



An Overview of the use of Gene Therapy in Cancer Treatment

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Abstract

Gene therapy is a novel tool for treating many illnesses. It was first heavily used in research projects in 1989, and since then, significant progress has been made in this treatment. Since most gene therapy research focuses on cancer, it was only a matter of coincidence that the first commercial gene therapy was developed in 2003 to treat neoplasia. However, a few unfavourable incidents involving the use of this medication led to its stringent monitoring and to the marketing of safer treatment plans. There are currently many different kinds of gene therapy ideas about a large number of anticancer molecular pathways in an effort to potentially open the door for incredibly potent treatment choices. Although there have been significant advancements in gene therapy in the fight against cancer, its practical use, safety, and efficacy remain restricted. It is anticipated that these challenges will be consistently overcome.

Keywords: Immunotherapy, Transference Method, Gene Therapy, Therapeutic Genes

Introduction

Cancer is a serious global health issue that claims the lives of over 8 million people annually. It is a complex, multidimensional illness with alterations to DNA that are controlled by interactions between the host and environment [1]. Characteristics including self-sufficiency in boom signals, resistance to anti-boom signals, ability to invade and metastasize tissue, limitless potential for replication, persistent angiogenesis, and evasion of apoptosis are shared by the majority of malignancies [1]. The tumour microenvironment, which is made up of a range of non-malignant cells that express various regulatory proteins and the extracellular matrix, is essential to the initiation and development of malignancies. Gene therapy aims to stimulate a healing response by expressing genetic material transferred into target cells or tissue.

An Overview of Gene Therapy for Cancer

Rogers *et al.* were among the first to show a preliminary proof-of-concept for virus-mediated gene transfer. He confirmed that viruses may be used to introduce foreign genetic material into hobby cells [3]. Motivated by the outcomes, he carried out a similar investigation on humans. Rogers is the first business to use this technology in a human gene therapy experiment. In that investigation, Rogers used a wild-type Shope papilloma virus, which permits the insertion of the arginase gene into girls with urea cycle abnormalities, or hyperargininemia [4,5].

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He hypothesised that the Shope papilloma virus might encode the arginase interest gene, and that the patients should be exposed to the virus in order to transmit this gene. Unfortunately, the trial's ultimate results were not favourable. Neither the arginine levels nor the scientific explanation of the sickness showed any variation in those people. Even while Rogers' "out of the box" concept began to make sense, it was eventually doomed to fail when it was found that the Shope papilloma virus genome no longer encoded the arginase gene.

In 1989, the US Food and Drug Administration (FDA) approved and launched the first gene therapy programme. There were lymphocytes that had been taken from superior cancer and were known to infiltrate tumours.

After being raised in vitro, patients were reinfused with a marker gene that had been transduced ex vivo and was no longer a healing gene [6]. In the subsequent year, the first scientific investigation on the majority of cancers with a curative aim began, treating patients with advanced cancer with ex vivo genetically engineered tumour infiltrating cells that expressed tumour necrosis factor [6].

The work by Cline et al. produced yet another important breakthrough in the realm of gene therapy. In order to treat thalassemia patients, bone marrow cells were taken out, transfected ex vivo with plasmids containing the human globulin gene, and the patients were then given these cells back. Not because it was unsuccessful, but rather because it was carried out without the appropriate approval from the University of California, Los Angeles (UCLA) Institutional Review Board, this project represents a turning point in the history of gene therapy. This example demonstrated the paucity of knowledge at the time and demonstrated that human gene therapy had more ethical and technological difficulties than first thought.

Techniques for Gene Transfer and the Vectors Used in Gene Therapy

The objective of gene therapy endeavours is to transfer a suitable quantity of genetic material into designated cells or tissues and sustain gene expression for a predetermined period of time. The delivery of genetic material to target cells or tissues can be achieved by a variety of techniques, including physical, viral, non-viral, and bacterial

or yeast-based methods. Physical techniques include things like gene gun delivery, ultrasound, and electroporation. While non-viral gene transfer techniques employ synthetic carriers like liposomes or nanoparticles, viral vectors use biological carriers, such as viruses, to transfer genetic material. Regarding transduction effectiveness, gene expression efficacy, length of transgenic expression, and safety profiles, each vector has distinct characteristics. Different vectors may be used for different therapeutic reasons, depending on the requirements.

For in vivo gene transfer, viral vectors are currently thought to be the most efficient gene delivery technique. A gene transfer vector should ideally target a particular tissue with high transduction efficiency and sustain sustained, regulated gene expression free from immunogenic reactions or unfavourable effects. All these requirements are not met by any of the gene delivery vectors that are currently in use. While systemic administration of a vector can result in extensive expression throughout the body, local injection of a vector usually produces a precise and confined effect area. In order to attain focused distribution and boost transduction efficiency, changes have been made to vector design and administration techniques. In spite of this, a lot of viral vectors have a natural tendency to favour particular cell types or tissues, which can be used therapeutically.

Vectors of Virals

Adenoviral vectors, lentiviruses, retroviruses (including HIV), vaccinia viruses, adeno-associated viruses (AAV), and baculoviruses are the most often used viral vectors for gene transfer. The transgenic capabilities, immunogenicity, expression profiles, cellular tropisms, and longevity of transgene expression of these vectors differ.

Viral vectors can be classified as integrating or non-integrating vectors in addition to their place of origin. Non-integrating vectors, such as baculoviruses and adenoviruses, are unable to integrate their genome and, hence, the transgene, into the host genome. On the other hand, integrating vectors like as lentiviruses, retroviruses, and AAVs can integrate into the host genome. With non-integrating viral vectors, transgenic expression is often transient (lasting a

few weeks), whereas with integrating vectors, transgene expression is usually long-term (months to years). However, since integration can happen in actively expressed areas (insertional mutagenesis), especially with retroviral vectors, integrating the transgene into the host genome raises questions about safety.

