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REVIEW ARTICLE ON: GENE THERAPY IN VARIOUS CARDIOVASCULAR DISEASES

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ABSTRACT

Gene therapy is revolutionizing the treatment of genetic and acquired ailments by modifying or replacing defective ancestry. Utilizing both fervid and non-viral delivery systems, this approach addresses circumstances such as cancer, cardiovascular diseases, and genetic disorders. Advances in nanotechnology and ionizable drug delivery systems have enhanced nucleic acid transport, improving safety and efficiency. Innovative therapies show promise in restoring heart function, while therapeutic angiogenesis using Vascular endothelial growth factor, Platelet-Derived Growth Factor and Hepatocyte growth factor aims to improve blood vessel development. CRISPR-associated protein 9 gene editing is emerging as a precise tool for genetic modifications and it breakthroughs for β -thalassaemia, sensorion's gene therapy for hereditary deafness, and retroviral cytokine therapy for cancer treatment. Ex-vivo gene therapy has successfully corrected familial hypercholesterolaemia, demonstrating long-term cholesterol improvements. In neurology, low-intensity focused ultrasound has enabled blood brain barrier penetration, facilitating gene therapy for Parkinson's disease, while Adeno associated virus -based therapy has improved unit function. Regulatory milestones, such as the Food and Drug Administration approval of Vyjuvek, highlight the growing clinical acceptance of gene therapy. As analysis progresses, gene remedy continues to progress, offering transformative solutions across neurology, cardiology, oncology, and metabolic disarrays, paving the way for personalized medicine and improved patient outcomes.

I. INTRODUCTION

GENE Unit of inherent information that occupies a fixed site (locus) on a chromosome. Ailment achieve their effects by directing the synthesis of proteins. Genes are composed of deoxyribonucleic acid (DNA), A DNA molecule is composed of two chains of nucleotides that wind about

each other to resemble a twisted ladder. The sides of the ladder are made up of sugars and phosphates, and the rungs are formed by connected pairs of nitrogenous bases such as adenine (A), guanine (G), cytosine (C), and thymine (T). Gene concern is often used to describe a biochemical action, such as receptor ligand or DNA-binding transcription activator, and this commotion

can be influenced by the cellular spot of the protein. ^[1]

Gene remedy involves the launch of mint genes into cells, to reinstate or add gene expression, for the purpose of treating disease. Most recurrently a mutated gene is replaced with DNA encoding a utility copy. Alternatively, DNA encoding a therapeutic protein drug may be advance. Gene therapy works by Substituting altered genes, Anchoring transformed genes. Thus, increasing the blatantness of infected cells to the body's defence method. Putting it up, the endogenous genome is influenced. ^[2]

GENE DELIVERY SYSTEM:

Gene delivery is a key sector of drug delivery since it offers the possibility for direct and in some cases permanent adapt of cell and organ functions.

Nanoparticles seem to be the right choice for this impetus since they have similar sizes compared to undeniable viruses which are the natural but pathogenic gene delivery systems. Due to safety reasons, natural virus-based gene delivery systems have rather a slim prospect to be mainly used for gene delivery. ^[3] The viral gene delivery systems have discussed for the viral value based on DNA, RNA and oncolytic viral vectors. The non-viral gene delivery systems have also treated for the physicochemical approaches such as corporal methods and chemical methods. Several kinds of successful gene delivery systems have briefly discussed on the bases of the descent delivery systems such as cationic polymers, poly(L-lysine), polysaccharides, and poly(ethylenimine)s. The gene analysis has currently examined only for diseases that have no other cure techniques.

In order to get a successful design of gene delivery system, it must be required the

complete agreement of interaction between targeting cell and gene delivery system. The gene delivery systems consist of the three integrant such as a plasmid-based gene expression methodology that controls the concern of a gene within the targeting cell, a gene that encodes a specific therapeutic protein, and a gene delivery system that controls the delivery of the gene expression plasmid to specific location within the body. ^[4] Gene therapy is one of the most revolutionary medical technologies developed with DNA recombination enginery and gene cloning technology. It is a biomedical treatment method ground on changing human genetic material. For genetic diseases, gene therapy can directly repair or even replace the disease-causing genes at the molecular level, restoring defective protein. After decades of development, gene therapy has shown great potential in treating significant diseases caused by inherent defects and inherited abnormalities such as malignant tumours, acquired immunodeficiency syndrome, and cardiovascular diseases. Viral vectors are the most widely used delivery vehicles for gene therapy *in vivo* and *in vitro* due to their high transfection efficiency and stable transgene expression. With the expansion of nanotechnology, novel nanocarriers are gradually replacing viral vectors, materializing superior performance. The primary snag to be solved for gene therapy drugs is delivery, which is the bottleneck of gene therapy today. ^[5]

