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REVIEW

Gene Therapy: A Double-Edged Modality with Few Propitious Targets against Cardiovascular Disorders like Heart Failure, Hypertension and Infarction

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ABSTRACT

Cardiovascular diseases like that of congestive heart failure, hypertension and infarction have reached epidemic proportions, and even though many novel pharmacological formulations and devices have improved survival, a real cure is yet to be found. After extensive research and trials (both preclinical and clinical), gene therapy is seen as an important upcoming tool against cardiovascular disorders. Advancements in the vector technology and in the molecular understanding of various diseases like that of heart failure, ischaemic heart diseases and even polygenic diseases like hypertension have opened doors to a new era of cure. With the improved understanding of the pharmacodynamics and the pharmacokinetics of gene transfer, there is a substantial growth being seen in the treatment of cardiovascular disorders using gene therapy with an increasing number of potential targets (genes), especially in the post-human genome era. Few potential targets have been identified for gene therapy from various molecular pathways, which along with the newly developing delivery systems will accelerate and strengthen the fight against heart failure and ischaemia (therapeutic angiogenesis), in which at present most of the clinical trials are going on. But at the same time, all the potential adverse effects and safety concerns arising with these new modalities should also be assessed before enforcement.

Key words: Gene therapy/transfer, genetic targets, delivery systems

Introduction

Gene therapy is a therapeutic modality, which involves replacement of altered or non-functional gene with a healthy one. Indians have a genetic disadvantage when it comes to being affected by coronary disorders, because as an ethnic race, it tends to have a high lipoprotein(s) content compared to other races in the Asian region like that of Chinese[1]. At present, the situation can be compared as a coronary epidemic, and the fact that in the past 30 years the average age of first heart attack in India decreased by 20 years (out of which men dominated the figures with over 50% of them being below 55 years and 25% being below 40 years) supports the statement [1]. Heart being a localised organ makes it a potential target for surgical (or with the help of catheters) local in vivo gene delivery. The cardiomyocytes being

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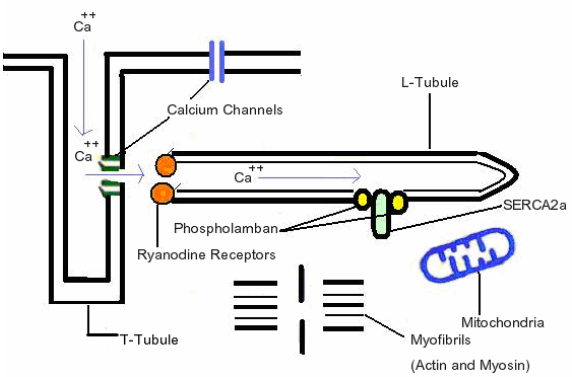
post-mitotic cells require a prolonged and efficient gene expression, which is mainly met by vectors like adenoviruses, adeno-associated viruses and lentiviruses. The molecular pathways are again essential to identify the targets for the gene therapy for heart failure and also form the backbone for planning or bringing gene therapy into clinical practice.

Targets for Gene Therapy for Heart Failure

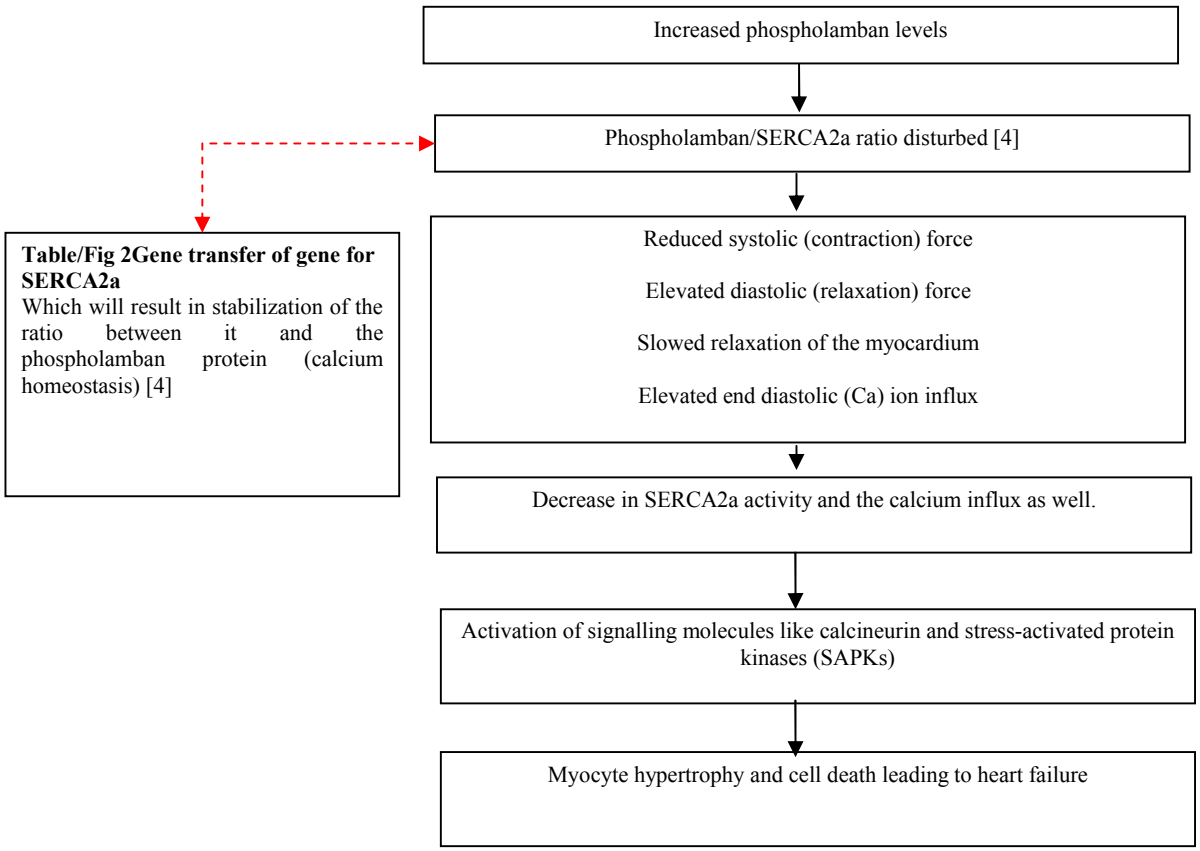
Target 1 – calcium channels (levels of calcium in the body)