Ex vivo gene transfer techniques are another way to distribute genetic material; in this method, genetic material is first injected into isolated autologous cells outside of the patient and is subsequently reintroduced into the patient.

As of right now, the most common gene delivery vectors utilised in gene therapy are adenoviruses. Adenovirus serotypes numbering in the hundreds and are categorised into six subgroups (A–F). Serotypes 2 and 5 are the most often utilised in gene therapy among them. Nevertheless, a drawback of adenoviruses is that 97% of people have detectable amounts of pre-existing antibodies, which may have an impact on transduction efficiency and treatment results.

Not-Viral Vectors

Although viral vectors have been shown to be effective gene transfer agents, they have certain disadvantages, including the potential for immunogenic and inflammatory reactions and quick elimination from the bloodstream when used systemically. New synthetic gene delivery vectors have been created as a result of this. Non-viral technologies, in particular naked plasmid DNA, have shown great promise as viable substitutes because of their low toxicity and affordability. They are less effective at transfection than viral vectors, though. In order to prevent this, plasmid DNA can be condensed using cationic polymers or lipid formulations, which also improve absorption and transfection. By varying the size of the micro- or nanoparticles, these formulations provide flexibility in customising attributes like focusing on particular tissues or cells and affecting biodistribution and cellular absorption. Non-viral gene therapy has encountered difficulties in practical applications despite these developments, in part because of its lower transduction efficiency in comparison to viral vectors—which have undergone lengthy evolutionary processes. Overcoming the several extracellular and intracellular hurdles that affect the effectiveness of gene delivery, such as cellular

uptake, endosomal escape, nuclear uptake, and gene expression, is essential for the success of non-viral gene therapy.

Clinical Gene Therapy Effectiveness

Different gene transfer vectors and gene therapy techniques have been investigated for the treatment of cancer. Among these methods are apoptosis induction, oncolytic virotherapy, immune modulation, anti-angiogenic therapy, repairing gene defects, blocking tumour invasion, using gene therapy to improve chemotherapy and radiotherapy, myeloprotective gene therapy, pro-drug activation/suicide gene therapy, and antisense and RNA interference (RNAi) based techniques. Only a small number of these techniques, meanwhile, have advanced to clinical use.

Using a spontaneous mutation in the p53 protein is a frequently employed strategy in cancer gene therapy. An adenoviral vector containing the tumour suppressor gene TP53 was used by Lang *et al.* in a phase I clinical trial in 2003 to treat patients with recurring malignant gliomas. In this trial, en bloc tumour resection and post-resection cavity treatment were performed on 15 patients after intratumoral stereotactic injection of the adenoviral vector using an implanted catheter. Minimal toxicity was seen, despite the fact that the tumour response could not be thoroughly assessed in this investigation. The maximum dose that could be tolerated was not achieved, and there was no indication of systemic viral spread. Furthermore, little transgene expression was observed in the vicinity of the injection site in tumour specimens analysed.

Another noteworthy study that employed Gendicine™ was comparable to the methodology of Lang *et al.* Gendicine™ is a replication-incompetent adenovirus that treats different types of cancer by expressing the TP53 gene rather than the viral E1 gene. Being the first gene therapy medicine authorised for clinical use, Gendicine™ earned prominence. Twelve patients with laryngeal cancer participated in a phase I clinical trial in which Gendicine™ showed therapeutic potential; over the five-year follow-up period following therapy, none of the treated patients experienced tumour relapse. 132 patients with head and neck squamous cell carcinoma participated in a phase II/III trial,

which further demonstrated Gendicine™'s favourable safety profile. Fever was the most frequent adverse event in this experiment, as reported by 32% of the patients. A synergistic effect of the combination therapy was demonstrated by the fact that 64% of patients with Gendicine™ in combination with radiation showed total regression and 29% showed partial regression, while only 19% with radiotherapy alone showed complete regression and 60% with partial regression.

Shanghai Sunway Biotech's Oncorine™ is the second gene therapy product to be approved for sale by the Chinese SFDA. Adenoviral E1B 55K gene deletion results in the conditional replication of Oncorine™, a kind of adenovirus. Because of this deletion, the virus is unable to attach to and deactivate the wild-type p53 protein, which is a crucial part of the host's defence against viral infection. The virus can only multiply preferentially in cells without functioning p53, like malignant cells, but it cannot replicate in normal cells in the absence of E1B 55K activity. Its potential as a cancer treatment for solid tumours stems from the focused viral growth that causes oncolysis.

Oncorine™ is noteworthy because ONYX-1/2, a comparable medication created by Onyx Pharmaceuticals, was never approved for sale. In contrast to Oncorine™, ONYX-1/2 was unable to show any therapeutic advantages in clinical settings. For instance, ONYX-1/2 was proven to be safe and to have no significant side events linked to it in a Phase I dose-escalation trial carried out by Chiocca *et al.*, in which 24 patients with recurrent malignant glioma received injections of the oncolytic virus into 10 distinct sites of resected tumours. All individuals did, however, exhibit tumour growth. Two patients who had a second resection exhibited immune cell infiltration at the injection site, and one patient with anaplastic astrocytoma had stable illness.

Significant safety results for a range of malignancies, including gliomas, head and neck, pancreatic, and ovarian cancers, have been presented by ONYX-1/2 and ONcorine™, suggesting an acceptable safety profile. Fever, soreness at the injection site, nausea, hair loss, low white blood cell count, and flu-like symptoms were among the frequent side effects.

More therapeutic proteins have been added to oncolytic viruses to increase their effectiveness. A second-generation oncolytic herpes simplex virus (HSV) that has been modified to create the therapeutic protein granulocyte-macrophage colony-stimulating factor (GM-CSF) is called OncoVEXGM-CSF. According to a Phase I safety research, OncoVEXGM-CSF injections intravenously were safe and well-tolerated in patients with cutaneous or subcutaneous deposits of gastrointestinal, head and neck, and breast malignancies as well as malignant melanoma that had not responded to prior therapy. Additionally, the study revealed signs of an anticancer impact, which was corroborated by a Phase I/II trial in which patients with untreated stage III/IV squamous cell carcinoma of the head and neck received OncoVEXGM-CSF in addition to radiation and cisplatin.

