

Fetal Therapy for Alpha and Beta Thalassemia Major

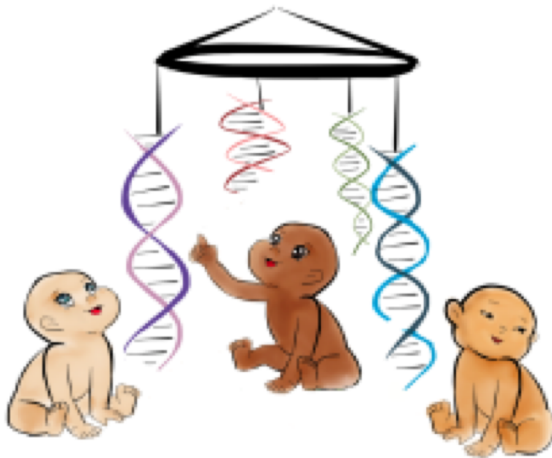
Tippi MacKenzie, MD

Professor of Surgery

**Co-Director, Center for Maternal-Fetal
Precision Medicine**

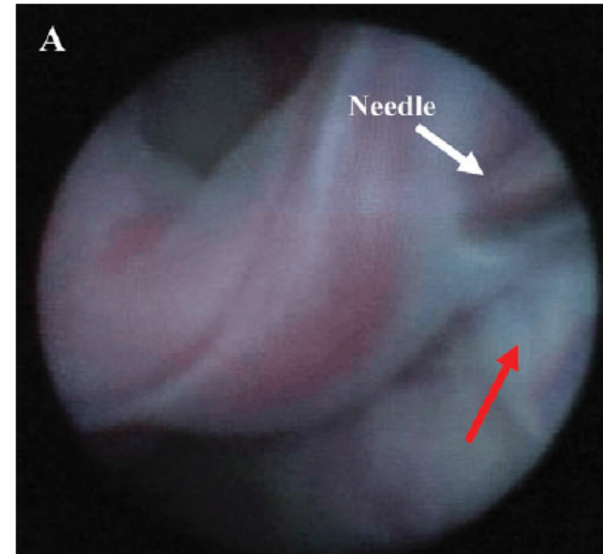
UCSF

UCSF Center for Maternal-Fetal
Precision Medicine

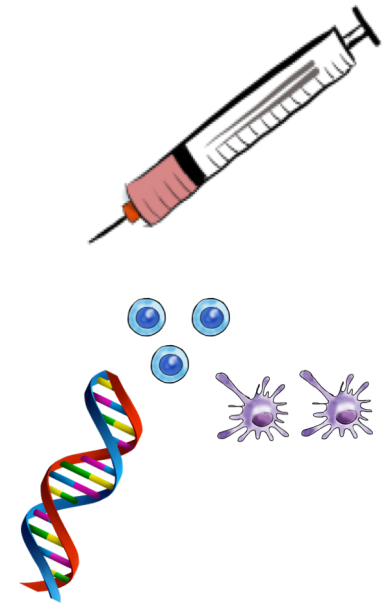
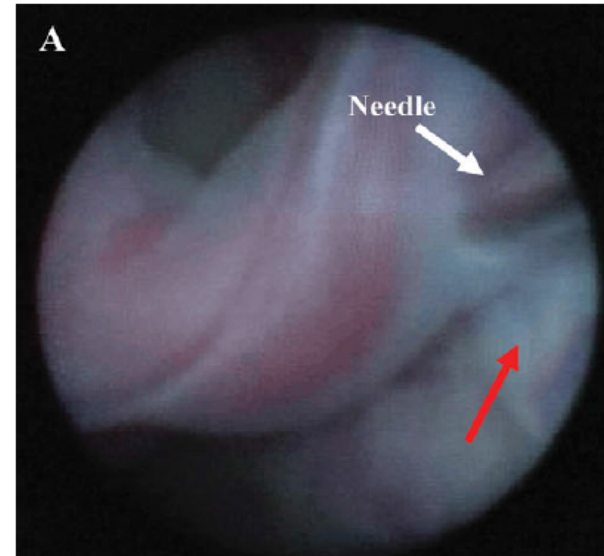


The Fetal Treatment Center
THE BIRTHPLACE OF FETAL SURGERY

Fetal Surgery was invented 30+ years ago...



