GeNeXpreSS

Breakthroughs in Genetics: Success Stories of Gene therapy in 2017-18

Priyanka Srivastava, Shubha R Phadke

Department of Medical Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Correspondence to: Dr Priyanka Srivastava *Email:* srivastavapriy@gmail.com

Gene therapy for permanent cure of genetic diseases is the ultimate aim of Genomic Medicine. The year 2017-18 was a promising year for Genomic Medicine with a few major successes in gene therapy. Below are some of the major breakthroughs in gene therapy in 2017-18.

Beta globin gene therapy cures Sickle cell disease (Ribeil et al., 2017)

Ribeil et al. published a paper in The New England Journal of Medicine in March 2017 about a 13 year-old-boy in France who was successfully cured of sickle-cell disease after receiving an experimental gene therapy (HGB-205) developed by Bluebird Bio. He was treated with a lentiviral vector which was used to introduce an anti-sickling β-globin gene (βA87Thr:Gln) into autologous hematopoietic stem cells. This anti-sickling variant has the ability to restore normal beta-globin expression and function. It also inhibits the polymerization of HbS and is distinguishable from other globin chains using reverse-phase high-performance liquid chromatography. Fifteen months post treatment, the boy had high levels of therapeutic anti-sickling β-globin (approximately 50% of β-like–globin chains) and did not develop any episodes of sickle cell crisis.

Gene therapy for beta thalassemia: Hope with promising result (Alexis et al., 2018)

After the positive outcome of gene therapy for Sickle cell anemia, Thompson et al., made an attempt to treat beta thalassemia by gene therapy in 22 patients between 12 and 35 years of age. They transduced the bone marrow cells ex vivo with lentiviral vector with HbAT87Q and reinfused it into the patients (sponsored by Bluebird Bio). Correction of biologic markers of dyserythropoiesis was achieved in evaluated patients and their hemoglobin levels were in near-normal ranges. Out of the 22 patients treated, 15 patients who had severe symptoms no longer required monthly blood transfusions. There was a decrease in the number and volume of transfusions required for the rest of the patients. This study provides hope for patients with thalassemia as it has the potential to provide them a life free of blood transfusion.

Childhood leukemia and adult large B–cell lymphoma: CART therapy (Ruella & Kenderian, 2017)

Food and Drug Administration (FDA) approved a therapy in August 2017, which works for both childhood leukemia and for adult large B-cell lymphoma. This therapy was named as "CART therapy" (Chimeric antigen receptor T cells) which works by genetically modifying a patient's own blood cells to turn them into cancer killers. The only limitation was that it required patient-specific manufacturing. The University of Pennsylvania-designed CD19-directed CART cell therapy (Kymriah - Tisagenlecleucel) became the first CART therapy for acute lymphoblastic leukemia. Two months after Kymirah, FDA approved another cutting-edge immunotherapy to treat aggressive non-Hodgkin lymphoma in adults. This therapy was named as Yescarta (Axicabtagene ciloleucel). A patient's T cells are extracted and genetically engineered to produce specific T cell receptors. The resulting CARTs direct the T cells to target and kill cancer cells with a specific antigen on their surface. The genetically modified cells are then infused back into the patient. This therapy carries a risk of cytokine release syndrome and neurological toxicities.

Luxturna: Ray of hope to end darkness

(Dias et al., 2018)

In December 2017, FDA approved another gene therapy for treating a rare inherited form of blindness (Leber congenital amaurosis), a condition that is caused by biallelic mutations in *RPE65* gene. Spark Therapeutics (manufacturer) brought out this first in vivo gene therapy and named it Luxturna (Voretigene neparvovec). Luxturna is an Adeno-associated virus (AAV2) vector containing human RPE65 cDNA with a modified Kozak sequence. This therapy is not exactly a treatment of blindness but it improves the vision in treated patients. The basic concept was to deliver the corrected copy of the gene *RPE65* to retinal cells. It has the potential to achieve definitive treatment by replacing or silencing the causative gene and to produce the deficient enzyme. Luxturna is the first ocular gene therapy approved in the US to directly target mutations in one specific gene.

Gene therapy: Regeneration of skin

(Hirsch et al., 2017)

Hirsch et al. have published a study wherein an entire, fully functional epidermis was regenerated in a seven-year-old child with severe junctional epidermolysis bullosa through autologous transgenic keratinocyte cultures. The child had a homozygous acceptor splice site mutation (IVS 14-1G> A) in intron 14 of the *LAMB3* gene. Skin biopsy was performed on a part of the child's body that wasn't blistered, skin stem cells were isolated from the biopsy tissue and normal copies of the *LAMB3* gene were introduced into the cells. These cells were then grown into small sheets and were transplanted back onto the patient. This study paves the way for further gene therapy for other genodermatoses.

References

1. Alexis A, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med 2018; 378:1479-1493.
2. Dias MF, et al. Molecular genetics and emerging therapies for retinitis pigmentosa: Basic research and clinical perspectives. Prog Retin Eye Res 2018; 63:107-131.
3. Hirsch T, et al. Regeneration of the entire human epidermis using transgenic stem cells. Nature 2017; 551: 327-332.
4. Ribeil JA, et al. Gene Therapy in a Patient with Sickle Cell Disease. N Engl J Med 2017; 376: 848-855.
5. Ruella M, Kenderian SS. Next-Generation Chimeric Antigen Receptor T-Cell Therapy: Going off the Shelf. BioDrugs 2017; 31: 473-481.