Chapter 30
Gene Therapy

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Gene therapy may provide an alternative for those individuals with severe forms of PIs, who may be treated with Hematopoietic Stem Cell Transplantation (HSCT) from a haplo-identical parent or unrelated donor. These types of transplants may be complicated by a problem called graft versus host disease (GVHD) where the body tries to reject or fails to accept the new cells. In contrast, GVHD is not a problem after gene therapy because the individual is transplanted with their own Hematopoietic Stem Cells (HSC), negating the need for a HSC donor.

To add a normal copy of the gene, we take advantage of the ability of some viruses (retroviruses) to penetrate into cells and to insert their genes into the individual's own DNA. For the purpose of gene therapy, viruses have been modified so that their own genes have been removed and replaced with the normal copy of the human gene that is causing the PI. The genes carried into HSC by the virus are permanently in the stem cell's DNA and will be passed on to all of the blood cells made from the HSC, giving them the normal gene. The new gene does not go into other cells of the body besides the blood cells and will not prevent an individual from passing the disease gene on to their future offspring. Because PI is caused by gene defects that affect blood cells, this can be sufficient to treat the disease in the affected person. To directly fix genes that carry mutations, techniques have been developed to directly edit genes in human cells to repair mutations. Gene editing uses designer proteins, such as the CRISPR system, to find a single gene among the entire human genome in each cell, and modify that gene to correct a mutation causing PI. Gene editing in HSC has advanced to clinical trials for several conditions (such as HIV, thalassemia) and is coming to the clinic for several more conditions, including some types of PI, sickle cell disease, and other illnesses.

To perform gene therapy, the individuals with PI are both the donors and recipients—their own stem cells are collected, the gene is corrected in the cells, and then their cells are given back into them (by an intravenous infusion). HSCs are first isolated from their bone marrow or from their peripheral blood, and the cells are then cultured in the laboratory for a few days, usually with some growth factors to activate them. During this time, the gene is added or edited in the cells. The gene-corrected cells can then either be transplanted back to the individuals directly, or frozen and given back later. The cells that have the added gene or the fixed gene of interest in their chromosomes will pass it to all the cells that will be generated when these cells divide. Most gene therapy has used chemotherapy to support the engraftment of the corrected stem cells, but generally less chemotherapy is necessary for gene therapy than is needed for transplants from another donor.

Until now, gene therapy has been used to treat individuals with Severe Combined Immunodeficiency (SCID) secondary to adenosine deaminase (ADA) deficiency (ADA-SCID), X-linked SCID, X-linked Chronic Granulomatous Disease (XCGD), and Wiskott-Aldrich Syndrome (WAS). The first clinical trial of gene therapy was at the National Institutes of Health in 1990 and treated a 4-year-old girl with ADA-SCID. The design of this first trial did not attempt to correct the defective HSC, only the T cells. This girl is now clinically well and still has about 25% of her circulating T cells carrying the corrected ADA gene more than 20 years after her treatment. After this initial clinical trial demonstrated that gene therapy could be carried out safely and that gene-corrected T cells could survive for years and function normally, follow-up trials were initiated attempting to treat other children with ADA-SCID by targeting HSC from the bone marrow for gene correction. The results have been excellent, with most of the nearly 100 individuals with ADA-SCID attaining a significant long lasting increase of the T and B cell count and a remarkable improvement of immune function. Importantly, no episodes of serious adverse reactions have occurred in the individuals with ADA-SCID treated by gene therapy.

The next type of PI to be treated by gene therapy was X-linked SCID. These trials also targeted the HSC using a retrovirus to deliver the gene. Beginning

with a groundbreaking study in Paris followed by a similar experience in London, there were 20 babies with X-SCID treated with gene therapy. In these infants, gene therapy was performed without any chemotherapy prior to the transfusion of HSC that had been cultured with the virus. Eighteen of these individuals are currently alive. In 17 of these 18 children gene therapy alone was sufficient to restore development of T cells and immune function, and no other treatment was needed.

Unfortunately, while the X-SCID was corrected, six of these individuals developed leukemia as a complication of the retrovirus vector. Five of the children's leukemia was able to be treated, but one child died. More recent trials for X-SCID have used the next generation viruses designed to avoid the risk of leukemia and have led to similar immune benefits as in the early trials, but without any cases of leukemia to date.

Clinical trials of gene therapy for WAS and XCGD are ongoing. Gene therapy trials, using either viral addition or editing, are also ongoing or under development for individuals with other types of PI including: Artemis-deficient SCID, Leukocyte Adhesion Deficiency, RAG 1/2 deficiency SCID, X-linked Hyper IgM Syndrome (XHIGM), X-linked Agammaglobulinemia (XLA), Immunodysregulation-Polyendocrinopathy-Enteropathy-X-linked disease (IPEX), and more. One of the limitations of gene therapy, compared to HSCT from a related donor or tissue matched unrelated donor that can be used for any PI, is that gene therapy is a more personalized medicine and requires a specific virus or editing system to be developed for each different form of PI. Gene therapies have not yet been tested for more complex diseases like Common Variable Immune Deficiency (CVID) where all the responsible genes are not yet known, and there are many different genes that have been found among individual patients.

Overall, the growing experience with gene therapy for ADA-SCID, XSCID, WAS, and XCGD has demonstrated that it is possible to successfully treat PI by inserting a normal copy of the gene into the individual's HSC. Clinical trials are ongoing for many types of PI. It is likely that a larger number of types of PI will be treated by gene therapy in the future.