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A Review :Drug–Gene Interactions in Precision Cancer Therapy: Emerging Roles of Immunotherapy, Suicide Genes, and Molecular Editing Tools

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A b s t r a c t

Cancer remains one of the major threats to human fitness, and although there are many treatments available to address this problem, conventional treatments including radiotherapy and chemotherapy have significant adverse effects and are by no means ideal. Gene therapy is a newly developed treatment modality that provides superior targeting with fewer adverse effects than conventional treatments. To change the expression of gene products, foreign genetic material is injected into the host tissue during gene therapy. Gene therapy provides the opportunity to influence the course of many diseases. Therefore, reliable and safe gene products and vector application coupled with advanced biotechnology will be crucial in the treatment of various diseases in the future. Gene therapy is a treatment strategy of opportunity that has been extensively studied recently. The therapeutic genes are implanted at the specified site. Cell or tissue specific to the majority of tumors these compounds have the ability to either induce cell death or inhibit the rate of cell proliferation. Of most types of cancer. Many viral and non-viral genes and vectors are being used in investigations because this treatment uses unique approaches that involve either silencing inactivated or unwanted genes or activating recovery genes. Activation of tumor suppressor genes is a crucial mechanism that helps control the growth of tumors and suppress them, and controls the function of oncogenes and inhibits their activation. Our explanation in this article covers gene therapy, methods of treating most tumors using genes, the use of approved genetic drugs to treat most malignant tumors, and the future of gene therapy for cancer. . Gene therapy no longer meets the criteria to completely replace conventional treatments. But with a deeper understanding of the process behind cancer treatment, one can choose the optimal course of action and target for future gene therapy, either alone or in combination with other therapies.

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1. INTRODUCTION

Globally, cancer remains one of the most serious public health challenges and continues to be a leading cause of mortality in the twenty-first century, despite recent advances in prevention and treatment. The American Cancer Society (ACS) estimated that approximately 600,000 cancer-related deaths would occur in the United States in 2022 (Siegel et al., 2022). In addition, approximately 58 million Americans today have a history of cancer and this is expected to reach a higher

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number of over 22.1 million by 2030, which is mainly attributed to population increase and the aging process. (Miller et al., 2019). The use of conventional cancer treatment methods which involve chemotherapy, radiotherapy and surgery is associated with less than ideal results due to high mortality rates, high side effects on the body and long term problems like tumor metastasis and recurrence. These restrictions emphasize that there is a dire necessity of new and more specific therapeutic interventions..

Gene therapy has become one of the most promising advanced therapeutic methods over the last 30 years and is currently viewed as a significant supplementary method to the traditional cancer therapies. Gene therapy; a type of therapeutic intervention used in contrast to conventional therapy, includes the therapeutic transfer of exogenous or intact genes into host cells to selectively kill precancerous or malignant cells, sparing normal tissues. (Pan, Liu, & Shi, 2018). Interaction of two or more genetic mutations in a cell results in complex gene-gene interactions, which usually cause unanticipated phenotypic effects.. A negative or synthetic genetic interaction results where two mutations applied alone are non-lethal, but by combining with each other, the resulting mutation is lethal, and is used in the treatment of cancer to selectively kill tumor cells. On the contrary, positive genetic interactions are where mutations that happen simultaneously lead to a smaller phenotype than expected which is an indication of functional compensation between genes. The knowledge of such interactions is crucial to discovering the most important molecular targets and unmeasured hidden genetic processes of human diseases.

Gene therapy has shown therapeutic promise in a very wide range of diseases, such as viral disease, inherited diseases, and cancer. Many gene delivery mechanisms have been formulated such as non-viral and viral vectors. (Griesenbach, 2007; Carlin, 2011). Currently, gene therapy mainly is under investigation on the diseases that cannot be treated easily by conventional methods. This is possible by successful gene molecule delivery to the nucleus of host cells, which leads to its therapeutic expression in the form of somatic cell production of a given therapeutic protein that is able to correct or regulate genetic abnormalities. Consequently, the creation of effective communication among target cells and delivery systems is a vital factor towards effective gene transfer. (Gonçalves et al., 2017).

One of the biggest advances in the clinical translation of gene therapy was when the European Medicines Agency granted approval to the first gene therapy drug, Alipogene Tiparvovec (Glybera), in Western medicine. (Kaufman, Kohlhapp, & Zloza, 2015). The cornerstone findings to this historical breakthrough include the explanation of the DNA-double helix structure that formed the basis of the establishment of contemporary genetic-based treatment. Within the past 10 years, the latest molecular technologies have permitted the accurate editing of DNA and mRNA alteration by means of post-transcriptional effects.

Gene therapy works by administering certain genetic content that controls the expression of a gene or altering the biological characteristics in target tissues. Genetic therapy is a potent alternative to peptide-based therapies in the event of low bioavailability, instability, toxicity and high cost of production. (Bulaklak & Gersbach, 2020). This mode of therapy acts based on a few mechanisms, that is, replacing the bad genes, silencing of bad genes or transfection of therapeutic genes. With the help of specialized vectors, either viral or non-viral, genetic material, DNA or RNA, is delivered to target cells to produce the desired therapeutic effect.

Gene therapy is a relatively new treatment method due to its rapid acceptance as a feasible approach to treat various medical and health conditions, such as rheumatoid arthritis, since the early 1990s, diseases of cardiovascular, infectious, and various malignancies (Wirth, Parker, & Ylä-Herttuala, 2013; Ma et al., 2020; Sudhakar & Richardson, 2019; Deng et al., 2020; Neves et al., 2020; Sims et al., 2020). The genes that play a role in the initiation and progression of cancer are currently the subject of extensive research in both experimental and clinical studies, and the domain of cancer gene therapy is experiencing rapid growth. (Ma, Cui-Cui, et al., 2020).

Recent developments in gene therapy products emphasize the importance of safe delivery and long-lasting genetic stability by utilizing innovative systems like lipid nanoparticles, polymer-based carriers, CRISPR-Cas delivery platforms, and self-amplifying RNA vectors.These systems improve transfection efficiency, minimize toxicity, and enhance the intracellular stability of therapeutic genes, especially in treatments based on drug-gene interactions.

Together, These advancements pave the way for gene therapy as a highly promising approach for the future treatment of cancer and a wide range of other human diseases.