Methods of Gene Therapy to Activate the Immune System

The topic of immunotherapy has drawn a lot of attention lately. Generally, the aim of immunotherapy is to enhance the visibility or appeal of tumor-related antigens (TAAs). Unfortunately, aside from the herbal tolerance to TAAs and the highly immunosuppressive tumour microenvironment, there aren't many uncommonly difficult conditions that have been addressed with the use of immunotherapies. In particular, there has been a great deal of study done on T cell genetic engineering [28]. One example of T cell genetic engineering is the development of a T cell receptor (TCR) directed against a recognised TAA. An example of this method can be found in the scientific publication by Morgan *et al.*, wherein they used retroviral vectors to transduce normal peripheral blood lymphocytes (PBLs) with an anti-MART1 TCR transgene that became isolated from tumour infiltrating lymphocytes (TILs) of cancer patients [29]. There, they demonstrated that 15 patients had sustained T cell engraftment at tiers higher than 10% of peripheral blood lymphocytes for at least months following mobile infusion. Additionally, 365 days following infusion, they found high sustained levels of circulating, engineered PBLs in patients who had all achieved goal remission of metastatic cancer lesions. T cells have been transduced with a TCR targeting

the antigen NY-ESO-1 in another scientific study. This antigen is expressed in a variety of malignancies and is present in most cancers/testis (CT) [30]. Furthermore, on this trial, an objective Patients' scientific response became resolute, providing evidence that developing a TCR focused on a TAA is a feasible option for the treatment of the majority of malignancies.

Similar to introducing a TCR, T cells can also be stimulated using a synthetic T cell receptor, often known as a chimeric antigen receptor, or CAR. In clinical settings, the use of CAR to direct T lymphocytes against cancer cells has produced impressive response rates, especially against haematological malignancies. For example, a clinical phase I trial was carried out by Kochenderfer *et al.* to evaluate the safety and viability of adoptive transfer of genetically engineered T cells that express CAR against CD19.

Herman *et al.* assessed a different strategy to boost an anti-tumoral immune response in patients with locally advanced pancreatic cancer who were enrolled in a randomised phase III clinical study. For this goal, an evaluation was conducted on a second-generation replication-deficient adenovirus of serotype 5, which carries the TNF- α cDNA under the early growth response protein 1 (Egr-1) promoter. The transgene's expression is restricted to the radiation field by the promoter Egr-1, which is activated by ionising radiation. In this study, 304 patients were randomised 2:1 to get conventional care plus gene therapy—that is, an adenovirus that codes for TNF- α —as opposed to receiving normal care alone. The findings showed that while standard of treatment in addition to gene therapy was safe, patients with locally advanced pancreatic cancer did not benefit in terms of survival. On the other hand, a study by Malmström *et al.* that looked at the immunostimulating effects of gene therapy using adenoviral vectors expressing CD40 ligand showed a more encouraging result. Belonging to the TNF gene superfamily, CD40L is well-known for its ability to stimulate T helper 1 cells' immunological responses. Eight patients with invasive bladder cancer were recruited for this study's phase I/IIa trial, which evaluated the antitumor responses, immunological effects, safety, and effectiveness of gene transfer. The

findings demonstrated a decrease in circulating T regulatory cells and an increase in IFN- γ presence in tumour samples. Following adenoviral CD40L gene therapy, additional histologic assessment revealed a decrease in the load of malignant cells in the bladder. Chiocca *et al.* conducted a trial in which 11 patients received stereotactic injections of adenoviruses producing interferon- β at different doses into their tumours. Four to eight days later, the tumour was surgically removed, and the tumour bed was injected with more adenovirus. Regrettably, after 4 months of treatment, all patients had disease progression and/or recurrence. 9.3 weeks was the median time to tumour progression, while 17.9 weeks was the median overall survival.

Apart from the previously described tactics, a pro-drug activating suicide gene therapy is another method that has been thoroughly investigated in pre-clinical and clinical settings for the treatment of cancer. This will be covered in more detail later on.

Pro-Drug Activating Gene Therapy for Suicide

Prodrug activating suicide gene therapy works on the basis of inserting a transgene into the tumour that codes for an enzyme that is either nonexistent or present in mammalian cells but in an inactive state. The injected inactive prodrug is changed into its active form by the enzyme made by the transduced cells, which causes the cells that express the therapeutic gene to die. The bystander effect, in which nearby non-transduced cells perish as well, is essential for the effectiveness of therapy. Because brain tumours are isolated, localised lesions of rapidly dividing cells in a backdrop of non-dividing cells and frequently return near the initial lesion, they are particularly well-suited for prodrug activating gene therapy.

This strategy produced negative early results, mainly because of low transduction efficiency, which was probably caused by the first use of retroviral vectors. Adenoviral vectors, on the other hand, have demonstrated significantly greater transduction efficiency and transgenic expression. Adenoviruses have the ability to transduce both quiescent and proliferating cells, which is useful because cancer cells do not all multiply within a tumour at the same time.

The prodrug activating enzyme Herpes simplex virus-thymidine kinase (HSV-tk) packaged into an adenovirus was used in the first phase I clinical trial by Eck et al. in 1996 to treat patients with recurrent gliomas. Sandmair et al. announced the results of the first extensive trial using adenovirus HSV-tk in patients with malignant glioma in 2000. In order to treat primary or recurrent gliomas, the effectiveness of adenovirus-mediated HSV-tk gene therapy and retrovirus-packaging cells for HSV-tk was evaluated in this work. Compared to the retrovirus-packaging cell group, the adenovirus HSV-tk group's mean survival time was noticeably greater. The retrovirus-packaging cell techniques demonstrated no efficacy, despite their safety.

