

## Evaluation of vector mediated gene therapy as a novel approach to mitigate cardiovascular diseases; A short review

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Article Review

### ABSTRACT

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Positioning in the top list of mortality and morbidity, cardiovascular disease (CVD) is required new approaches to mitigate the risk and prevalence. Recombinant DNA (rDNA) technology and genome sequencing explore the new horizon to treat CVD through modified therapy. Gene transfer mechanism eventually angiogenic gene therapy provides efficacy in early-stage heart failure. Targeted gene delivery system depicts the novel therapeutic pattern for both genetic disorder and pathophysiological deficit and opens the pathway of early diagnose and treatment. Despite some limitations of a specific vector (viral vector) mediated gene transfer, these new approaches make hope on CVD treatment rather than the surgery and other ways. Furthermore, some vectors are less hazardous than viral vectors to suggest successful non-viral gene modulations to Cardiovascular tissues and perform in the clinical trial. However, plasmid-mediated gene transfer method along with genome editing technology might be the best possible approach for future CVD prognostics and diagnostics.

*Penyakit kardiovaskuler (PKV) yang menempati posisi tertinggi dalam daftar kematian dan kesakitan memerlukan pendekatan baru untuk memitigasi risiko dan prevalensinya. Teknologi DNA rekombinan dan sekuensing genom membuka cakrawala baru untuk mengobati PKV melalui terapi termodifikasi. Mekanisme gen transfer dengan menggunakan terapi gen angiogenik menyediakan efikasi bagi gagal jantung pada tahap dini.*

*Sistem delivery gen target menggambarkan dan membuka jalur diagnosis dini dan terapi awal pada kasus gagal jantung. Meskipun terdapat beberapa keterbatasan dari transfer gen yang diperantarai vektor spesifik (vektor viral), pendekatan baru ini membuat sebuah harapan pada terapi perawatan PKV selain pembedahan dan cara lainnya. Adanya Beberapa vektor yang lebih aman dibandingkan dengan vektor viral bisa digunakan untuk melakukan modulasi gen non-viral yang sukses pada jaringan kardiovaskuler pada uji klinik. Namun demikian, penggunaan plasmid pada gen transfer bersama dengan teknologi penyuntingan gen (gene editing) mungkin bisa menjadi pendekatan yang lebih baik untuk prognosis dan diagnosis PKV pada masa yang akan datang.*

#### INTRODUCTION

Over recent years, there have been substantial advancements in the development of gene therapy strategies and vector technology for the treatment of cardiovascular disease which is

the most common cornerstone of mortality in the developed world.<sup>1</sup> In fact, it holds a major public health problem with increasing prevalence, poor clinical results, and huge health care costs. Nearly 1-2 % of the grown-up population in developed

countries undergo heart failure (HF), with prevalence rising to  $\geq 10\%$  among individuals aged 70 years or older.<sup>2</sup>

On the other hand, conventional pharmaceutical and invasive therapies for CVD have shown the shortening of symptom and unhurried disease progression. Consequently, this limitation in currently emerging therapies has fuelled extensive investigation into new treatment modalities.<sup>3</sup> The molecular pathways and causative genes involved in the induction and progression of CVD have been elucidated through advances in molecular cardiology. These promising insights move towards the use of gene therapy as a novel treatment modality for CVD and HF, escalated by the emerging clinical success in the field significantly. Besides, cardiovascular diseases are variegated and as such have unique traits demanding precise tailoring of gene therapy strategies to particular diseases. In this review, we will point out the gene therapy approaches that have been rummaged in clinical trials or are approaching clinical translation.<sup>4</sup>

#### **Vector mediated gene delivery system in cvd treatment**

Gene therapy is nothing but an outstanding approach of inserting genes to a target cell or organ to treat or prevent the diseases by altering the genetic makeup.<sup>5</sup> Therapeutic competence of gene delivery method is the most considerable phenomenon which relies on the settlement of the desired gene in the target region.<sup>6</sup> Though in a precise manner gene delivery method is denoted as transduction where genes are incorporated in the target organ, the delivery approach can be implied intermittently such as the discharge of a hormone or growth factor owing to the transduction of a few cells. Vectors are the inevitable carrier of potential gene delivery tools where many vectors are reported in this regard. There is a remarkable development in both viral and non-viral vectors based gene delivery method has been performed throughout the years.<sup>7</sup>

