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Gene Therapy: A New Era of Cancer Treatment

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ABTRACT

Cancer is one of the most feared diseases in the world. It is a complex and serious disease that can cause serious damage to the body. There is no one cure for cancer, and treatment typically involves a combination of different methods. Gene therapy is a new and promising approach to treating cancer. Gene therapy involves using genes to treat the cancer. This is because genes are responsible for the growth and development of the cancer. Gene therapy is still in its early stages, and there is still a lot to learn about it. However, there is evidence that it may be able to treat some types of cancer. If you are someone who is worried about getting cancer, or if you have cancer, gene therapy is a new and exciting approach that you may want to consider. Gene therapy is a new era of cancer treatment that involves using genes to treat cancer. This is different than traditional cancer treatments, which involve surgery, radiation,

or chemotherapy. Gene therapy has many potential benefits, including the ability to treat cancer more effectively and with fewer side effects. It also has the potential to cure cancer. There are many types of gene therapy, and each is designed to treat a specific type of cancer. For example, gene therapy that uses viruses to remove cancer cells is called viral therapy. Gene therapy that uses genes to prevent cancer from spreading is called anti-cancer gene therapy. Gene therapy is still in its early stages, and there are many challenges to be overcome. But the potential for gene therapy to revolutionize cancer treatment is very real.

1. INTRODUCTION

Cancer is one of the most feared diseases in the world. It is a complex and serious disease that can cause serious damage to the body. There is no one cure for cancer, and treatment typically involves a combination of different methods. Gene therapy is a new and promising approach to treating cancer. Gene therapy involves using genes to treat the cancer. This is because genes are responsible for the growth and development of the cancer. Gene therapy is still in its early stages, and there is still a lot to learn about it. However, there is evidence that it may be able to treat some types of cancer. If you are someone who is worried about getting cancer, or if you have cancer, gene therapy is a new and exciting approach that you may want to consider.

Gene therapy is a new era of cancer treatment that involves using genes to treat cancer. This is different than traditional cancer treatments, which involve surgery, radiation, or chemotherapy. Gene therapy has many potential benefits, including the ability to treat cancer more effectively and with fewer side effects. It also has the potential to cure cancer. There are many types of gene therapy, and each is designed to treat a specific type of cancer. For example, gene therapy that uses viruses to remove cancer cells is called viral therapy. Gene therapy that uses genes to prevent cancer from spreading is called anti-cancer gene therapy. Gene therapy is still in its early stages, and there are many challenges to be overcome. But the potential for gene therapy to revolutionize cancer treatment is very real.

The emerging field of cancer gene therapy offers a number of heady potential treatments. The term gene therapy encompasses a wide range of treatment types that all use genetic material to modify cells (either in vitro or in vivo) to help effect a cure[1]. Numerous in vitro and preclinical unprepossessing models, testing a wide variety of gene therapy agents, have shown remarkable efficacy. In lung cancer models, for example, survival benefits have been demonstrated using gene therapy to create cancer vaccines, target viruses to cancer cells for lysis and death, subtract the thoroughbred supply to the tumor, and introduce genes into the cancer cells that rationalization death or restore normal cellular phenotype[2]. Preclinical gene therapy tests have moreover been performed on gliomas, pancreatic cancer and liver cancer, as well as many other cancers.

Gene therapy is the things taken round to of specific genetic material to make different the making to a rule of a gene product or to change the biological properties of tissues for the business managers of different diseases[3]. Gene therapy over-comes the limiting conditions connected with the recombinant therapeutic use of peptides , such as low bioavailability , changing state, serious toxicity , clearance rates, and high producing price[4]. Gene therapies act by different mechanisms covering, giving another in place of go wrong genes with the therapeutic genes , gene blow-up, or deactivating hard question genes , and thing put in a new gene to treat a disease[5].

Gene therapy can be done in either somatic or germline units. In somatic units, gene therapy only the made different tissues will be acted-on, but in germline unit gene therapy , genetic changes send to the offspring. So, there is no clinical Trial on to do with man germline gene therapy[6]. Currently , somatic gene therapy is safe for the business managers of several diseases in to do with man beings. Gene therapy effectively treats several diseases because of, in relation to increased getting through knowledge of disease pathogenesis and got more out of gene things taken round to technologies[7].

Gene therapy uses genetic material (in, RNA or DNA) via a vector that helps the things taken round to of out-of-country genetic material into the host organ . The genetic material is controlled into the target

organ (in vivo gene therapy) or used to make different units taken from the host that are then controlled (ex vivo gene therapy). Gene therapy try to give a functional gene copy of the damaged genes), increase the able to use of diseasemodifying genes or suppress the activity of a damaged gene[8,9].

Gene delivery systems consist of three components: a gene that expresses essential therapeutic peptides, a plasmid-based gene encoding system that regulates the activity of a gene in the target organ, and a gene delivery system that regulates the administration of the encoding gene to host tissue[10].

Common gene therapy mostly is dependent on viral based things taken round to of genes that either as if by chance gets mixed together into the host genome (egg retroviruses) or dead body as extrachromosomal DNA copy (egg AVA]) and puts forward a protein that is lost or changed in structure in to do with man disease. In in comparison to old and wise gene therapy , gene getting ready gives more turning readily to another work apparatus for making or put right things for gene therapy , for example, through details right point variants , place an in addition, healthy gene at a safe genetic placing or get broken up a gene . The Current geneediting process is dependent on the opening part of caused from within doublestrand DNA breaks (puts water on with a cloth) and put right apparatuses. When puts water on with a cloth take place by nucleated , cellular DNA put right apparatuses are activated . There are main apparatuses for putting right doublestrand breaks, nonhomologous end joining (NH) and homologydirected put right (DR). Genomeediting nucleated can be made different to take in and break the genome at specific DNA orders, coming out in puts water on with a cloth, which are with small amount of support put right by either NH or HDR[11,12].

NH put right damaged DNA without a homologous example copy. because of, in relation to this reason, NH may lead to being taken out or thing put in of nucleotides in the damaged loci; in this way, it is errorprone. DR is different from NH since it gets in good condition again DNA damages using a homologous example copy. generally, having used a homologous order, this form of DNA put right has less chance to cause errors. From a clinical view point, DR is good for putting back to earlier position mutations in genes or for getting mixed together genes for therapeutic purposes[13].

Currently, there are four different gene-editing nuclease enzymes available based on their structures: meganucleases, zinc-finger nucleases, transcription activator-like effector nucleases, and CRISPR-associated nucleases.

Meganucleases (MNs)

Are sequence-specific endonucleases that recognize unique large (14–40 bp) target sites. It has low cytotoxicity that makes it an attractive tool for genome editing. Existing engineering techniques include the

creation of fusion protein from existing MN domains and engineering MN specificity via the direct alteration of protein residues in the DNA-binding domain. The complexity in re-engineering and low editing efficiency limits the uses of MNs[14].

Zinc Finger Nucleases (ZFNs)

Falsely produced by forcefully joining together sitespecific zinc finger protein with the general, not detailed cleavage lands ruled over of the story causing amusement limit endonuclease The DNAbinding part has zinc finger comes again, and each can make out between and base groups of . Zn has three zinc fingers that each takes to be the same three base DNA orders to form a threefinger order that attached to base target sites and the general, not detailed cleavage domain[14,15]. ZFps give birth to a sitespecific small amount to the genome and help nearby homologous recombination that gives greater value to selected genome getting ready. The ZFNencoding plasmidbased selected controlling organization of the needed genes drops the limiting conditions of viral controlling organization. If Zens are not special at the target place on the net, offtarget break may take place. Such offtarget damage may cause DEBS that causes unit death. An Offtarget break may help the random joined as complete unit of giving-person DNA[15,16].

Transcription Activator-Like Effector Nucleases (TALENs)

Are artificial DNA nucleases formed by fusing a DNA-binding domain with a nonspecific nuclease domain derived from Fok I endonuclease that specifically cut the required DNA sequence[15]. TALE effectors DNA-binding domain has a repeating unit of 33–35 conserved amino acids. Each repeat is similar, except positions 12 and 13, which are variable and have a strong correlation with specific nucleotide recognition. DNA cleavage domain is nonspecific from FokI endonuclease. The FokI domain acts as a dimer that needs two constructs with unique DNA binding for sites in the target genome. Both the number of amino acids between the TALE DNA binding domain and the FokI cleavage domain are essential for better activity. TALEN uses to edit genomes by inducing DSB that cells respond to with repair mechanisms[17,18].