HSV-tk gene therapy was found to be effective in later phase II clinical studies, where patients who received the treatment had a higher survival rate than those who did not. Historically, this was the first trial to show a survival benefit employing an adenoviral vector and the HSV-tk prodrug activating suicide gene in a randomised, controlled setting. Motivated by these findings, a multicenter randomised phase III clinical trial with standard care control was started, enlisting 250 patients who were randomised to the standard care or experimental group.

In the experimental organisation, the median time to death or re-intervention increased to 308 days, compared to 268 days in the manipulation organisation. Interestingly, the chance ratio (HR) increased to 1.72 ($p = 0.008$) in a cohort of patients with non-methylated regions of the DNA repair gene MGMT (O6-alkylguanine DNA alkyltransferase). Nevertheless, there is no statistically significant difference found in the average survival of the organisations [41]. The results of the study suggested that the use of HSV-tk gene therapy following tumour resection can accelerate the time to death or re-intervention in patients with recently discovered supratentorial glioblastoma multiforme, even though the study did not indicate development of ordinary survival. This study also shows that more domestically generated gene therapy for glioblastoma is necessary, especially for patients who will not respond to traditional chemotherapy. Because it is based only on the suicide gene treatment with

HSV-tk, this study is by far the only adenoviral vector study to complete a section III clinical trial.

Gene therapy safety

The protection statistics gathered from unique human gene therapy trials have been consistently excellent, despite the terrible situation of Jesse Gelsinger, who perished as a result of gene treatment using adenoviral vectors. It should be noted, nevertheless, that since the viral vectors used in gene therapy are usually human infections, pre-existing antibodies against the viral vector may exist, which could result in an unfavourable immune response. An injection of adenoviral vectors, for instance, will result in an initial non-specific immune response in the host, such as the release of several cytokines aided by the use of a specific antibody and a mobile-mediated immune response targeted against transduced cells. Nonetheless, the response to adenoviruses varies depending on the serotype. For instance, a study utilising Thoma et al. demonstrated that the macrophages' spontaneous cytokine response in response to viral stimulation varies depending on the adenovirus serotype, making it serotype-specific. In particular, Ad11 caused no/moderate toxicity and Ad5 caused moderate/excessive toxicity in a long-term study where both adenovirus serotypes 5 (Ad5) and 11 (Ad11) were injected intraperitoneally [42].

However, there are generally no longer many long-term protective data about the use of viral vectors in humans. However, a number of meta-evaluations have already been conducted on adenoviruses, showing a sufficient level of protection in humans [41, 43]. The side effects of adenoviral vectors have generally been mild and have not been connected with any serious adverse events; the tolerance of these vectors has been excellent.

Various techniques have been employed to improve the safeguarding of gene remedies. One method is to intensify targeted strategies to improve the beauty of gene transfer vector movement and, in turn, extend and improve the effectiveness of gene expression. Generally speaking, lack of specificity to target cells and low transduction efficiency are two of the main drawbacks of gene therapy. Over time, increasing transduction efficacy and/or specificity may potentially lead to a better protective profile. As a

result, as vector technologies—such as repurposing viral vectors through the use of molecular evolution, chemical modification, and epitope insertion—have advanced, so too has the transduction efficacy of gene transfer vectors [44]. An example of this was investigated in a phase I clinical study conducted by Kim *et al.*, wherein they modified the RGD fibre knob on adenoviruses, thus enhancing the viral infectivity of the majority of cancer cells [45].

A great deal of study has been done on the role of innate immunity as well as the activation of T and B cells in response to the vector and its transgenic product. In particular, subjects that need to be similarly evaluated are the possible effects of gene transfer vectors and/or their produced proteins on neighbouring lymph nodes. Since quite some time, the pre-existence of neutralising antibodies (e.g., against many adenovirus serotypes or AAVs) has been documented. It is believed that these pre-existing neutralising antibodies can considerably reduce transduction efficiency [46].

Viral floor proteins had been used to improve transduction efficiency as well as selectivity.

modified, removed, or swapped out. For example, lentiviral vectors were created, where a cell

The viral envelope has been combined with a specific kind of ligand or antibody (also known as pseudotyping) [47]. This has the disadvantage that during lentivirus production, special tweaks resulted in low vector titers [13]. Additionally, it has been demonstrated that concentration may undoubtedly jeopardise the vector's ability to enter the cell [13,47]. Conversely, instead of concentrating on viral vectors exclusive to one cell type, pseudotyping can be employed to cultivate the tropism of the viral vector to diverse cell types. For example, the Vesicular Stomatitis virus G-protein (VSV-G) is frequently pseudotyped into retroviruses and lentiviruses in order to increase their tropism and production yield [48].

Utilising tissue-specific or conditional promoters is another method for increasing the specificity of viral vectors to their target cells. The application of hypoxia-particular regulatory structures, which aim to induce and constrain gene expression to ischemic tissues, is an example of conditionally structured gene expression [49]. These hypoxia-specific regulatory structures are commonly

applied to various ischemia illness models, such as ischemic myocardium, stroke, and injured spinal cord, but they can also be used in the majority of cancer gene therapies [50]. As was already indicated in the case of OncorineTM, gene expression can also be modulated depending on a genotypic trait (e.g., a mutant TP53 gene in most malignancies cells).