2.GENE THERAPY

The technology encompasses the incorporation of Putting outside DNA into cells, be it inside a living body or not Outside the body, used to help treat or find health issues Whatever the goal in lab work might be clinical gene therapy, the primary challenge persists in attaining effective cellular uptake of the therapeutic gene Yet ensuring controlled gene activity remains key for one or the other Spells that come and go. Or stick around longer than expected. (Iglesias-Lopez et al.,

2019 Inside cells, genetic fixes come through strands like DNA or RNA. These pieces step in where broken genes cause illness. Messenger RNA delivers instructions anew. Tiny siRNA blocks trouble messages quietly. Antisense bits redirect faulty signals one by one. Each molecule plays its part without fanfare.

Picking a nucleic acid depends on what job it needs to do inside the body. For swapping out broken genes, scientists lean toward DNA since it can carry working copies right into cells. When quick but brief protein creation is needed, messenger RNA steps in, turning on proteins without changing inherited code. On another path, siRNA along with antisense strands dial down gene activity, putting harmful signals like MYC on pause. To check if that quieting effect took hold, researchers turn to qRT-PCR, tracking how much message molecule vanishes after treatment - this number often tells the story. Such precision makes these molecules key players when studying tumor targets or how medicines shape genetic behavior. (Iglesias-Lopez et al., 2019) . Starting off differently - gene therapy medicines fall under a special group called advanced therapies, according to the European Medicines Agency. These treatments face strict review because of how complex they are biologically. That detail comes from Liang and Wang's work back in 2020Neuhaus, Schaudien, & Dehmel, 2023). These technologically sophisticated agents may carry therapeutic, preventive, or diagnostic genes and are widely employed in tissue regeneration, correction of metabolic deficiencies, restoration of physiological functions, and the inhibition of undesirable gene expression (Cesur-Ergün & Demir-Dora, 2023; Cesur, 2019; D'Aria et al., 2020). Gene therapy can be executed through several principal molecular strategies (Neuhaus, Schaudien, & Dehmel, 2023):

1. Replacement of mutated genes with functional counterparts,
2. Gene Action of aberrant, suppression
3. Inhibition of undesirable gene expression,
4. Compensation for missing genes, and
5. Targeted delivery of therapeutic genes to specific tissues.

Gene suppression and inactivation techniques—especially those utilizing antisense oligonucleotides and nuclear RNA-mediated silencing—have proven effective in blocking oncogene activity and curbing the growth of cancer cells. In suicide gene therapy, a specific gene is delivered into tumor cells to enable the conversion of a harmless prodrug into a toxic agent directly within the cancerous tissue. This approach, termed gene-directed enzyme prodrug therapy, improves the precision of treatment and reduces harmful side effects on healthy tissuesFully working versions of broken genes get delivered into cancer cells, different from other methods. Vectors carry these replacements carefully inside. Normal cell behavior starts returning once the fix takes hold. This approach fixes errors at their source instead of just managing symptoms.

Flying genes from one place to another needs special shuttles - these helpers go by the name of gene delivery systems, using either viruses or non-virus options. Even though virus-based and synthetic methods get the job done, more scientists now lean toward the man-made kind. Safety steps up a level without viral parts onboard. The body's alarm system tends to stay quiet when artificial carriers arrive. Factories also find it easier to crank out copies of these lab-built tools compared to growing actual viruses. (D'Aria et al., 2020). Gene transfer strategies are additionally categorized based on the type of target cells, which can be somatic or germ cells, as well as the method of delivery, which may be ex vivo or in vivo. (Chen et al., 2022). Gene therapy is fundamentally focused on modifying gene expression and the biological behavior of living cells for therapeutic aims. (Dora, 2021). Gene therapy has the potential to address both somatic and germ cells, the current clinical focus is solely on somatic cell therapy of gene, which is non-heritable and therefore regarded as ethically and legally acceptable (Goswami et al., 2019).

Traditional gene therapy approaches involve the genetic modification of autologous or allogeneic T cells, transplantation of hematopoietic stem cells (HPSCs), and the engineering of chimeric antigen receptor T cells (CAR-T) through ex vivo transduction, in addition to direct in vivo gene delivery into patient tissues. Still, once tools like zinc-finger nucleases showed up - along with TALENs and CRISPR - fixing broken genes got a whole lot more accurate. What shifted the game was aiming straight at broken DNA pieces. No more hoping - now fixes land exactly on target. With every leap forward, changes turned crisper, simpler, trustworthy. Where clumsy tries once failed, accuracy finally took hold (Motta et al., 2019).Fair accuracy marks where ZFNs land in DNA, although setting them up means long hours plus steep expenses. Hardly a quick fix, their complexity bogs progress in extra steps. Hitting targets more reliably, TALENs open wider paths forward but remain slow to assemble and costly just the same. Then comes CRISPR-Cas - precision climbs, design simplifies, cost drops, speed rises. Exact changes matter when fixing DNA in cancer care - CRISPR delivers just that, hitting only what needs correction. Watch a cell shift after silencing one stubborn gene; responses reveal how medicines might work better when guided precisely. (Motta et al., 2019).System of gene therapy comprises setup includes three main parts:

1. Active copy of a gene, designed to produce the protein needed
2. A small circular piece of DNA that includes a region controlling whether genes are turned on or off.
3. A tool moves the treatment package into the body's cells (Mali, 2013). One method carries ge netic material where it needs to go inside living tissu e (Mali, 2013).