In particular, during the global outbreak of coronavirus disease 2019 (COVID-19), the successful evolution and entreaty of the mRNA jab highlighted the advantages, accelerated the development process, and predicted broad prospects of gene therapy. However, safe and systematic delivery systems, optimized design and preparation process forum commercial production

standards are still the main factors affecting its clinical application and industrial development for a long time. To overcome these difficulties, researchers have been making unremitting efforts. In 2016, scientists found an appropriate panacea by developing the chemical modification of nucleic acid monomers as a key gear to decode the problems of stability, off-target effects and immune provocation effects of nucleic acids. [6] The most critical contributor to this great breakthrough is the application of ionizable nanocarriers in the transfer of nucleic acids. With the emerging development of ionizable nanomaterials, such as ionizable lipids, ionizable phospholipids and ionizable polymer-lipids, the ionizable drug delivery systems (IDDSs) have been extensively investigated and become currently the most sophisticated carriers for the delivery of nucleic acid medications for protection, uptake, and performance, there has been a renovation in the viral carriers for them to be utilized in gene-specific remittance. [7] The norms can be said to be of two types based on their cell entrance, one that enters the cell's core and the other that stays in the cytoplasm to show action. These vectors or carriers are obtained from deoxyribonucleic acid or ribonucleic acid; non-viral nucleic acid carriers are used to haul genes to various cells and groups of cells. Non-viral vectors show properties like being easier to pick out, safe to stockpile, form to be copious, and can possibly be customarily given, showing finite defence by the body against them. The cellular internalization of exogenous nucleic acids (NA) requires efficient haulage vehicles to overcome their inherent pharmacokinetic drawbacks, e.g. electrostatic repulsions, enzymatic degradation, limited cellular uptake, brisk

clearance, etc., Nano-technological preferment have enabled the use of polymer-based nanostructured biomaterials as safe and potent gene delivery systems, in addition to fervid vector delivery methods. Among the plethora of polymeric nanoparticles (NPs), this review will provide a comprehensive and in-depth precis of the polyester-based nano vehicles, including poly (lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA) NPs, used to deliver a diversity of foreign NA, e.g. short interfering RNA (siRNA), messenger RNA (mRNA), and plasmid DNA (pDNA). Notable attention will be given to the pivotal role of nanotechnology in tackling emerging infections such as coronavirus disease 2019 (COVID-19): ground-breaking mRNA vaccines delivered by NPs are used worldwide to fight the pandemic, pushing the boundaries of descent therapy. [8] Gene therapy has been experiencing a breakthrough in recent years, targeting copious specific cell coterie in numerous therapeutic areas. However, most recent clinical studies maintain the use of traditional viral vector systems, which are challenging to manufacture cost-effectively at a commercial scale. Non-viral vectors have been a fast-paced research topic in gene delivery, such as polymers, lipids, inorganic particles, and combinations of contrasting types. Although non-viral vectors are low in their cytotoxicity, immunogenicity, and mutagenesis, beguiling more and more researchers to explore the auspicious delivery system, they do not carry ideal characteristics and have faced critical challenges, including gene transfer efficiency, specificity, gene expression term, and safety. [9]

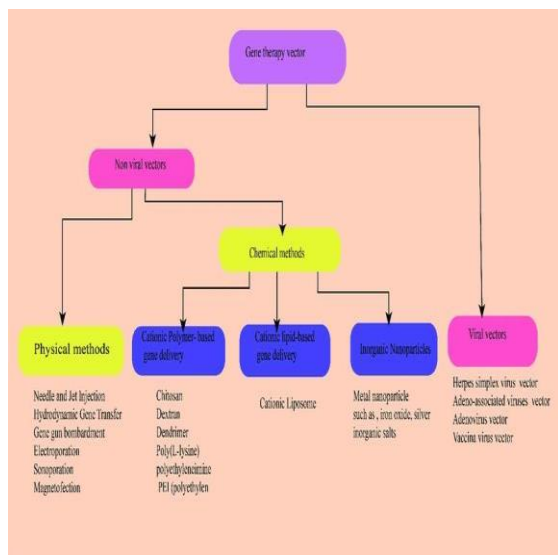


Fig (1)

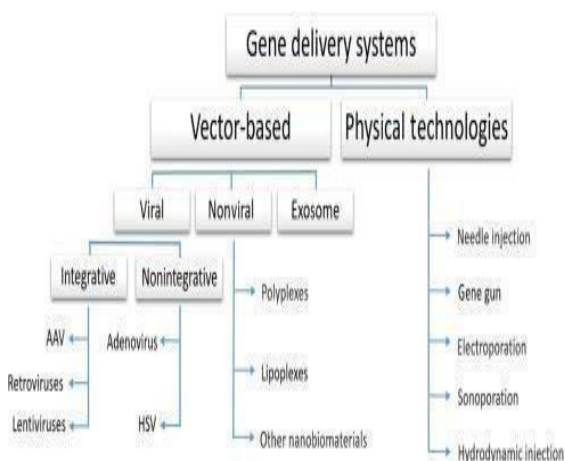


Fig (2)

Benefits

In the future, inbred therapies may be used to avert, treat, or cure certain inherited disorders, such as cystic fibrosis, alpha-1 antitrypsin deficiency, haemophilia, beta thalassemia, and sickle cell disease. They also may be worn to treat cancers or sepsis, including HIV. Genetic therapies that are currently approved by the FDA are available for mortals who have Leber congenital amaurosis, a rare inherited condition that leads to blindness. CAR T-cell therapy external link is FDA ratify for

mankind who have blood cancers, such as acute lymphoblastic leukaemia (ALL) external link and diffuse large B-cell lymphoma.