Insertional mutagenesis using integrating vectors poses a risk to protection. retroviruses,

Examples of viruses that integrate their genome into their host chromosomes are lentiviruses and AAVs. By doing this, there's a chance that those vectors might also merge into transcriptionally active regions or gene regulatory regions, respectively, which could potentially lead to insertional mutagenesis and oncogenesis. Numerous methods had been developed to get around those issues. Thus, one of the most important topics in cutting-edge vector enhancement has been the targeted integration of transgenes to predefined genomic websites. Better homologous recombination via DNA double-strand breakage is the main green strategy for achieving centred integration into human cells [51]. Additionally, the development of lentivirus/transposon hybrids allowed for the possibility of insertional mutagenesis to be decreased [52]. One interesting method that allows for robust transgene integration through transposition into the target mobile genome is the Sleeping Beauty transposon machine [53, 54]. The advantage of the Sleeping Beauty transposon machine is that the inverted repeats have very little residual promoter/enhancer activity and no longer exhibit a drive for integration inside active genes. One of the main arguments against human gene therapy has been the possibility of genotoxicity or mutagenesis. Nevertheless, it is sometimes overlooked that the majority of conventional cancer treatments, such as chemotherapy and radiation therapy, can also cause genetic alterations. It is a fact that a number of chemotherapeutic medications, in addition to radiation therapy, may cause genetic alterations and oncogenesis in patients [55–57].

The protective profile of gene switch vectors may also be enhanced with the help of expanding the production of gene switch vectors (i.e., improving the manufacturing of mobile phone lines,

manufacturing techniques, in addition to the purification procedures). For instance, gutless adenoviral vectors are vectors in which every other gene is removed, with the exception of those essential for the production of the virus, and replaced with the desired gene, which is pushed with the help of a suitable promoter. Because of this, gutless adenoviruses still exhibit high transduction efficiency and similar tropism to previous vectors, but they are far less immunogenic than adenoviral vectors from the first generation. However, co-contamination with a helper adenovirus is required because gutless vectors lack all of the viral genes. This provides the necessary proteins for the genome replication, packaging, and capsid formation of the virus. Since the viral capsids of helper and gutless vectors are identical, separation should be handled before purification, which is time-consuming and hasn't always been done without difficult circumstances [58].

Recent advancement in gene therapy

Gene Therapy
Since the discovery of DNA as the fundamental component of heredity, medicine has aimed to modify specific regions of the human genome. The ability to improve genes through the rectification of changed (mutated) genes or site-specific alterations with the goal of therapeutic treatment is known as gene therapy. Afterwards, many approaches that are frequently employed for this aim are discussed. Gene therapy is still primarily used in research labs today, and its applications are still experimental. The majority of trials are carried out in Australia, Europe, and the United States. With the ability to treat diseases brought on by acquired genetic illnesses like cancer, certain viral infections like AIDS, and diseases caused by recessive gene disorders including sickle cell anaemia, muscular dystrophy, haemophilia, and cystic fibrosis, the approach is comprehensive. Recombinant DNA technology is one of the most widely used methods; it involves inserting a healthy gene or gene of interest into a vector, which can be plasmidial, nanostructured, or viral; the latter is most frequently used because of its effectiveness in invading cells and introducing its genetic material. A few gene therapy protocols that represent the illness, the target, and the kind

of vector utilised are compiled, authorised, and published for clinical usage [104]. The process of gene therapy is very complicated, and new developments are still needed for many procedures, despite the success of numerous protocols. It should be possible to identify and reach the precise bodily cells that require medical attention. The diseases and their tight genetic ties must be fully known, and a method for delivering the gene copies to the cells must be available. The target cell type of gene therapy, which is now separated into two major groups—gene therapy of the germline and gene therapy of somatic cells—is another crucial issue. In germline gene therapy, functional genes are inserted into the stem cells, such as those found in the sperm and egg, to alter them. The alterations are inherited and are passed down to the next generation. Theoretically, this strategy should be quite successful in combating inherited and genetic illnesses. Gene therapy using somatic cells involves transferring therapeutic genes to a patient's somatic cells. Any changes or consequences are unique to that patient and are not passed down to subsequent generations.

Procedure for gene therapy: the gene's release
In gene therapy, an aberrant gene that causes a particular disease is replaced with a normal gene by inserting it into the genome. The technique presents a number of problems, but one of the biggest is getting the gene released into the stem cell. In order to release the gene, a molecular carrier known as a "vector" is utilised. This vector must be highly specific, exhibit efficiency in releasing one or more genes of the sizes required for clinical applications, elude immune system recognition, and be purified in large quantities and high concentrations in order to be produced and made widely available. After the vector is implanted, the patient cannot experience an allergic reaction or an inflammatory response; instead, it should improve normal functions, address deficits, or prevent harmful activity. In addition, it need to be safe for the experts handling it as well as the surroundings and the patient. Lastly, over the duration of the patient's life, the vector should be able to express the gene generally.

While the effectiveness of viral vectors has been established, new research has shown that there are

a number of drawbacks to using these carriers. The plasmid's viral genetic material is a potent aggravating factor because, in addition to potentially causing an oncogenic transformation, it can trigger an immediate immunological response. There are now two primary methods for altering a cell's genetic makeup: virus-mediated and physical mechanisms using preparations made using cutting-edge nanotechnology methods. Included in this context are polymers that create networks, such as cationic polymers, DNA microinjections, cationic liposomes, and particle bombardment, that capture a gene and release its content when they enter the cells. Because of their great potential for lifespan and ability to self-renovate, hematopoietic stem cells have emerged as promising candidates for gene transfer. The synthesis of gene transfer vectors for the generation of induced pluripotent stem cells (iPS), which allows for the differentiation of the iPS and the provision of an extra phenotype from this differentiated derived cell, is one example of this coupling of gene therapy and stem cells. Individuals who need a liver transplant and have chronic liver disease as well as viral infection (hepatitis B and hepatitis C, for example) may receive mature or iPS-derived hepatocytes transplanted into their livers. In addition to genes, another necessary step in the process of turning stem cells into hepatocytes could be the transfer of a vector encoding a short hairpin RNA that targets the hepatitis virus. This would give the transplanted cells resistance, or "immunity," against reinfection. Over time, resistant cells can replenish the liver and return it to normal hepatic function[105].