Normally when an excitation impulse reaches the sarcoplasmic reticulum (SR) through the transverse (T) tubule, the voltage-gated calcium channels, longitudinal (L) type, open and allow small amount of calcium influx, which contributes to the calcium released by the SR through the Ryanodine receptors, which

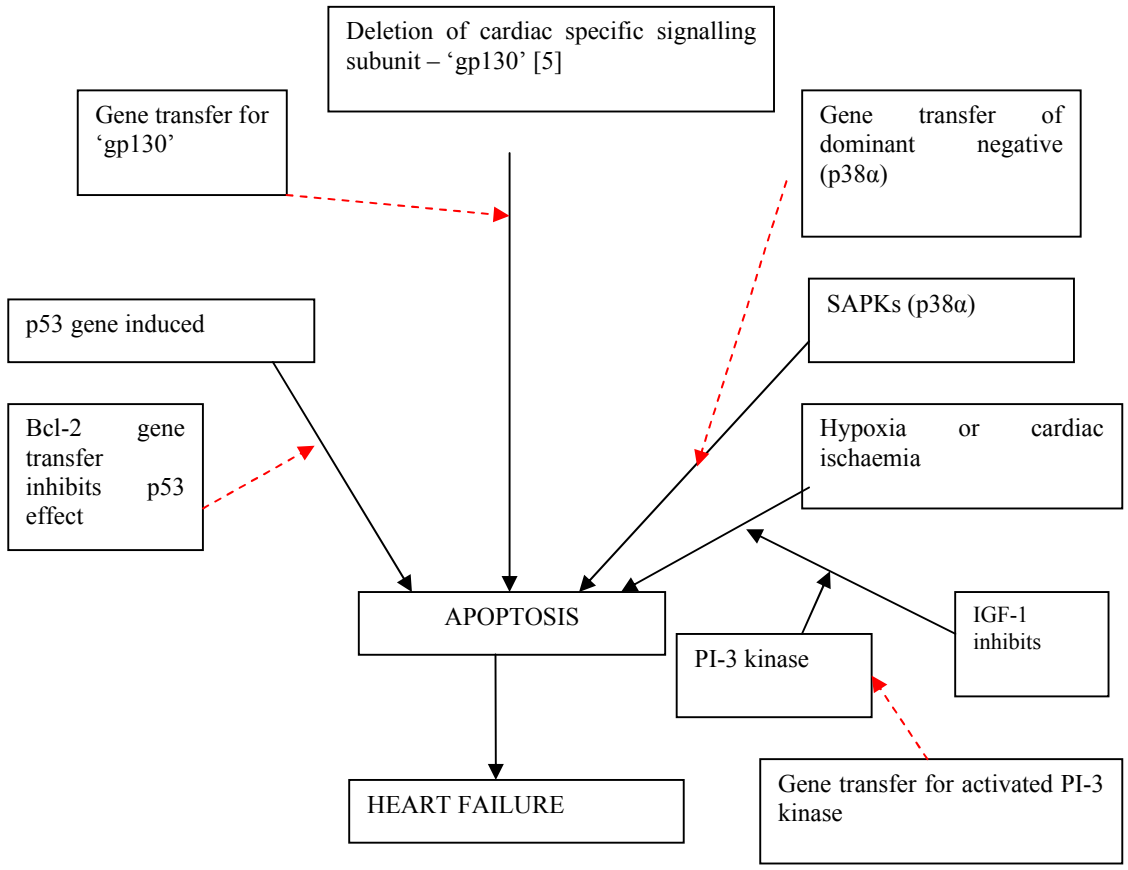


Table/Fig 1 Shows functional sarcoplasmic reticulum and the location of Ryanodine receptors, phospholamban and SERCA2a units.

activates the myofilaments causing contraction of the myocardial muscle (Sliding Filament theory) [2]. During relaxation, the SR re-accumulates the calcium back through the sarco-endoplasmic reticulum calcium ATPase pump



Table/Fig 2Gene transfer of gene for SERCA2a
Which will result in stabilization of the ratio between it and the phospholamban protein (calcium homeostasis) [4]



Table/Fig 3: Shows the various molecular pathways that lead to apoptosis of the cardiac myocytes, which in turn cause heart failure. Various points in these pathways are potential targets for gene therapy against it. Red (broken) arrows show these targets [2].

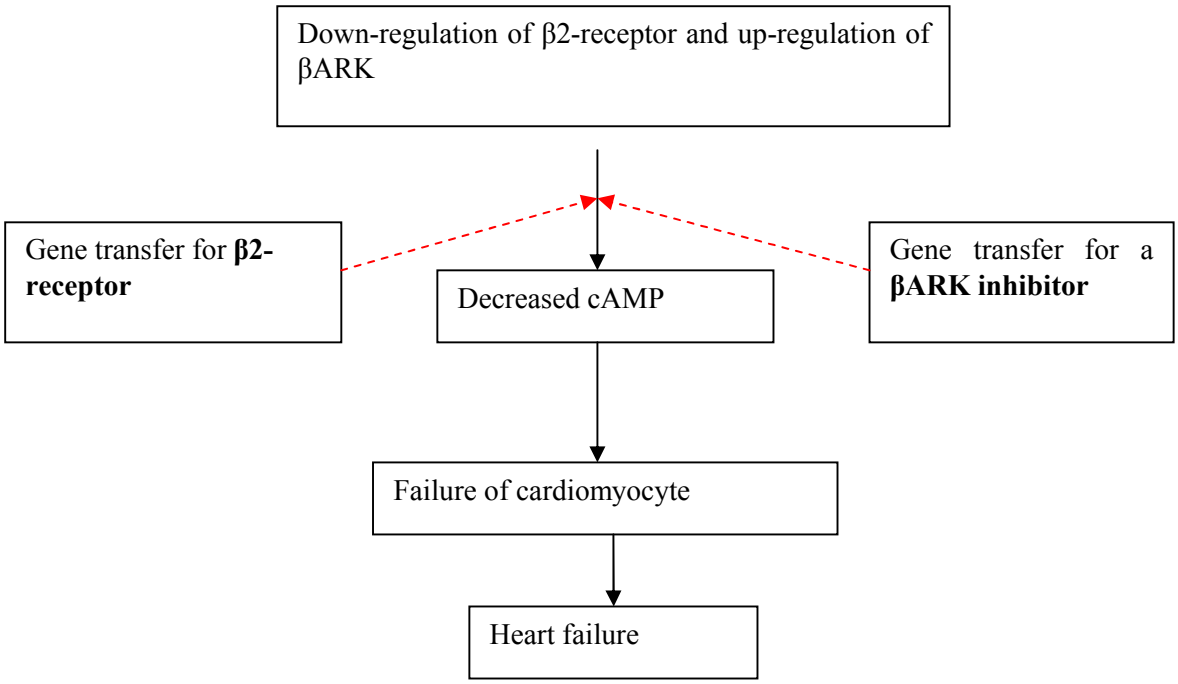
(SERCA2a), and then this calcium is pumped out extracellularly by the sarcolemmal Na/Ca exchanger. In humans ≈75% of the Calcium is removed by the SERCA2a, while the remaining removed by the Na/Ca exchanger [3]. This action of SERCA2a is inhibited by phospholamban protein (unphosphorylated state), while the phosphorylated state (cAMP and Ca-Calmodulin–dependent protein kinase) reverses this inhibition [4][Table/Fig 2]. The architecture of a functional sarco-endoplasmic reticulum with the location of the key players is shown in [Table/Fig 1].