Risks

Genetic therapies hold oath to treat many diseases, but they are still new approaches to treatment and may have risks. Dormant risks could include certain essence of cancer, allergic reactions, or damage to organs or tissues if an injection is involved.^[10]

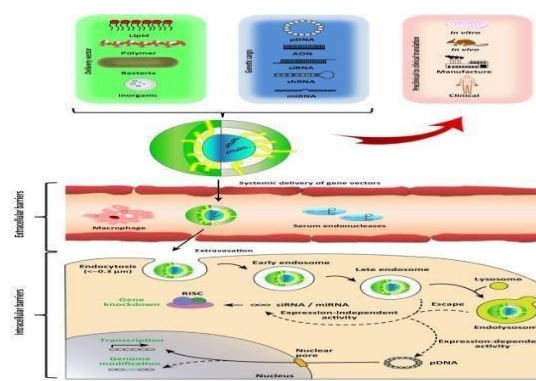


Fig (3)

II. TYPES OF GENE THERAPY IN CARDIOVASCULAR DISEASES:

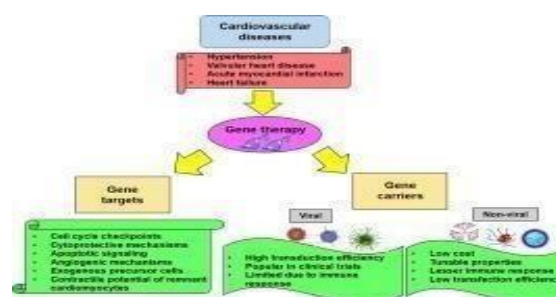


Fig (4)

In 2022, a group of researchers famed the promising results of an experimental gene therapy for heart failure. When oversee to

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pigs with induced cardiomyopathy, the treatment restored normal heart functioning with a single dose.

Heart failure is a life-threatening and highly pervasive syndrome characterized by the impairment of the heart's ability to pump blood. It affects more than 64 million people worldwide. But mounting affirmation suggests the gene therapy developed at

CVRTI (cardiovascular research and training institute) has the potential to reverse the condition, helping victim avoid cardiac convey and other invasive procedures. The treatment works by ramping up production of a protein called cBIN1 the levels of which fall precipitously when hearts fail. Normalizing cBIN1 levels, may "allow mangle heart muscles to heal".

When cBIN1(cardiac bridging integrator1 protein) is knocked out in engineered lab mice, the animals have defective microdomains, and are at heightened risk of arrhythmias. The team later reported that cBIN1 proteins in blood also bestow useful insights into cardiac health. They developed a diagnostic and prognostic biomarker.

The largest clinical suit before this, the CUPID2(calcium up- regulation by percutaneous) study, had targeted a gene called *SERCA2a*, which has roles in calcium cycling. Calcium helps to mesh the electrical impulses that drive heartbeats, and deficiencies in *SERCA2a* are associated with heart fiasco progression.

But during the CUPID2 study, *SERCA2a* gene therapy didn't revamp clinical outcomes. In the study, *SERCA2a* was delivered in a viral capsid with limited affinity for heart cells, which may have accord to the trial's outcomes, says

Matthew Killeen, CVRTI's senior advisor in translational probing and entrepreneurship.

SERCA2a is also one of many possible targets apropos to failing hearts. "From a clinical perspective, heart failure therapy should focus on the altered trafficking hubs of heart muscle cells, which are composed of manifold proteins important for heart contraction and relaxation.

cBIN1 offers important advantages over previous gene therapy targets. Where *SERCA2a* is

one of many molecular players that affect calcium signaling, cBIN1 is a master regulator that collects and organizes all the important proteins, including *SERCA2a*, that make a heart contract and relax. Gene therapy with cBIN1 "treats all forms of heart failure, both genetic and acquired". And the gene will be delivered with adeno-associated virus 9 (AAV9), a newer vector that has greater tropism for heart muscle cells. [\[11\]](#)

Intra myocardial delivery of genes and cells derived from bone marrow has been evaluated in several small studies of 'no-option' symptomatic patients with chronic ischemic coronary artery disease. Clinical experience with intra myocardial gene delivery is limited to genes encoding isoforms of vascular endothelial cell growth factor. Availability of novel viral vectors, such as the adeno-associated viruses, with an improved safety silhouette, long-term efficacy, and tissue selectivity has greatly contributed to advancements of cardiac gene therapy. [\[12\]](#)

Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris, Results from a phase II trial

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suggest that vascular endothelial growth factor (VEGF) gene transfer is safe and might produce an anti-ischemic effect in patients with chronic, stable myocardial ischemia. [\[13\]](#)

Gene remedy is proving likely to be a viable alternative to conventional therapies in coronary artery disease and heart failure. Phase 1 clinical trials indicate high levels of safety and clinical benefits with gene therapy using Angiogenic growth factors in myocardial ischaemia. Although gene therapy for heart debacle is still at the preclinical stage, experimental data indicate that therapeutic angiogenesis using short-term gene uttering may elicit functional improvement in affected individuals. [\[14\]](#)