A component of the gene therapy system consists of three main parts. One part delivers the genetic material, while another targets specific cells. The third element ensures stability once inside the body

A working copy of a gene, designed to produce the needed protein, A small DNA circle carrying a control segment for turning genes on or off, A tool moves the treatment package into the body's cells (Mali, 2013). One method carries genetic material where it needs to go inside living tissue (Mali, 2013). This approach shuttles a designed sequence across cell boundaries (Mali, 2013). The process involves guiding engineered DNA into target areas of an organism (Mali, 2013). Moving helpful genes relies on such transport setups (Mali, 2013). Modern gene therapy rests on these linked systems, built molecule by molecule. Their combined actions explain how treatments now reach cancer care with greater accuracy. Step by step, they shape the way therapies match individual patients. From one cell to another, function follows form in tailored medical approaches

2.1. Advantages of gene therapy

Advantages of gene therapy in cancer treatment involve various methods such as using plasmid Deoxyribonucleic acid with curative nucleotides, modulating gene expression, and utilizing RNA intrusion (Liu et al., 2019) Gene therapy offers benefits like high efficacy, specificity, low off-target toxicity, and multiplexed delivery of genes targeting cancer tumor genesis, recurrence, and drug resistance (Ni et al., 2022)The effectiveness of gene therapy in cancer treatment has been greatly enhanced by genomics editing techniques. Gene therapy has become a common practice in medicine. Its key features include gene addition, gene excision, and transgenes is. Unlike viral vectors, gene therapy is limited to facilitating the addition of genes. For instance, Cell therapy for adoption employs The process of gene delivery is employed to modify T cells, resulting in a targeted antitumor response. This approach aims to enhance the body's antitumor immune response through artificial means, leading to a sustained and potent antitumor effect. A remarkable advancement in the field of adoptive cell therapy, chimeric antigen receptor T-cell therapy has been devised to effectively combat a wide range of malignant hematological tumors and solid tumors. (D'Aloia et al., 2018). Suicide gene therapy, on the other hand, involves By introducing a suicide gene into targeted tissues, like tumors, it is possible to trigger cell death through the production of Distinct enzymes, toxins, or pro-apoptotic proteins. within cancer cells. (Zhao et al., 2021). This therapy can also increase the sensitivity of cancer cells to chemotherapy (Li et al., 2020) by utilizing a specific tumor promoter to regulate gene expression in cancer cells (Qiu et al., 2021).

However, despite the significant advantages of CRISPR/Cas9-based gene editing, major challenges remain, including unintended off-target DNA cleavage and substantial barriers to efficient delivery in solid tumors, which limit its full clinical translation (Guo et al., 2023).

2.2.Gene delivery technologies.

Ensuring the safe and effective delivery of genetic products has proven to be quite a challenge ever since the emergence of recombinant DNA methods. Gene delivery depends on vectors to transport the gene into specific tissues, ensuring proper delivery of a suitably sized genetic construct to achieve accurate expression. Different methods including viral vectors, non-viral vectors, and bacterial systems are employed for gene transfer. Recent reviews have shown that both viral and non-viral vectors remain central to gene therapy development, each with distinct advantages and trade-offs (Butt et al., 2022; Taghdiri et al., 2024).

.2.2.1Systems Utilizing Viral Gene Therapy

Viral vectors have emerged as a highly promising tool in the field of gene therapy technology. due to their significant potential and efficient gene transfer capabilities. They can be administered locally and/or systemically, The delivery of genes into human cells in a pathogenic manner is regarded as a valuable technique by scientists, as it allows for the substitution of accessories of the viral genome with the desired the rapeutic gene, resulting in increased efficiency(Raty et al., 2008)Despite the need to address various shortcomings before clinical use, viral gene therapy has progressed through recent trials and approvals for treating head and neck carcinoma, skin cancer, and Deficiency of lipoprotein lipase. Ongoing clinical development includes combinations of viral gene therapy such as AAV, lentivirus, and retrovirus. While viruses are the primary vectors under investigation, research has expanded to explore non-viral alternatives due to ongoing safety concerns(Liu & Kirn, 2008) (Kaufman et al., 2010) (Scott, 2015) (Shaw & Suzuki, 2019)

2.2.Systems Utilizing Non-Viral Gene Therapy

Non-viral vectors, such as liposomes or polymers, utilize a positive charge from cationic liposomes or polymers to bind to DNA, which carries negative charges on the phosphate group. Another method for creating DNA nanoparticles is through calcium phosphate coprecipitation (Hosseinkhani & Tabata, 2006) While co-precipitation of plasmid DNA with calcium phosphate is used for cell transfection, the efficiency is lacking. There is a necessity to enhance the materials used. Polycation technology relies on the interaction of cells through a simple and constant electrostatic force (Hosseinkhani et al., 2004) (Abedini et al., 2011) (Hosseinkhani et al., 2015) (Abdullah et al., 2010)(Abedini et al., 2010) (Shi et al., 2020)

2.2.3. Risks affiliated with viral vectors

The primary worries linked with viral vectors include the potential for ignition, insertional mutations, and off-target effects (Chattopadhyay & Sen, 2017) (Stolberg, 1999)The case of Jesse Gel singer's death in 1999 serves as a notable example of infection caused by an adenovirus overdose. Insertional mutagenesis poses a significant obstacle that needs to be addressed when employing gene therapies. Occasionally, vectors may align with undesired sections of the genome. To mitigate this issue, it is advisable to utilize a non-integrating vector (Alnasser, 2021)

3.Effectively Employing Gene Therapy Strategies In The Field Of Cancer Treatment

Cancer is a complex and diverse disease characterized by the uncontrolled growth and invasion of cells in the body. The appropriate treatment for cancer depends on various factors such as the specific type of cancer, its stage of progression, and the individual patient. There are several treatment options available, including chemotherapy, surgery, radiotherapy, hormonal therapy, and photodynamic therapy .Other treatment options to consider include High temperature, Immune therapy, stem cell planting, Directed treatment, and gene therapy. Gene therapy, in particular, stands out from conventional treatments as it has the potential to be applied with minimal side effectsA range of strategies for gene therapy in cancer comprise suicide gene therapy, tumour suppressor gene activation, and immunotherapy., and gene suppression. Furthermore, gene therapy can also be used to activate oncogenes and for antiangiogenic purposes. (Rajakumar et al., 2022)

3.1. Immunotherapy

To date, the primary focus of cancer gene therapy research has been on immunotherapy. This approach utilizes the patient's own immune system to identify and attack cancer cells (Riley et al., 2019)Cancer cells possess immunogenic properties and contain intracellular cancer antigens, making T-cell-mediated cellular immunity more crucial than B-cell-mediated hum oral immunity. However, a regular immune response is insufficient to completely eliminate cancer cells. The ability of cancer cells to evade the immune system is dependent on factors such as the secretion of immunosuppressive substances, antigen expression, and down-regulation. In gene immunotherapy, various immune molecules are employed to stimulate a potent antitumor immune response (Feins et al., 2019) For example, genes encoding various cytokines are introduced into cancer cells either ex vivo or in vivo. as a result, Cancer cells produce proteins from the transfected genes in the tumor microenvironment. These Alarm clocks of the immune system alter the tumor microenvironment, ultimately boosting the immune response to fight against cancer. (Alnasser, 2021)