Target 2 – apoptosis

In [Table/Fig 3], various signalling cascades are shown, which contribute to the mechanism of apoptosis (programmed cell death) of the cardiac myocytes, which in turn causes heart failure. These cascades include mitogen or stress-activated phospho kinases (SAPK) like p38, the *p53* gene, and certain growth factors like insulin growth factor (IGF) 1, which inhibits other contributors like ischaemia and hypoxia.

Target 3 – β2 adrenergic receptors

There is quite a difference in the consequences of β2 adrenergic receptor (AR) stimulation and the β1AR formas, the basis of it being used as a target against failing heart [Table/Fig 4]. Stimulation of the β1AR has an apoptotic arrythmogenic potential, whereas the β2AR signalling pathway is devoid of these negative effects [2]. Therefore, using gene transfer for β2AR and βARK inhibitor will restore the cAMP levels, resulting in increased functionality of the cardiomyocytes.

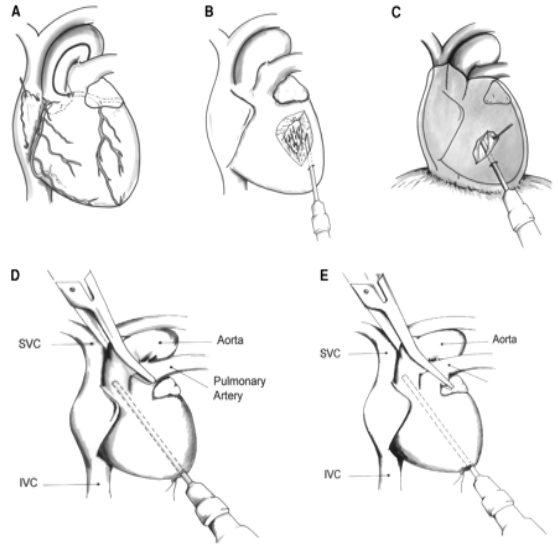


Table/Fig 4: Shows the targets for heart failure (*eight adrenergic receptors*) [2] (red broken arrows depict the gene targets).

Delivery of the gene therapy for heart failure

The vector of choice for this purpose is none other than recombinant adenovirus (including the helper dependent), which has a range of carrying capacity and is capable of transducing the non-dividing cells as well. But the immune response which it is capable of provoking is the main reason for the search of a better vector. Since heart is a localised organ, various mechanical methods have been tried to deliver the virus locally into the heart muscle/myocardium. Using the epicardial approach, recombinant adenoviruses were injected into the ventricular wall. Though the results showed high gene expression, but this effect was localised to the injected area (i.e. some of the area around the point of injection). Also there was even damage caused to the myocardial fibres by the needle. Then intra-coronary catheterisation was tried, which resulted in expression in areas supplied by the coronaries. Intra-myocardial delivery using the intraventricular approach with retro-perfusion of the coronary veins also resulted in localised gene expression [6]. In rodents, the pericardial approach was tried, which again showed the expression only in the pericardial layers, but the effect was much better with the addition of collagenase and hyaluronidase [4]. All the above-mentioned methods were not useful as effective gene therapies for heart failure, as gene expression throughout the whole heart (myocardium) is required. Donahue et al. [7] identified few conditions that increase the efficiency of gene transfer and expression in explanted hearts using intra-coronary perfusion. Conditions included use of crystalloid solution instead of whole blood, temperature, high coronary perfusion, viral concentration and exposure time. To achieve this gene transfer in vivo, a catheter was introduced through the apex of the rodent's heart and pushed beyond the aortic valve; then a high concentration of recombinant adenovirus was injected through the catheter [Table/Fig 5], with the clamping of the aorta and the pulmonary artery for 10–40 seconds distally to the catheter. This resulted in homogeneous gene expression in both the ventricles. Maurice et al. [5] used the same technique for expression of β-adrenergic receptors, but they instead clamped only the aorta as shown in [Table/Fig 5]. And moreover, their results basically showed mainly epicardial gene expression, thus highlighting the importance of clamping of both the vessels,

which restrict the increase in left ventricular end-diastolic pressure resulting in more efficient transfection of the endocardium by the adenovirus. Thus, it is now known that optimisation of conditions not only is important in ex vivo gene delivery but also plays equally important role in in vivo gene delivery, specially local in vivo gene delivery.



Table/Fig 5: Shows different mechanical methods under trial for localised in vivo gene delivery for the gene therapy for heart failure. (A) Coronary perfusion. (B) Intramyocardial injection. (C) Pericardial injection. (D) Aorta clamping. (E) Cross clamping of both aorta and pulmonary artery. IVC – inferior vena cava, SVC – superior vena cava. (Taken from Ref. [2].)

Hypertension

Background

Hypertension is one of the most common cardiovascular disorders that result in death, in the developed nations. It causes complications like stroke, myocardial infarction, atherosclerosis, and end-stage renal failure, which in turn contributes to the mortality rate due to it. Systemic hypertension is a multifactorial disorder and its polygenic basis has resulted in doubts of the gene therapy for it being successful at all or not. Primary pulmonary hypertension is a progressive disorder due to intimal hyperplasia and in situ thrombosis, resulting in increased pulmonary circulation resistance, and which in turn results in right-sided heart failure. The biggest advantage and the need for gene therapy for hypertension are because of the fact that the present-day drug therapy only suppresses the disorder and its effects and that also only if there is patient compliance (main reason for its failure), i.e. the patient takes these drugs regularly as prescribed. And since it is a long-term therapy, there are chances of drug resistance and adverse effects of the drugs (as they are non-specific).

