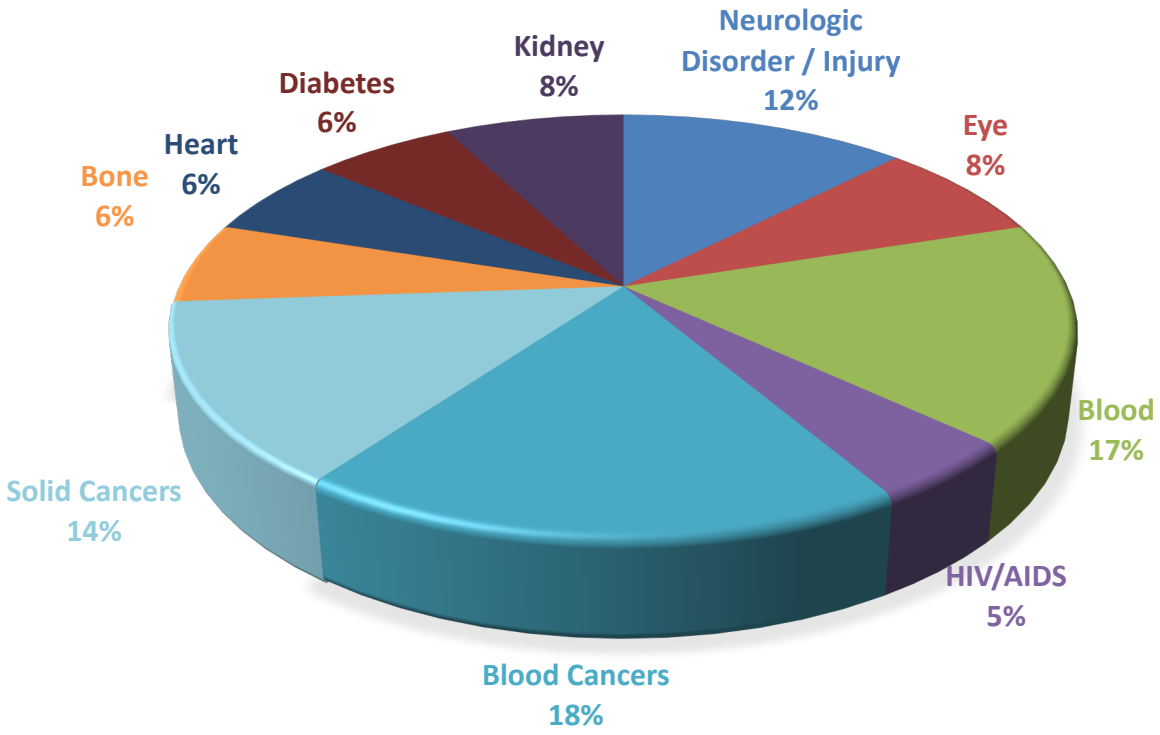
MISSION

CIRM's Mission

Accelerate stem cell treatments to patients with **unmet medical needs.**

CIRM
CALIFORNIA'S STEM CELL AGENCY

Diverse Therapeutic Portfolio

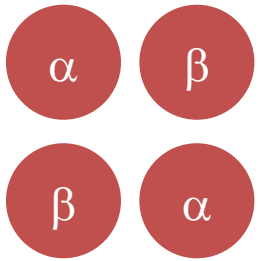


49 Clinical Trials (40 active)

12 Preparing IND

CIRM-FUNDED HEMOGLOBINOPATHY PROGRAMS

Hemoglobinopathies: A Family Of Severe Or Fatal Diseases



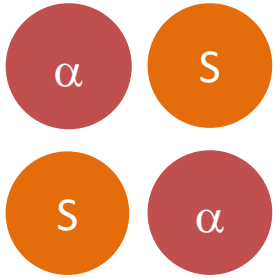
Hemoglobin is a multi-subunit molecule in red blood cells that carries oxygen throughout the body

- Sickle cell disease: Defective β-hemoglobin
- Beta thalassemia: Too little β-hemoglobin
- Alpha thalassemia: Too little α-hemoglobin

Sickle Cell Disease (SCD) Unmet Need

- Affects 100,000 in the U.S.
- Higher rates in African Americans, Hispanics
- Anemia, severe pain, stroke, organ damage
- Average lifespan in U.S. ~ 40 years

Hemoglobin "S"

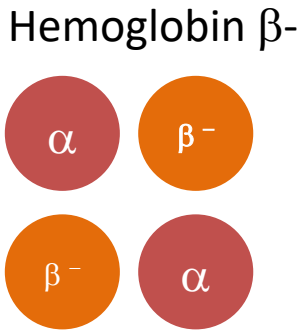


- **CIRM funds four SCD therapeutic programs**
  - Kohn (UCLA): Phase 1 trial
  - Rosenthal (City of Hope): Phase 1 trial
  - Porteus (Stanford): IND-enabling
  - Walters (CHORI): Translational

CIRM
CALIFORNIA'S STEM CELL AGENCY

Beta Thalassemia Unmet Need

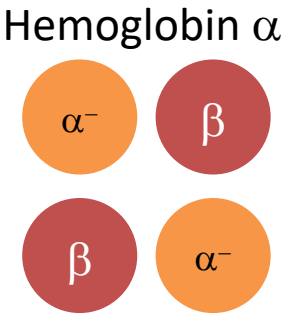
- 60,000 new cases each year, worldwide
- Higher rates in Middle East, Africa, Central Asia
- Severe life-long anemia
  - Requires frequent blood transfusions
  - 20% of *treated* patients have lifespan < 40 years