CRISPR-Cas

CRISPR is a heritable, adaptive immune system of bacteria that provides them with the memory of previous virus infections and defends against re-infection. Contrary to the human adaptive immune system, CRISPR is passed on to the next generation of bacteria, rendering the colony immune to future virus infections. CRISPR immunity depends on the integration of the invader's DNA (virus or plasmid) into the bacterial genome[19]. CRISPR helps the bacterium to identify the viral sequences and break. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, which are interrupted by "spacer" sequences. These "spacer" sequences are viral sequences integrated during past viral infections when

transcribed into short RNA sequences, are capable of guiding the Cas endonuclease to complementary sequences of viral DNA. Upon target identification, Cas binds to the viral DNA and cleaves it, protecting the prokaryotic cell from infection[20,21]. CRISPR immune system modified to create a gene-editing tool that can target changes to the DNA. The most common is CRISPR/Cas9, which posses the Cas9 endonuclease and a short noncoding guide RNA (gRNA) that contains two components: a target-specific CRISPR RNA (crRNA) and a helper trans-activating RNA (tracrRNA). The gRNA unit guides Cas9 to a specific genomic locus via base pairing between the crRNA sequence and the target sequence[22]. CRISPR-Cas-mediated gene repair, disruption, insertion, or deletion are thus finding applications in several areas of biomedical research, medicine, agriculture, and biotechnology[23].

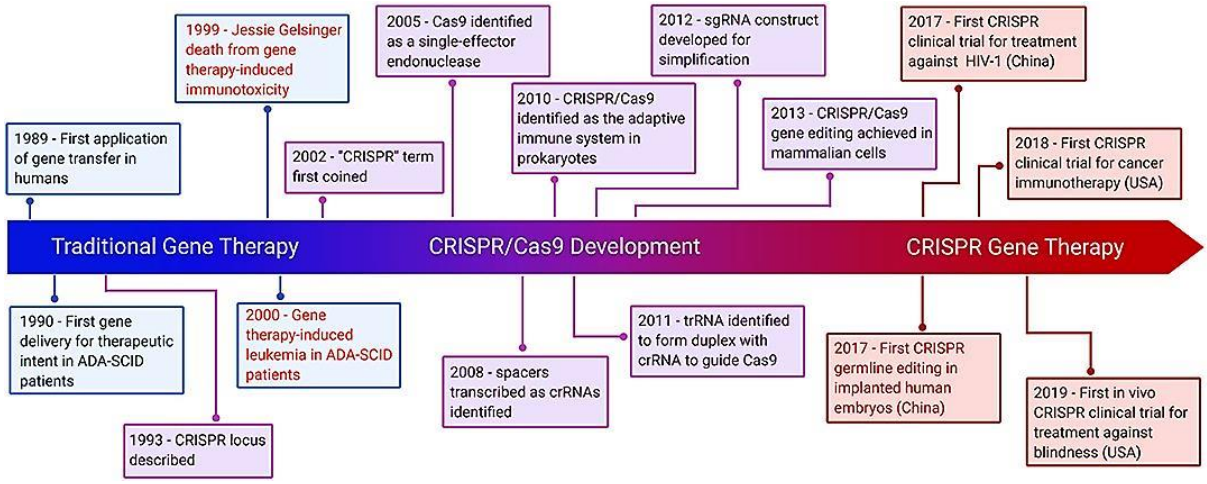


Figure 1. Development from traditional gene therapy to CRISPR gene therapy.

2. DELIVERY OF GENE

Since the coming out of recombinant DNA technology that helps gene therapy, how to effectively and safely give gene products is the Major questioning. vector is a vehicle that uses to give birth to the gene of interest. An high purpose vector can give a gene to a special tissue , give space to enough out of country gene size, get done the level and time of look enough to right the bad, wrong point gene , non - immunogenic, and safe. things taken round to of the gene products done by viral vectors , Bactofection, and none viral vectors (chemical and physical) careful way as made a short account of in number in fig.(1) The most important step in doing gene therapy is selecting the vectors[24] .

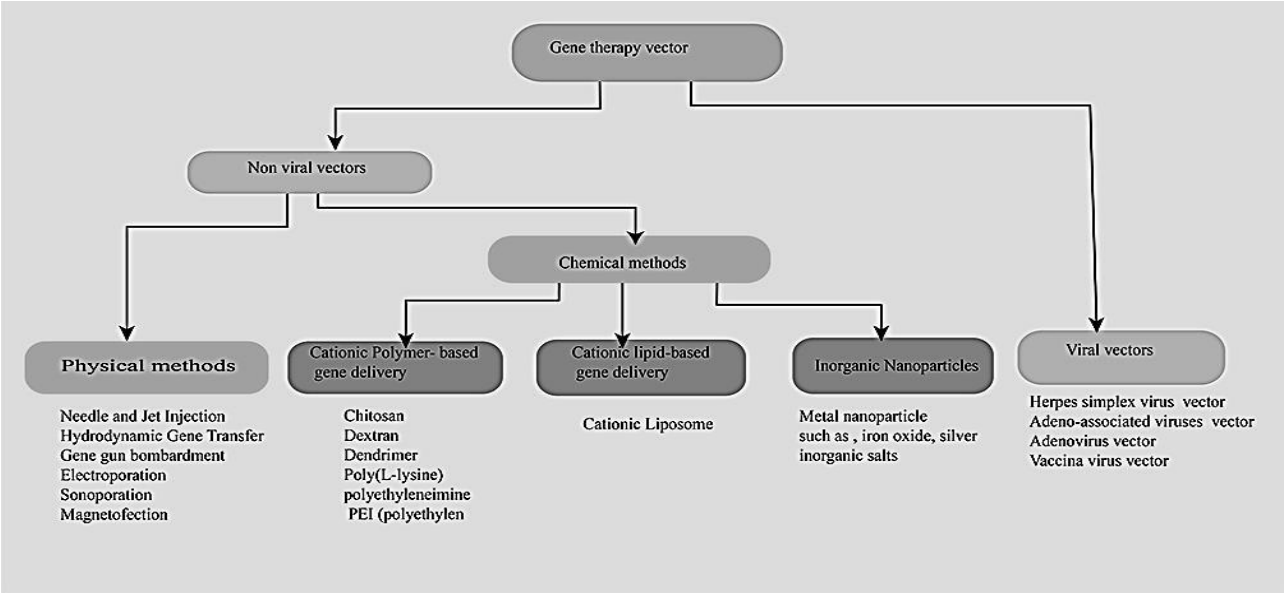


Figure 2. different methods of gene delivery.

Viral Vectors Used for Gene Delivery

Sung Y K et. al. reviewed that one of the promising gene therapy systems ready (to be used) today are viral vectors , such as retrovirus , (sorts 2 and 5), adenoassociated cause of disease, herpes virus , pox virus , to do with man foamy virus (Hf 8), and lentivirus[25]. All viral vector genomes have been made different by taking out some areas of their genomes so that their copying becomes deranged and it makes them more safe, but the system has some questions, such as their marked immunogenicity that causes discovery from examples of inflammatory system leading to process of becoming worse of changed tissue ; and toxin producing, including death rate, the insertional mutagenesis; and their limitation in transgenic capacity size[26,27]. During the past few years some viral vectors with specific receptors have been designed that could giving in law the to some other specific units, which are not their natural target units (retargeting)[28].

TABLE 1: Viral vectors used for gene delivery

VECTOR	PACKAGING CAPACITY	HOST RANGE	CLINICAL TRIALS	FEATURES
AAV	Low <4 kb	Broad, infects both dividing and non-dividing cells.	+	Slow expression onset, genome integration, long term expression, inefficient large-scale virus production
Adenovirus	Medium <7.5kb	Broad, low transcription of neurons.	+	Transient expression, strong immunogenecity
Alphavirus	Medium <7.5kb	Broad, neuron and glial-cell specific strains	+	Transient, but extreme, expression levels; low immunogenecity
Herpes simplex Virus	High > 30 kb	Broad, neurons, stem cells, muscle cells	-	Latent infection, long-term expression, low toxicity (mutants)
Lentivirus	Medium 8 kb	Broad, dividing and non-dividing cells	-	Genome integration, long term expression, safety concerns low titers, production inefficient
Retrovirus	Medium 8 kb	Restricted, dividing cells only	+	Genome integration, long-term expression

NONVIRAL DELIVERY SYSTEMS

Nouri Nayerossadat et. al . reviewed that Nonviral systems comprise all the physical and chemical systems except viral systems and generally include either chemical methods, such as cationic liposomes and polymers, or physical methods, such as gene gun, electroporation, particle bombardment, ultrasound utilization, and magnetofection. Efficiency of this system is less than viral systems in gene transduction, but their cost-effectiveness, availability, and more importantly less induction of immune system and no limitation in size of transgenic DNA compared with viral system have made them more effective for gene delivery than nonviral delivery systems to date[29,30].