Targets for Gene Therapy for Hypertension

Target 1 – renin–angiotensin system (RAS)

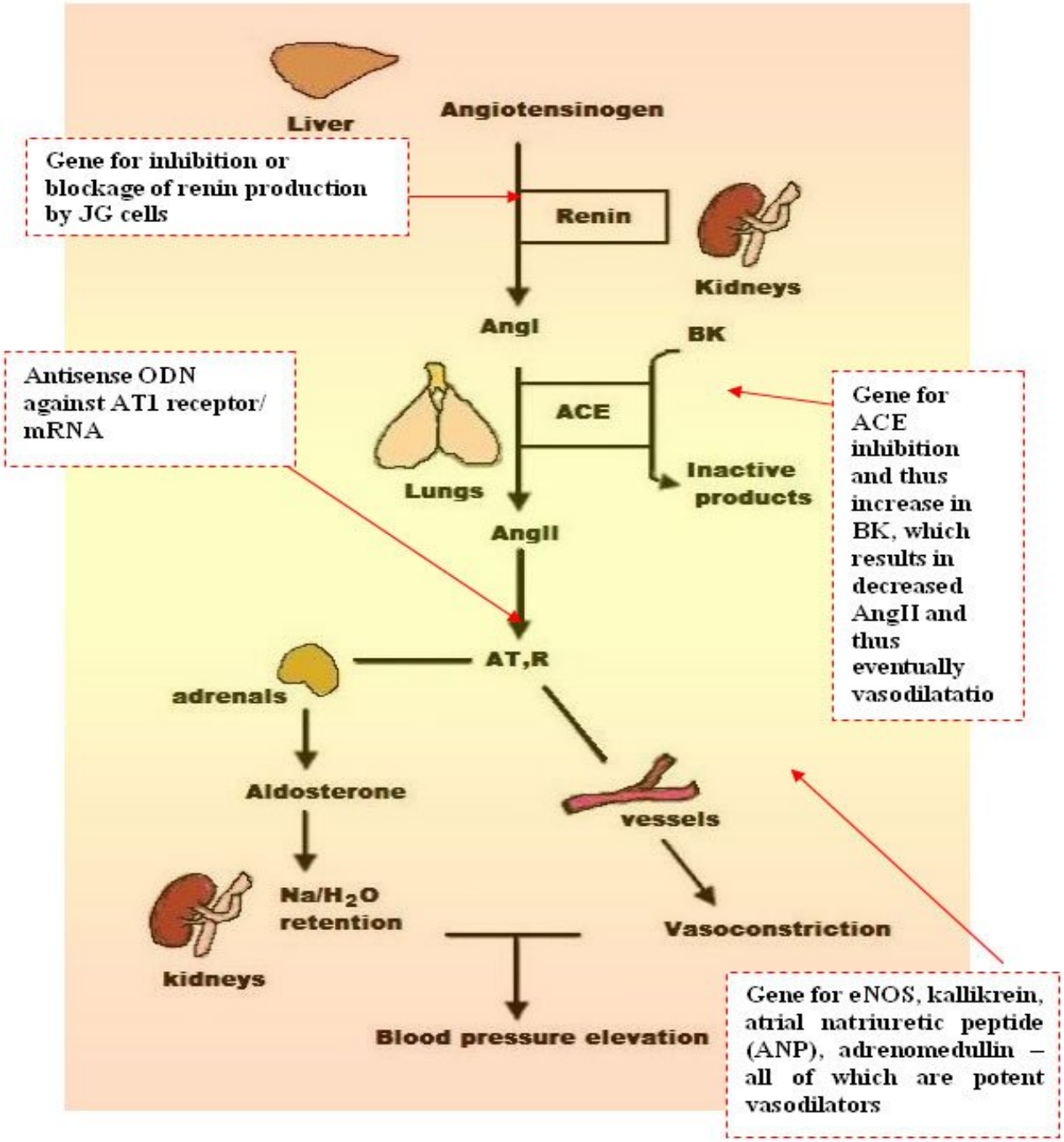
The RAS is the central regulator of both the cardiovascular and the renal homeostasis, i.e. its components are the key controllers for the regulation of blood pressure and fluid levels in the body. It is basically an endocrine system, in which the key product angiotensin II regulates the major actions [Table/Fig 6]. Recently, the discovery of human analogue of angiotensin-converting enzyme (ACE), known as ACE2 has given us one more very potential target for gene therapy against hypertension. This ACE2 is a central regulator of both the cardiovascular and the renal homeostasis and acts through various pathways for regulating the blood pressure in our bodies [8] ([Table/Fig 7]).

Target 2 – genes for vasoactive peptides

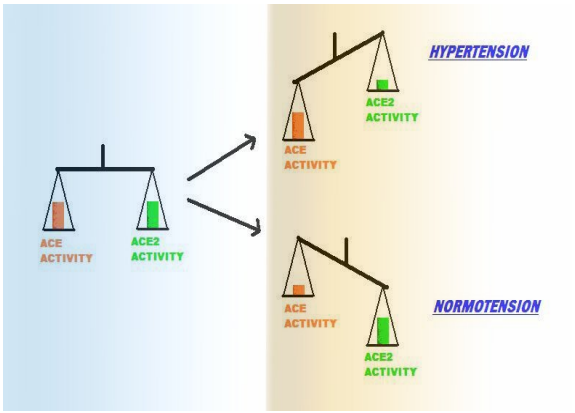
There are many vasoactive peptides that have been studied as potential targets for the gene therapy against hypertension. *Human kallikrien* (HK) is one of them. It cleaves kininogen to produce kinin, which is a potent vasoactive peptide that regulates both cardiovascular and renal functions. Other vasodilatory genes are that of *atrial natriuretic peptide* (ANP), *adrenomedullin*, and *endothelial nitric oxide synthase* (eNOS), which is useful for both systemic and pulmonary hypertension. Other vasodilator genes that are useful for pulmonary hypertension are *calcitonin gene-related peptide* (CGRP) and *prostaglandin I synthase* (PGI) [9].

