Gene Therapy with an Anti-Sickling Gene for Correction of Sickle Cell Disease: A Novel Approach

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The Cause of Sickle Cell Disease

- ***Cause of Sickle Cell Disease***: a mutation in the HBB gene (that produces the adult hemoglobin protein in red blood cells) causes production of a mutant hemoglobin termed sickle hemoglobin.
- ***Sickle Hemoglobin Results in*** rigid, sickle-shaped red blood cells, which clog blood vessels and are destroyed rapidly.
- ***The disease causes*** severe pain episodes/pain crisis and weakness/fatigue from anemia.

Gene Therapy: Adding Working Genes

- Before birth, humans produce ***Fetal Hemoglobin***, which prevents red blood cell sickling.
- Normally the Fetal Hemoglobin gene switches off shortly after birth
- Adding a modified Fetal Hemoglobin gene that ***cannot switch off*** and ***preferentially makes Fetal Hemoglobin over the faulty Sickle Hemoglobin*** can prevent red blood cells from sickling

How is Gene Therapy Typically Done?

1. Ex-vivo (outside the body) gene transfer

- Blood stem cells (blood-making cells) are removed from the body.
- A lentiviral vector delivers the anti-sickling gene into the blood stem cells
- The vector is a virus because it can get inside the cell – but the viral genes are fully removed and replaced with the anti-sickling gene

- Once the gene gets inside the cell, the functioning Fetal Hemoglobin gene will prevent sickling of red blood cells despite the presence of the faulty globin

How is Gene Therapy Typically Done?

2. Typically, very high dose chemotherapy is given to completely destroy faulty blood stem cells and make space for corrected blood stem cells

- Then the gene-corrected cell product is given back via a vein
- A month or more later, the corrected stem cells start producing red blood cells that do not sickle

We tested a new gene therapy approach with reduced-dose chemotherapy because red blood cells from corrected stem cells outcompete the faulty sickle red blood cells

- This approach makes the transplant process less complicated
- Causes fewer chemotherapy-related immediate and long-term side effects
- Reduces hospitalization and costs

Preliminary results of Gene Therapy with a functional Fetal Hemoglobin Gene using a Reduced-dose chemotherapy

- 2 patients were treated 21 and 15 months back with the fetal Hemoglobin gene cell product (ARU-1801). The 3rd patient is enrolled and many interested.
- Both recovered from acute side effects of transplant within 7-12 days (typical recovery with full dose chemotherapy is 1-2 months).
- Both have had a >95% reduction in disease symptoms
  - 0 and 2 pain crises in 15 and 21 months, as compared to 20 crises and 48 crises in patients 2 and 1 in the 18 months prior
  - Both have relief from their chronic daily pain, allowing discontinuation of daily opioids.
- Anti-sickling hemoglobin levels were 22% and 30% (> 20% provides benefit to patients).

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