3.2.Suicide gene therapy

Utilizing gene therapy is a revolutionary way to address genetic and acquired diseases that do not respond well to conventional treatments (Duarte et al., 2012)Suicide gene therapy involves introducing a specific gene, referred to as a "suicide" gene, into tumors to trigger the conversion of a prodrug into a potent and lethal substance(Ketola et al., 2004)

3.2.1Suicide gene therapy systems

Suicide gene therapy represents a targeted therapeutic strategy in which a specific gene is introduced into cancer cells to convert a non-toxic prodrug into a cytotoxic compound, thereby selectively inducing tumor cell death. The delivery of genes into human cells using One reason viral vectors stand out? They move genes effectively, work reliably inside cells, leave lasting effectsFaster than most, adenoviruses appear frequently - retroviruses tag along - not far behind, herpes simplex tags in - each slips through cell walls easily, pulled toward tumors as if guided. Though imperfect by design, their structure keeps them lingering near cancerous zones on intent. When precision counts, their ability to infect turns useful without trying. Finding their way inside cells comes naturally to these, which is why researchers keep coming back. Not merely active but driven, they track cancer spots much like a beacon guiding without pause.

A piece of the herpes virus works when combined with a specific drug, according to research. Since it targets only some cancer cells, the added gene produces an

enzyme activating ganciclovir. This initial step creates ganciclovir monophosphate thanks to a viral protein at work. Within the cell, regular enzymes keep altering it until reaching ganciclovir triphosphate. Resembling one piece used in DNA construction, this transformed compound gets woven into growing DNA chains. When the mimic joins replication, DNA creation stops. Because of this, rapidly dividing cancer cells break down on their own (Shi et al., 2016).

Outside virus-based tricks, some try shaking genes together with chalky stuff, linking them to rubbery bits, or tucking them inside oily shells - often quieter on the body's alarm system, gentler too. Still, getting every gene inside a cell remains a puzzle. For sharper results, teams reshape polymer skins, craft miniature carriers one piece at a time, adjust how fat pockets form - each change nudging genes toward smoother entry, tougher survival, quicker escape after arrival. With these shifts, synthetic helpers now move DNA with strength close to natural invaders, widening paths to fight tumors minus viral baggage. When heat from radiofrequency is applied, cancer cells respond differently to gene therapy with HSV-TK and GCV. Because of the warmth, drug entry improves as the cell surface changes shape. With temperature on its side, genetic treatment finds an easier path inside. Mice and rat studies recorded clear drops in tumor size under these conditions. Working side by side, rather than solo, the two approaches press further into abnormal tissue. Heat shapes how well treatment travels through tissue. Evidence shows gains come from motion, not molecules. Tests on living creatures show tighter control when fever leads the way. What matters most is order - warmth opens paths before medicine follows. Results hold promise, arriving quickly where they’re needed (Li et al., 2020).

3.2.2.Mesenchyme stem cells (MSCs) designed as vectors

Mesenchymal stem cells (MSCs) have emerged as promising tools in anti-tumor gene therapy because of their unique biological advantages, including tumor-homing ability and immune privilege, which enable them to migrate selectively toward tumor microenvironments (Shah, 2012; Ding et al., 2021). These characteristics make MSCs attractive candidates for delivering therapeutic genes particularly suicide genes directly to solid tumors while minimizing damage to surrounding healthy tissues. One approach tested a lot uses the CYP2B6TM-RED gene setup to turn cyclophosphamide into an active drug. This gene, when placed in stem cells near tumors, changes the medicine right where it's needed. Inside the tumor, those altered cells make powerful cancer-killing substances. Mice getting these modified stem cells directly into their tumors showed full shrinkage in one third of cases. Six months passed without signs of return in those successful instances. The results point toward real impact against cancer growth. A sharper immune reaction also appeared alongside the shrinking masses. Earlier experiments back up what was seen again recently. Findings from 2014 and another set in 2020 support the pattern.

Not built by accident, MSCs are adjusted using various ways to reach their target. While viruses show up a lot due to how well they enter cells, they bring dangers such as tumors and immune trouble - slowing down real-world treatment use. For this reason, research has shifted slowly toward non-virus methods, considered kinder to biology and more flexible when tuning MSC behavior (Amara et al., 2016).MSCs can be harvested from accessible tissues such as bone marrow and adipose tissue, making them practical for clinical translation. When engineered, MSCs produce tumoricidal byproducts that selectively kill cancer cells within the tumor microenvironment (Amara et al., 2014). Furthermore, the clinical evaluation of gene therapy vectors, such as Ad5-yCD/mutTK (SR39)-ADP combined with gemcitabine, demonstrated acceptable safety and tolerability in pancreatic cancer patients, reinforcing the feasibility of MSC-based gene delivery in cancer treatment (Engeland, 2022).Despite these promising outcomes, careful consideration must be given to the potential effects of activated prodrug metabolites on surrounding non-malignant tissues to ensure therapeutic precision and safety.

3. 3.Gene activation for tumor suppression.

A lone flaw in a gene copy rarely shuts down tumor suppressors - these keepers of order demand both versions harmed to lose function. Running strong, they halt unchecked expansion, sometimes halting cell progress or launching self-destruct sequences. Take Rb: it jumps in during G1, hitting pause. Damage found? Then p53 takes charge, enforcing strict rules. Certain ones, like CDK inhibitors, dampen growth cues at critical gates. Different types, including BRCA1 and BRCA2, help fix broken DNA strands accurately. Their combined work keeps mutations in check, reducing chances of cancer forming (Tamura et al., 2020).

Among these, the p53 gene is the most important and extensively studied tumor suppressor. It functions as a genomic gatekeeper by detecting DNA damage and activating DNA repair pathways or inducing apoptosis when damage is irreparable (Ibnat et al., 2019). Experimental studies have demonstrated that p53 gene transfection results in significant tumor growth inhibition and regression in animal models, confirming its therapeutic potential (Zhang et al., 2018).Now scientists are tuning how p53 shows up in cells, thanks to sharp new tools like CRISPR/Cas9 and TALENs.

