Gene Therapy for Fanconi Anemia

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What is Gene Therapy?

Any therapy where the benefit is achieved by the transfer of genetic material (a “gene”) into a patient’s cells.

For FA patients, the primary goal of gene therapy is to prevent bone marrow failure without the risk of GVHD.
Gene Therapy in Blood Stem and Progenitor Cells

Therapeutic Gene

Self-renewing stem cell

Lymphoid progenitor

Thymus

Natural killer (NK) cell

B lymphocyte

T lymphocyte

Granulocyte-monocyte CFU

Monocyte

Dendritic cell

Macrophage

Erythrocytes

Platelets

Basophil

Eosinophil

Neutrophil

Megakaryocyte

Erythroid CFU

Myeloid progenitor

Pluripotent stem cell

Patient
Ex Vivo Gene Therapy: Putting Functional Genes Into Bone Marrow Stem Cells Outside of the Body

- Bone Marrow Harvest
- Isolation of Bone Marrow Stem Cells
- Virus-Mediated Gene Transfer of Functional FA Gene

GOAL: Gene modified bone marrow stem cells engraft and produce new blood cells for the life of the patient without the risk of GVHD.

- SCID
- WAS
- ALD
- MLD
1. Successful gene therapy for other monogenic diseases demonstrates ex vivo gene therapy of bone marrow stem cells can work (SCID-ADA, X-linked SCID, ALD and MLD).

2. Rare evidence for somatic mosaicism in Fanconi anemia: natural gene therapy improves marrow function.

Cartier et al. 2009, Science
Clinical Study of FA Gene Therapy: A History

1. First gene therapy trial for FA(C) patients initiated.
2. First retrovirus carrying FA(A) reported.

1997

First report of retroviral FA(C) gene correction indicates that improvement is only transient.

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First report of retroviral transduction to assign complementation group.

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1. First reported successful in vitro correction using lentivirus.
2. First report of successful mobilization and peripheral blood stem cell collection in FA patients.

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Report of improved gammaretroviral FA(C) gene correction in mice.

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2006


2007

Report of diminished stem cell availability in FA-A patients treated with FA-A gene therapy using a gammaretrovirus with only transient benefit.

2010

Lentivirus gene therapy trial utilizing improved culture conditions and FA GTWG recommendations initiated for FA-A patients.

2011

1st International FA Gene Therapy Working Group Meeting report issued.

2012
Previous Trials: Outcomes

1. 1999 (Liu) Gammaretroviral-mediated delivery of FA(C) gene into CD34+ HSCs in FA(C) patients.
   - no long-term engraftment observed; published report

2. 2000 (Wagner) Retro-viral-mediated delivery of FA(C) gene into mobilized peripheral blood HSCs.
   - poor mobilization and blood stem cell survival ex vivo; no report

3. 2006 (Williams) Gammaretroviral-mediated gene delivery of FA(A) to CD34+ BM HSCs in FA(A) patients.
   - transient gene correction; published report
Advances in Gene Transfer Process Should Improve Safety and Engraftment

1. Improved *ex vivo* culture conditions
   - Hypoxia (1-5% O$_2$)
   - Antioxidant co-culture

2. Improved lentiviral vector design
   - SIN (self-inactivating) to prevent turning on harmful genes nearby
   - Successful and safe in gene therapy for other genetic diseases

3. Shorter transduction protocol
   - Shorter *ex vivo* culture time = greater potential to make new blood cells
Phase I: Study of Gene Transfer for Patients with Fanconi Anemia Complementation Group A (FANCA).

FA-A patients (≥ 4 years) with confirmed FA of the A complementation group

**First Day**
- **Bone Marrow Harvest** to collect ≥ 1 x 10^6 bone marrow stem cells/kg body weight
- Isolate the bone marrow stem cells (CD34*)

**Second Day**
- Gene Transfer: put in a correct version of the FA-A gene
- Gene Modified Cells Infused Through IV

**First 4 Weeks After Infusion**
- Check patient blood and bone marrow for the presence and function of gene modified cells

**Up To 15 Years After Infusion (depending on how well the gene modified cells work)**
- Check patient blood and bone marrow for the presence and function of gene modified cells

At Home

In Seattle
What We Hope To Learn:

1. Can we collect enough stem cells?

2. Do the improved culture conditions and reduced time outside the body allow for better engraftment?
   - If not, we will try low-dose conditioning

3. Do the gene corrected stem cells produce blood cells after infusion?

4. How safe is this approach in FA-A patients?
Who Can Enroll?

FA-A patients ≥ 4 years old who meet the following criteria:

- have normal or near-normal kidney, liver and lung function
- have normal or near-normal bone marrow cytogenetics
- have adequate blood cell counts
  - ANC ≥ 500/mcL
  - Hemoglobin ≥ 8 g/dL
  - Platelets ≥ 20,000/mcL
- are able to understand the consent form or have a parent/legal guardian who understands the consent form
- do not have an active or ongoing infection
- do not have another cancer with limited survival (<2 years)
- do not have another significant disease such as uncontrolled diabetes or heart disease or haemophilia
- not pregnant or HIV+
- not undergoing a BMT with a matched sibling donor
What Can I Expect if I Enroll?

1. Travel to and from Seattle, Washington.
2. ~6 weeks in Seattle:
   a. Testing before treatment if needed (1-2 weeks).
   b. Bone marrow collection and infusion of gene modified cells (2-days).
   c. Post-infusion monitoring including regular blood draws and one bone marrow aspirate after infusion of gene modified cells (4 weeks).
3. Monitoring after returning home (done locally):
   a. For the first 2 months, blood draws every two weeks.
   b. For the next 9 months, blood draws once per month.
   c. If gene modified cells are found in blood at 1 year, blood draws at least annually; bone marrow samples if needed.

Costs: All study-related treatments while in Seattle are covered by the clinical trial. Any treatments that are standard for FA are still covered by patients and/or their insurance carrier. Travel and lodging for time in Seattle are not covered by the study, but FARF can help!
Why Should I Participate?

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2. First report indicating that hypoxia promotes FA BM progenitor growth *ex vivo*.

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You are here?
Thank You for Your Attention!
Lentivirus-Mediated FA-A Gene Delivery

Cell

Nucleus

Genomic DNA

Integration

Transcription

dsDNA

Reverse Transcription

Viral RNA containing FA-A Gene

Cytoplasm

Viral Particle

Translation

Functional FA-A Protein