Agenda Item #12
ICOC Meeting
June 15, 2016

CIRM 2.0
CALIFORNIA'S STEM CELL AGENCY

Hematopoietic Stem Cell Gene Therapy

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Hematopoietic Stem Cell (HSC) gene therapy

- Background about HSC
- Challenges in HSC transplantation
- Gene therapy plus HSC transplantation
- CIRM HSC gene therapy portfolio

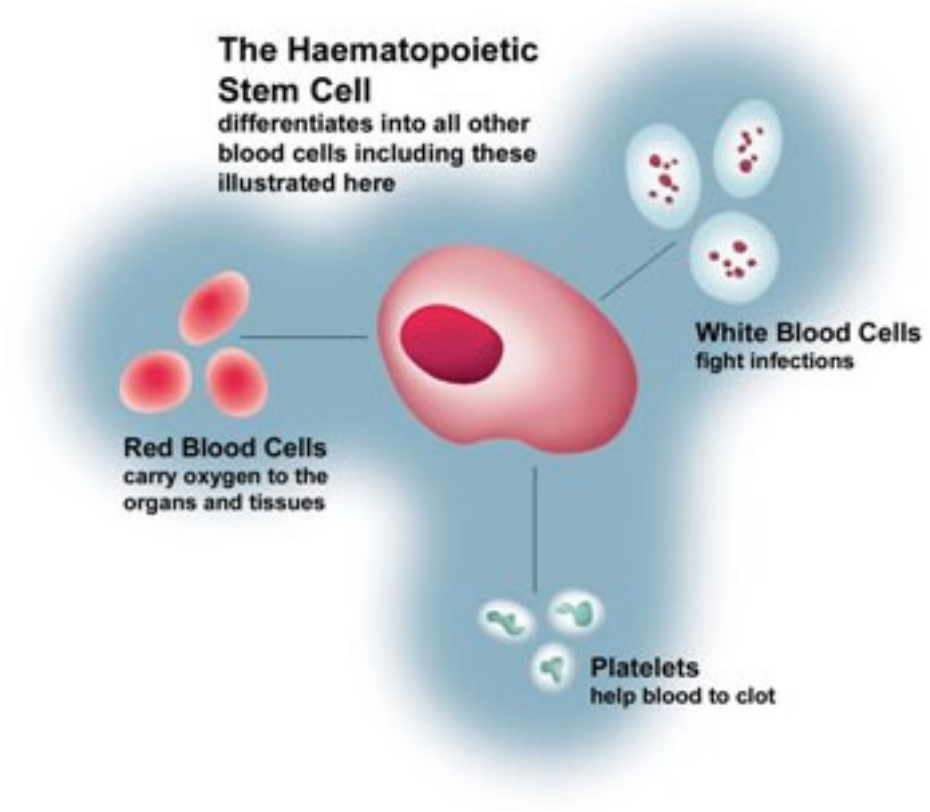
Hematopoietic Stem Cells (HSC) produce all of the blood cells

HSC come from:

Bone Marrow,

Umbilical Cord,

or Blood Stream

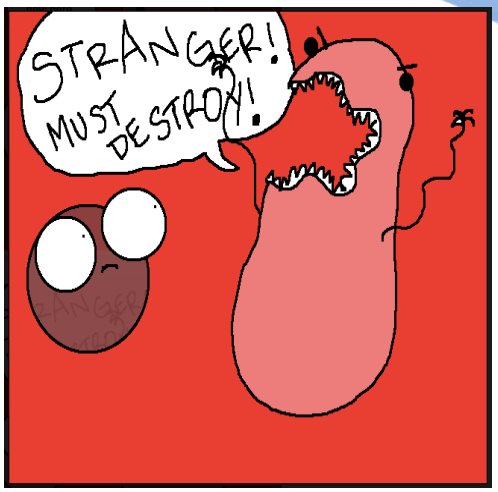


Clinical uses of stem cell bone marrow transplantation

- HSC have been in clinical use for over 50 years
- Replace damaged bone marrow with healthy bone marrow from a donor
  - High dose chemotherapy
  - Radiation
  - Genetic disease
  - HIV (Berlin Patient)