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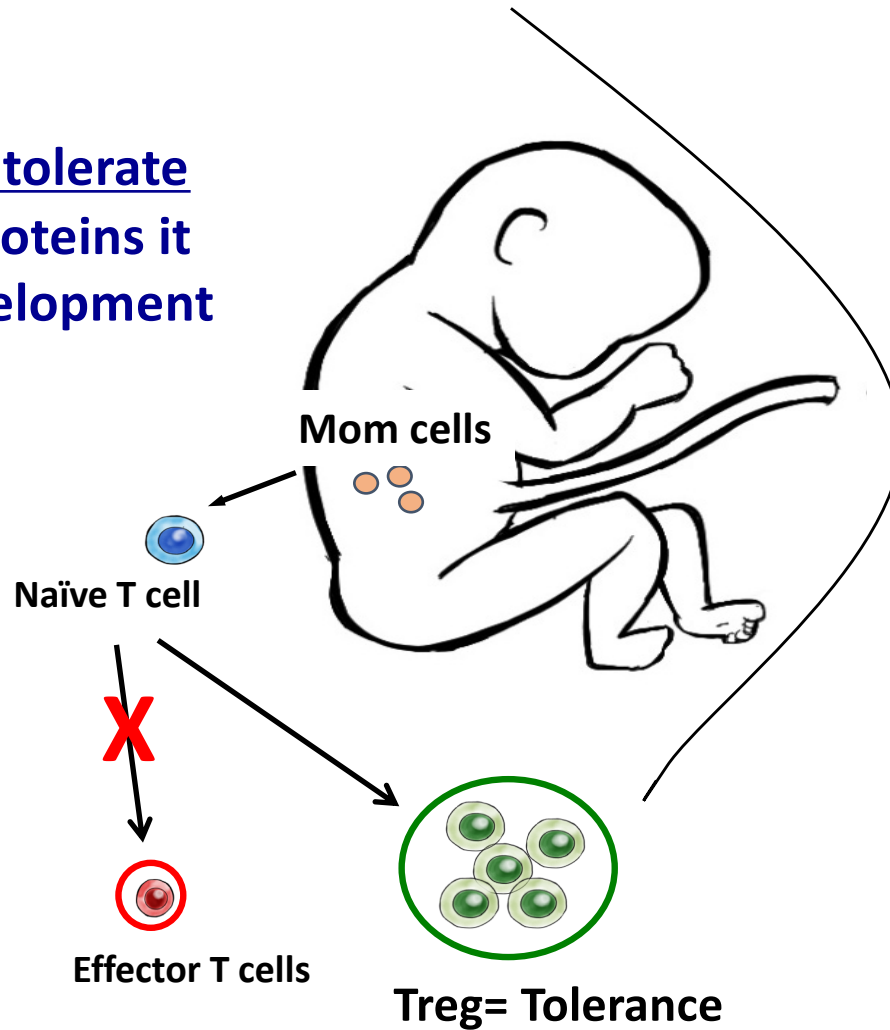