- **CIRM funds one beta thalassemia program**
  - Conner/Sangamo: Phase 1 trial

Alpha Thalassemia Unmet Need

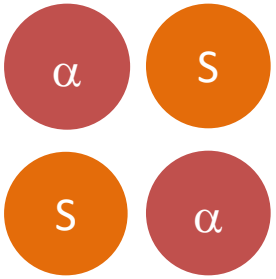
- 1000s of fetuses annually worldwide; >100/year in the U.S.
  - Most die of heart failure or are terminated
  - Survivors to birth require regular red blood cell transfusions



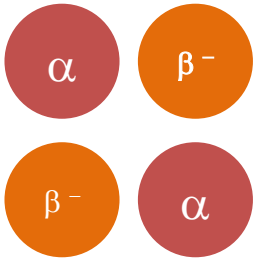
- **CIRM funds one clinical stage program**
  - MacKenzie/UCSF: Phase 1 trial

Potential Cures for Hemoglobinopathies

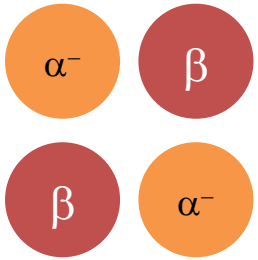
Hemoglobin "S"



Hemoglobin β-



Hemoglobin α

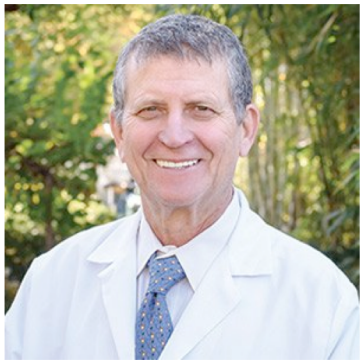


CIRM funded hematopoietic stem cell transplant approaches:

- Half-matched (related donor) transplant (2)
- Gene addition to patient's own blood stem cells (1)
- Gene editing of patient's own blood stem cells (3)

HALF-MATCHED BLOOD STEM CELL TRANSPLANT

Treatment Of SCD By Induction Of Mixed Chimerism And Immune Tolerance Using CD4+ T-Depleted Haploidentical Blood Stem Cell Transplant



Investigator:
Joseph Rosenthal, MD

Institution:
City of Hope

Stage

- Phase 1 trial

Approach

- Transplant genetically half-matched donor blood stem cells after chemical conditioning
- Mild conditioning to allow more patients to be treated

Goal

- Primary: Safety, feasibility
- Secondary: Induction of mixed chimerism

HALF-MATCHED BLOOD STEM CELL TRANSPLANT *IN UTERO*

In Utero Hematopoietic Stem Cell Transplantation For The Treatment Of Fetuses With Alpha Thalassemia Major

Investigator:
Tippi MacKenzie, MD

Institution:
UCSF

Stage

- Phase 1 trial

Approach

- Transplant maternal blood stem cells to fetus in the womb

Goal

- Primary: Safety of mother and fetus
- Secondary: Feasibility; efficacy (maternal/fetal blood chimerism)

GENE ADDITION TO PATIENT'S OWN STEM CELLS

Clinical Trial Of Stem Cell Gene Therapy For Sickle Cell Disease

Investigator:
Don Kohn, MD

Institution:
UCLA

Stage

- Phase 1 trial

Approach

- Transplant patient's own gene-modified blood stem cells

Goal

- Primary: Safety, feasibility
- Secondary: Hematopoietic recovery; RBC function; Quality of life assessment

GENE EDITING OF PATIENT'S OWN STEM CELLS

A Phase 1/2 Study Of ST-400 Autologous HSC Transplant In Transfusion-Dependent Beta Thalassemia

Investigator:
Ed Conner, MD

Institution:
Sangamo Therapeutics

Stage

- Phase 1/2 trial

Approach

- Transplant patient's own blood stem cells after gene editing with zinc finger nucleases

Goal

- Primary: Safety
- Secondary: Levels of fetal hemoglobin, frequency of transfusions required

Genome Editing Of Autologous Hematopoietic Stem Cells To Treat Sickle Cell Disease

Investigator:
Matthew Porteus, MD

Institution:
Stanford University

Stage

- IND-enabling studies

Approach

- Use CRISPR/Cas9 gene editing to correct defective beta globin gene in patient's own blood stem cells

Goal

- Complete pre-clinical safety studies and manufacturing of cell product for a trial
- File IND application with FDA

Curing Sickle Cell Disease With CRISPR-Cas9 Genome Editing

Investigator:
Mark Walters, MD

Institution:
Children's Hospital of Oakland Research Institute

Stage

- Translational

Approach

- Use CRISPR/Cas9 gene editing to correct defective beta globin gene in patient's own blood stem cells

Goal

- Optimize gene editing conditions in stem cells
- Establish clinical grade manufacturing protocol
- Hold pre-IND meeting with FDA

Development of a Noninvasive Prenatal Test for Beta-Hemoglobinopathies for Earlier Stem Cell Therapeutic Interventions

Investigator:
Cassandra Calloway, PhD

Institution:
Children's Hospital of Oakland Research Institute

Stage

- Translational (Diagnostic)

Approach

- Sequence fetal DNA in mother's blood to screen for beta thalassemia and sickle cell anemia mutations

Goal

- Develop a clinical grade non-invasive prenatal test for beta hemoglobinopathies

Conclusions

- Cures for hemoglobinopathies are a major unmet need
- Multiple approaches to a cure are being investigated
  - Safer treatments
  - Available to many more patients
- Success can translate to other genetic blood diseases

Questions?