Challenges in donor HSC transplantation

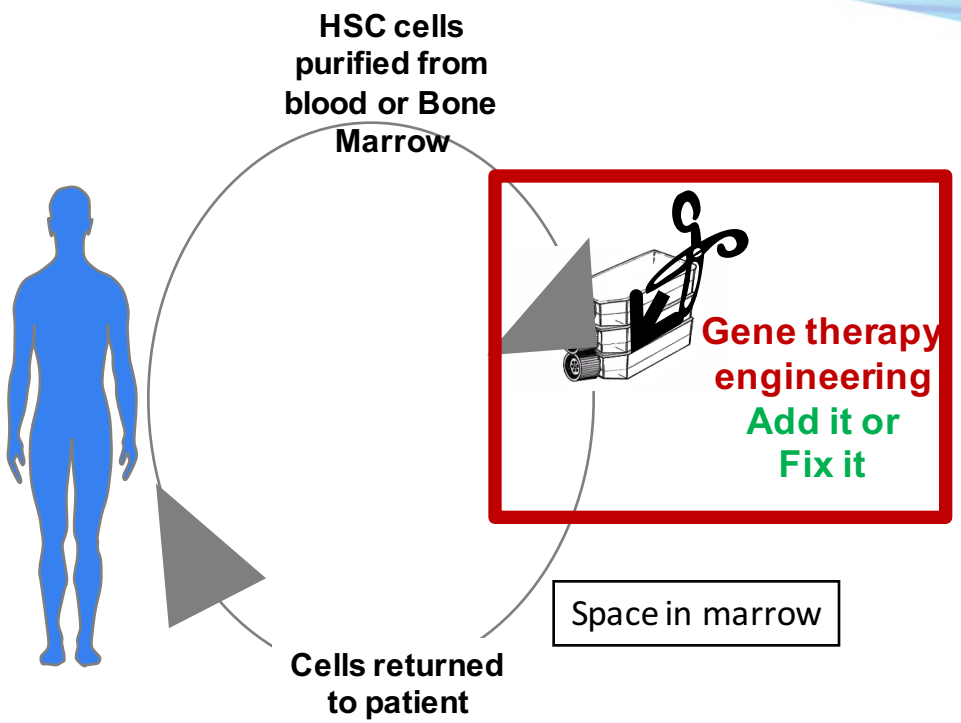
- Highest potential for success if the HSC comes from a closely matched donor
- Fewer than 15% have a sibling who is a full immunological match
- Risks for immune complications (GVHD and rejection) from less well-matched donors



Strategies to Overcome Challenges

- Use patient's own HSC
- Gene correction of patient's cells with normal gene
- No immunological complications of donor HSC transplantation

HSC gene therapy



Applications of HSC gene therapy

- Primary immune deficiencies:
  e.g. “Bubble baby” disease
- Inherited blood disorders
  e.g. Sickle Cell Disease, Thalassemia
- Inherited metabolic disorders:
  e.g. Adrenoleukodystrophy (ALD)
- HIV/AIDS Therapy