Conclusion

Most cancers can be treated using gene therapy, which is an intriguing and effective method for treating a variety of diseases. At the moment, the majority of gene therapy procedures are limited to ex vivo gene switch techniques or the close control of the gene switch vector. The minimal dispersion of the vector within the tissue and low transduction efficiency continue to be challenging circumstances in gene therapy. It is imperative to stress that awareness needs to shift not just to the vector improvement process itself but also to the vector production process. It has been difficult to deal with the high cost associated with the

production of viral vectors, which is the product of laborious downstream purification processes. Furthermore, the concept of using gene therapy as an unmarried agent medication has not shown to be as successful as anticipated. Therefore, combined treatment with other novel medicines or current orthodox modalities needs to be considered and can yield additional benefit in the majority of malignancies treated with gene therapy.

References

1. The characteristics of the majority of malignancies, Hanahan, D.; Weinberg, R.A. 2000; *Cell* 100: 57–70.
2. M.J. Bissell and W.C. Hines ask, "Why don't we get more cancers?" A suggested stance by the microenvironment in halting the growth of the majority of malignancies. *Nat.* 2011; *Med.* 17, 320–329.
3. Viruses as carriers of genetic information delivered: Rogers, S.; Pfuderer, P. 1968; *Nature*, 219, 749–751.
4. Colombo, J.P.; Terheggen, H.G.; Rogers, S.; Lowenthal, A.; Induction of arginase pastime using the A patient with arginineemia's tissue lifestyle cells contained the Shope papilloma virus. *J. Exp.* 1973, 137, 1091–1096. *Med.*
5. Rogers, S.; Terheggen, H.G.; Lowenthal, A.; Lavinha, F.; Colombo, J.P.; Ineffective trial of replacement gene in the absence of arginase. *Z. Kinderheim.* 1975, 119, 1-3.
6. Aebersold, P.; Cornetta, K.; Kasid, A.; Morgan, R.A.; Moen, R.; Karson, E.M.; Lotze, M.T.; Yang, J.C.; Topalian, S.L. Gene switch into humans—Tumor-infiltrating lymphocytes were used in immunotherapy for patients with superior melanoma, but the method was altered through retroviral gene transduction. *N. Engl.* 1990; *J. Med.* 323, 570–578.
7. P. MacMillan. The Cline Scandal. *Nurs. Times*, 78, 383 (1982).
8. Beutler, Edward. The Cline incident. *Mol. Ther.* 2001, 4, 396–397.
9. Raty, J.K., Lesch, H.P., Wirth, T., Yla-Herttuala, S. Enhancing gene remedy protection. *Curr. Drug-Safe.* 2008, 3, 46–53.
10. Baker, A.H.; Coughlan, L.; Nicklin, S.A.; Parker, A.L.; Bradshaw, A.C.; McNeish, I.A. Tropism-amendment methods utilising adenoviral

- vectors for centred gene transfer. 2010, 2, 2290–2355. *Viruses*.
11. E. Montini. Seeking safety at AAValon. 2011, 117, 3249–3250 in *Blood*.
12. Plati, T., Rubagotti, E.; Biffi, A.; Bartolomae, C.C.; Cesana, D.; Cartier, N.; Aubourg, P.; Ranzani, M.; Cesani, M.; Benedicenti, F.; et al. In preclinical settings, lentiviral vector integration websites are not uncommon, and a scientific trial reflects a benign integration bias and no longer oncogenic selection. 2011, 117, 5332–5339 in *Blood*.
13. J. Matrai, M.K. Chuah, and T. VandenDriessche. Recent developments in the development of lentiviral vectors as well as uses. *Mol. Ther.* 2010, 18, 477–490.
14. Anand Sharma, Xia Li, D.S. Bangari, and S.K. Mittal Adenovirus receptors and their consequences in gene transfer. 2009, 143, 184–194. *Virus Res*.
15. Heyde, M.; Shakesheff, K.M.; Howdle, S.M.; Oreffo, R.O.; Partridge, K.A.; Garnett, M.C. Applications for tissue engineering employ gene therapy. *J. Pharma. Pharmacol.* 2007, 59, 329–350.
16. Pathak, A., Patnaik, S., and Gupta, K.C.: Current trends in gene transfer mediated by non-viral vectors. *Biotechnological. J.* 2009, 4, 1559–1572.
17. Learning from the viral journey: Entering cells and overcoming intracellular barriers to reach the nucleus (Mudhakir, D.; Harashima, H.). *AAPS J.* 2009, 11, 65–77.
18. Teissie, J.; Rols, M.P.; Escoffre, J.M. Gene switch: How can the organic constraints be overcome? *J. Membr. Biol.* 2010, 236, 61–74.
19. Chang, S.; Berger, M.S.; McDermott, M.W.; Kunwar, S.M.; Junck, L.R.; et al. Lang, F.F.; Bruner, J.M.; Fuller, G.N.; Aldape, K.; Prados, M.D. Phase I study of p53 mediated by adenovirus Gene therapy for recurrent glioma: Scientific and biological outcomes. *J. Clin. Oncol.* 21, 2508–2518 (2003).
20. Yla-Herttuala, S.; Wirth, T.; Pikkarainen, J.T.; Raty, J.K. Gene remedy: the principal authorized scientific indications, molecular mechanisms, and gene-based pharmaceuticals. *Curr. Mol. Pharmacol.* 2008, 1, 13–23.
21. Wang, Q.; Ni, X.; Chen, X.H.; Pan, J.H.; Han, D.M.; Huang, Z.G.; Zhang, W.; Yu, Z.K.; Wang, H. Recombinant adenovirus p53 injection's efficacy against the majority of laryngeal cancers: Phase I scientific experiment and adhere to it. *Yi Xue Za Zhi Zhonghua* 2003, 83, 2029–2032.
22. Peng, Z. Recombinant human Ad-p53 agent for cancer treatment: the current status of genetics in China. *Hehe. Gene ther.* 15, 1016–1027, 2005.
23. Kirn, D.H.; Williams, A.; Heise, C.; Horn, S.; Muna, M.; Ng, L.; Nye, J.A.; Bischoff, J.R.; A. Fattaey; A. Sampson-Johannes; et al. A mutant adenovirus that replicates only in human tumour cells with low p53. *Science* 264, 373–376 (1996).
24. Hochberg, F.H.; Barker, F.; Kracher, J.; Chiocca, E.A.; Abbed, K.M.; Tatter, S.; Louis, D.N.; Carson, K.; Fisher, J.D.; Grossman, S.A., et al. a phase I open-label, dose-escalation, multi-institutional study involving the injection of ONYX-015, an E1B-attenuated adenovirus, into the peritumoral region of malignant gliomas that recur within the adjuvant context. *Mol. Ther.* 2004, 10, 958–966.
25. Oncolytic adenovirus clinical trials in China, Yu, W.; Fang, H. *Curr. Cancer.* 2007; *Drug Targets* 7, 141–148.
26. Hu, J.C.; Harrington, K.J.; James, N.D.; Love, C.A.; McNeish, I.; et al.; Coffin, R.S.; Davis, C.J.; Graham, N.J.; Groves, N.; Guest, P.J. I watch a portion of OncoVEXGM-CSF, a herpes simplex virus with second-generation oncolytic infection that expresses granulocyte macrophage colony-stimulating factor. *Clin. Cancer Res.*, 12, 6737–6747 (2006).
27. Thway, K.; Sibtain, A.; McNeish, I.A.; Harrington, K.J.; Hingorani, M.; Tanay, M.A.; Hickey, J.; Bhide, S.A.; Clarke, P.M.; Renouf, L.C.; et al. Phase I/II study of chemotherapy plus radiation plus cisplatin for oncolytic HSV GM-CSF in untreated level III/IV squamous cell carcinomas of the head and neck. *Clin. 2010; Cancer Res.* 16, 4005–4015.
28. M.H. Kershaw, J.A. Westwood, and P.K. Darcy. Gene-engineered T cells as a treatment for most malignancies. *Nat. (2013) Rev. Cancer* 13, 525–541.
29. Royal, R.E.; Topalian, S.L.; Kammula, U.S.; Restifo, N.P.; Morgan, R.A.; Dudley, M.E.; Wunderlich, J.R.; Hughes, M.S.; Yang, J.C.; Sherry, R.M.; et al. Patients who switched to genetically altered lymphocytes experienced a

