🦫 Healthcare industry BW

The use of human genes as medical products

In contrast to medications used for treating disease, gene therapy does not use chemical agents to alleviate or cure disease symptoms. Instead, it involves the introduction of a normal copy of a mutated gene to restore the function of a protein. Gene therapy could also be described as a way of restoring the body's self-healing process. It is an extremely smart idea that enables the sustainable treatment of diseases which cannot usually be achieved with standard drugs. Gene therapies have been undergoing clinical testing for around thirty years now. There have been successes as well as some setbacks.
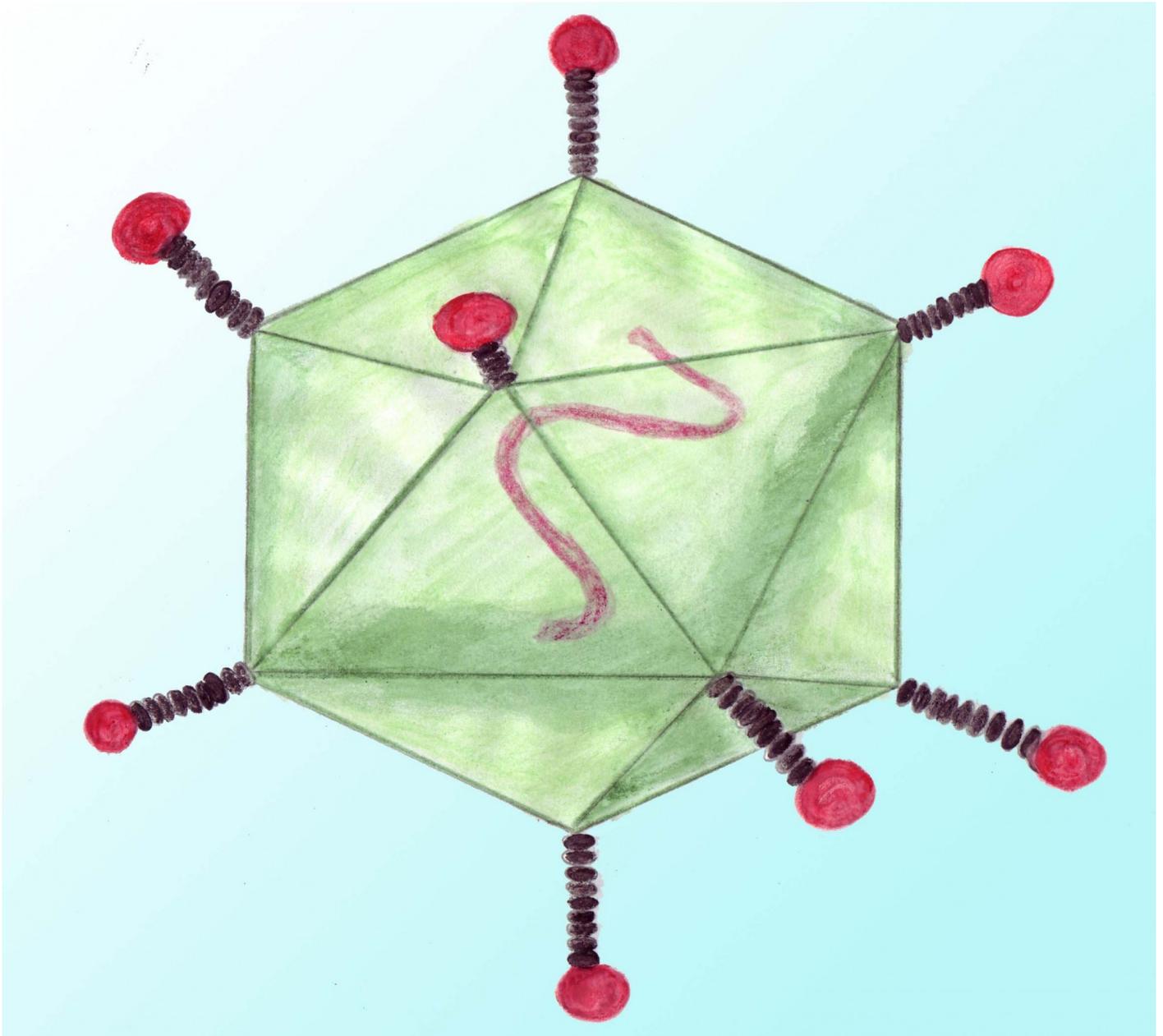
Gene shuttle on the test: The use of adenoviruses is not associated with a permanent effect as their genetic material is not incorporated into the DNA of the host cell. Their use can potentially lead to adverse effects in the form of severe immune reactions.
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In 1990, the first ever successful gene therapy was performed at the National Institutes of Health (USA) on four-year-old Ashanti DeSilva. The girl was born with a rare immunodeficiency due to an enzyme whose absence prevents B and T lymphocytes from maturing and the body from generating an immune response. The girl's defective gene was replaced with a functional variant, with the result that the number of T cells rose to near-normal values, meaning that the therapy was at least partially able to restore Ashanti's immune system. Ashanti is now able to lead a normal life, her condition is stable, but she is not completely cured. Although researchers still continued to find cells that were able to produce the missing enzyme five years after she had received the first corrected cells, Ashanti still has to be given regular injections of corrected blood cells that are able to produce the vital enzyme.