Gene therapy has been extensively studied in peripheral and cardiac ischemia, heart and vein graft failure, and dyslipidaemia, but most clinical trials failed to show their efficacies despite good outcomes in preclinical studies. So far, 2 gene therapies for dyslipidaemia and one for critical limb ischemia in peripheral artery disease have been approved. In critical limb ischemia, gene therapy using proangiogenic factors has transpire as a novel therapeutic modality for promoting angiogenesis. Initial researches mainly focused on vascular endothelial growth factor, fibroblast growth factor, or hepatocyte ballooning factor. However, only a phase III clinical trial of the intramuscular injection of hepatocyte growth factor plasmid DNA has shown successful outcomes, and it was recently approved in Japan for treating patients with critical limb ischemia who have ulcers and for whom no alternative therapeutic values.

DNA vaccine is another promising modality of gene therapy. An antitumor vaccine suppressing angiogenesis through

the inhibition of proangiogenic factors and an

antihypertensive vaccine inhibiting the renin–angiotensin system are representative DNA (Deoxyribonucleic acid) vaccines. The advantage of DNA vaccine is its long-term effectiveness with a few vaccinations; however, the benefits and risks, such as adverse T-cell reaction against self-antigen or long-term side effects, of DNA vaccines should be carefully evaluated in PAD, the intramuscular injection of naked plasmid DNA encoding hepatocyte growth factor (HGF) gene (Collategene) was not long ago approved by the Japan Ministry of Health, Labour and Welfare for the treatment of CLI(critical limb ischemia) in patients with PAD(Peripheral Artery Disease) or Buerger disease who have ulcers and for whom no viable alternative therapeutic options, such as endovascular treatment or bypass graft surgery, are available. The therapeutic inhibition of angiotensinogen with antisense oligonucleotides, which are single-strand and DNA-like synthetic nucleic acids designed to hybridize to specific RNAs or pre-mRNAs, has been proven to have antihypertensive effects in rodent models, but the requirement of weekly or monthly dosing may be disadvantageous compared with DNA vaccine. However, the long-term effectiveness of DNA vaccine has a risk of longterm hypotension or adverse immunologic reaction to self-antigen.

Thus, the balance between the risks and benefits of vaccines should be carefully examined. Although gene therapy is also at an early phase, several clinical trials using angiogenic growth factor genes have recently been conducted in PAD (Peripheral Artery Disease), including successful and unsuccessful trials. The widely used

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method is to transfer a target gene to the skeletal muscle or myocardium in the ischemic region using plasmid DNA or viral vector, such as adenovirus and AAV (Adeno-associated virus vector) vector, although some studies delivered it through intra-arterial or intracoronary injections. The transfected muscles or cardiomyocytes secrete encoded proteins, which enhance angiogenesis.

FGF indicates fibroblast growth factor; HGF, hepatocyte growth factor; IC, intracoronary arterial injection; IMY, intramyocardial injection; and VEGF, vascular endothelial growth factor.

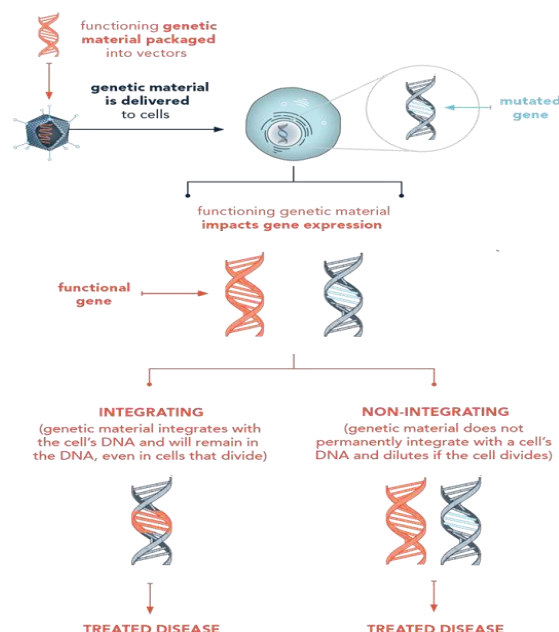


Fig (5)

Table 1. Clinical Trials of Gene Therapy in Peripheral Artery Disease

Trial or Author Name	Vector	Route	Phase	Enrolment	Outcomes
Baumgartner <i>et al</i>	phVEGF165	IA	I	9	Tolerated
Mäkinen <i>et al</i>	phVEGF165	IM	II	54	Tolerated, increased vascularity
RAVE	AdVEGF121	IM	II	95	improvement in exercise performance or QOL
Deev <i>et al</i>	AdVEGF121	IM	IIb/III	100	increase in PWD, ABI, and BFV
Comerota <i>et al</i>	phFGF-1	IM	I	51	Tolerated
TALISMAN	phFGF-1	IM	II	125	Reduction in the amputation rate
TAMARIS	phFGF-1	IM	III	525	improvement in QOL or ABI and no reduction in the