- regression in their cancer. *Science*, 314 (2006), 126–129.
30. Wunderlich, J.R.; Nahvi, A.V.; Helman, L.J.; Mackall, C.L.; et al. Robbins, P.F., Morgan, R.A., Feldman, S.A., Yang, J.C., Sherry, R.M., Dudley, M.E., et al. The application of genetically modified lymphocytes reactive with NY-ESO-1 results in tumour regression in patients with metastatic synovial mobileular sarcoma and carcinoma. *J. Clin. Oncol.* 2011, 29, 917–924.
31. Treating B-cellular most malignancies using T cells that express anti-CD19 chimeric antigen receptors Kochenderfer, J.N.; Rosenberg, S.A. *Nat. Rev. Clin. Oncol.* 2013, 10, 267–276.
32. Dudley, M.E.; Feldman, S.A.; Wilson, W.H.; Spaner, D.E.; Maric, I.; Stetler-Stevenson, M.; Phan, G.Q.; Hughes, M.S.; Sherry, R.M.; et al. Kochenderfer, J.N. B-cell depletion, cancer remissions, and cytokine-related damage in a study using T cells transduced with anti-CD19 chimeric antigen receptor. 2012; *Blood*, 119, 2709–2720.
33. Chang, K.J.; Taylor, G.E.; Donehower, R.C.; Herman, J.M.; Wild, A.T.; Wang, H.; Tran, P.T.; Ziegler, M.A., Pawlik, T.M., Cai, H., et al. Randomised multi-institutional section III examination of Final results for TNFerade biologic combined with fluorouracil and radiation therapy for pancreatic tumours that are superior domestically. *J. Clin. Oncol.* 2013, 31, 886–894.
34. Malmstrom, P.U.; Fransson, M.; Wanders, A.; Loskog, A.S.; Lindqvist, C.A.; Mangsbo, S.M.; The first AdCD40L immunogene treatment for bladder cancer was developed by Gardmark and Totterman. trial in section I/IIa. *Clin. Cancer Res.* 2010; 16, 3279–3287.
35. A section I trial of Ad.hIFN-beta gene therapy for glioma was conducted by Chiocca, E.A., Smith, K.M., McKinney, B., Palmer, C.A., Rosenfeld, S., Lillehei, K., Hamilton, A., DeMasters, B.K., Judy, K., and Kirn, D. *Mol. Ther.* 2008, 16, 618–626.
36. Packman, C.H.; Koeplin, D.S.; Moolten, F.L.; Freeman, S.M.; Abboud, C.N.; Whartenby, K.A.; Abraham, G.N. Tumour regression while a portion of the tumour mass is still present: The "bystander effect" genetically altered. 1993; *Cancer Res.* 53: 5274–5283.
37. Hurskainen, H.; Tyynela, K.; Turunen, M.; Vanninen, R.; et al. Sandmair, A.M.; Loimas, S.; Puranen, P.; Immonen, A.; Kossila, M.; Puranen, M. Thymidine kinase gene therapy for human malignant glioma, employing adenoviruses or replication-poor retroviruses. *Hehe. Gene ther. Eleven*, 2000, 2197–2205.
38. Judy, K.; Mollman, J.; Phillips, P.C.; Eck, S.L.; Alavi, J.B.; Alavi, A.; Davis, A.; Hackney, D.; Recombinant adenovirus H5.010RSVTK treatment of superior CNS malignancies: a section I trial (Wheeldon, E.B.; Wilson, J.M.). *Hehe. Gene ther.* 1996, 7, 1465–1482.
39. Rainov, N.G. A section III scientific evaluation of ganciclovir gene therapy and herpes simplex virus type 1 thymidine kinase as a supplement to radiation therapy and surgical resection in adults with glioblastoma multiforme that had not previously received treatment. *Hehe. Gene ther. Eleven*, 2000, 2389–2401.
40. The study conducted by Immonen, A., Vapalahti, M., Tyynela, K., Hurskainen, H., Sandmair, A., Vanninen, R., Langford, G., Murray, N., and Yla-Herttuala, S. found that intravenous ganciclovir combined with the AdvHSV-tk gene therapy enhances survival in human malignant glioma patients. *Mol. Ther.* 2004, 10, 967–972.
41. Adenovirus-mediated gene therapy with stimagene ceradenovec monitored by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): A randomised, open-label, phase three trial Westphal, M.; Yla-Herttuala, S.; Martin, J.F.; Warnke, P.; Menei, P.; Eckland, D.; Kinley, J.; Kay, R.; Ram, Z. *Lancet Oncol.* 2013, published in press.
42. Adenovirus serotype eleven causes significantly less prolonged intraperitoneal irritation than serotype five: Implications for the treatment of ovarian malignancies Thoma, C.; Bachy, V.; Seaton, P.; Green, N.K.; Greaves, D.R.; Klavinskis, L.; Seymour, L.W.; Morrison, J. 2013, 447, 74–83 in *Virology*.
43. Safety profile of plasmid/liposomes and virus vectors in scientific gene remedy: Wirth, T.; Hedman, M.; Makinen, K.; Manninen, H.; Immonen, A.; Vapalahti, M.; Yla-Herttuala, S. *Curr. Drug-Safe.* 1, 253-257, 2006.
44. Molecular engineering of adeno-related virus serotypes is the next stage in gene delivery, according to Wang, J., Faust, S.M., and Rabinowitz, J.E. *J. Mol. Cell. cardiac.* 2011, 50, 793–802.