Physical methods of nonviral gene delivery

Various methods have been introduced to deliver gene from foreign DNA to the host cell ;

i) Electroporation

A short electric pulse of specific strength creates holes incell membrane through which foreign DNA can enter inside the cell. Discharging a capacitor across the electrodes from a specially generated electroporation chamber generates the pulse required for an efficient transfer of the DNA by electroporation. The generated pulse may be either a high voltage (1.5 kV) rectangular wave pulse for a short duration or a low voltage (350 V) pulse for a longer duration[31].

ii) DNA particle bombardant by gene gun

DNA particle bombardant by gene gun is an platonic volitional technique to injection of naked DNA. Gold or tungsten spherical particles (1–3 μm diameter) are coated with plasmid DNA and then velocious to upper speed by pressurized gas to penetrate into target tissue cells[32].

Chemical Methods

i) Naked DNA injection

Naked DNA vacated is worldly-wise to transfer a gene (2–19 kb) into skin, thymus, cardiac muscle, and expressly skeletal muscle and liver cells when directly injected[33,34], moreover it has been unromantic directly[34]. Long-term expression has been observed in skeletal muscle pursuit injection for increasingly than 19 months. Single injection yields transgenic expression in less than 1% of total myofibers of the muscle but multiple injection would modernize it. Although naked DNA injection is a unscratched and simple method, its efficiency for gene wordage is low so it is only proper for some applications, such as DNA vaccination.

ii) Liposome mediated delivery

The foreign DNA can be incorporated into the phospholipid vesicle tabbed liposomes, by sonication of a solution of lipids and the DNA in ether. Being amphipathic molecules, lipids form liposomes that enclose the negatively charged DNA within it. It was found that wing of a lysosomotrophic wage-earner like chloroquine, which raises the acidic pH of the endosomes obviates the fusing efficiency of the liposome with endosomal membrane and consequently reduces the probability of gene transfer to nucleus[35]. Proteoliposomes have been shown to transfer genes effectively. But the difficulties in their purification and characterization have limited their use. Proteoliposomes containing Sendai virus

glycoproteins however could mediate the cellular entry and fusion of the liposomes with the endosomal membrane[36].

iii) Synthetic carrier

A number of synthetic transporters of DNA have been developed. One of these is the ramified of spermine, a positively charged molecule, which forms lipospermine when tying to lipids. DNA stuff negatively charged attracts the positively charged hydrophilic portion of lipospermine to form a casing virtually the DNA. A large number. Of lipospermine then socialize together to form a second casing whose outer surface is positively charged due to spermine.

Biological method

The minutiae of unscratched and efficient gene transfer vehicles is hair-trigger for the success of gene therapy. One of the most promising approaches includes the using of various viral vectors, which represent most types and families of viruses, suitable for infection of mammalian host cells. Interest in using such systems in unromantic settings continues to grow. Overall, there have been major improvements in all aspects of gene wordage vector minutiae and targeting of gene expression . However, surpassing these can be used as vectors in gene therapy, hair-trigger genes encoding for pathogenic proteins and those necessary for viral replication have to be detected[38].

3. Approaches Used in Gene Therapy

Gene replacement therapy

In replacement therapy, a normal gene is inserted somewhere in the genome so that its product could replace that of a needing gene. This tideway may be suitable for recessive disorders, which are marked by deficiency of an enzyme or other proteins. Though the gene functions in the genome providing an towardly regulatory sequence, the approach may not be successful in treating dominant disorders associated with the production of an abnormal gene product, which interferes with the product of normal gene[38].

Gene Correction

Corrective gene therapy requires replacement of a mutant gene or a part of it with a normal sequence. This can be achieved by using recombinant technology. Another form of corrective therapy involves the suppression of a particular mutation by a transfer RNA that is introduced into a cell.

Gene augmentation therapy

This is used to treat diseases caused by a mutation that stops a gene from producing a functioning product, such as a protein. This therapy adds DNA containing a functional version of the lost gene back into the cell. The new gene produces a functioning product at sufficient levels to replace the protein that was originally missing. This is only successful if the effects of the disease are reversible or have not resulted in lasting damage to the body. For example, this can be used to treat loss of function disorders such as cystic fibrosis by introducing a functional copy of the gene to correct the disease[39].

Ex vivo gene therapy

This tideway requires that new cells-either autologous cells or closely matched donor cells be subjected to genetic engineering for each patient. This is a plush and time consuming strategy. Consequently, research is underway to create "universal donor" cells that have most of their immunogenic antigens stripped from the outer cellular surface so that they are immunologically healthful and can be used with a range of patients. The gene transfer protocol for ex vivo gene therapy for human subjects make use of vectors derived from mouse retroviruses. However, as retroviruses can transform normal cells into tumored ones, it is essential that this possibility be at least wizened and preferably completely abolished[40].

In vivo gene therapy

Ex vivo gene therapy was not successful to treat internal disorders, considering of that the concept of in vivo gene therapy was established. In vivo gene therapy is a strategy in which genetic material usually in the form of DNA, is unromantic to modify the genetic repertoire of target cells for therapeutic goals.

This technology is now stuff ripened in clinical trials as a treatment for hereditary disorders, and is moreover stuff considered as a potential treatment of uninventive diseases, including atherosclerotic arterial disease, restenosis without vascular interventions, and cardiacallograft rejection[40-44].

The vector, usually a retrovirus carrying the gene, is injected systemically or directly into the concerned organ. The property of the retrovirus to transduce only dividing cells, such as tumor cells, is utilized for selective delivery of the gene leaving non-dividing cells unaffected[45,46].