**Why in utero:
-fetus doesn't reject new cells**

*We are now moving from anatomic problems to genetic diseases like
thalassemia*

Harnessing Fetal Tolerance

Fetus learns to tolerate foreign cells/proteins it sees during development



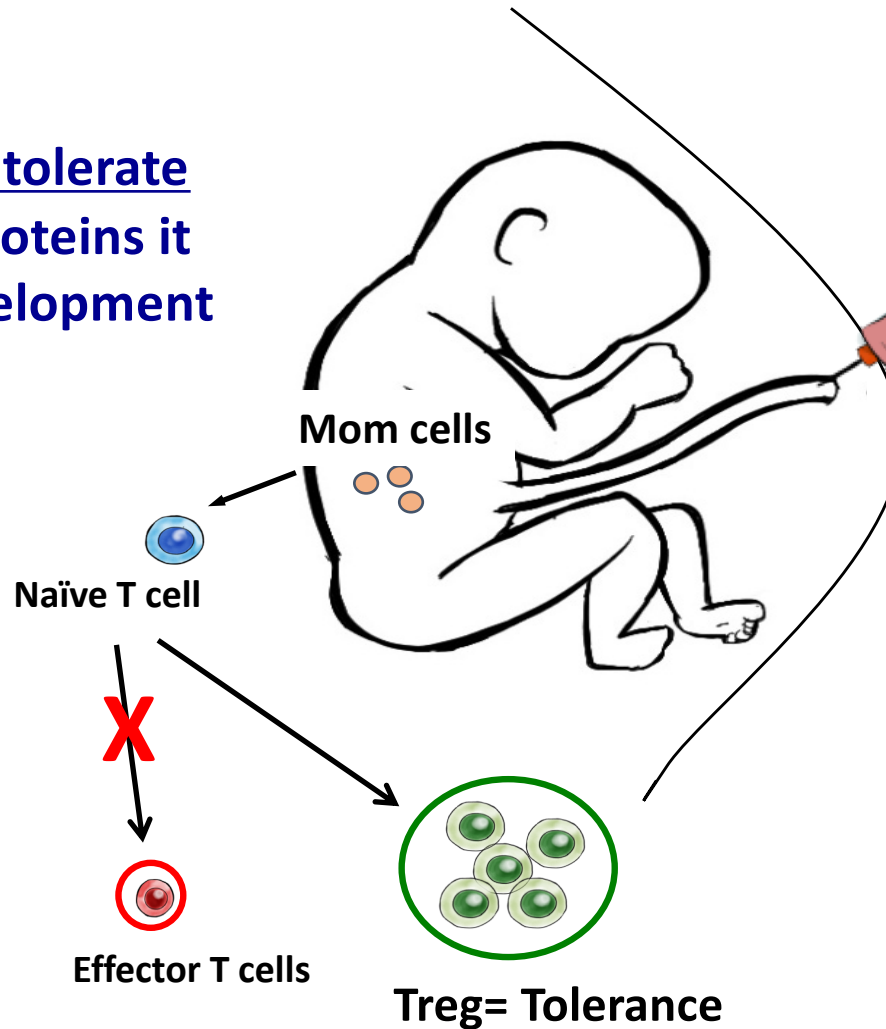