#### **Viral vectors**

Viral vectors are the most recurrently used application tools than their non-viral counterpart to transfer genes into cardiac myocytes for the treatment of CVD. Several viral vectors are frequently used in this method. Those viral are retroviruses, adenoviruses and adeno-associated viruses.<sup>8</sup> Retroviruses encode RNA-dependent DNA polymerase named reverse transcriptase that converts ss RNA to ds DNA which is subsequently inserted to the host chromosome.<sup>9</sup> Despite being deficient transduction to cardiomyocytes as they require active cell division for integration and function, retroviruses(RV) have been used for several non-cardiac applications. However, cell division is not mandatory for Lentiviruses(LV), which makes LV more competent for extensive use in cardiac treatment. Though the inability to generate adequate concentrations of viral treatment through coronary perfusion is a great challenge yet, there is an evidence of a successful example of LV gene transfer to the heart through intramyocardial injection.<sup>10</sup>

Many favourable distinctiveness of Adenovirus (ADV) suggested that these vectors are tremendously utilized for gene transfer. The efficiency of ADV is strikingly prominent as AV vectors are capable of infecting non-dividing cells. Though DNA remains as an episomal portion rather than being incorporated with host cell chromosome, the period of persistence of the episomal genes is unidentified. Recently, vectors are primarily derived from other possible stereotypes or non-human AV to avoid the potential problems regarding immunity that primarily exist in the human body.<sup>12</sup> Moreover, inflammatory and immune responses are included as limitation as we have talked earlier; this was because of the short duration of gene expression. Some modifications like deletion were introduced into some regions of vectors which evade the immune response over the conventional vectors. The advantages of the modifications over earlier generation AV vectors

have occurred in a two way. Firstly, as viral coding sequences are deleted from the vector genome, where no viral proteins are expressed from the vector and this modification is competent to reduce its toxicity. Finally, the absence of the viral coding sequence simultaneously increased the capacity for the incorporation of heterologous DNA as well as expressed several genes and regulatory elements. Additionally, the expression of transgene was corrected after the modifications of the AV genome.<sup>13</sup> Adeno-associated virus (AAV) is classified as a human parvovirus as this is not capable of replicating unless helper virus comes. We can make examples of AAV, such as Herpes or AV that is present on the same cell. Nevertheless, there are six known human serotypes where AAV-2 has been the major focus of interest.<sup>14</sup> State of the art illustrates that besides ADV, AAV is also mostly studied in the cardiovascular gene therapy, since both possess great effectiveness

in vascular vessels, cardiac muscle and so on.<sup>15</sup>

### Nonviral Vectors

Besides viral vectors, some non-viral vectors are also observed for the frequency of their performances. Positively charged lipid vesicle made a tie with a negatively charged DNA molecule. Though plasmid DNA is released in the cytoplasm, only a small proportion might enter the nucleus.<sup>16</sup> Liposomes have the favourable characteristics as they have no viral sequences. Furthermore, cell division is not required for the transfection process. Reduced efficiency of myocardial gene transfer is treated as a limitation. Interestingly, liposome-mediated gene transfer of interleukin-10 was much higher than their counterpart of ADV mediated gene delivery system.<sup>17</sup> We may compare among the credentials of vector-mediated gene therapy in response to their efficacy, efficiency and other properties which are listed below.

Table 1: Comparison among salient features of vectors used in gene therapy.

Gene therapy by vectors	Ease of production	Infection of non dividing cells	Infection into host genome
Retrovirus	+	---	++
Adenovirus	++	+++	---
Adeno-associated virus	+++	+++	+++

Note: "+" denotes the lowest magnitude while "+++" denotes the higher magnitude and "---" denotes absence of the parameter.

