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Gene Therapy: a New Treatment Pillar

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In less than three decades, gene therapy has gone from science fiction to now being a reality with the first products approved. Considering the ongoing research and advancements in the field we are in the early innings of this revolutionizing treatment paradigm for a number of diseases.

Genes carry the information needed to make proteins that are the building blocks of the human body. Genes are made of a chemical called DNA (deoxyribonucleic acid), which consists of the four chemical letters that write the human gene code (A, T, G, C). All cells in the body carry a copy of the DNA, also called the human genome. DNA can be incorrectly copied during life, a process called mutation, which is one of the main drivers for evolution, but it can also cause problems. If genes are damaged through mutation, it can lead to disease conditions. Gene therapy is a technique, by which DNA is altered in cells within a patient's body, to prevent or treat a genetic disease. Depending on the problem gene therapy can be used in different ways:

- To replace a faulty gene with a healthy copy of the gene
- To inactivate a gene that is functioning incorrectly and causing symptoms
- To introduce a new gene into the body that may be needed for normal function

Gene therapy can be used to modify cells inside or outside the body. When it is done inside the body the gene will be directly injected into the part of the body that has defective cells. When cells are modified outside the body (blood, bone marrow and other tissues), specific cells are harvested, the gene is introduced and then the cells transplanted back into the patient again. Diseases which are caused by one mutation are considered easier to cure than diseases caused by several altered genes. There are many rare diseases caused by single mutations. One of the most familiar is the bleeding disorder hemophilia, caused by defects in the factor VIII or factor IX gene carried on the X-chromosome. One of these defects is enough to prevent the blood from clotting and patients can bleed to death by a small wound. Cancer is also caused by the accumulation of mutations in cells, either through aging or through external factors such as smoking or sunlight or chemicals. The first gene therapy experiment was done in late 1989. The scientific excitement was extraordinary and has continued to be high since. However, only a few products have so far been successfully manoeuvered through clinical trials, reached pre-determined end-points, and finally been approved by regulators.

From the publicly available database Gene Therapy Clinical Trials Worldwide, between 1989 and 2017, 2,597 gene therapy clinical trials have been completed, were ongoing or approved worldwide. The number of clinical trials has increased steadily over time and it reached its highest peak so far in 2015 (169 trials). Almost 95 pct. of the trials were in early phases (phase I-II) of development and a total of 98 clinical trials (3.8 pct.) were in phase III. The United States undertook 63 pct. of gene therapy clinical trials. Most gene therapies clinical trials identified targeted cancer diseases (65 pct.).

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Currently, gene therapy can be used for single mutation conditions. For example, to correct a disease like hemophilia, in which a clotting factor is damaged, the addition of the gene for production of the clotting factor would fix the underlying problem of the disease. In many cases, harmless viruses are used as carriers for the new gene. Viruses are used since they invade cells as part of the natural infection process. When used this way, the viruses are called 'vectors' and their own genes have been removed and replaced with the working human gene. Once the gene is correctly placed, it can be switched on to provide the working 'instructions' for correct function.

Although much of this may still sound like the realm of excited scientists toying with the human body, gene therapy is a method or technique that is being used to benefit patients with certain types of cancer using specific chimeric antigen receptor T-cell therapy to fight the disease.

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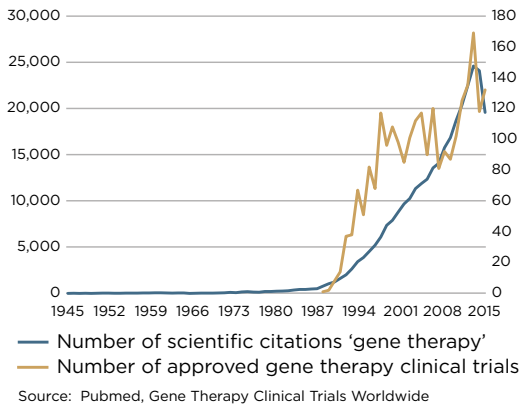
The first gene therapy ever approved in Europe was Glybera priced at EUR 1 million by UniQure in 2012 for the treatment of the rare disease, lipoprotein lipase deficiency. The drug was a commercial failure and withdrawn from the market last year. Two T-cell therapy drugs for blood cancers were approved in 2017 in the US. Novartis Kymriah for treatment of acute leukemia in children and Gilead Sciences Yescarta for the treatment of late-stage non-Hodgkins Lymphoma. They are both made by the gene manipulation of immune cells outside of the body and then re-introducing them. This technology is called CAR-T (chimeric antigen receptor T-cell therapy). Also, recently approved was the first "true" gene therapy, Luxturna, by Spark Therapeutics, in which the gene vector is injected directly into the eye. It has proven to improve vision in a rare disease caused by a single mutation, which without treatment leads to blindness. The drug was priced at USD 850,000, but the company will only charge patients which are responding to the treatment.

It is necessary for gene therapy to have a high price tag for it to be commercially viable, since it will probably be used as a one-time treatment. One approved treatment has further to compensate financially for all the failures in this complex research-intensive area. The price can be motivated if patients are cured and get a better life, or, if other medical costs, such as lifelong medication or a life dependent on caregivers, are avoided. Gene therapy can eventually in the future also be used to correct deficiencies in the brain, such as dopamine production in Parkinson's disease, and restore components needed for normal blood cell function in those with certain blood diseases, such as hemophilia and beta-Thalassemia, and cure cystic fibrosis or other degenerative diseases. More recently FDA approved a gene therapy for patients with a rare inherited type of blindness.

Thousands of medical conditions are the result of gene disorders. Gene therapy holds promise for treating many different diseases including cancer, diseases in the nervous system and rare diseases. If some of these genetic problems can be corrected, individuals suffering from these diseases may be cured and able to live long productive lives with contribution to society, improved quality of life and leading to overall lower costs for the healthcare system.
That gene therapy is a rapidly advancing area is shown by the graph in figure 1. It shows the number of scientific citations with the search query 'gene therapy' (blue line, lhs; Pubmed), and the number of approved gene therapy clinical trials (yellow line, rhs; Gene Therapy Clinical Trials Worldwide).

Figure 1: **Gene therapy, a advancing area**



Source: Pubmed, Gene Therapy Clinical Trials Worldwide

At C WorldWide, we are following the development in the gene therapy space closely, and monitor companies exposed to this exciting growth area. If you want to follow more of our thoughts and insights, please visit our website: cworldwide.com.

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