One of the most recent and effective targets has been ACE2, for the effective delivery of which two factors have played an important role: firstly, the engineered ACE2, i.e. the secretory human ACE2 (shACE2) rather than the plasma membrane-bound ACE2, and secondly, the development of an efficient vector for intramuscular gene delivery like that of

lentiviruses [10] [Table/Fig 8]. Also the use of cell-penetrating peptides (CPP), which are at present being studied as potential vectors for gene therapy, may in future also make local and sustained gene expression of the target genes possible



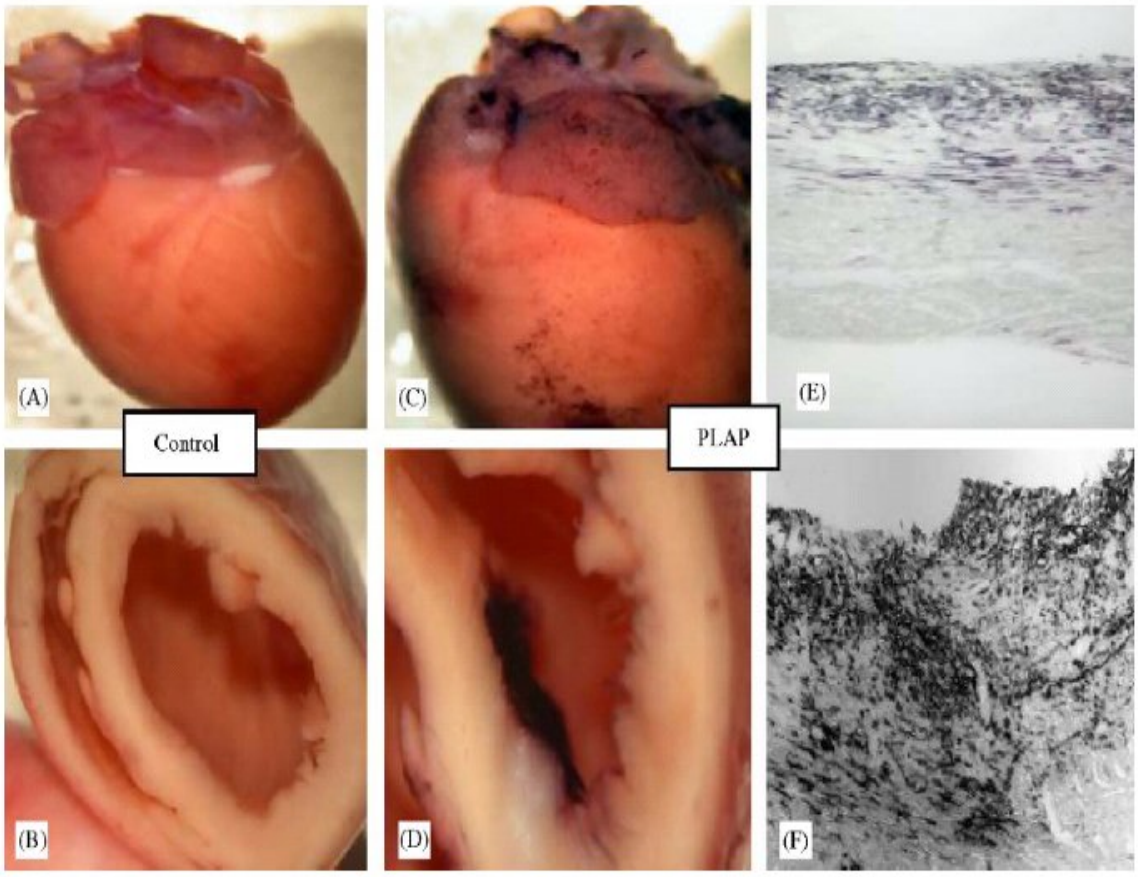
Table/Fig 6 : Shows the potential targets in the RAS (reticulo-angiotensin system) against hypertension [10].



Table/Fig 7: Shows the role of ACE2 in blood pressure regulation and comparison of ACE and ACE2 with their actions [10].

Delivery of gene therapy for hypertension

One of the most recent and effective targets has Studies on ACE and AT1R using the down-regulation antisense approach of these genes on animal models have shown very positive results [11],[12] and is one of the most widely used approaches against hypertension. It is very important to know that down-regulation of genes is not as sensitive as their over-expression (e.g. vasoactive peptides). Another important limitation to the antisense approach is the body's



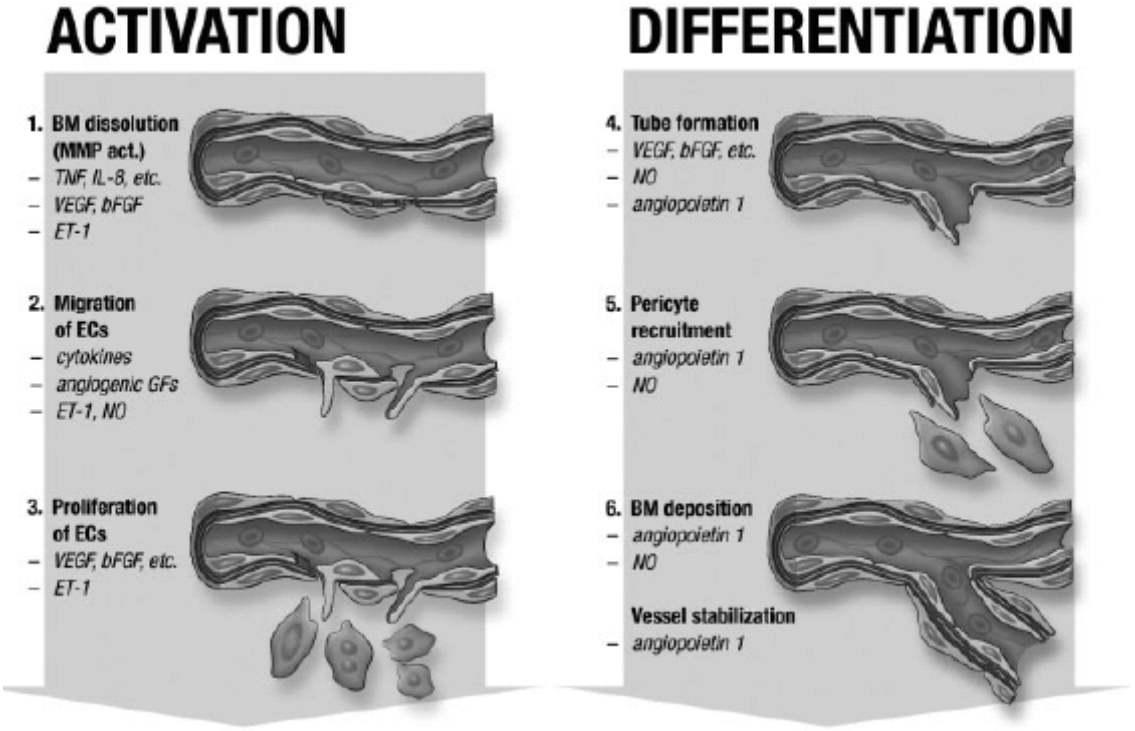
Table/Fig 8: Shows the efficiency of the lentiviral vector system in transferring the gene. It uses placental alkaline phosphatase (PLAP) as a reporter gene (results seen after 10 days of injection) [10]. (A) Shows global view of heart (control) - no staining. (B) Shows ventricular cross-section (control). (C) Shows efficient transduction by lentivirus (atria and ventricles) of the whole heart. (D) Shows magnified view of ventricular cross-section. (E and F) Shows histological sections with PLAP marker transduced by lentiviral vector.