Maternal-fetal tolerance



Healthy Pregnancy

Harnessing Fetal Tolerance

Fetus learns to tolerate foreign cells/proteins it sees during development



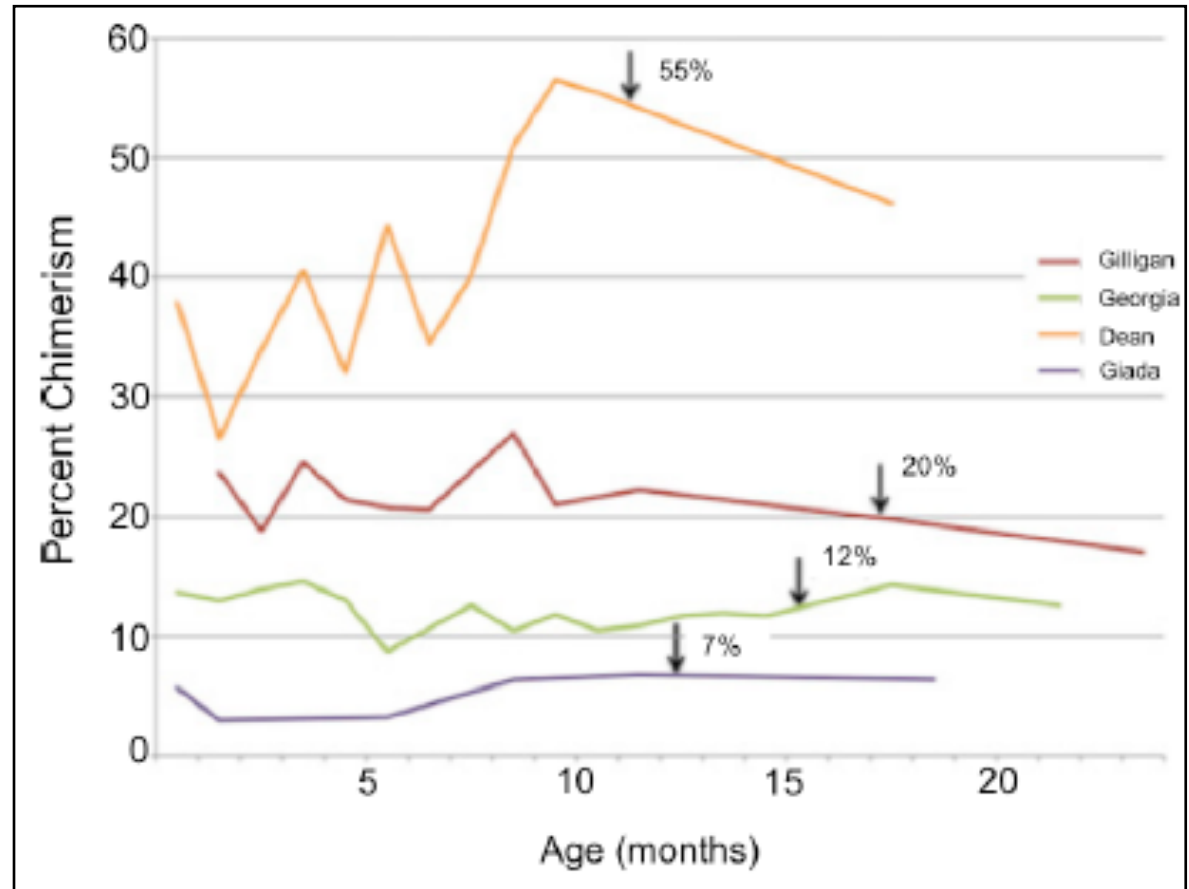
We can transplant mom's cells into fetus!

Every patient has a "matched" donor- while they are a fetus...