Instead of a blunt approach, these methods fix broken p53 bits right where they need it - inside cancerous tissue - with far less drift elsewhere. What helps? Better carriers, both virus-based and synthetic, that steer the healthy version of p53 straight to tumors without scattering. Precision grows when delivery learns where to go.People in cancer tests did better when researchers slipped synthetic p53 into chemotherapy using viruses. Higher survival rates popped up - beyond what scientists had predicted. The real surprise? Results stayed strong month after month. Gains crept ahead, steady in every group studied. Even when past therapies did not work, doctors saw shifts in tough patient cases (Ma, Ma, & Xing, 2017). Pooled findings across research point to p53 playing a key role in fighting cervical cancer. Because it guides cell division and triggers cell death, unchecked tumor expansion is less likely. That kind of regulation proves vital in halting irregular tissue development (Valente, Queiroz, & Sousa, 2018). For these reasons, methods using gene therapy to adjust p53 levels remain among the more effective paths being explored in oncology (Siddiqui et al., 2020). Popping into the system early, adenoviruses arrive fast - retroviruses tag along not long afterward. Soon after comes herpes simplex, sliding into cells the way rain slips down glass. As if pulled by whispers, they drift toward tumors without rush. Designed with quirks on purpose, they linger near cancer spots more than anyone thought. What makes them spread so easily becomes crucial when precision counts, operating on their own. Deep within cells they always land, pulled in as naturally as air into breathing. This force keeps researchers coming back, drawn by what it reveals. Not merely traveling, they seek out cancer spots much like sunlight reaches clearings. When paired with a certain medication, part of the herpes virus becomes active, studies show (Wang et al., 2020).

3.4Antiangiogenic gene manipulation for therapy

How tumors grow ties closely to blood vessel creation, which feeds them oxygen and needed resources. That link makes blocking new vessels a key angle in fighting cancer. Not every method tries to ramp up VEGF or angiopoietin. Some turn instead to reinforcing the body’s own stop signs - substances like endostatin, angiostatin, interleukin-12, or the p53 protein. Delivering these precisely where required? Still a puzzle, mostly because today's delivery tools miss the mark too often. A newer tactic slips in a split virus built to haul both human endostatin and angiostatin at once, tripping up rogue blood vessel formation more completely. In tests on liver cancer setups, this setup slowed tumors sharply while stretching out life spans in lab mice (Fallah et al., 2019).

Monoclonal Antibodies Targeting VEGF

Two decades back, a handful of lab-made antibodies targeting blood vessel growth got the green light from U.S. regulators to stop VEGF signals - bevacizumab leads that group. Even though they work, their impact fades fast inside the body, plus the price tag keeps many from using them regularly or broadly over time.

Lentiviral Anti-VEGF Antibody Gene Expression Systems

Now, with a gene-based anti-VEGF monoclonal antibody delivery system, the problem has been resolved to some extent. It has become possible to produce antibody continuously following a single administration.The results indicated that using such a lentivirally mediated gene expression system, functional bevacizumab could be produced in modified HEK293T cells, with stable and persistent inhibition of VEGF effects (Zhou et al., 2019).This makes effects that were not previously possible a reality. This development represents in essence one step forward for long-term antiangiogenic therapy with less frequent administration and lower cost.

Exosome-Mediated miRNA Delivery in Angiogenesis Suppression

Recent studies have shown that miR-155 can influence the production process of blood vessels in stomach cancer through its control over FOXO3a. Once gene expression is reduced to a critical level, tumour growth tends to lessen instead of rising fast--this relationship holds true even on closer examination. Those minuscule balls of fat and protein--exosomes, which were originally thought to be refuse from cells--are in fact packed with treasure. Like a shuttle service, they carry molecules and traffic through bodily fluids with remarkable precision. Such molecular delivery within these spaces is essential for the tenuous interaction between miR-155 and the protein FOXO3a that regulates new blood vessel growth in gastric cancers(cell line: Bao et al., 2014). As one day they may shuttle approaches that starve blood supply lines for tumors so effectively to their destinations.

Combined Drug and Gene Therapy Approaches

Once treatments stop building nuclei for fresh aphid infestations, a new phenomenon arises in tumors. This new phenomenon, however, may not be as tough to deal with as people think. As course, it depends where the drug goes after it gets inside. Mixing genetic switches with drugs in a PEI ploy has so far had quite good suppressive effect on tumor growth--early signs seem to suggest this (Prados et al., 2012).

4. Enhancing The Therapeutic Impact By Integrating Gene Therapy With Complementary Cancer Therapies

4.1.Maximizing Treatment Efficacy through the Integration of Gene Therapy and Chemotherapy

many people still end up facing even with big progress in cancer treating, spread of the illness, often beyond cure. For these individuals, body-wide chemo stays the go-to option. Some mixtures of drugs work better than others depending on tumor type - yet using multiple chemicals at once, though it may help live longer, tends to bring strong harm along with it. Because of this, scientists now push harder to make poison-based therapies strike smarter without wrecking healthy tissues.

Sending genes into cells is becoming a useful way to boost cancer drug effectiveness, especially against stubborn or spreading tumors. Alongside standard chemo, genetic treatments have worked well in increasing how strongly medicines stop cancer growth - seen clearly in lung, bladder, pancreas, colon, and breast types. Finding an inhibitor of programmed death cells or RNA cutters that can take away maligenant genes, with therapy combined such killers still more many types of cancer cells will die. (Lin et al., 2023)Chemotherapy is a combined action strategy using conventional drugs that can be participated with gene therapy. Advanced drug delivery technology enables the agent to target and greatly elevate its effect throughout the body. Clinical trials have tried several gene-based agents given alongside chemotherapeutic drugs (Xu et al., 2018). For example, TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) is a member of the TNF family. TRAIL plays a unique role in programming cells for destruction. It effectively promotes cancer cells to kill themselves by connecting with death receptor DR5 and death receptor DR4; both are overexpressed in many malignant tumors. Also, TRAIL encoding gene therapy exerts a bystander effect with significant antitumor activity in vivo (Amreddy et al., 2018).Yet the triumph has been hampered by the impossibility of cancerous tissues to combat death receptors.In the face of this enemy, scientists took on a new line of defense: HuR. With its strong links to tumour genesis, cancer progress and spread, HuR was deemed a promosingtreatment target (Qin et al., 2020).Targeting HuR could increase the sensitivity of a tumor sample to genes that induce apoptosis, so increasing the combined effect of gene therapy and chemotherapy.