45. Rudge, T.L.; Peggins, J.O.; Broadt, T.L.; Ryan, M.J.; Estep, J.E.; Miniard, B.M.; Kim, K.H.; Preuss, M.A., Siegal, G.P., Wang, M., et al. Adenovirals with improved conditional replicative ability and a new age of serotype chimeric infectivity: the protective profile of ad5/3-Delta24 in an improved phase I clinical trial in patients with ovarian cancer. *Hehe. Gene ther.* 2011, 22, 821–828.

46. Wang, L.; Siegel, D.L.; Wilson, J.M.; Grant, R.L.; Calcedo, R.; Bell, P.; Lin, J.; pre-existing immunity during gene transfer using adeno-related virus 8 vectors to nonhuman monkey liver. *Hehe. Gene ther.* 22, 2011, 1389–1401.

47. Barnett, B.G., Crews, C.J., and Douglas, J.T. Adenoviral vectors with a target. *Biochim. Biophys. Acta* 2002, 1575, 1–14.

48. Changing the tropism of lentiviral vectors through pseudotyping Cronin, J.; Zhang, X.Y.; Reiser, J. *Curr. Gene ther.* 2005, 5, 387–398.

49. Hypoxia-unique gene expression for the ischemia disease gene Kim, H.A.; Mahato, R.I.; Lee, M. *cure. Adv. Drug Deliv.* 2009, 61, 614–622. *Rev.* 50. Adenovirus-mediated hypoxia-centered gene repair using HSV thymidine kinase Harvey, T.J.; Hennig, I.M.; Shnyder, S.D.; Cooper, P.A.; Ingram, N.; Hall, G.D.; Selby, P.J.; Chester, J.D. and genes that activate prodrugs through bacterial nitroreductase both in vivo and in vitro. *Cancer Gene Ther.* 2011, 18, 773–784.

51. Using Rebar, E.J., Zhang, H.S., Holmes, M.C., Gregory, P.D., and Urnov, F.D., genome enhancing zinc finger nucleases with engineering. *Nat. Mr. Genet.* 2010, 11, 636–646.

52. Hybrid lentivirus-transposon vectors with a random integration profile in human cells: Staunstrup, N.H.; Moldt, B.; Mates, L.; Villesen, P.; Jakobsen, M.; Ivics, Z.; Izsvak, Z.; Mikkelsen, J.G. *Mol. Ther.* 17, 1205–1214 (2009).

53. Acosta-Sanchez, A.; Mates, L.; Chuah, M.K.; Belay, E.; Jerchow, B.; Manoj, N.; Grzela, D.P.; Becker, K.; Schmitt, A.; Matrai, J.; et al. Evolution of its molecules in a single hyperactive sleeping In vertebrates, beauty transposase enables robust, robust gene switching. *Nat. Genet.* 2009, 41, 753–761.

54. The field of pluripotent stem cells and the emerging potential of transposons for gene therapy are explored by VandenDriessche, T., Ivics, Z., Izsvak, Z., and Chuah, M.K. 2009; *Blood* 114: 1461–1468.

55. Sarcoma caused by radiation, Patel, S.R. *Curr. Handle. Oncol Options.* 2000, 1, 258–261.

56. The carcinogenicity of anticancer drugs: A risk assessment in humans Harris, C.C. 1976; 37: 1014–1023. *Cancer.*

57. Post-chemotherapy secondary malignancies after most cancers Boffetta, P.; Kaldor, J.M. *Acta Oncol.* 34, 591–598 (1994).

58. Chillon, M.; Bosch, A.; Alba, R. Gutless adenovirus: Adenovirus for gene therapy of the last era. *Gene ther.* 2005, 12, S18–S27.

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