Transplanting mom's cells into fetus works in animal models



In utero transplant of maternal CD34 cells in fetal dogs
-chimerism
-tolerance

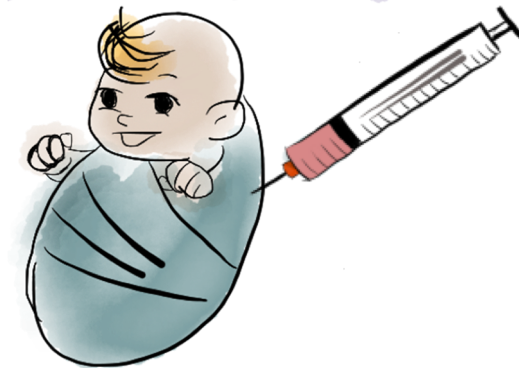
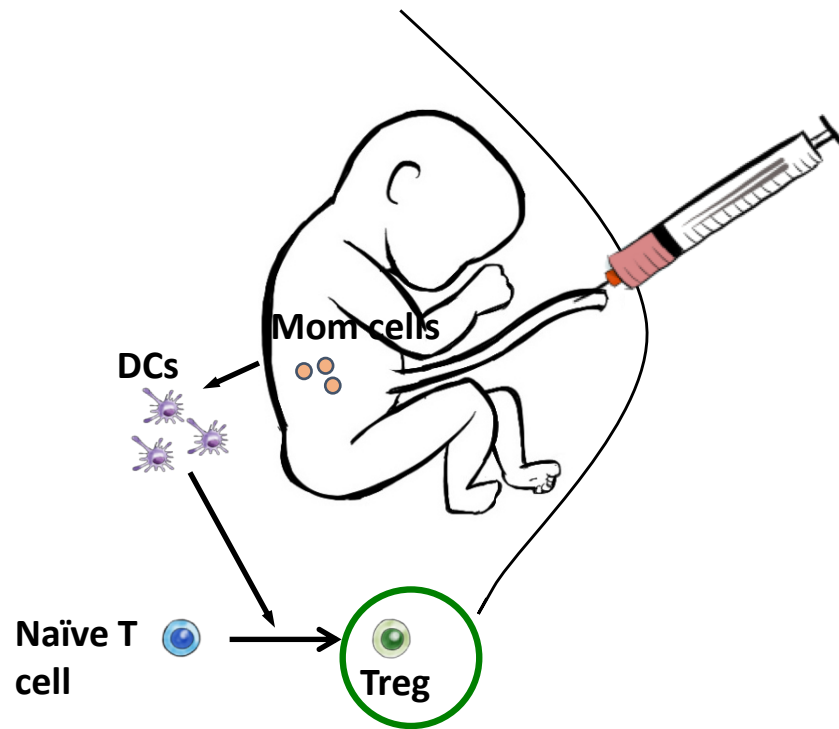


Engrafted animals tolerate a kidney transplant from the same donor.

We can do a 2-step approach

Fetal transplant extends tolerance after birth

“Booster” transplant after birth improves chimerism to cure the disease

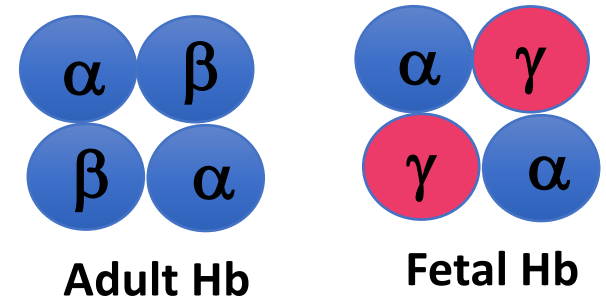


***We are now doing a clinical trial of fetal
therapy in patients -
Starting with alpha thalassemia***

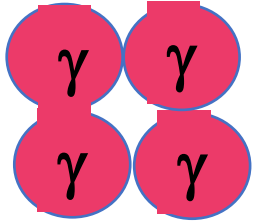
***Planning to expand to beta thalassemia
in 2020***

Alpha Thalassemia Major

- --/-- = Hemoglobin Bart's; no alpha hemoglobin chain
- Fetal hydrops due to in utero hypoxia
- 5% carrier rate worldwide
- China, Southeast Asia: $\geq 15\%$ carrier