4.2.Gene Therapy Combined with Phototherapy: A Powerful Treatment Approach.

The latest medical methods to fight illness Light is also now turning on gene remedies. ”Not only does this construct ship habile genes, it brings them active wherever that may be required. At the right moment triggery medical repairs pour into body continually with illumination help. Instead of expansive results, through a thin line of light control The two separate ideas of once stand now more closely linked than before. The one side provides them with genetic apparatus and the other side uses the rays to get on line again. Because two methods thereby combine each other's capacities, the weakened effect and raised stability Treatment then gets the upper hand without spreading, precise effective for target areas. Merging these two modalities into a synergistic platform facilitates targeting gene activation at specific sites of disease. The result has both greatest efficacy and minimal effect on surrounding healthy tissues.The concept of combining gene therapy with phototherapy has shown great promise for treating a variety of medical conditions, including cancer, genetic diseases and infections. In the field of gene therapy for caner, an artificial gene can be introduced into tumor cells so that it only attacks them, and a new approach also uses phototherapy in order to turn on genes One way to express this is to make highly focused local destruction for malignant cells while sparing normal ones.Two major types of phototherapy are generally recognized.Photothermal therapy (PTT, which in fact does not use light at all) Photodynamic therapy (PDT) are both effective in the treatment of specific cancers, albeit at a high cost (Stahel & Zangemeister-Wittke, 2003).In photothermal therapy, light-induced heat generated by near-infrared radiation is used to destroy cancer cells, while at the same time minimizing any damage to nearby healthy tissue (Kim et al., 2016). Compared to conventional modes of treatment, PTT has a number of attractive advantages: minimal invasiveness, deep tissue penetration and a low procedural trauma (Kim et al., 2020).On the other hand, Photodynamic therapy (PDT) is a new type of cancer treatment, that uses visible light to activate a photosensitizer (PS)--a light-sensitive molecule that turns into reactive oxygen species (ROS) following its activation -- ultimately resulting in cancer cell death (Cai et al., 2020). PDT is especially successful in treating surface tumors like esophageal cancer, bladder cancer and melanoma. The many advantages it possesses--such as low invasiveness, targeted cytotoxicity and minimal side effects--contribute greatly to its clinical success. (Chen, Luo & Zhang, 2019; Revia & Zhang, 2016).

4.3.Combined approach of gene therapy and magneto thermal therapy

This method that relies on a particular magnetic field makes the little particles inside of tumors begin to heat up. Only sick cells get burned--the rest are okay, even if they do have a fever. Energy from outside causes these small materials to sway back and forth, making everything nice and warm where it should be. The temperature rise pushes damaged cells to self-destruct, without bursting the buds too tightly. This treatment is precise: the effect follows where the particles are put. Only those places where particles have gone get warm. Nearby healthy tissue feels next to nothing at all; shift a tumor cell, and the results show up in the 1960s research of Tay et al. As for where the magnetic nanoparticles goes to in the body? Frequently, magnetic particle imaging needs to take over this chore, as Yang et al. proved in 2022. The heat inside a tumor caused by a magnetic field has worked well - little side effects, deep infiltration - and is now on trial patients with the number NCT02033447. To succeed, we must maintain our success in keeping the heat between 43 and 46 degrees Celsius. This is achieved if we can place enough particles where they are needed precisely where we want them. (Gavilán et al., 2021).

Thirty years ago, researchers started looking at the possibility of using heat from magnets to treat hard balls in the body. Now, tests focus on small iron-made particles to stop lumps in the head or pelvic region. Inside just such approaches, little particles actually get deposited right into the troubled tissue and then exposed to a slight wave field at roughly 100,000 cycles per second. Moreover, although such particles have already been approved for the sake of scanning, and to cure low blood counts others for heating alone must be made with more rigorous physical qualities. They need an adjusted magnetism, stable external layer, and predictable agglomeration so as efficiently turn the field into heat will deliver heating with precision. Big strides have been made in recent times in creating the next-generation magnetic nanoparticles for treating hormone-related cancers. And this transformation is removing obstacles to combining magnetic heating with chemo, radiation, immune treatment, light-driven methods of treatment, or gene therapy -opening up multi-faceted methods for dealing with tumours. Work still proceeds on how heat spreads in the centre of a tumour and keeping the target temperature exact during treatment, gradually improving both reliability and effect without making more noise (Stahel & Zangemeister-Wittke, 2003).

5.Current Molecular Methodologies Used In The Field Of Cancer Gene Therapy

Scientists have also developed a new way of moving around genes that means very different medicine is likely as well. This has may well support existing therapies while opening up entirely fresh ones for action. keep coming out, Out of this shift - perhaps net delimited by the double entitled stripped or semi-narrative blog post which rules left by science but otherwise ignored and unread over time - has emerged a number of novel cancer strategies. With genetic material shifting its goal: analytics have gone haywire and TALENs take the foreground, iRNA appears in conjunction with CRISPR-like DNA repeats. Up near ZFNs attend local settings looking for damage while recycled DNA units, self-destructing genes, and repeat patterns similar to CRISPR move into labs on bite wheels more and more frequently.

5.1.Antisense technology is a captivating and auspicious way to treat cancer

One of the most promising strategies for treating cancer is antisense technology. Inthis approach, particular sequences of antisense oligonucleotides (ASOs) are used to bind specifically to corresponding target mRNA, thereby inhibiting gene translation. Furthermore, thisinteraction's high specificity arises from Watson–Crick base pairing, which allows ASOs to be powerful tools for target validation, gene regulation, andspecific therapeutic interventions in cancerand genetic diseasesthe specificity of this interaction is receptor-legated by Watson–Crick base pairing, making antisense oligonucleotides powerful tools for target validation, gene regulation, and selective therapeutic intervention.

Prime targets for antisense-based therapy might be ones that havetheir expression governed by certain slew genes, which are implicated inthe comport of cancer cells. Only one antisense compound has been accorded topical registration to date, but clinical trials are now in progress. These are looking at antisense-based treatments for cytomegalovirus-inducedretinitis, as well as experimental therapies targeting the people key oncogene mRNAs Bcl-2,protein kinase C-α (PKC-α),c-raf, was (Dias and Stein, 2002:550).Antisense oligonucleotides by binding to their respective mRNAtargets can trigger distinct molecular mechanisms of action (Le et al., 2019; Lundin, Gissberg, & Smith, 2015).