The alteration or distortion of some promoters when they are fixed in an adenoviral genome is one of the key barriers of tissuespecific promoter system. Furthermore, the intermingling between the promoter components enhancer stuff or transcription set-up lines within the adenoviral sequences flanking the transgene expression cassette, which can activate transcription in non-target cells.<sup>18</sup>

Based on the fix-up of genes to the endothelium of either native coronary vessels or coronary artery bypass grafts or the myocardium cardiac gene delivery can be accomplished. The myocardial gene can be carried out either via direct myocardial injection or via the coronary

vasculature. Manifold injections generating noticeable levels of gene expression within a 1.5-cm radius of the site of injection is needed for direct myocardial injection.<sup>19</sup>

Nevertheless, one discernible shortcoming is the phase of cross-clamping to a matter of seconds is interrupted by the acute pressure surplus of the LV. Considering this barrier, direct catheterization of the right or left coronary artery is more pertinent clinically. Notwithstanding, one drawback is the scanty exposure of the heart to the virus. Current approaches demand high infusion pressure to inject the virus, which could cause endothelial or myocardial injury.<sup>20</sup>

Another comprehensive process of gene

delivery during CPB has been revealed which is incessant circulation of an adenoviral vector solution through the heart. However, the development of two separate circuits and oxygenators indifferent to standard approach is needed. Besides, as a means of gene transfer has been implemented by the insertion of retrograde delivery of vector through the coronary sinus in a porcine beating heart model.<sup>21</sup>

### **Recent updates on Gene delivery for the treatment of CVD**

Database research conducted by prominent Australian, British and Swedish researcher in 2018 revealed that the inclusive course of clinical trial performance in the field of gene therapy is obvious, with the flourishing vindication of clinical advantages over a progressive number of disease targets. The hopeful message is that gene therapy could be a new gateway for angiogenesis treatment, myocardial shielding, resuscitation and recuperation, therapeutics of restenosis following angioplasty, restraint of bypass graft failure and risk-factor regulation.<sup>22</sup>

However, to defeat some of the impediments that have tormented the field of gene therapy for decades, two American scientist Morgan Maeder and Charles Gersbach in 2016 reconnoitred their views slightly different pathway named Genome Editing Technology. They concluded likely genome editing has transformed the demarcation of gene and cell therapy and has been a key factor in the recent resurgence of this field, but there is still considerable rudimentary and translational work to ascertain the full assurance of these technologies for widely treating human disease.<sup>23</sup>

While the exquisite analysis by Bradshaw and Baker in a review paper in 2012 showed that with progressive improvement of futuristic surgical revascularization approaches and the obvious upliftment that have been made in distinguishing the molecular principle of cardiovascular disease, it is transparent that these advancements will flourish in coming years to more feasible gene therapies for vascular implementation.<sup>24</sup>

Gene therapy has some risks. Problems that are currently raised include inadequate delivery

and expression, immune response to the viral vector or transgene leading to inflammation and cardiotoxicity (alter signal transduction presented arrhythmia although in small number), off-target effects resulting from uncontrolled expression, insertional mutagenesis, limited duration gene expression although these some risks can be resolved by improved gene transfer vector and the possibility of causing leukaemia. Recently many problems are still inherent to either the transgene or delivery method.<sup>25</sup>

An exciting prospect for translating much work from animal models to human studies has been opened up by the recent demonstration of quantitative imaging of transgene expression in living animals. However, it must be remembered that still having many problems of gene therapy in regards of CDV such as immune response leading to inflammation and toxicity, uncontrolled expression of the transgene in a different organ, and the possibility of causing a tumour for example leukaemias. Thus, any genes that appear to cause enhanced cardiac function must undergo extensive toxicity studies in animals before similar experiments being performed in human subjects. Although many issues remain unresolved, the techniques described in peer's paper may be utilized in the future to deliver various genes, targeted to combat many different diseases mostly CVD.

### **CONCLUSION**

Gene therapy is a plighting genre for the amelioration of inherited and acquired cardiovascular diseases. The findings of the molecular footing engaged in the pathophysiology of cardiac disease administrated to fostering preclinical gene therapy studies in small and large animal model and tracked down to significant pitfalls such as neutralizing antibodies are present to initiate cellular immune responses directed against the viral vector and/or the gene-modified cells along with the insufficient gene expression levels and the limited gene transduction efficiencies as well that leads recent research trends into new clinical trials based on the delivery of the targeted protein.

However, hopefully, new cutting-edge paradigms agglomerated into miRNA regulation or genome editing technology that has opened new therapeutic perspectives for fruitful remedies of CVD.

#### CONFLICT OF INTEREST

None declare

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None declare

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