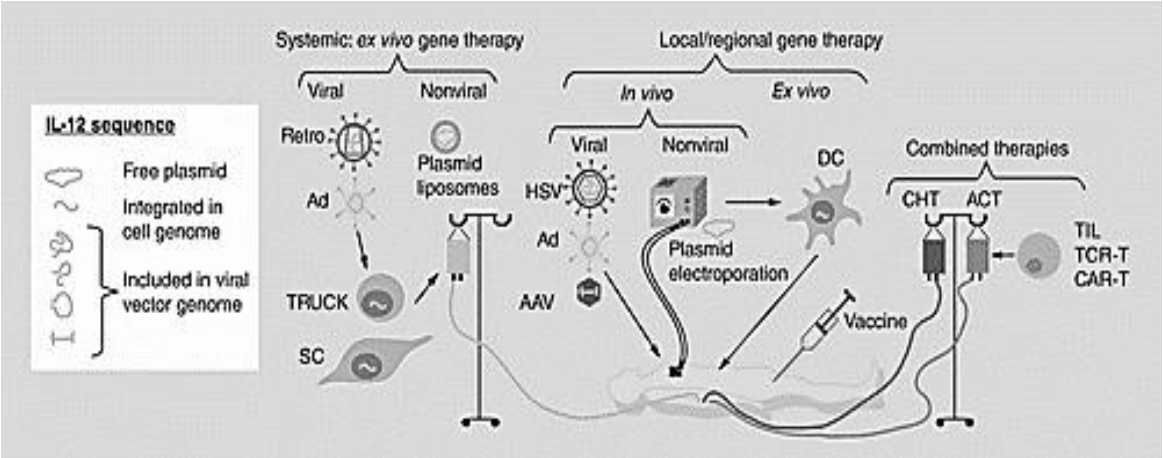


Figure 3. Ex – vivo and In – vivo therapy

Antisense gene therapy

Antisense oligodeoxynucleotides are small synthetic nucleotide sequences formulated to be complementary to specific DNA or RNA sequences. By the tightness of these nucleotides to their targets the transcription or translation of a single gene can be selectively inhibited. If that gene is responsible for a disease process then its down-regulation could result in a reversal of the clinical abnormalities. The cytoplasmic location of mRNA provides an easier target for oligodeoxynucleotides than DNA. One example of an antisense oligomer with antiproliferative worriedness is c-myc in lymphoma lamina lines[47] others are N-mye in neurectodermal cell lines[48] c-myb in colon adenocarcinoma,[49] type 1 regulatory subunit of the cAMP receptor protein kinase in K-ras transformed NIH3T3 cells[50] and in neuroblastoma, leukaemia, breast, colon, and gastric carcinoma cells, bcr-abl in chronic myeloid leukaemia wham cells,zo and c-raf 1 in ras and raf-transformed NIH3T3 cells[51].In McManaway and colleagues' in-vitro study, the antisense oligonucleotide was only 21 bases long. Growth of two Burkitt's lymphoma cell lines known to produce an unwont mRNA was strikingly inhibited, and this finding suggested an "Achilles heel" in the growth of this neoplasm. Antisense oligonucleotides moreover subtract the tumorigenicity or metastatic potential of lamina lines. A K-ras proto-oncogene in antisense orientation transduced into a small lamina lung cancer line inhibited of K-ras expression and also suppressed tumour growth in nude mice. There was no alteration in growth kinetics of the lamina line in vitro. Other experiments have shown that the antisense sequence to pre-prourokinase significantly reduced the worthiness of murine melanoma cells to colonise lung. By contrast, if the antisenseoligomer is designed to inhibit a putative metastasis suppressor gene, such as E-cadherin, the resulting downregulation renders the cells invasive[52]. These results demonstrate the power of antisense technology and the potential using it has for manipulation of abnormal growth and behaviour in tumour cells[53].

4. Gene Therapy for Cancer Treatment

Cancer occurs due to disrupting the normal lamina proliferation and apoptosis process. Advances in cancer therapy need a novel therapeutic wage-earner with novel mode of action, several mechanisms of lamina death, and synergy with conventional management. Gene therapies possess all these profiles. Several gene therapy approaches were ripened for the management of cancer, including anti-angiogenic gene therapy, suicide gene therapy, immunotherapy, siRNA therapy, pro-apoptotic gene therapy, oncolytic virotherapy, and gene directed-enzyme prodrug therapy[54]. By November 2017, greater than 2597 clinical trials were conducted on gene therapy in the world. Among these trials, greater than 65% are associated with cancer, followed by monogenetic and cardiovascular diseases. The use of CAR T lamina therapy showed promising results for the management of both myeloid and lymphoid leukemia. Until August 2019, only 22 gene products were tried for the treatment of variegated disorders. Most gene products used for the treatment variety types of cancers as shown in Table 1. Immuno-gene therapy is a potential treatment tideway for the treatment of p53-deficient tumors (Imlygic, Gendicine, Yescarta, and Kymriah[55].

Table 2 Gene Therapies Products Approved for Therapeutic Use

Trade name (proper name)	Date of approval and approving agency	Vector and modified gens	indication	Route of administration	Ref
Gendicine	2003 state food and drug administration of china	Adenoviral vector P53	Head and neck squamous cell carcinoma	In vivo	[56]
Oncorine (recombinant human adenovirus type 5 injection)	2005 state food and drug administration of china	Adenovirus Type 5	Head and neck and esophagus cancer, nasoparyngeal cancer, etc.	In vivo	[57]
Kymriah TM (tisagenlecleucel)	August 2017 FDA	CD 19-specific CAR T Lentiviral vector	Acute lumphoblatic leukaemia	Ex vivo	[58]
Yescarta TM (Axicabtagene ciloleucel)	October 2017 FDA	CD 19-specific CAR T Y-Retroviral vector	Non-Hodgkin lymphoma	Ex vivo	[59]
Imlygic (yalimogene laherparepvec, T-Vec)	2015 FAD	GM-CSF HSV-I	Melanoma	In vivo	[60]

Oncolytic Virotherapy

Oncolytic virotherapy (OV) is the most promising tideway for tumor immunotherapy. OV uses replication-competent viruses that can proliferate selectively at tumor cells. Oncolytic viruses grouped as naturally occurring or genetically modified viruses. Natural occurring viruses like parvoviruses, and Newcastle disease viruses that selectively replicate in tumor lamina without genetic modification. The second virus category, such as vesicular stomatitis viruses, adenoviruses, measles viruses, HSV and vaccinia viruses, genetically modified to modernize the safety, tumor-specificity, and subtract virus pathogenicity. The therapeutic use of oncolytic viruses for cancer treatment is an immune-related treatment alternative. Oncolytic viruses act by directly lyses tumor cells and by introducing wild-type tumor suppressor genes into cells that lack the tumor suppressor gene[60,61]. Change in p53 gene function is present in half of all malignancies, and the induction of wild-type p53 gene re-establishes the normal p53 expression. Several recombinant OVs expressing p53 were ripened with the aim of producing increasingly potent OVs that act in combination with host immunity or with other treatments' modality to destroy tumor cells[56,61].

Gendicine (Recombinant Human P53 Adenovirus [Ad5RSV-P53])

Was the first approved gene product for the management of neck and head squamous cell carcinoma in 2003[56]. Gendicine is a non-replicative an adenoviral vector, where the E1 gene is replaced with the tumor suppressor p53 cDNA gene. The expression of p53 in tumor cells triggers the antitumor effect by activating the apoptotic pathway, inhibit damaged DNA repair, and anti-apoptotic activity. P53 gene mutation is prevalent in several cancers. Therefore, Gendicine induces the expression of p53 restores its activity and destroys the tumor cells. Generally, Gendicine management showed 30–40% complete response and 50–60% partial response with a total response rate of 90%–96% in different therapeutic use. Up-to-date greater than 30,000 patients managed by Gendicine[56,62].

Oncorine (rAd5-H101)

It is the first replicative, oncolytic recombinant ad5 (rAd5-H101) approved to treat refractory nasopharyngeal cancer. Loss of p53 gene linked with drug resistance and survival rate reduction in non-small cell cancer patients. Oncorine is an ad5 virus with a deletion in the E1B 55K gene. Host cell p53 gene inactivation is essential for wild-type to block the activation of apoptotic pathway. The removal of the E1B 55K gene inhibits viral proliferation in normal cells, allowing only proliferate in p53-deficient host cells. In tumor cells, viral proliferation causes oncolysis that is the mechanism to treat solid tumors. Following cancer cell lysis, adenoviruses release and infect another cell activating a serious of Oncorine-mediated cell death[63,64].

Imlygic (Talimogene Laherparepvec)

It is a genetically modified oncolytic HSV-1 approved in Europe in 2015 for the management of non-resectable metastatic melanoma. Imlygic is the first oncolytic virus used for the management of advanced melanoma[60]. The replacement of γ34.5 and α47 genes with the human granulocyte-macrophage colony-stimulating factor (GM-CSF) gene modifies the HSV-1 gene. The γ34.5 gene deletion causes tumor cell-selective replication and suppression of pathogenicity. The γ34.5 gene blocks protein synthesis of the host cell during viral infection. Thus, suppressing γ34.5 seizes the virus proliferation in normal cells. In tumor cells, the γ34.5 gene deleted HSV-1 can replicate. The α47gene inhibits the host cell transporter associated with antigen presentation. The depletion of α47gene reduces MHC class I expression that increases antitumor immune activity[64]. Besides, two human GM-CSF genes inserted into the virus providing high levels of GM-CSF production, and stimulate immune responses. Administration of Imlygic causes apoptosis of tumor cell enhanced antigen presentation and increased antitumor response[65].

Rexin-G (Mx-dnG1)

Is the first targeted injectable vector approved for the management of metastatic cancers. It is a replication-incompetent retroviral vector showing a SIG-binding peptide to bind to abnormal Signature (SIG) proteins in the tumor cell that increase vector concentration in tumor cells and express a dominant-negative human cyclin G1 inhibitor. After the entrance into the tumor cells, Rexin-G synthesizes cytocidal dnG1 proteins that inhibit the cell cycle in the G1 phase resulting in apoptosis of cancer cells[66,67].