compensatory mechanisms, which will affect the efficiency of this approach on long-term basis. Over-expression of vasoactive peptide genes like ANP, kallikrien, and eNOS, when they were transferred via naked DNA or viral vectors in a spontaneously hypertensive rat (SHR), showed a drop of about 20–30 mmHg over a period of 6–12 weeks, whereas intracardiac injections of viral particles containing antisense ODN of AT1R or angiotensinogen resulted in a drop of 30–60 mmHg for a period of 36 days, while the retroviral ACE antisense delivery resulted in drop for 100 days [9] ([Table/Fig 3]).

Therapeutic Angiogenesis

Background

Today, at present, most of the ongoing human clinical trials on gene therapy (about 90%) are based on the gene therapy against therapeutic angiogenesis. For an effective gene therapy against therapeutic angiogenesis all that is required is a transient gene expression of the therapeutic gene to alter the physiological response as a result of the disorder; in this case, it is formation of new blood vessels (angiogenesis) in the infarcted tissue ([Table/Fig 6]). Not only the requirement of a transient gene expression of the therapeutic gene is sufficient to bring about the desired change, but it also keeps the safety issues in mind, i.e. prolonged gene expression of these therapeutic genes will not only alter the disease but with it give us the risk of having newer problems (discussed later).



Table/Fig 9: Shows sequential events in the process of angiogenesis [14].

Targets for Gene Therapy for Angiogenesis

There are first-generation angiogenic peptides, which include fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and the second-generation angiogenic peptides, which include hypoxia inducible factor (HIF)-1α.

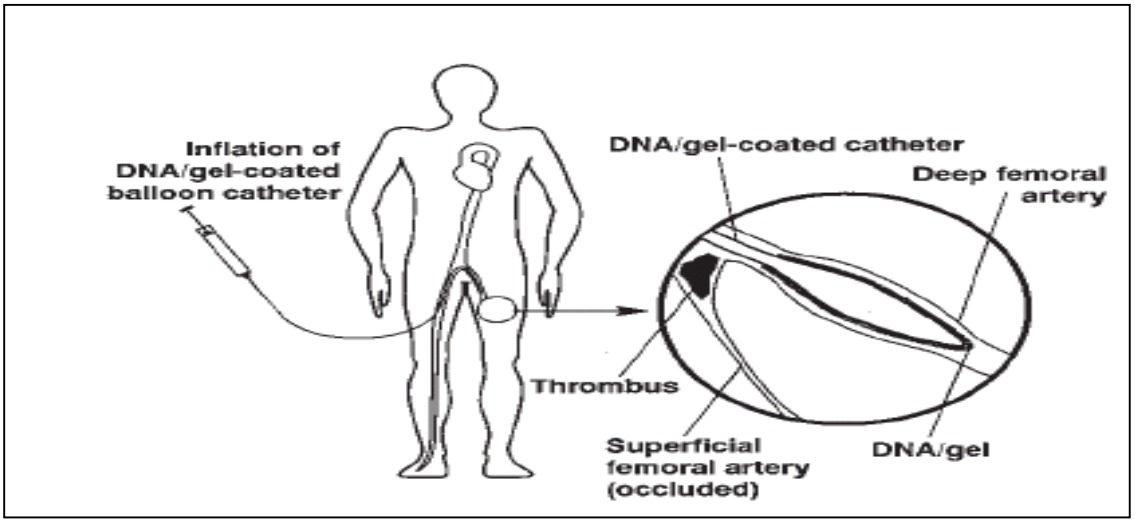
Target 1 – fibroblast growth factor

The first clinical trial on cardiovascular disease began in 1994 and it involved the intramuscular injection of plasmids carrying the FGF, for angiogenesis against the peripheral arterial

occlusion. There are 22 structural homologues of this protein, which bind to the FGF receptors, and talking of receptors there are four types of them, having extracellular immunoglobulin-like domain having cytoplasmic tyrosine kinase activity [13]. Out of these 22 types, FGF1 and FGF2 are the ones that lack these signalling peptides that the others possess, which directs them out to the extracellular matrix. It is because of this that these two have the maximum angiogenic potential and are mostly used. It is because of this diversity in the receptors and structure of FGF that at times the desired effect is not reached, as they are more prone to be antagonised (known as knock-out transgenes), thus producing a milder effect or no effect at all. The main mechanism by which FGF2 (best studied) acts is by stimulating the proliferation and migration of endothelial stage (see [Table/Fig 6] stages 2 and 3). They also act as mitogens for vascular smooth muscle cells (VSMC) and macrophages. Both these actions are synergistic and results in massive new blood vessel formation, compared to one that only stimulates the endothelial cells.

Target 2 – vascular endothelial growth factor

Out of the various isoforms generated as a result of alternating splicing of the peptide, only VEGF 121 and VEGF 165 are the ones that are used the most for angiogenic purposes, simply because of their diffusing properties. VEGF as a secreted diffusible protein has various actions and the major one being stimulation of proliferation of endothelial cells; therefore, it is one of the candidate genes for gene therapy for angiogenesis. There are two receptors that have been identified for angiogenesis and they are VEGFR-1 and VEGFR-2. Both these receptors are found in the endothelial cells and macrophages and account for the specificity of the VEGF. These receptors have accessory isoform receptors like neuropilin-1 (NPL1) and the integrins that facilitate their action [14] ([Table/Fig 7]).