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					amputation rate or death
Morishita <i>et al</i>	phHGF	IM	I/IIa	22	Tolerated
HGF-STAT	phHGF	IM	I/IIa	104	Improvement in TcPO ₂
Powell <i>et al</i>	phHGF	IM	II	27	Decreased rest pain and a tendency of complete ulcer healing
Shigematsu <i>et al</i>	phHGF	IM	III	40	Improvement in rest pain and ABI and reduction in ulcer size
Henry <i>et al</i>	phcHGFdHGF	IM	I	12	Decreased VAS score
Kibbe <i>et al</i>	phcHGFdHGF	IM	II	52	Complete ulcer healing and improved TcPO ₂

ABI indicates ankle–brachial index; BFV, blood flow velocity; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IA, intra-arterial injection; IM, intramuscular injection; PWD, pain-free walking distance; TcPO₂, transcutaneous oximetry; VAS, visual analog scale; and VEGF, vascular endothelial growth factor.

Table 2. Clinical Trials of Gene Therapy in Coronary Artery Disease

Trial Name	Vector	Route Phase	Enrolment	Outcomes
AdVEGF121	IMY	I	21	Tolerated
AdVEGF121	IMY	I/II	17	Safe but no effects in exercise capacity and perfusion

AdVEGF121	IMY	II	67	Improvement in exercise time to 1-mm ST-segment depression, total exercise duration
phVEGF121	IMY	II	80	Improved regional wall motion
AdVEGF165	IC	II	103	Safe and increased perfusion but no differences in the restenosis rate or minimal lumen diameter
phVEGF165, GCSF	IMY	II	48	Safe but no effects
phVEGF165	IMY	II	93	No improvement in perfusion
AdHGF	IC	I	18	Safe
AdVEGF-D ^{dNdC}	IMY	I	30	Safe and well-tolerated, increased perfusion
AdFGF-4	IC	III	532	No difference but genderspecific effects in the exercise tolerance test

The concept of vaccine for hypertension was first introduced by the reported inhibition of renin by a peptide vaccine. However, the development was stopped due to the adverse autoimmune responses in the kidneys in animal models. An Ang I vaccine (PMD3117) was also found to reduce the blood pressure (BP) in rat and mouse models; however, a clinical study did not show the effectiveness of the vaccine in reducing the BP. It was suggested that the feedback pathway between Ang II (Angiotensin II) and renin was responsible for its failure. An Ang II vaccine (AngQb-Cyt006) was also found to reduce the BP to a similar level as ramipril by producing anti-Ang II antibodies in rodents. [\[15\]](#)

Human gene therapy has undergone rapid development since Theodore Friedmann and Richard Roblin published the first accounts on its potential and challenges in 1972. Since then, scientists have strived to develop a safe, long-lasting, and effective method for modifying and manipulating human cells to achieve therapeutic effects for various heritable diseases in the field of cardiology, some pioneering studies of gene therapy were first performed in 1990, in which a murine retrovirus was used to deliver a recombinant betagalactosidase gene into the wall of an arterial segment in 1996, Dr Jeffrey Isner used a plasmid containing vascular endothelial growth factors, which was suspended in a hydrogel polymer and coated onto an angioplasty

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balloon that was applied to the distal popliteal artery to induce angiogenesis.

In 2007, the first gene therapy clinical trial for patients with heart failure aimed to determine the effects of delivering a gene expressing SERCA2a through an AAV to improve calcium handling within cardiomyocytes where the Ca^{2+} ATPase was downregulated. Unfortunately, the treatment failed to improve clinical outcomes. [16]

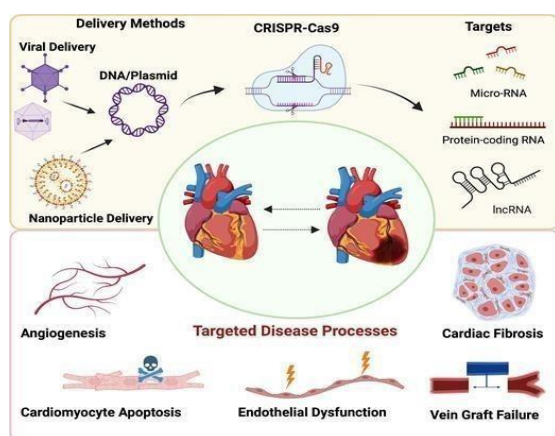


Fig (6)

Gene therapy-mediated therapeutic angiogenesis could help those who have not gained sufficient symptom relief with traditional treatment methods. Especially patients with severe coronary artery disease and heart failure could benefit from gene therapy. Some clinical trials have reported improved myocardial perfusion and symptom relief in CAD patients, but few trials have come up with disappointing negative results. However, promising new methods for transducing the cells, such as retrograde delivery and cardiac-specific AAV vectors, hold great promise for myocardial gene therapy. [17]

Platelet-derived growth factor (PDGF) family members, PDGF-A, PDGF-B, PDGF-C and PDGF-D, have also been

shown to have angiogenic properties. Since they most likely act as vascular stabilizers, they have also been studied in combination with endothelial cell activators, such as VEGF-A, HIF-1 α or FGF-2.