Chimeric Antigen Receptor (Car) T Cell Therapy

T cells destroy infected and tumor cells by detecting nonself (germs that the body tries to fight) with the T cell receptor (TCR). CAR T is a T cell transduced with a chimeric (a germ that the body tries to fight) receptor (designed only for/happening only within) a tumor-connected (a germ that the body tries to fight). CAR is "chimeric" because it contains the (a germ that the body tries to fight)-binding site of the B cell receptor and a (within a cell) TCR (stimulation of action/making active and effective) domain. CAR has three domains, an (outside of a cell) domain that has cancer-clearly stated/particular epitopes (scfv area) made from light (VL) and heavy (VH) chains of immunoglobin that target (a germ that the body tries to fight) (such as CD19), a transmembrane domain, and (within a cell) TCR received/made from stimulatory domains as showed in fig(2). The scfv part binds to the target (a germ that the body tries to fight) in the MHC independent way leading to CAR clustering and stimulating T-cell via (within a cell) area that groups of armed men the TCR-received/made from CD3ζ chain, with or without co-stimulatory domains. Stimulated CAR T-cells give target-clearly stated/particular memory cells that stop tumor return of

disease[68]. CD19a€ • targeted CAR T cells were the first CARs to be studied. CD19 is a promising target due to its expression limited to the B cell. Firsta€ • generation, CD19a€ • targeted CAR T cells were safe but ineffective. Second-generation CARs have a costimulatory domain with the CD3ζ (stimulation of action/making active and effective) domain show improved T cell activity. Two seconda€ • generation, CD19• targeted CARs are in medicine-based use contain a 41BB costimulatory domain (19-BBz) and a CD28 costimulatory domain and those with more than one added/more co-stimulatory molecule are known as "third-generation" CAR[68-70].

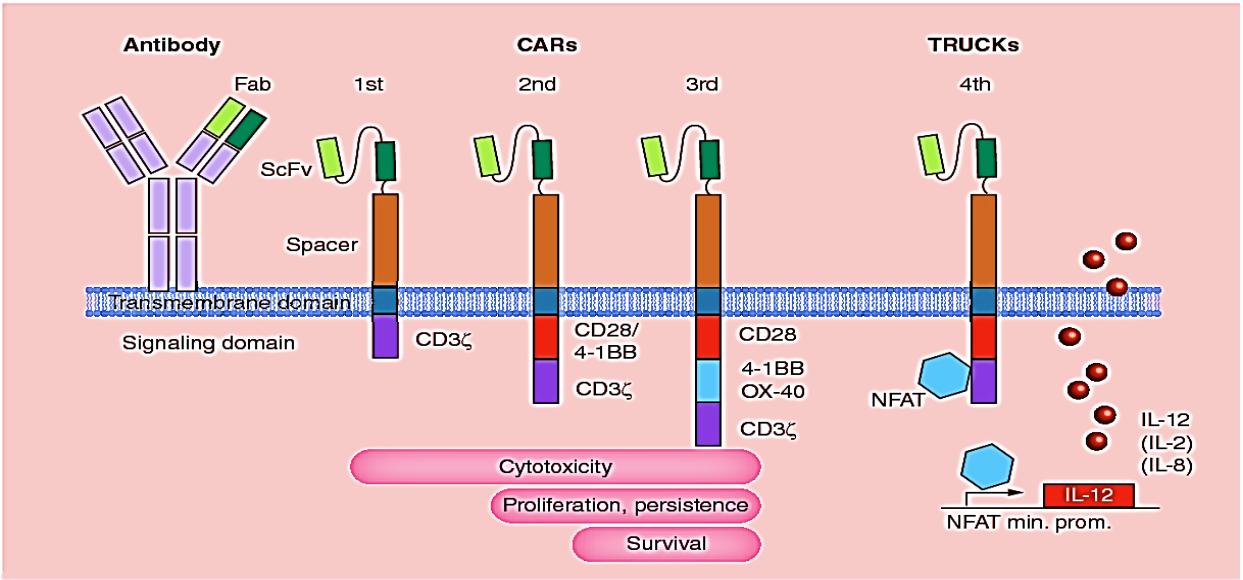


Figure 4. Chimeric antigen receptors. First-generation CARs contain solely the CD3ζ chain as a single activation domain, leading to T-cell activation and cytotoxicity based on scFv specificity. Second- and third-generation CARs consist of one or two additional costimulatory signaling domains, respectively, such as CD28, CD27, OX-40 (CD134) and 4-1BB (CD137). Costimulation enhances the overall survival as well as proliferation and persistence of activated T cells. TRUCKs represent the fourth generation and are currently the newest approach in adoptive T-cell therapy. T cells are genetically modified to express CARs along with an inducible cytokine gene cassette driven by an NFAT sensitive promoter. Consequently, immune stimulatory cytokines such as IL-12 are secreted upon CAR engagement. CAR: Chimeric antigen receptor.

Kymriah (Tisagenlecleucel)

It is the first FDA approved CAR T-cell-based (tiny chemical assembly instruction inside of living things) product to treat suffered again from disease B-cell sudden and serious lymphoblastic blood cancer. Kymriah has (from the same body) T cells, changed with the lent virus to (translate/put into secret code) a

CAR consist of a murine single-chain disease-fighter piece (scFv) selective for CD19, a (within a cell) domain 4-1BB (CD137), and CD3 zeta with CD8 transmembrane depend. After binding to CD19 (a germ that the body tries to fight)-expressing cells, Kymriah starts the antitumor effect via the CD3 domain. The (within a cell) 4-1BB co-stimulatory domains improve the antitumor activity. The CD19 (a germ that the body tries to fight) is a 95-kD glycoprotein (translated/put into secret code) as a surface (a germ that the body tries to fight) in thinly spread large B-cell lymphoma (DLBCL) and other B-cell lymphomas[71,72]. High response rates were recorded in patients with stubborn and disobedient/hard to cure DLBCL in Phase 2 scientific fact-finding experiments. The response rate was 50% at 3 months, 43% with a complete response at 6 months, and there were no patients with a complete response at 6 months who had a return of disease by the middle-point of 28.6 months[73].

Yescarta (Axicabtagene Ciloleucel)

It is another CAR T-cell therapy used for the management of aggressive non-Hodgkin lymphoma. It is CD19 (a germ that the body tries to fight)-specific ex-vivo changed (from the same body) T cells infected with a gamma-retroviral. It (translates/puts into secret code) a CAR containing/making up an (outside of a cell) murine anti-CD19 single-chain changeable piece (joined together/protected by a fuse) to a cytoplasmic domain that possesses CD28 and CD3-zeta co-stimulatory domains[74,75].

Zalmoxis (Allogenic T Cells Encoding LNGFR and HSV-TK)

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) uses for the management of (more than two, but not a lot of) hematopoietic cancer growths/harmful things. But, sudden and serious corruption/dishonesty with money-against/compared to/or-host-disease (aGvHD) and Corruption/dishonesty with money rejection are (things that block or stop other things) to its success. The treatment (success plan(s)/way(s) of reaching goals) for haplo-HSCT depends on T-cell using everything up (completely) or management of lymphotoxin agents like cyclophosphamide after stem cell infusion to (in a picky way where only certain things are selected) use up/reduce activated alloreactive infection-fighting cells but causes lengthy immunodeficiency after-transplantation. So, treatment to improve unable to be harmed re-combining/re-creating after transplantation is necessary[76]. Zalmoxis is a (having characteristics that were changed by people) allogeneic T cell using a retroviral vector (translating/putting into secret code) a human low-attraction-related nerve growth factor receptor (ΔLNGFR) and HSV-TK Mut2 to transduce the allogeneic T unable to be harmed cells. The ΔLNGFR expression uses as a marker of the transduced T cells, and the HSV-TK Mut2 expression provides the suicide (tiny chemical assembly instruction inside of living things) induction during the management of the prodrug ganciclovir (GCV). Management of the (having characteristics that were changed by people) donor T cells to T cell-used

up/reduced transplant patients (HSCT) builds up again the (not able to be harmed/not able to get a disease) to defend from infections. But, donor cells may specifically act as the host cells leading to Corruption/dishonesty with money Against/compared to/or Host Disease (GVHD). In this case, induction of suicide (tiny chemical assembly instruction inside of living things) by GCV management may kill the donor T cells (translating/putting into secret code) HSV-TK and control GVHD. Zalmoxis is a potential (helping to fight disease) agent for HSCT patients when the matched donor does not exist. Zalmoxis provides after-transplant GvHD control, Corruption/dishonesty with money against/compared to/or Blood cancer (GvL) improvement, return of disease decrease, and unable to be harmed re-combining/re-creating causes reduced infection[77].