CIRM HSC Gene Therapy

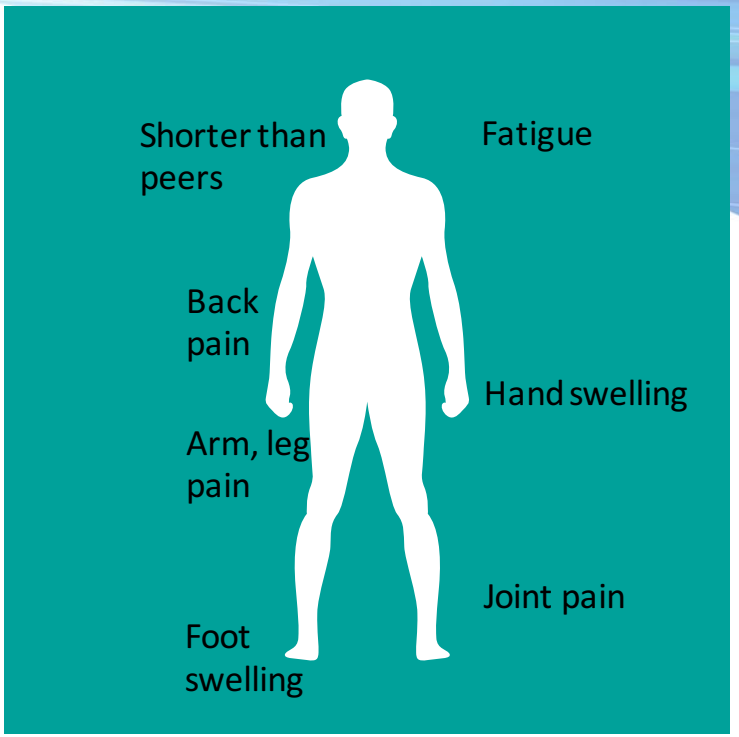
AWARD # PI INSTITUTION	CIRM FUNDING (MM)	APPROACH	DISEASE/INJURY	PROJECT GOAL
CLIN2-08231 Kohn UCLA	$7.4	Stem Cell Gene Therapy	X-linked Chronic Granulomatous Disease.	Phase 1/2
DR3-06945 Kohn, UCLA	$13.1	Stem Cell Gene Therapy	Sickle Cell Disease	Phase 1
DR2-05365 Shizuru, Stanford	$20.0	Stem cell + Mab	X-linked SCID	IND, Phase 1/2a
PC1-08111 Porteus, Stanford	$1.0	Stem Cell Gene Therapy	SCID	Pre-IND
CLIN1-08363 Puck/Cowan, UCSF	$4.2	Stem Cell Gene Therapy	Artemis- SCID	Preclinical/IND

CIRM HSC Gene Therapy - HIV

AWARD # PI, INSTITUTION	CIRM FUNDING (MM)	APPROACH	DISEASE/INJURY	PROJECT GOAL
DR1-06893 Symonds, Calimmune	$8.27	Stem Cell Gene Therapy	HIV/AIDS	Phase 1/2a
Abedi, UC Davis	$8.5	Stem Cell Gene Therapy	AID- Lymphoma	Phase 1
Zaia, City of Hope/Sangamo Biosciences	$5.58	Stem Cell Gene Therapy	HIV/AIDS	Phase 1
Zack, UCLA	$5.30	Stem Cell Gene Therapy	HIV/AIDS	Preclinical

Sickle Cell Disease (SCD)

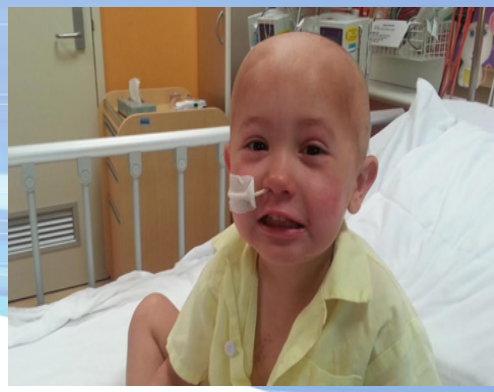
- Affects 100,000 in the US
- Disproportionately African Americans
- Severe medical complications
- Average lifespan – around 40 years



Stem cell gene therapy for SCD: Kohn, UCLA

- Patient's own marrow HSC gene modified
- Phase 1 trial
- 10 patients – first one 9/28/15
- Patient discharged at day 24 after transplant
- No drug related adverse event
- Next patient scheduled - August

Chronic Granulomatous Disease (CGD)



- Primary Immune Deficiency
- Repeated bouts of infection
- Estimated 1 in 200,000 births in the US
- Primarily affects males

Stem cell gene therapy for X-CGD: Kohn, UCLA

- Patient's own HSC gene modified
- Multicenter Phase I/II trial
- 6 Patients, first patient treated 12/18/15
- No adverse events
- Discharged from hospital on day +24.
- Remains clinically well (5 months S/P)
- Next patient July

Gene modified CD4+ T lymphocytes and CD34+HSC in HIV+ adults; Calimmune

- Patient's own white blood cells and HSC gene modified to create HIV-resistant blood/immune system
- Phase I/II trial. 3 dose cohorts
- 12 patients – 9 treated
- No evidence of severe adverse events

Conclusion

Gene editing technologies combined with HSC provides a new approach to developing stem cell treatments