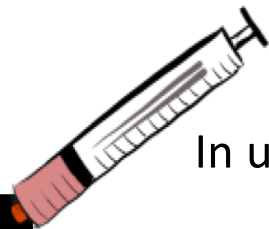


UCSF In Utero Stem Cell Transplantation Clinical Trial



Alpha Thal
Major

Need fetal blood transfusions
to survive to birth



In utero transfusion
+
STEM CELL TRANSPLANT

- Maternal Bone Marrow stem cells
- 18-25 weeks, umbilical vein

FDA Approval - October 2016

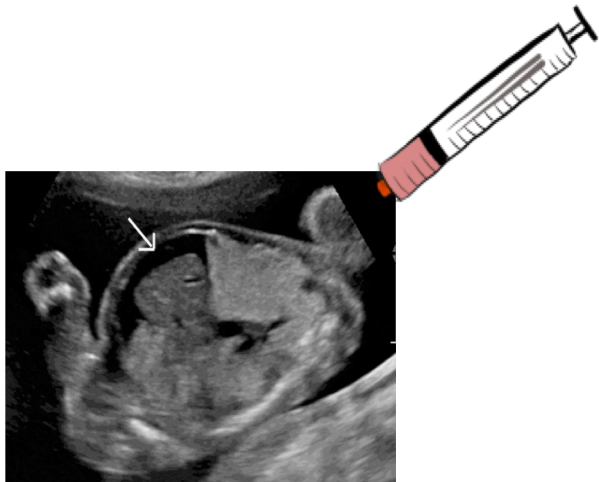
Grant funding (CIRM)- June 2017

First patient transplanted Oct 2017

Currently recruiting patients for enrollment

First patient transplanted October 2017

- Presented with hydrops at 18 weeks
- Transplanted at 22 weeks
- Continue transfusions every 3 weeks (5 total)



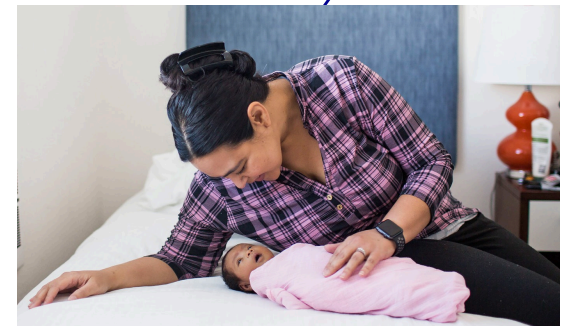
Safety:

- Born at 36 3/7 weeks- no preterm labor
- Hydrops resolved

birth

What we learned:

- Hydrops resolves with careful transfusions
- Clinical protocol is feasible; appears safe



New York Times May 2018

International Prospective Registry



We are trying identify patients with
alpha thalassemia major-
not as rare as we think!

Goals:

- *Patient and provider attitudes regarding fetal therapy vs termination*
- *Neurologic outcomes of fetuses who had adequate transfusions*

1-800-RX-FETUS

Alpha Thal Major is NOT FATAL



**Another option:
In Utero Transplant
Clinical Trial**

Fetal is diagnosed with alpha thal major

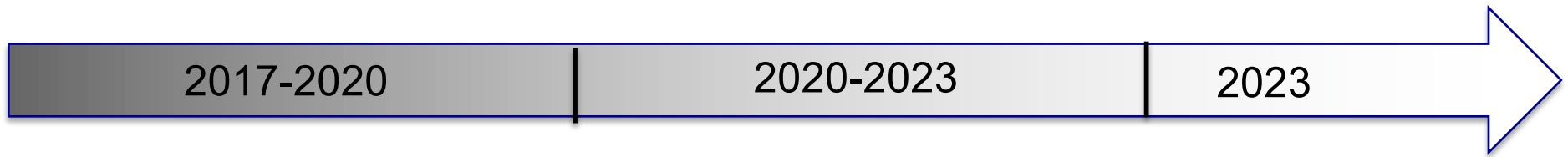
Ending pregnancy

(expectant management)

**In Utero Transfusions
Common, safe**

**After birth: like Beta Thalassemia
monthly transfusions or
stem cell transplant**

Long Term Plan- Fetal Therapy

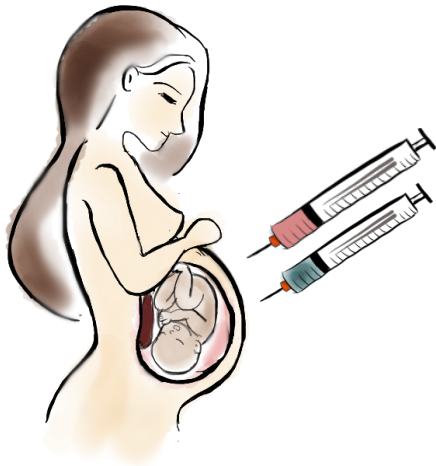


Stem Cell Transplant

Alpha Thalassemia Major

Beta Thal Major/Sickle Cell

Others



Fetal Gene Therapy

We continue to do research to improve these therapies

Ethical considerations



ETHICS

- Non-directive counseling
- Cultural sensitivity
- Marginal corrections vs fetal demise
- Access to care

Patient representation critical for planning therapy

How can you get involved?