Table/Fig10: Shows local gene delivery (in vivo) of VEGF to arteries as seen in case of gene delivery for therapeutic angiogenesis [14].

Target 3 – second-generation angiogenic peptides [hypoxia-induced factor (HIF) 1α, angiopoietins 1 and 2]

HIF1α protein is a second-generation angiogenic peptide and basically used in arteriogenesis, which, unlike the simple angiogenesis, involves a coordinated action of multiple factors in the formation of a new vessel. Its action is basically of a regulatory gene. It is a rapidly degraded transcription factor that, in presence of hypoxia, stabilises and causes expression of the angiogenic genes (mainly the first generation) and also genes involved with the glycolysis pathway [14].

Delivery of the gene therapy for therapeutic angiogenesis

Local gene delivery including intra-coronary and intra-myocardial injections has been proved to be one of the best options for therapeutic angiogenesis, as is it not only more efficient but also more safe. Both viral (mainly adenoviral)

and non-viral (plasmid and liposomes) have been used.

Risk Associated with Cardiovascular Gene Therapy

Background

For cardiovascular gene therapy clinical trials, whether using viral or non-viral vectors, so far no evidence of any complication, as a result to the vector being used, has been produced. The fact that there has been increase in clinical trials for cardiovascular disorders, especially with ones using non-viral vectors, is an indication in itself that the risks associated with it are very less compared to other gene therapy trials [6]. Also the increasing use of naked DNA for cardiovascular gene therapy reflects on the safety issues involving viral vectors, without compromising on the efficiency of gene transfer, as it can be optimised to be as efficient as the adenovirus, by modifications in the backbone of the vector[15] and/or with changes in the mode of physical delivery (for e.g. ultrasound exposure) [16]. Inflammation is another complication reported after certain preclinical trials [17], but this does not result in any diseases as such. Fever and abnormal liver function tests (LFT) have been reported with adenoviral gene transfer of VEGF and FGF genes [18].

Mortality

As stated earlier, the clinical trials for cardiovascular gene therapy had been carried out on set of people who are so severely ill that even if the therapy fails they have very little to lose. Patients of limb ischaemia and end-stage coronary artery disease (CAD) patients were chosen for the purpose. After this selection of people, the main question was to differentiate the cause of death (if occurred) in them, i.e. whether the death was due to the gene transfer (procedure or due to the transgene) or due to the underlying disease. It was shown that none of the deaths were due to the gene transfer [Table/Fig 11] and [Table/Fig 12].

Morbidity

Like most of the interventional modalities, gene therapy also had many morbidity problems. The most common morbidity problem reported in relation to cardiovascular gene therapy is lower extremity oedema, but there has been no report as yet on it being lethal. There are few others that are discussed below.

Neoplasms

The main reason for neoplasm to be postulated as a risk factor was simply because of the therapeutic angiogenesis gene, which was seen to increase the blood supply not only in the targeted tissue but also in dormant neoplasms in the body, which as a result would become active. However, there is a very little chance of this happening, as firstly it is seen that the gene transfer is localised to the target tissue and secondly even if the viral particles do enter the systemic circulation, they are in so low amounts (pictogram per millimetre range) that they cannot contribute towards activation or formation of a neoplasm. Moreover, these particles can stay in circulation for about less than 4 weeks. So with so less amount and that too for such a less period of time, it is very unlikely to contribute towards a neoplasm. But it remains a potential risk for it when it comes to gene therapy involving the endothelial cell mitogen [6]. However, two new neoplasms were found in patients who had undergone VEGF gene transfer through plasmid/liposomes (VEGF P/L), and they were a malignant glioma and hypernephroma [19]. There was also a case of hypernephroma reported in a patient with VEGF transfer. This tumour was resected and patient remains alive without reoccurrence 3 years after the procedure. In the VIVA and the TRAFFIC trials, neoplasm found in patients was either from controlled or from placebo group [6]. However, we must not forget that patients (elderly group) have a certain prior risk for cancer, and longer follow-up to increase the understanding of the relation between cardiovascular gene therapy and neoplasms [19] is essential.

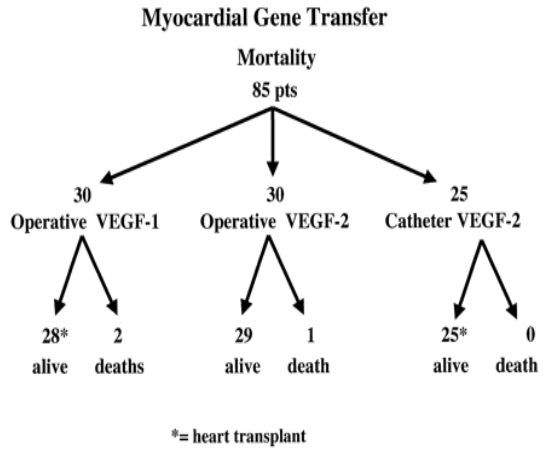
Retinopathy

Although VEGF and FGF have been implicated in the proliferative retinopathies, there is no evidence as such that gene transfer of these genes causes it. Again in the VIVA and the TRAFFIC trials, there were three cases reported in total, all of which were either from controlled or from placebo group. Moreover, diabetes is very commonly seen in patients enrolling for the angiogenic gene trials, but even in this high-risk group and in patients who had retinopathy before, there is no evidence of any contribution as such even on long duration follow-up [6].