Hypoxia-inducible factors, HIF-1 α and HIF-2 α , have been shown to promote angiogenesis and myocardial perfusion without causing oedema. In a pig model of chronic myocardial ischaemia, HIF-1 α has been shown to promote small and large vessel growth, improving myocardial perfusion and function of the hibernating myocardium.

Hepatocyte growth factor (HGF) is downregulated in myocardial ischaemia, and HGF gene transfers have been shown to induce blood vessel growth in rat ischaemic myocardium. HGF's ability to rehabilitate post-infarcted myocardial function has also been demonstrated in swine. Combination of two HGF isoforms, HGF-723 and HGF-728, has been shown to cause more potent effects than either isoform alone.

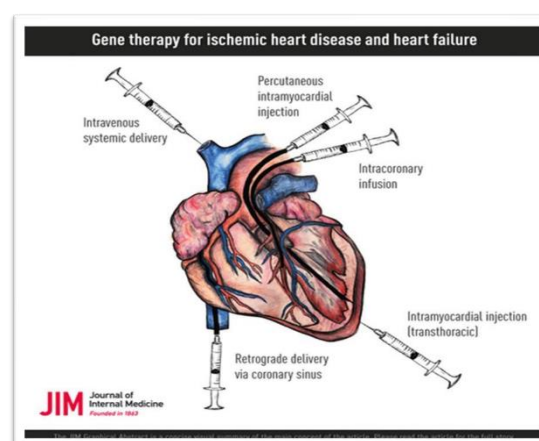


Fig (7)

In brief, rAAV gene therapies provide the new opportunities for CVD patients, targeted therapy for refractory diseases is

likely to have a far-reaching impact, which also implies that the optimization of viral capsid protein sequences and promoters will be a promising research direction in future preclinical trials. These strategies may better reap the potential benefits of rAAV gene therapy and more adequately address the distress and troubles of CVD patients. Researchers from the University of Texas Southwestern Medical Centre believe a new CRISPR-Cas9 gene editing therapy can both help treat heart disease and repair damaged tissue immediately after a heart attack via a mouse model. Gene editing provides scientists with a way to alter a person's DNA. ^[18]

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 Trusted Source is one of the technologies used in gene editing. By using this technology, scientists can "turn on and off" specific genes in a person's cells. They can also "cut out" or add to cellular DNA. Using a mouse model, Dr. Olson and his team studied their new CRISPR-Cas9 gene editing therapy. In order for the components of the gene editing system to reach the heart, they were packaged into a viral delivery system that targets the heart of mice and large mammals.

"CRISPR-Cas9 gene editing. The guide RNA corresponds to a specific region in the genome and acts to bring the base editor in close contact to a specific gene. The base editor precisely modifies the gene. In our approach, we used a specific guide RNA to target the base editor to the CaMKII δ gene. The base editor modified this gene to prevent chronic over activation of the CaMKII δ protein that is an inducer of cardiac disease. ^[19] Cardiovascular diseases remain a large global health problem. Although several conventional

small-molecule treatments are available for common cardiovascular problems, gene therapy is a potential treatment option for acquired and inherited cardiovascular diseases that remain with unmet clinical needs. Among potential targets for gene therapy are severe cardiac and peripheral ischemia, heart failure, vein graft failure, and some forms of dyslipidaemia. The first approved gene therapy in the Western world was indicated for lipoprotein lipase deficiency, which causes high plasma triglyceride levels. With improved gene delivery methods and more efficient vectors, together with interventional transgene strategies aligned for a better understanding of the pathophysiology of these diseases, new approaches are currently tested for safety and efficacy in clinical trials. ^[20]

Novartis Gene Therapies has developed a reproducible manufacturing process. The AAV platform is robust, which allows for flexibility in downstream purification techniques. The optimal AAV serotype can be chosen for different clinical applications in the future. A triple transfection of the cells produces adeno-associated viruses, or AAV vectors, which serve as vehicles to get therapeutic genetic material into a patient's cells. These are known as transgenes and are specifically designed to replace the function of a gene that patients need. Novartis Gene Therapies efficiently produces a supply of gene therapy. Redundant raw material suppliers are used, and operations run 24/7 and 365 days a year. ^[21]

Revolutionary Strategies for Cardiovascular Repair:

Gene therapies are gaining significant attention for their potential in treating vascular diseases, such as ex vivo gene

therapy for bypass grafts. They also hold promise for boosting the growth of new blood vessels in the heart and other body parts, known as angiogenesis. Additionally, gene therapy could aid in regenerating and strengthening heart muscle cells after a heart attack, particularly in patients with heart failure. Furthermore, researchers are exploring gene editing techniques to address genetic abnormalities that affect the heart. These areas of focus highlight the wide-ranging possibilities of gene therapies in improving cardiovascular health and combating cardiac conditions. Coronary bypass surgery improves blood supply to the heart muscle in people with coronary heart disease. However, vein grafts used in the procedure often fail over time due to the narrowing caused by a complex pathological remodelling of the Graft. ^[22]