Nine years later, 18-year-old Jesse Gelsinger was the first person publicly identified as having died as a result of gene therapy. The young man suffered from a mild form of liver disease and was able to survive on special medication and a special diet. He wanted to help others who suffer from a more severe form of the disease and volunteered for a gene therapy trial. He was injected an infusion consisting of several billions of adenoviral vectors carrying a corrected gene. Gelsinger died of multiple organ failure four days after he had received the corrected gene because his body was unable to trigger an immune response against the large number of viruses. In addition, the investigators of the trial failed to report that other patients had experienced serious side effects. Due to these issues, the American FDA decided to stop any gene therapy trials involving adenoviruses.

Exchange of defective genes

Researcher using molecular biology methods to assess whether the correction of the gene of interest was successful.
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Gene therapy is generally applied to patients with diseases that are caused by a single defective gene. The gene therapy of these so-called monogenic diseases involves the replacement of the disease-causing gene with a healthy, functional gene. In order to do this, cells are removed from the patient, and a functional gene is transferred to the cells. The corrected cells are put back into the patient. In general, viral vectors are used to carry the DNA inside cells. Depending on the disease treated, either adeno- or retroviruses are used. All viral genes that might cause disease are removed and the therapeutic gene incorporated into the viral genome. The viral genes that allow the virus to inject its genome and activate the corrected gene in the host's genome must be left intact.

The use of viruses is associated with several problems: in addition to the flu-like symptoms that gene therapy can trigger, the greatest risk associated with the use of viruses is the integration of the corrected gene at a random, i.e. inappropriate, site in the host genome. In addition to the expression of the corrected gene, this could also lead to the activation of genes that are involved in cell cycle regulation. Retroviruses incorporate their DNA into the host cell genome at a random site; the integration of the DNA could lead to the disruption of a gene that inhibits uncontrolled cell division. It might also be incorporated close to a gene that promotes cell division. Its activation could then lead to the uncontrolled division of cells. In both cases, the cells could end up dividing in an uncontrolled manner and degenerate, resulting in cancer or leukaemia. Adenoviruses do not permanently integrate their genes into the host cells, which is why large quantities of adenoviral shuttles must be injected into the patient in order to achieve the desired effect. The consequences might be a greater risk of inflammation and severe immune reactions.

New approaches with gene shuttles

Much research is still required in order to assess the efficiency and side effects of gene therapy, which offers hope to many patients suffering from diseases for which no cure is currently available.
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Gene therapy trials undertaken to treat Wiskott-Aldrich syndrome or X-SCID, a severe X-linked immunodeficiency disorder, were initially highly promising, but eventually had to be aborted as the patients developed blood cancer due to the unintentional activation of cellular genes involved in initiating blood cancer.

Researchers are therefore pursuing an approach that involves the use of so-called gene scissors to cut the DNA at defined sites. This is done outside of the human body (ex vivo). The cell membranes are made temporarily permeable using a method known as electroporation; the gene scissor mRNA and the DNA donor required for the correction of the defective gene are then injected into the cells, and the corrected cells retransplanted into the patient.

Considerable progress has also been made with regard to artificial gene shuttles where the genetic cargo is included in liposomes. Liposomes can carry encapsulated antigens, cytokines, tumour suppressor genes, suicide genes as well as missing genes into the host cells.

More than 60 percent of all gene therapy trials are focused on the fight against cancer. A recent study carried out by the German Cancer Research Center in Heidelberg is aimed at exploiting the special properties of parvoviruses for cancer therapy. Parvoviruses are so small that they are able to cross the blood-brain barrier and they only replicate in dividing cells (e.g. cancer cells). The researchers found that parvoviruses are able to fully eliminate glioblastoma (a highly aggressive type of brain tumour).

Glybera® - the first ever gene therapy approved

Despite the setbacks experienced over the last few years, gene therapy is one of the beacons of hope in medical research. Research is mainly focused on rare diseases. In 2012, Glybera® became the first gene therapy approved by regulatory authorities in the Western world. It is the first medication approved for patients with severe pancreatitis caused by a metabolic disorder known as lipoprotein lipase deficiency (LPLD). The intramuscular application of the gene shuttle used to transport the functional gene is close to receiving regulatory approval.

The European Medicines Agency (EMA) has strict requirements relating to the group of medications known as "advanced therapy medicinal products" (ATMPs). ATMPs need to undergo three clinical testing phases and are assessed by two independent committees before the EMA will issue a positive recommendation. However, the final decision is made by the European Commission, and authorisation to market the drug is usually only granted for a specific period of time; the manufacturer of the drug is required to carry out further studies in the future. In 2013, forty gene therapy proposals were submitted to the EMA. The routine application of gene therapy is not yet in sight and a great deal of research is still needed to clarify important aspects. However, gene therapy has great potential, especially in the field of oncology.