These mechanisms can be broadly classified into two major categories:

1. mechanisms that promote RNA degradation, and
2. mechanisms that inhibit RNA function by steric blockade without inducing RNA degradation.

Regardless of the specific pathway involved, the therapeutic application of antisense oligonucleotides demonstrates significant potential for effective and selective cancer treatment (Bennett et al., 2017; Karim et al., 2018).

5.2.RNA molecules with interfering properties

The advent of RNAi can be dated to 1998 with its first observation in Caenorhabditis elegans (C. elegans) (Fire et al, 1998), Before long, RNAi has emerged as an efficient gene silencing technology with important implications for treating cancer.This is called RNA interference. It is a post-transcriptional gene regulation mechanism mediated by double-stranded RNA (dsRNA). dsRNA only binds complementary copies of malicious HIV virus RNA sequence while leaving your own cellular machinery undisturbed. In three major groups of small regulatory RNAs have been found in animal,you will normally find: small interfering RNAs (siRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs) (Schuster, Miesen, & van Rij, 2019; Sun et al., 2023).

SiRNA-based RNA interference holds great promise as a potential therapy for cancer. Yet currently the use of this method in a clinical setting is hampered by key complications such as metabolism instability, limited targeting specificity towards tumours and problems with getting into cells. A potential way around this is to structurally change the siRNA using synthetic nucleic acid bases so that it is more stable in vivo. In this study, we produced and tested functionally modified siRNAs containing different numbers of the hydrophobic F base. We systematically studied the interactions between F-base modified siRNA (F-siRNA) and plasma protein human serum albumin. The F bases significantly improved the tumor-targeting capability of those siRNAs, their lifetime in the body and also their ability to penetrate tissues. Mechanically, the F bases serve to stabilize siRNA–albumin complexes so that this combination can preferentially achieve selective translocation to and retention in tumors through the enhanced permeability and retention (EPR) effect. Meanwhile, the F bases increase siRNA binding to transport proteins in cell membranes and so promote broad uptake by cells. The data underscore that F-base modified siRNAs dramatically improve the stability, conveyance efficiency and selective tumor accumulation of siRNAs deposited in new liposomes like those investigated here as potential cancers treatments. (Feng et al., 2023)

A tumor-targeting fluorescence probe for the near-infrared region was developed in order to narrow down targets even further.The probe f-CRI is designed to detect RNA, and is targeted to tumors through a cyclic RGD peptide, a furan furan group for modifying mtRNA (mitochondrial ribosnucleic acid), and was covalently linked with monoxide-sensitive IR780 receptors. When f-CRI is irradiated by an 808 nm laser, photoactivation occurs and it is covalently bonded to mitochondrial RNA (mtRNA) with a prolonged residence time in the targeted tumor. This covalent modification destroys mitochondrial function and induces significant regression of tumor.

The f-CRI Strategy's new

What really sets the f-CRI system apart is its ability to direct, RNA-level targeting of mitochondria--it's a great improvement over traditional photothermal therapy (PTT) or photodynamic therapy (PDT). With traditional PTT and PDT, at the cellular level, all they really do are induce thermal damage or cause damage with reactive oxygen species (ROS) generation. In contrast, direct covalent modification of mtRNA by the f-CRI probe disrupts tumor metabolism at its genetic and mitochondrial nucleus. Such a mechanism greatly increases the precision of therapy done by these molecular agents as well as improves the spatial control they offer. And best of all? There's far less harm to surrounding healthy tissue that results from off-target effects-- making f-CRI a next-generation monogenic photogene therapy.

6.CONCLUSION AND FUTURE PERSPECTIVE

Cancer is among the most complex and insoluble problems now because of its genetic differences, diverse direction of development resistance to normal treatment methods Despite the existence of many different routes to therapy, there is an increasing optimism that advanced molecular techniques in particular gene therapy will help turn cancer into history over coming decades. At present, most gene-based clinical experiments are in a relatively early stage. Although gene therapy cannot meet the current criteria to replace traditional treatments such as chemotherapy and radiotherapy, it shows wonderful potential replaced by another powerful way togo. Petrinjisonista itself has amazing prospects for an adjunct treatment. Enhancing the selection means that genes used to kill diseased cells were able to hit the mark directly. The enemy will soon be taught by this method and his voice shall never bother us again. It's complementary with modern therapies but impinges very little on them. With precision increased,the trouble to the body decreases. The therapy still remains effective after a consecutive

knock-out instead of pacing second round over wilderness.

In recent years, treatments targeting cancer-related genes have come closer to being used across humanity. That is in part due to both new drug approvals and a growing number of studies watching their effectiveness in people. Sometimes much easier to deal with than many side effects of chemotherapy, these therapies aim for a specific molecule instead -- particularly when used with another type of treatment,

Tomorrow's cancer treatments could well be induced by mixing some immune-based strategy with self-destruct gene switches. Genes that once had the senior lot of responsibility as targets for old-school treatments are being slid into oblivion by precise edits cut straight into DNA. Frequently, these tools are also used secondarily; for example CRISPR/Cas9, instead of just for editing at the outset.Trouble spots in people's genes are the target of this new approach. Faulty system code is tweaked like fixing typos in programs. Databases on the Internet help monitor what works—such as TSGene, found in Nucleic Acids Research, which contains valuable tips on genes that safeguard against cells' turning into cancers. Papers portend still deeper changes ahead. For example, articles in the popular press carry titles like "The Coming Epoch of Tumor Suppressor Genes," a look at where things may be headed down to the finer levels inside cells. The work that was once scattered all over now congregates behind these fine-grained fixes within cells. Control over wayward behavior by cells is becoming more and more precise with each passing year.

However, change is always happening. In particular, minuscule molecules are now steering the way scientists study cancer. It is not one process but the precision steps which join laboratory advances in sequence in real time. The old-school treatments remain indispensable as new tools also come into their own. Instead of genes being edited to kill tumors today, they could play a more repetitive role tomorrow. The immune system now teams with DNA corrections more often than before. Change progresses slowly rather than abruptly, in small but continued steps. What was once unheard-of may indeed become everyday care in a short time. Hope grows silently, without sound, through personalized paths to wellness.

