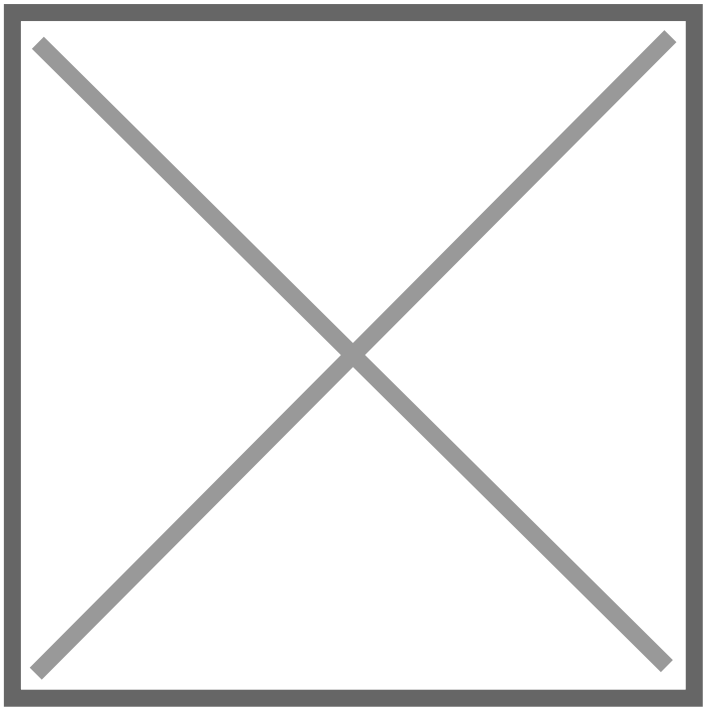
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Gene therapy, a dream technology

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As a doctoral student in late 80s and early 90s, I remember thinking that I was very fortunate to be studying diseases and molecular biology in Madison, Wisconsin, as those were exciting times for biologists. Cells and cellular processes were being unraveled at a molecular level and the understanding that pathologies are a result of specific molecular perturbations was becoming well accepted. It was also a period during which genomes of several organisms were sequenced and the human genome sequencing was initiated. It was felt that that we would soon have novel therapies for all diseases and gene therapy was considered to be the Ã¢â?¬Å?future medicineÃ¢â?¬?.

At the turn of the century, I remember listening to Dr Francis Collins addressing a group of gene therapy researchers in Seattle, WA. He was then the Director of National Human Genome Research Initiative at NIH, and predicted that by the year 2010 predictive genetic tests would exist for many common diseases and we would have gene therapies for a few of them. He said in the future, physicians will need to study molecular biology, as they would be handicapped unless they understand diseases at a molecular level. By the year 2020, he predicted, we would have designer gene-based drugs for diabetes, Alzheimer's, hypertension and many other diseases. We have come a long way in the last decade with many ups and downs for gene therapy technologies but are not quite at the stage where we have off-the-shelf gene medicines. China approved its first gene therapy product, Gendicine, for head and neck cancer in 2004. However, the rest of world is still working on developing safe and efficacious gene therapy products.

Gene therapy or therapeutic gene transfer is a process by which new or modified genes are inserted into a person's cells to treat or prevent disease. Although conceptually very simple, it is difficult to accomplish safe delivery of a therapeutic gene only at the desired site, expressing the right amounts of protein at the right time. Since viruses are very efficient at entering, releasing their genetic material and expressing their proteins in host cells, they have been used as vectors to ferry therapeutic genes.

Viruses are first made innocuous by removing all the undesirable parts of their genome and replaced with nucleic acid containing the therapeutic gene. The virus shell is prepared in specialized cells, which express the required viral proteins. In the past two decades, major strides have been made in the development of this revolutionary medicine. We have a range of

viral vectors to choose from depending on target cell type and the need for transient or stable expression of the therapeutic gene. When viral vectors are used, a common problem is immune response against the vector. Our body recognizes the viruses as foreign and mounts an immune response that may make the therapy ineffective or cause an adverse reaction like the one that resulted in death of Jesse Gelsinger.

We hope it will be possible to treat an array of inherited and acquired diseases, which are untreatable today, using gene medicines in the foreseeable future. There are over a dozen cancer treatments and a heart treatment in phase III clinical trials apart from several gene therapy products in early development. One of the most advanced therapies, Glybera, is under review for marketing approval in Europe. It has provided a significant benefit to patients suffering from lipoprotein lipase deficiency (LPLD) in phase III clinical trials. LPLD is a seriously debilitating and potentially lethal orphan disease caused by mutations in LPL gene that result in absence or very low levels of functional protein. It is characterized by abnormal breakdown of fats in the body and massive accumulation of chylomicrons, the large circulating fat carrying molecules seen in blood. Deficiency of LPL leads to pancreatitis, is associated with severe morbidity and mortality, and has no approved therapy so far. Glybera may very well become the first gene medicine for any inherited genetic disorder and comprises AAV (adeno-associated virus) vector delivering LPL gene to muscle. Using a similar vector system, experimental gene therapy trials have improved the vision of people suffering from a hereditary degenerative retinal disease resulting in blindness called Leber's congenital amaurosis (LCA). Mutations in as many as 14 genes have been causally associated with LCA. One of the genes, RPE65 has shown promise in treating patients with a mutation in the gene. The same gene was used to treat and cure 50 dogs suffering from LCA, including Lancelot that was born blind.

Another inherited fatal brain disorder that was recently shown to be treatable in initial trials is X-linked Adrenoleukodystrophy (ALD), a disease featured in Ã¢â?¬Å?Lorenzo's OilÃ¢â?¬?. Using a lentiviral vector (HIV vector), ALD gene was transferred into patients' hematopoietic stem cells outside the body (ex-vivo) and the gene-modified cells were transferred back into the patients after destroying their bone marrow. The results are very encouraging with the patients showing neurological improvement and a delayed progression of the disease. Two years later the healthy ALD proteins are still detectable in their blood. The protein was expressed in only about 15 percent of blood cells and there is scope for further development of better gene therapy approaches.

Several gene therapy products are in advanced clinical trials for cancers and cardio-vascular disorders. Viral vectors can provide an effective and lasting gene expression in host cells but one of the potential drawbacks is the possibility of inactivation of an important (tumor suppressor) gene in the host cells or activation of a proto-oncogene. Non-integrating viral and non-viral gene delivery helps alleviate the problem but does not provide a lasting expression. Recently, scientists have successfully developed a human artificial chromosome (HAC) by deleting regions of a chromosome that are non-essential for replication. This approach, if used effectively, would allow lasting episomal expression of therapeutic genes in the patient's cells.

An elegant way of tackling the non-specific integration problem would be to change the existing gene sequence by a process of editing or inserting a healthy copy of the gene in the place of the original faulty gene. A new technology developed by Sangamo BioSciences uses zinc finger proteins that are designed to recognize specific sequences in the genome and has the potential to achieve the desired solution. Scientists have used the technique to disrupt the gene for CCR5, a receptor for HIV in patients' T cells, and put the cells back in the patient.

The hope is that the modified cells will repopulate the patient's immune system and defeat the virus. In mouse experiments, the genetically modified cells had a strong growth advantage as they were immune to the constant onslaught of HIV virus. It remains to be seen if it would prove beneficial to HIV-infected patients. This technique may also be useful to insert several genes for beneficial traits at a safe location on the chromosome, for instance, and holds promise for generating genetically engineered plants as well. There is a constant endeavor to improve gene transfer technologies to make them simpler, efficient, safe and affordable.