Table/Fig 11: Patient deaths after cardiovascular gene transfer [6]

Patient (indication)	Sex	Age at death (y)	Vector/transgene	Mode of delivery	Interval from gene transfer to date of death	Nature of death
1 (CLI)	M	56	NV/VEGF$_{165}$	IA	3 y	?MI
2 (CLI)	M	61	NV/VEGF$_{165}$	IA	11 mo	?MI
3 (CLI)	M	84	NV/VEGF$_{165}$	IA	3½ y	?MI
4 (CLI)	F	73	NV/VEGF$_{165}$	IA	2 y	Cardiac arrest
5 (CLI)	M	88	NV/VEGF$_{165}$	IA	2 mo	Cardiac arrest
6 (CLI)	F	77	NV/VEGF$_{165}$	IM	7 mo	Severe coronary atherosclerosis and interstitial myocardial fibrosis
7 (CLI)	F	65	NV/VEGF$_{165}$	IM	5 mo	Suicide
8 (CLI)	F	57	NV/VEGF$_{165}$	IM	13 mo	Suicide
9 (CLI)	M	73	NV/VEGF-2	IM	16 mo	Severe accidental head trauma
10 (restenosis)	M	76	VEGF$_{165}$	IA	58 mo	Cardiac arrest
11 (restenosis)	M	83	VEGF$_{165}$	IA	70 mo	Lung cancer
14 (CAD)	F	71	NV/VEGF$_{165}$	IMyo(op)	4 mo	Respiratory insufficiency, renal failure
15 (CAD)	M	59	NV/VEGF-2	IMyo(op)	1 d	CAD/cardiogenic shock
16 (CAD)	M	65	Ad/FGF-4	IC	145 d	Sudden death
17 (CAD)	M	68	Ad/FGF-4	IC	267 d	Colon cancer
18 (CAD)	M	61	Ad/VEGF$_{121}$	IMyo(op)	40 d	MI, pneumonia, lung abscess
19 (CAD)	F	85	Ad/VEGF$_{121}$	IMyo(op)	5 d	Ileocolic necrosis
20 (CAD)	NR	NR	Ad/VEGF$_{121}$	IMyo(op)	5 mo	Sudden death

CLI indicates critical limb ischemia.
CAD, coronary artery disease; M, male; F, female; NR, not reported; NV, nonviral; IA, intra-arterial; IM, intramuscular; IMyo(op), intramyocardial (intraoperative); IC, intracoronary; and MI, myocardial infarction.



Results obtained from data for myocardial gene transfer clinical trial. [6]

Oedema

VEGF is seen as a potent factor that increases the vascular permeability, thus resulting in complications like that of ascites (abdominal filling with fluid) in malignancies. Oedema in the lower extremities has been documented in patients who have undergone VEGF transfer peripheral vascular diseases. But this oedema responded well to diuretics and was resolved within weeks. But this complication is one of the limitations with the VEGF gene therapy [14].

Hypotension

Gene therapies involving the VEGF and FGF transfers cause increased production in nitric oxide, which is a potent dilator, thus causing the risk of hypotension. But this complication is so far not documented both for animal and for human trials because of low circulating levels of

the gene product versus the high circulating levels of the recombinant protein [6].

Arrhythmias

Gene therapy involving gene transfer for heart failure like that of β1-receptors and that for calcium channels may be potential risk for the development of arrhythmias in patients, along with patients in whom myocardial gene transfer of angiogenic growth factors is done [6].

Accelerated atherosclerosis

There are sufficient data from animal models that delivery of angiogenic cytokines like that of recombinant human (rh) VEGF causes accelerated atherosclerosis, although data from the clinical trials till date do not give any such relation between the two [6].

Vascular malformations

Various vascular malformations have been reported with injection of high dosage of VEGF like haemangiomas and telangiectasia [6].

Discussion

Experimental data and the information received from various ongoing clinical trials on gene therapy for cardiovascular disorders (many more in addition to the ones discussed in this dissertation) have been very encouraging, but again the searches for an ideal vector system, and even for the right gene, are still few of the major obstacles in our quest for a safe and efficient therapeutic modality against these disorders. For complex disorders like that of hypertension, more than one gene needs to be targeted and so what we can call a 'therapeutic gene cocktail' [20] should serve the purpose. The clinical trials for vascular gene transfer have not only shown it to be safe but also with lot of therapeutic potential when delivered intravascularly [20]. But for future clinical trials, we must first test and find an efficient vector and study model (keeping in mind the good manufacturing practices). Then after the protocol approval and toxicological testing, we should bring it in for clinical trials and try in patients and human tissues. From 1989 (the first gene transfer) till present date, the technology has seen rapid progress in terms of yielding novel vectors and also the progress in clinical trials. Up to 2004, there have been 76 clinical trials for cardiovascular gene therapy, out of which 64 were for therapeutic angiogenesis (mainly involving FGF and VEGF genes) [21]. At present, majority of the new trials in this field are in Phase I still, but with the development of specialised gene therapy units like that of University Of Pittsburgh (U.S.A.) and the A.I. Virtanen Institute for Molecular Sciences (Finland, Europe), to name a few, trials have entered phase II and some even phase III stages. The rationale at present against gene therapy as a therapeutic modality, especially after few setbacks like the famous Jesse Gelsinger death (which was attributed to the overdosage of drug), can be summarised by the joint statement issued by the American and European Gene Therapy Societies in response to an article in Nature, "*The field of gene therapy is working to develop new and better methods to treat a variety of severe disorders, including genetic diseases such as hemophilia and SCID, and also cancer and AIDS. The clear-cut therapeutic benefits seen in recent clinical trials of gene therapy for XSCID and ADA-deficient SCID warrant judicious consideration of the benefits and risks of this approach compared to imperfect alternatives, such as haplo-identical hematopoietic stem cell transplantation.*"

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GLOSSARY

Angiogenesis	Formation of a new blood vessel
AT1R/ATR	Angiotensin II type 1 receptor
ATP	Adenosine Tri-phosphate
Arrhythmia	Loss of normal rhythm
ANP	Atrial natriuretic peptide
Apoptosis	Programmed cell death
ß1ARK	ß1 adrenergic receptor kinase
Cardiomyocytes	Cells of the heart muscle
cAMP	cyclic adenosine mono-phosphate
Epicardium	Layer covering the heart
ECM	Extra-cellular matrix
FGF	Fibroblast growth factor
Glioma	Tumour of the glia (cells of the central nervous system)
Hypercholesterolemia	Increased levels of cholesterol
Hepatocytes/Kupffer cells	Cells of the liver
Hyperplasia	Increase in number of cells
Hypernephroma	Tumour of the kidney
Ischaemia	Lack of blood supply
Intraluminal	Inside the lumen
LDL	Low-density lipids
Mitogen	Substance that stimulates mitosis
Myofilament	Muscle filament
Neoplasms	Cancers or tumours
ODN	Oligodeoxynucleotides
Sarcoplasmic reticulum	Cell organelle that controls the calcium levels
Transgene	The gene used in the gene transfer
TGF	Transforming growth factor
Therapeutic gene	Gene that is used for the purpose of treating the disorder
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
Vector	Carrier of the protein/DNA (deoxyribonucleic acid)