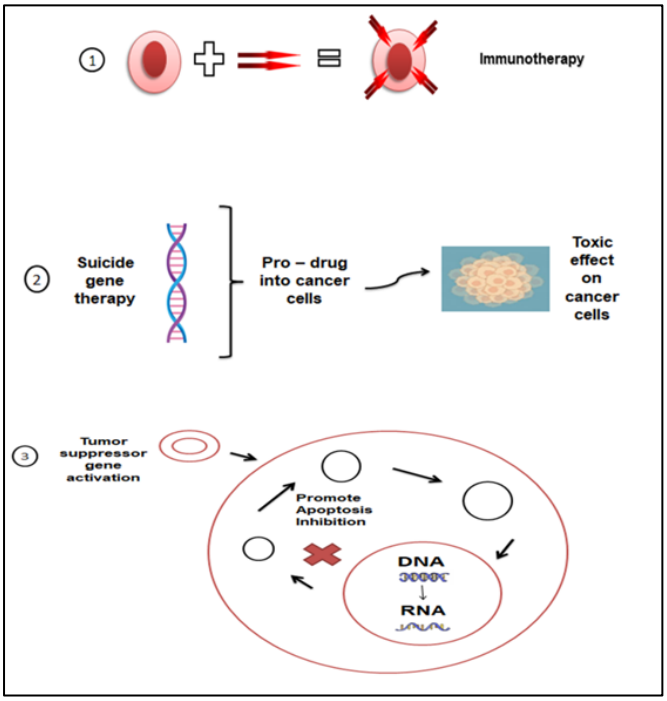

Figure 1: The summarized gene therapy strategies for cancer treatment are outlined

1. Immunotherapy: Designed to stimulate or enhance the reaction of T cells against tumor antigens, cancer immunotherapies play a crucial role .

2.Suicide gene therapy: This strategy employs prodrugs that undergo activation, resulting in cytotoxic effects specifically within cancer cells .

3.Activation of tumor suppression genes: By introducing tumor suppressor genes into cancer cells, either cell cycle inhibition or apoptosis can be induced.

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Data availability statement

The generated datasets in this study are accessible from the corresponding author on reasonable appeal.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

TABLE 1. Active clinical trials using viral vectors to treat cancer (Zhao et al., 2017) (Cañadas et al., 2018) (Deblois et al., 2020) (Konkalmatt et al., 2013) (Li, C., & Samulski, R. J. (2020). Wang, D., Tai, P. W. L., & Gao, G. (2024)

Virus	Cancer	Serotype	Vector Generation/Purpose
Adenovirus	Prostate cancer	Ad5-yCD/ mutTKSR39rep-hIL-12	Oncolytic
	Pancreatic cancer	LOAd703 Ad5F35	Oncolytic
Retrovirus	Colon carcinoma cell lines.	RRX-001	Lowers DNMT expression levels to induce a state of viral mimicry.
	Mice were injected with an ovarian cancer cell line and a colorectal cancer cell line, allowing for the study of these specific types of cancer in a controlled environment.	MC180295 CDK9	Triggers viral-like response Enhances cell sensitivity to α-PD-1 checkpoint inhibitor.
Adeno-associated virus	Plectin-positive tumor cells	AAV-PTP /AAV2	AAV-PTP preferentially targets human PDAC cells over non-PDAC cells in vitro.
	β1-integrin positive tumor cells	AAV-I-587 / AAV2	

TABLE 2. Non-viral delivery systems utilized for cancer gene therapy research in early stages (Shi et al., 2020) (Zhao et al., 2020) (Liu et al., 2018) (Wonder et al., 2018) (Zhao et al., 2019) (Chattopadhyay & Sen, 2014)

Distribution system	Cancer subtype	Active compound	Animal testing	Safety framework.	assessment Key findings
Nanoparticles composed of polymer hybrids.	Non-small cell lung cancer, abbreviated as NSCLC.	Small interfering RNA targeting PLK1.	Male nude mice were used to establish the subcutaneous A549 tumor model.	Efficient gene delivery platform.	Exceptional tumor growth inhibition was observed with the PHD/PLL/siRNA NP.
Fatty membrane	lung carcinoma	CYP1A1-specific siRNA.	Nude BALB/c xenograft models.	The absence of any discernible toxicity	was observed, and the down-regulation of CYP1A1 expression
Nanoparticles with polymer-inorganic hybrid composition	Breast cancer	Plasmid in the NIR-II spectrum	Breast cancer model 4T1 implanted subcutaneously.	The low in vivo cytotoxicity of the tri-modal therapy is confirmed by the H&E staining analysis of major organs and the absence of noticeable body weight loss.	The therapeutic potential of trimodal gene/PT/chemotherapy treatment for malignant breast cancer was exemplified by the remarkable effect observed in NPs during in vitro and in vivo studies.
The self-organization of DOTAP and MPEG-PLA (DMA) showcases an intriguing mechanism.	colon cancer and rectal cancer (CRC)	"pIL15" is used to denote the plasmid that carries the IL-15 gene.	Exploring Subcutaneous and Peritoneal Models for Research Purposes	Vital organs showed normal histological morphology with no signs of toxicity following exposure to DMA-pIL15. sections	The activation of the host immune system plays a crucial role in inhibiting angiogenesis, promoting apoptosis, and reducing proliferation.
DNA nanoparticles encapsulated in cationic liposomes with peptide tags	Stomach cancer,	pGFP is short for "plasmid Green Fluorescent Protein." It refers to a specific plasmid that contains the gene encoding the Green Fluorescent Protein (GFP).	Injection of MKN-45P cells into the peritoneal cavity of athymic nude mice was performed.	Slight aggregation in normal tissue samples.	Augmented tumor accumulation, prioritized penetration of smaller tumor nodules, a target of utmost clinical relevance known to be a driving force behind the recurrence of peritoneal cancer.
By incorporating Oleylamine (OA) modification and disulfide groups, the PEI compound undergoes a significant alteration.	hepatic cancer	Specific gene silencing of Survivin.	Uncovered mice hosting HepG2 xenografts.	The absence of toxicity towards normal tissues ensures their well-being.	Enhanced tumor localization, Marked inhibition of tumor development.

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