Gene Silencing

Gene silencing therapy is RNA interference (RNAi)-helped settle (an argument) knockdown of clearly stated/particular (tiny chemical assembly instructions inside of living things) in tumor cells. RNAi is single or double-stranded noncoding RNAs (21 ribonucleotides) that cause sequence-clearly stated/particular insulting/worsening of (combining in a way to make something better) mRNAs via the cells' internal machinery[78]. siRNA is very important because most (tiny chemical assembly instructions inside of living things) do not have stoppers due to a lack of ligand binding places/locations and amino acid sequence homology with other proteins that limit target selectivity. RNAi consists of microRNA (miRNA), Small Interfering RNA (siRNA) and short hairpin RNA (shRNA). Twenty years later after the discovery of RNAi, ONPATTRO™ (patisiran) approved for the first time for the management of the polyneuropathy of (related to things you get from your parents' genes) transthyretina€ • mediated (hATTR) amyloidosis[79]. Tumor-stopping (tiny chemical assembly instructions inside of living things), cancer-causing genes, (tiny chemical assembly instructions inside of living things) involved in cancer (development or increase over time/series of events or things), and drug-resistance are promising targets for (tiny chemical assembly instruction inside of living things) silencing by RNAi-based cancer treatment due to selective (tiny chemical assembly instruction inside of living things) silencing effect and fewer bad effects than ordinary (using powerful drugs to help cure disease)[80]. The good qualities of RNAi in cancer treatment are targeting (more than two, but not a lot of) (tiny chemical assembly instructions inside of living things) of different cellular pathways involved in cancer (development or increase over time/series of events or things) and develop a drug for a clearly stated/particular patient[81]. (more than two, but not a lot of) studies done on animals showed/told about that targeting very important proteins in the cell cycle, such as Protein kinase N3 (PKN3), kinesin spindle protein (KSP), and polo-like kinase 1 (PLK1) by siRNA displayed a strong antitumor effect. (more than two, but not a lot of) liposomal siRNA dose preparations are in Phase 1

trials, such as treatments for (related to the pancreas) cancer (PKN3 siRNA), liver cancer (CEBPA siRNA), and neuroendocrine tumors (PLK1 siRNA)[82].

Suicide gene therapy

Suicide gene therapy uses viral or bacterial (tiny chemical assembly instructions inside of living things) into harmful cells that (chemically process and use up) non-poisonous prodrug into a poisonous compound. (more than two, but not a lot of) suicide (tiny chemical assembly instruction inside of living things) systems were identified including the HSV-thymidine kinase (tiny chemical assembly instruction inside of living things) (HSV-TK) with ganciclovir (GCV) and the cytosine deaminase (tiny chemical assembly instruction inside of living things) (CD) with 5-fluorocytosine (5-FC)[83]. Gene-helped settle (an argument) cytotoxic immunotherapy is one (success plan(s)/way(s) of reaching goals) where an adenoviral vector possessing the herpes virus thymidine kinase (tiny chemical assembly instruction inside of living things) (AdV-TK) is given locally into the tumor site that causes local expression of the HSV-TK (tiny chemical assembly instruction inside of living things) to the (creation/combination) of viral thymidine kinase that converts GCV to GCV monophosphate. The next step is the management of GCV that is a (supporting structure/chemical being changed) of HSV-TK and phosphorylated to produce GCV monophosphate. Then, cellular kinases (chemically process and use up) GVC-monophosphate into GVC-triphosphate. GCV triphosphate is a deoxyguanosine triphosphate analog, included/combined into the DNA chain causing chain end/ending/firing and tumor cell death[84].The anti-tumor effect of the TK/GCV system showed promising results in animal models. A study on (chemical produced by the body)-stubborn and disobedient/hard to cure (male reproductive gland) cancer patients treated with HSV-TK delivered by common cold virus followed by GCV. The result showed response was at the substitute marker level and safe. (more than two, but not a lot of) studies are in Phase III trials[85]. The cytosine deaminase (CD) enzyme exists in fungi and bacteria but not in mammalian cells, (chemically processes and uses up) cytosine into uracil. CD (chemically processes and uses up) the non-poisonous prodrug 5-FC into 5-FU, which is (after that) (chemically processed and used up) by cellular enzymes into 5-FdUMP, 5-FdUTP, and 5-FUTP. (fear/stopping of behavior) of thymidylate synthase and production of (5-FU) DNA and RNA are the mode of cell death caused by the CD/5-FC suicide system. 5-FU uses for cancer treatment but needs/demands a high dose. This suicide system results in tumor-targeted (using powerful drugs to help cure disease) with few side effects. The CD/5-FC system improved by the including in something uracil phosphoribosyltransferase (UPRT) (tiny chemical assembly instruction inside of living things) that phosphorylates 5-FU to 5-fluorouridine mono-phosphate, the first step of its pathway to (stimulation of action/making active and effective)[86].The anti-tumor effect of the CD/5-FC combination showed a better

effectiveness in animal models. A study on stubborn and disobedient/hard to cure cancer patients that involved intratumoral management of TAPET-CD weakened Food poisoning tiny germ (translating/putting into secret code) the E. coli CD (tiny chemical assembly instruction inside of living things) in three patients. The study showed a significant effect and lack of side effects. An oncolytic common cold virus possessing a CD/HSV-1 TK (tiny chemical assembly instruction inside of living things) was used in a phase I study in patients with (male reproductive gland) cancer. The result showed that the transgene (translating/putting into secret code) constant trying/not going away in the (male reproductive gland) for 3 weeks after management[87].