- Encourage family and friends to have screening
- Follow us on Facebook
- Connect us to families with alpha thalassemia
- Visit our booth and website
- Tell us what you think!!!



Tippi.Mackenzie@ucsf.edu

UCSF Focus Groups

for parents of children with
alpha or beta thalassemia major

Tonight, 5:15 pm-6:45 pm

OR

Tomorrow 11:30 am-1:00 pm

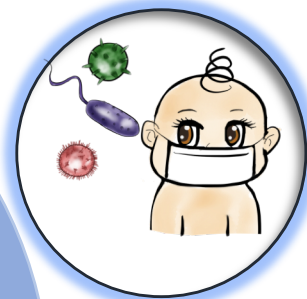
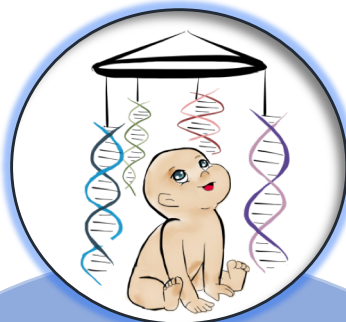
To participate:

- Visit the UCSF table outside OR
- Complete questionnaire on CAF mobile app

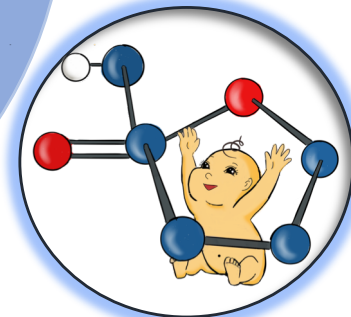
Participants will receive a **\$50 amazon gift card!**



GENETICS



FETAL IMMUNOLOGY



MOLECULAR
THERAPIES



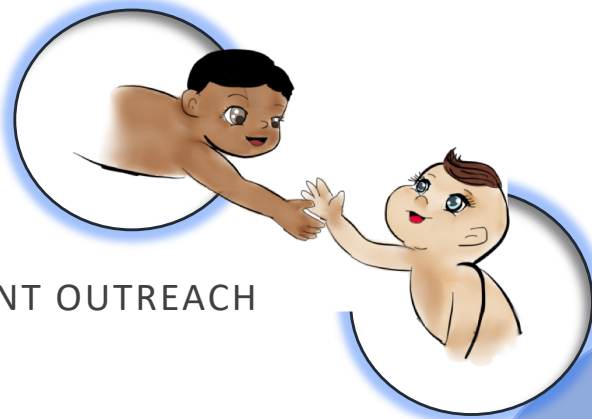
ETHICS



REGULATORY
AFFAIRS



PATIENT
EDUCATION



PATIENT
OUTREACH

Center for Maternal-Fetal Precision Medicine



CLINICAL TRIALS

Thalassemia Team

Elliott Vichinsky

Ashutosh Lal

Sandhya Kharbanda

Billie Lianoglou

Meghan Foe

Romobia Hutchinson

Mark Walters

Chris Dvorak

Craig Forrester

Juan Gonzalez

Roberta Keller

Anita Moon-Grady

Marla Ferschl

Questions?

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1-800-RX-FETUS

**THANK YOU TO
OUR PATIENTS
for their gracious
participation in
new therapies**



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THE BIRTHPLACE OF FETAL SURGERY