It is possible to artificially induce angiogenesis through the transfection of target tissues via viral or non-viral vectors, using encoding genes like VEGF and FGF, generally expressed during natural angiogenesis. Modified mRNA (modRNA) and naked plasmid vectors are easy to produce, eliciting low cytotoxic effects on target tissues, but both have issues with the degree of gene expression, duration of gene expression, or even both. Viral vectors provide much more efficient gene transfer and expression, but these do pose the risk of triggering moderate to severe immune responses. ^[23]

GENE THERAPY IN OTHER DISEASES

B-THALASSAEMIA

A human tRNA gene was converted to an amber suppressor by site-specific

mutagenesis of the anticodon. The mutated tRNA gene directed synthesis of a tRNA that suppressed the UAG amber nonsense mutation in β^0 thalassaemia mRNA. Such genes may be used to detect other nonsense mutations in mammalian cells and may provide an approach to gene therapy for β^0 thalassaemia due to nonsense mutations. ^[24]

β -thalassaemia is one of the most common monogenic disorders. The most common manifestations are similar to those of other severe β -thalassaemia, including anaemia, jaundice, hepatosplenomegaly, growth retardation, and thalassaemic facies. At present, a standard treatment for most thalassaemia patients is regular blood transfusions, with side effects such as iron overload and allo-immunisation. The only curative treatment is bone marrow transplantation, which is limited by the availability of human leukocyte antigen (HLA) matched stem cell donors. nic diseases with defects in the synthesis of β -globin, a component of adult haemoglobin, which is responsible for the oxygen delivery function of red blood cells. Over 300 mutations in and around the beta-globin gene have been identified as causes of β thalassaemia¹. HbE/ β -thalassaemia, a severe disease, affects over a million people worldwide, particularly in Asia in this study, we report a highly efficient genetic correction of HbE mutation in the SiBBE cells using the CRISPR/Cas9 system. The HbE-corrected clones restored β -globin production with reduced levels of HbE upon erythroid differentiation. Our approach provides a sustainable supply of corrected erythroid cells and represents a valuable model for validating the therapeutic efficacy of gene editing systems. ^[25]

Bilateral administration of human *OTOF* (*Otoferlin*) gene therapy appears safe, and preliminary data suggest that it could effectively treat a rare form of hereditary hearing loss by enhancing speech perception, sound source localization and overall auditory experience.^[26]

Gene therapy is a promising approach for hereditary deafness. We recently showed that unilateral AAV1-hOTOF gene therapy with dual adeno-associated virus (AAV) serotype 1 carrying human *OTOF* transgene is safe and associated with functional improvements in patients with autosomal recessive deafness (DFNB9). The protocol was subsequently amended and approved to allow bilateral gene therapy administration. Here we report an interim analysis of the single-arm trial investigating the safety and efficacy of binaural therapy in five paediatric patients with DFNB9. The speech perception and the capability of sound source localization were restored in all five patients. These results provide preliminary insights on the safety and efficacy of binaural AAV gene therapy for hereditary deafness. The trial is ongoing with longer follow-up to confirm the safety and efficacy findings.^[27]

Several establishments of micro metastasis, delivery of retroviral producer cells by the same route with a vector containing the *Escherichia coli* β -galactosidase (*lacZ*) gene demonstrated selective *in vivo* gene transfer to tumour deposits. By this approach, two retroviral producer cell lines encoding cytokines (IL-4 and IL-2) directed tumoricidal inflammatory responses to established metastases. Cytokine gene targeting inhibited metastasis formation and caused significant overall reduction in tumour burden. These results suggest a novel

therapeutic approach for the treatment of disseminated cancer.^[28]

An *ex vivo* approach to gene therapy for familial hypercholesterolaemia (FH) has been developed in which the recipient is transplanted with autologous hepatocytes that are genetically corrected with recombinant retroviruses carrying the LDL receptor. We describe the treatment of a 29 years old woman with homozygous FH by *ex vivo* gene therapy directed to liver. She tolerated the procedures well and *in situ* hybridization of liver tissue four months after therapy revealed evidence for engraftment of transgene expressing cells. The patient's LDL/HDL ratio declined from 10–13 before gene therapy to 5–8 following gene therapy, improvements which have remained stable for the duration of the treatment (18 months). This represents the first report of human gene therapy in which stable correction of a therapeutic endpoint has been achieved.^[29]

MYOCARDIAL REGENERATION

A substantial need exists for new treatments to prevent and treat cardiac dysfunction. In the 1990s, there was great hope for gene therapy in this regard. Since that time, the focus has switched to cell therapy—in particular, therapy—with the aim of inducing myocardial regeneration. Individually, gene and cell therapies still have substantial promise. Several gene products are currently being studied, including growth factors and chemokines that can modulate the survival and function of cardiac myocytes following an ischemic event and influence remodelling of the left ventricle. However, several issues remain, including the optimization and characterization of cell types, selection of vectors for gene transfer, and identification of appropriate strategies for delivery. Here,

we review the potential and need for cell-based gene therapy for the prevention and treatment of cardiac dysfunction and attempt to discuss the unresolved issues.^[30]