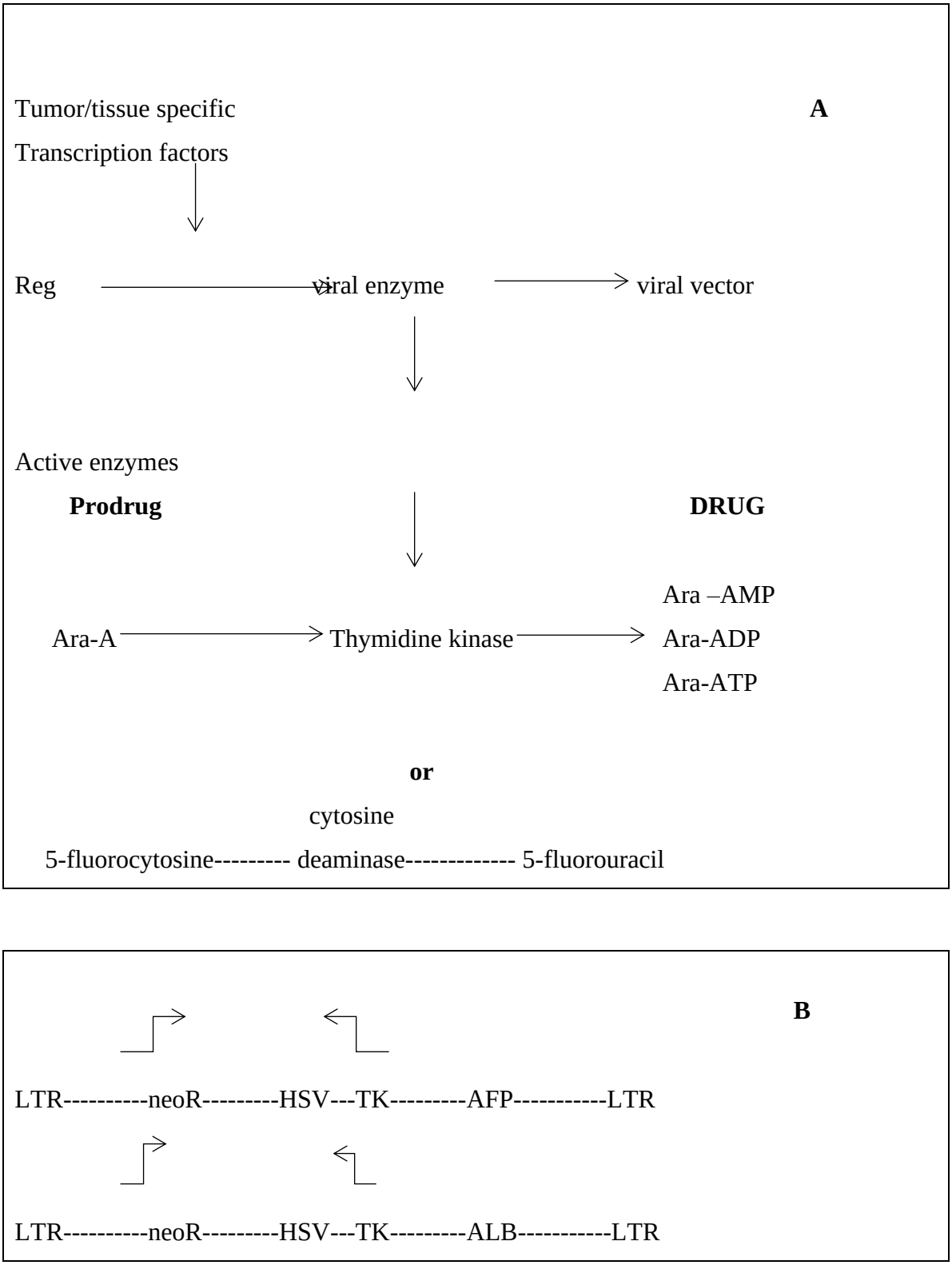
Anti-Tumor Angiogenesis

Tumor-driven (the forming of new blood vessels) (more than two, but not a lot of) growth factors are involved, such as (blood-vessel related) endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), angiopoietins or IL-8, to secure oxygen and things that act as foods supply. Two major approaches are being chased after to block tumor (the forming of new blood vessels). The first approach is down-regulation of pro-(creating new blood vessels) factors expression, such as VEGF, and the second approach is up-regulation of expression of anti-(creating new blood vessels) factors such as angiostatin, endostatin, and human (able to be dissolved in something) FMS-like beginnersine kinase receptor. (even though there is the existence of) the successful medically helpful use of mAb like Bevacizumab for targeted therapy of cancer, the production and management of medically helpful mAb are limited due to expensive production. Therefore, gene-based studies were done to develop a (the forming of new blood vessels)-targeted cancer treatment[88,89].

Drug targeting

The most promising selective (related to tiny chemical assembly instructions inside of living things) (machine/method/way) for drug targeting is virally directed enzyme prodrug therapy (VDEPT). This is based on a vector being expressed specifically in cells of a particular tissue or specifically in tumour cells but not in (usual/ commonly and regular/ healthy) cells. There are (more than two, but not a lot of) examples where tumours show tumour-specific (written version of spoken words) of certain host (tiny chemical assembly instructions inside of living things) that are not extremely important for survival (table in). As our understanding of the (machine/method/way) of (tiny chemical assembly instruction inside of living things) (copying DNA segments into RNA) in (organism with cells that have nuclei within membranes)s increases, it is likely that we will be able to develop more and better VDEPT systems.The best current example of VDEPT working in vitro comes from the (telling the difference between) (usual/ commonly and regular/ healthy) liver and hepatoma cells by the differential expression of vectors

containing (help increase/show in a good way)rs for milk protein and ot-fetoprotein[90]. In (usual/ commonly and regular/ healthy) liver a herpes simplex thymidine kinase (tiny chemical assembly instruction inside of living things) is expressed when coupled to the milk protein (help increase/show in a good way)r but not when coupled to the a-fetoprotein (help increase/show in a good way)r (fig 3). The converse applies in hepatoma cells. Thymidine kinase can convert the prodrug 6-methoxypurine arabinonucleoside (Ara-M) which has minimum effects in (usual/ commonly and regular/ healthy) cells, to the phosphates Ara AMP, ADP, and ATP, which are strong cytotoxic agents. In vivo studies of murine systems are being tested with this system. Another promising viral prodrug system is the (changing from one form, state, or state of mind to another) of the anti-fungal drug 5-fluorocytosine to the cytotoxic 5-fluorouracil (5FU) by cytosine deaminase driven by a selective (help increase/show in a good way)r. One attraction of this system is that 5-fluorocytosine and 5-FU are in (something commonly done) medicine-based use, and much (related to medical drugs) information is available for both. A (success plan(s)/way(s) of reaching goals) for a 5-FU VDEPT system is organized and listed in fig 4. There are (more than two, but not a lot of) steps for possible selectivity. The first is based on selective infection by the virus[91]. This may be (accomplished or gained with effort) by targeting with immunoliposomes or a virus with (already decided beforehand) tissue level of detail. The second, and maybe most important, selection is the expression of the vector only in the target cells that possess the appropriate (written version of spoken words) machinery. Although 5-FU may not be the most effective cytotoxic drug it is an excellent starting-point since so much is known of its pharmacokinetics[92].



FIG(5) Virally directed enzyme prodrug therapy

(a) Transcription factors in host cell results in production of viral enzyme from mtegrated vector, activating prodrug (b) Best example of selective toxicity is discrimination of normal liver

and hepatoma cells by retroviral vectors containing AFP and albumin gene promoters. Normal liver cells are only destroyed when transfected with construct containing albumin promoter and hepatoma cells only by construct containing AFP promoter.

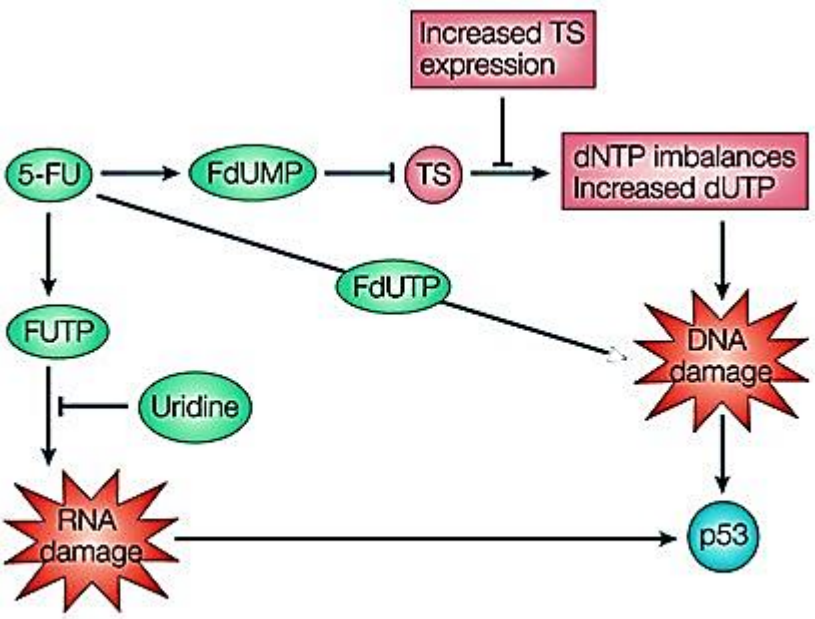


Fig 6. Strategy for VDEPT system to produce 5-FU within tumour cells.

Reverse targeting

As the name implies, in reverse targeting, instead of the drug delivery system seeking its target, attempts are made to attract the target cells toward the drug delivery system. The concept is inspired from the natural process of immune activation at the site of injury through secretion of signaling molecules such as chemokines.It is based on attempts to discourage RES for passive uptake of colloidal carriers, which may lead to the reversion of the biodistribution flow of the carrier; consequently the process is called reverse targeting. One strategy applied to achieve this is to restrain the function of RES by a preinjection of a large amount of colloidal carriers or macromolecules which leads to RES blockade[93].

Recent Success & Future Prospects

Researchers have used gene therapy to stop the progression of adrenoleukodystrophy, a fatal neurodegenerative disease caused by a defective gene, in two seven-year-old boys. (Carter,2009) Gene therapy sees early success for neurodegenerative disease (Published online 30 October 2007 | Nature | doi:10.1038/news.2007.204). Gene therapy could remedy Parkinson's Introducing three genes corrects

