The Breakdown: Gene Therapy for FA

What is gene therapy?

We know that FA is caused by defects in any one of 22 different genes called "FANC" genes. Thus, if we could somehow repair these defective FANC genes, we could treat or prevent FA disease.

Gene therapy is an investigational approach to do just that. The overall idea is to augment or replace defective FA genes with fully functional normal genes. Gene therapy addresses the root cause of inherited diseases like FA by "fixing" or "repairing" the disease-causing gene, enabling cells to produce normal FA proteins that are necessary for health. This should restore normal function to diseased stem cells and prevent bone marrow failure.

Gene therapy step-by-step

To deliver a fully functional normal gene into a cell, you have to first decide which cells need therapy. FA usually presents first with bone marrow failure, so we want to fix bone marrow cells to prevent failure. But more specifically, we want to fix a unique type of cell in the bone marrow called a "stem cell". Stem cells have the ability to generate all other types of blood cells in the body: white cells, red cells, platelets, everything! If we can fix the FA defect in stem cells, then all blood cells that come from a stem cell are also fixed.

To achieve this (see figure), blood or bone marrow cells are first drawn from a relatively healthy FA patient. Blood and bone marrow contain all types of cells, including rare stem cells. Stem cells are separated from other blood cells using a fancy stem-cell purification device.

A fully functional normal FA gene ("good" gene) is then added to create essentially normal, non-disease cells. These cells are then infused into the patient as soon as possible because when they are outside the body they risk degradation. After infusion, the repaired stem cells repopulate the patient's bone marrow, where they can generate normal blood cells and thereby prevent or delay bone marrow failure.

This sounds like it should work! Why aren't we using FA gene therapy now?

Well, it's complicated. Science is hard and doesn't always work in practice the same way it works in theory. For one, the stem cell population is reduced in FA, which creates challenges isolating enough stem cells to grow and manipulate in the laboratory. Another challenge is that stem cells are relatively fragile when removed from a patient, and FA stem cells appear particularly difficult to grow in the laboratory. And there is always the challenge of "engraftment"; can the stem cells with repaired FA genes repopulate the bone marrow and outgrow the diseased FA cells that are already there?

The Madrid and Seattle teams are making significant headway to overcome these challenges. Through collaborations, a potential biotech partnership, and open data exchange fostered by the International Fanconi Anemia Gene Therapy Working Group, key advances are happening. This is an area we all need to follow with hope and anticipation. The very best international scientists are working on gene therapy. Breakthroughs are certain, and FA scientists and physicians are at the forefront, well positioned to quickly implement these breakthroughs to improve the health of individuals with FA. ■