HYPOTHYROIDISM

The parathyroid hormone (PTH) (1-34) gene was inserted into a pcDNA3 promoter and *E. coli* competent cells were used to amplify the cDNA. C3H/10T1/2 stem cells were transfected with PTH (1-34) cDNA using Lipofectamine reagents. After G418 treatment live cells at a density of 4×10^7 were loaded onto a TheraCyt unit. Immunohistochemical staining and RTPCR were performed to find PTH (1-34)-positive cells and to detect PTH (1-34) mRNA. Serum calcium and PTH (1-34) levels were significantly higher in group A than in group B or C. PTH (1-34)-positive cells were found in the TheraCyt group 4 months after implantation. PTH (1-34) mRNA was detected in stem cells 48 hr after transfection and also in stem cells after transfection and 72 hr after G418 treatment. Implantation of the TheraCyt capsulated stem cells, which were transfected with PTH (1-34) cDNA can treat hypoparathyroidism.^[31]

EPILEPSY

Focal cortical dysplasias (FCD) are a common cause of drug-resistant epilepsy. A new study published in *Brain* shows that overexpression of potassium channels through gene therapy has an antiseizure effect in a mouse model of FCD. The therapy could be suitable for clinical translation to treat epilepsy in people with FCD. The researchers generated the FCD mouse model by in utero electroporation of frontal lobe neural progenitors with a plasmid carrying a constitutively active Ras homologue enriched in brain (*RHEB^{CA}*) gene. This model was

previously reported to recapitulate features of FCD type II, which is often caused by abnormal signalling of the mammalian target of rapamycin 1 pathway, downstream of RHEB.^[32]

PARKINSON DISEASE: Delivery of gene therapies across the blood–brain barrier (BBB) is a major challenge. In a new study, researchers used low-intensity focused ultrasound to temporarily open the BBB at specific locations in non-human primates and in individuals with Parkinson disease. The process was generally well tolerated and did not result in abnormalities detectable with MRI. In the non-human primates, the researchers administered a green fluorescent protein (GFP) expressing viral vector intravenously following the ultrasound. GFP was detected post mortem in targeted brain regions, indicating that the approach could facilitate delivery of gene therapies.^[33]

Parkinson's disease is a devastating neurodegenerative disorder, characterized by loss of dopaminergic neurons in the midbrain. Treatments such as dopamine receptor agonists or the dopamine precursor levodopa can alleviate some symptoms but this strategy lacks specificity as dopamine receptors are broadly distributed in the brain. Chen et al. developed a gene therapy approach that specifically targets striatal D1 medium spiny neurons (MSNs), which are affected in individuals with Parkinson's disease. The method uses retrograde adeno associated virus (AAV8R12) as a delivery vector, promoter sequences derived from the *GPR88* gene that are active in D1-MSNs, and a chemo genetic effector that ensures D1MSN activation after systemic ligand infusion. Application of this strategy to mouse and primate models of

Parkinson's disease was able to rescue locomotion, tremor and other motor skill problems. Although the safety and efficacy of this strategy remains to be tested in human patients and requires further development and assessment (such as the effect on non-motor symptoms), this work indicates that cell-type-specific targeting tools represent an exciting potential therapeutic avenue.^[34]

WOUND HEALING: The US Food and Drug Administration has approved the first treatment for the rare blistering skin disorder dystrophic epidermolysis bullosa. The therapy, V yjuvek (beremagene geperpavec), developed by Krystal Biotech, is also the first to use the herpes simplex virus type 1 (HSV-1) as a gene therapy vector. Patients with dystrophic epidermolysis bullosa experience painful and persistent skin wounds and rarely survive beyond age 30. The disabling skin wounds arise from mutations in the collagen gene *COL7A1*, defects in which cause loss of dermal and epidermal cohesion and lead to blistering, scarring and high rates of skin cancer. Vyjuvek replaces the mutated gene with two normal copies of the collagen type VII $\alpha 1$ chain (*COL7A1*) in keratinocytes and fibroblasts. This enables collagen type VII to form fibrils that anchor the epidermis and dermis together, leading to wound healing.^[35]

III. CONCLUSION

Gene therapy has emerged as a groundbreaking approach, reshaping vogueish medicine by providing innovative panacea for a broad range of genetic and acquired diseases. From targeted treatments for cancer, cardiovascular disorders, and metabolic conditions to CRISPR-Cas9 gene editing and stem cell

modifications, advancements in genetic engineering are paving the way for idiosyncratic medicine. The upshot of nanotechnology and ionizable drug delivery systems has further improved welfare, lethal, and coherence, remit key challenges in gene delivery.

While optimization of gene therapy remains an ongoing pursuit, therapeutic angiogenesis, blood-brain barrier penetration techniques, and AAV-based targeted therapies have expanded its potential applications, particularly for neurological and cardiovascular conditions. The FDA approval of Vyjuvek marks a significant milestone, reinforcing gene therapy's increasing aloof acceptance. As researchers rarefy freightage mechanisms and enhance therapeutic efficacy, gene therapy continues to evolve, offering transformative ministrations and expectancy for patients with previously untreatable conditions. With persistent innovation, descent therapy is poised to revolutionize disease directorate and usher in a new era of precision medicine.

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