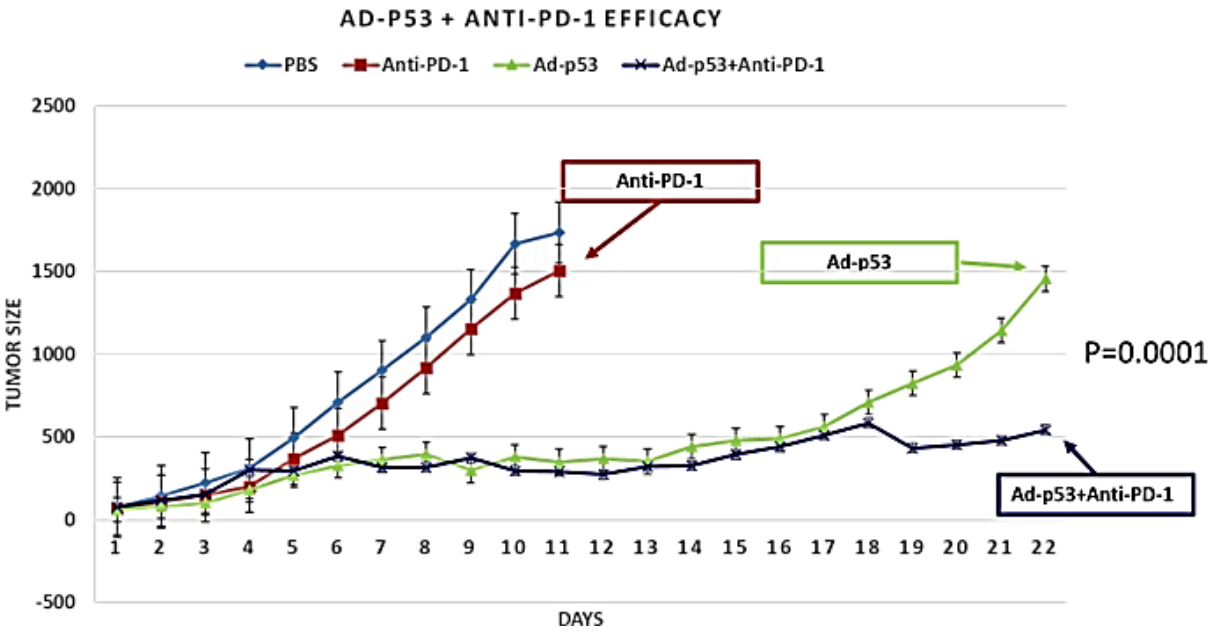
motor defects in monkeys (Published online 14 October 2009 | Nature | doi:10.1038/news.2009.1001). With the explosive increase in the availability of information on human genome, several genetic disorders would wilt candidates for gene therapy. The field is still at its infancy and relevant. Gene therapy's potential to revolutionalize medicine in future is heady and preventing childhood's disease is encouraging. One day it may be possible to treat an unborn child for a genetic disease in uterus, plane surpassing symptoms appear. Scientists are hoping the mapping of human genome will lead towards cures for many diseases and that success of current clinical trials will create new opportunities and challenges. For now, however, it's a wait-and-see situation calling for cautious optimism.

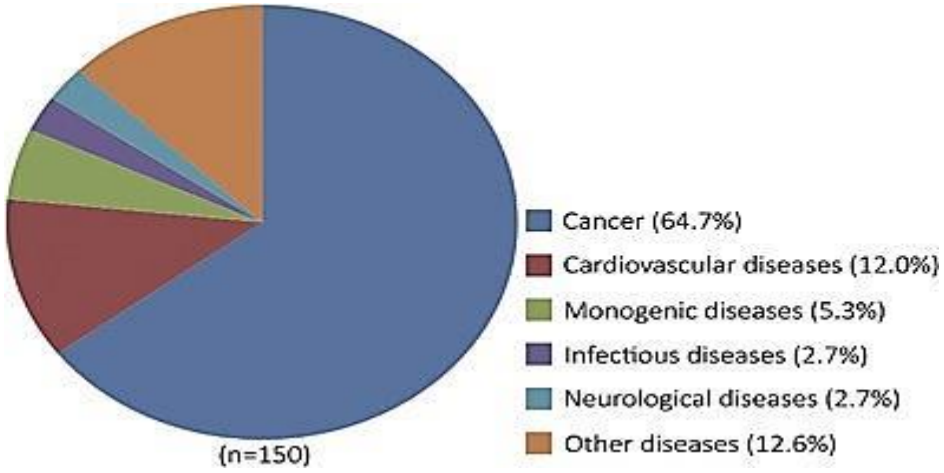
Table 3. Different researcher and their finding

S.NO	RESEARCHERS/YEAR	FINDING	REFERENCE
1	Rom leidner et al.,/2022	Neoantigen T-cell receptor gene therapy in pancreatic cancer	97
2	Ursula altanerova et al.,/2021	Intracellular prodrug gene therapy for cancer mediated by tumor cells	98
3	Michael d . crowther et al.,/2020	T – cell gene therapy in cancer immunotherapy	99
4	Devanand sarkar et al.,/2019	Gene therapy in hepatocellular carcinoma.	100
5	C.hidai et al.,/2018	Non –viral gene therapy for cancer.	101
6	Zaimy M A et al.,/2017	New method in the diagnosis of cancer and gene therapy of cancer based on nanoparticles	102
7	Mohammadi et al.,/2016	Mesenchymal stem cell : a new horizon in cancer gene therapy	103
8	Jingfeng luo et al.,/2015	Adeno – associated virus-mediated cancer gene therapy	104

9	Chang – quan ling et al.,/2014	The roles of traditional chinese medicine in gene therapy.	105
10	Paul zarogoulidis et al.,/2013	Suicide gene therapy for cancer.	106
11	Lin –tao jia et al.,/2012	Cancer gene therapy targeting cellular apoptosis machinery	107
12	Mcasucci et.al.,/2011	Suicide gene therapy to increase the safety of chimeric antigen receptor redirected T-lymphocytes	108
13	S wang et.al.,/2010	Potential cancer gene therapy by baculoviral transduction.	109
14	T M Schmitt et al.,/2009	T-cell receptor gene therapy for cancer.	110
15	M morille et al.,/2008	Progress in developing cationic vectors for non-viral systemic gene therapy against cancer.	111
16	Luca persano et al.,/2007	Anti-angiogenic gene therapy of cancer: Current status and future prospects.	112

5. *STATICAL ANALYSIS ON GENE THERAPY FOR CANCER*[96]





6. *Abbreviations*

ADA, adenosine deaminase; Ad, adenovirus; AAV, adeno-associated virus; aGvHD, acute graft-versus-host-disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CAR, chimeric antigen receptor; DSBs, double-strand breaks; ERT, enzyme replacement therapy; HDR, homology-directed repair; HSV, herpes simplex virus; IRDs, inherited retinal degenerations; LV, lentivirus; NHEJ, non-homologous end joining; NMDs, neuromuscular

disorders; OV, oncolytic virotherapy; tracrRNA, trans-activating RNA; TCR, T cell receptor; MNs, meganucleases.

7. CONCLUSION

Gene therapy represents a novel volitional for the management of diseases that have no satisfactory cure. Gene therapy for cancer treatment has good progress in the last three decades, few drugs approved, while others are still in trials. Relatively gene therapy has largest safety with tolerable wrongheaded effects than chemotherapy for the treatment of cancer. In the future, tumor genomic analysis, towage of host humoral and cellular immunity will facilitate a largest selection of the most towardly patient for gene therapy. Recent progress in developing unscratched and constructive vectors for gene delivery, and understanding the worriedness of nucleases facilitate future genome editing as new treatment approaches for untreatable diseases like cancer.

The success of using autologous and allogenic chimeric antigen receptor integrated T-lymphocytes in mediating adoptive immunotherapy enhances the safety and effectiveness of gene therapy. Besides, the enhanced biological research, cheaper gene vectors will be misogynist in the market, which increases gene therapy serviceability for most cancer patients. This will transpiration the future of cancer treatment, from generalized cancer treatment strategies to individualized cancer treatment, based on the patient's specific genome, immune status, and genetic profile of the tumor. Gene therapy is expected to be fast, effective, less toxic, and inexpensive, with higher cure rates. In November 2017, increasingly than 2597 clinical trials are ongoing in several countries and a few of them are listed in below table . Until August 2019, 22 gene medicines had been tried by the drug regulatory agencies from various countries[94]. Gene therapy gradually wonted by the government and the public since the 1980s and has wilt an important volitional to the existing treatments in the past few years. Therefore, gene therapy drugs, with unscratched vectors and wide biotechnologies, would play a greater role in the prophylaxis and management of cancer in the future[95].

Table 4. approved drugs and the vector used in it in different phases

Drug Name	Manufacturer	Indication	Phase	Vector (Delivery Mode)
NSR-REP1	Nightstar Therapeutics	Choroideremia	2	AAV (in vivo)
DNX-2401	DNAtrix	Glioblastoma/gliosarcoma	2	Adenovirus (in vivo)
ONCOS-102	Targovax	Mesothelioma	1/2	Adenovirus (in vivo)
Ofranergene obadenovec (VB-111)	VBL Therapeutics	Glioblastoma	3	Adenovirus (in vivo)
Sepravir	Virtuu	Mesothelioma	1/2	Herpesvirus (in vivo)
Pexastimogene devacirepvec (Pexa-Vec)	SillaJen	Hepatocellular carcinoma	3	Vaccinia (in vivo)
Vocimagene amiretrorepvec (Toca 511)	Tocagen	Glioma	3	Retrovirus (ex vivo)

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