https://doi.org/10.33472/AFJBS.2.3.2020.10-19 ISSN: 2663-2187

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Review Article **Open Access**

Viruses, the vehicle for cancer gene therapy: A Review

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Article Info

Volume 2, Issue 3, July 2020

Received : 02 October 2019

Accepted : 23 April 2020

Published : 09 July 2020

doi: 10.33472/AFJBS.2.3.2020.10-19

Abstract

Cancer diseases are among the world's leading causes of death, and this global burden is expected to rise in the next two decades. Researchers have been focusing on gene treatment strategy to curb this growing number. To guarantee the success of the gene therapy strategy, therefore, it is essential to develop a suitable delivery agent, notably a viral vector. Despite its benefits, there is also a disadvantage in viral vectors where viruses are hard to cope with their toxicity. Nevertheless, for their long-term expression and stability, viral delivery agents are preferred. To date, among the frequently used vehicles for gene transfer are adenovirus (Ad), adeno-associated virus (AAV), retrovirus, and lentivirus. Each one of these viruses has its own "pros and cons," rendering them a choice for gene therapy testing. A broad range of gene transfer technologies have been designed over these years, but all transferring technologies still have constraints in clinical applications, and there are no distribution systems that could be implemented *in vitro* and *in vivo* in all cell types without any limitations or side effects.

Keywords: *Gene therapy, Viral vector, Adenovirus, Retrovirus, Gene transfer*

1. Introduction

Cancer is said to be among the leading causes of mortality and morbidity with about 14 million new and 8.2 million cancer-related fatalities in 2012. It is anticipated that the burden of cancer will rise by about 70% in the next two decades (Dancey *et al*., 2012). Cancer is a complicated multifactorial disease integrated by the host and environmental interaction with modifications at the cellular and genetic levels. Two groups of genes are

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oncogenes and tumor suppressor genes in regulating the development of cancer. In accordance with genetic alteration, oncogene relates to any gene that converts normal cells into cancer cells lead to an abnormal proliferation of cells. There are more than 100 recognized oncogenes, most of which have been recognized in human tumors (e.g., ras). Over the previous few centuries, the ras gene has been widely studied and the most prevalent oncogene discovered in human cancer. The ras gene interrupts the cell division in which the normal cell is mutated and encourages cancer formation (Luo *et al*., 2012). While, tumor suppressor genes are normal genes that interrupt or inhibit an abnormal division of cells or cause the natural death of cells. Thus, if these genes are mutated, uncontrolled cell proliferation would not be inhibited and indirectly triggers the development of tumors (Zhao *et al*., 2013). Retinoblastoma (RB) and p53 genes are among the most common tumor suppressor genes and constitute the cell growth control's reverse side. Both the RB gene and the p53 gene have an impact on the protein p-RB and the protein p53 generated under these protein controls. These proteins generally prevent apoptosis induced by DNA replication and cell division (Engel *et al*., 2014; and Romli *et al*., 2017). This implies that if these genes are mutated, their proteins lose its functions and cause uncontrolled proliferation of cells, leading to cancer growth. A study has shown that in about 40% of human cancers, RB protein was inoperative (Engel *et al*., 2014). Similarly, in 50% of all tumor activity, the p53 gene was discovered to have extraordinary makeup (Morandell and Yaffe, 2012).

To date, surgery remains the most efficient type of cancer treatment by removing a big tumor that has not yet metastasized. In most cases, metastases found in patients freshly diagnosed with a solid tumor. Current approaches, such as chemotherapy and radiotherapy, often contribute to tumor resistance and have damaging effects on the surrounding normal cells (Romli *et al*., 2013). For instance, radiation therapy treats approximately 50% of cancer patients globally. Although radiation therapy does not cause systemic toxicity compared to chemotherapy, the continuous growth of resistance to this irradiation dose continues an anti-cancer challenge (Baskar *et al*., 2012). Cancer cells may have distinct origins, so this differs considerably in cell genetics, transcriptions, translations and cell profiles (Blanpain, 2013; and Ghaemi *et al*., 2017). This implies that it is crucial to specifically design the therapeutic methods based on the biology of tumor cells. All this shows the desperate need for therapeutic methods to progress.

2. Gene therapy

Gene therapy, a promising cancer treatment, has been the focus of attention in the field of cancer research and genomics for the last 20 years. Gene therapy shows the ability to be a healing agent for cancer that is predominantly gene-based as medicines (Wirth and Ylä-Herttuala, 2014). Gene therapy involves an experimental operation to alter cells for treating or curing illnesses genetically. There are three stages of gene therapy consisting of (i) the choice and construction of vector-carrying genetic components, (ii) the transfer of genetic components from the vector to the target cell, and (iii) the gene product expression in the target cells (Mali, 2013). The transmitted genetic components could be gene sequence, gene segment, or oligonucleotides that can be transmitted either *in vitro* or *ex vivo*. Researchers have been testing several methods throughout these years; (i) replacing a mutated gene that is accountable for a disease with a healthy copy of the gene, (ii) inactivating a mutated gene that works improperly with genome editing or, (iii) introducing a new gene into the cells that helps heal the disease (Nayerossadat *et al*., 2012). It has been indicated that the transportation of genetic products to tumor cells or normal cells to eradicate or decrease tumor mass is the main component in cancer gene therapy. Conventional cancer treatments such as chemotherapy and radiography generally lack the selectivity of cancer cells that could lead to normal cells being toxic where the strategy to gene therapy emerges as a successful alternative to this issue. Gene therapy can be used to target particular malignant cells as an anticancer agent, thus minimizing the side effect on normal cells (Naldini, 2015).

The strategy for gene therapy uses different kinds of techniques to transfer genetic products into the nucleus of target cells. The main achievement in intracellular transport system design is based on a deeper understanding of the mechanism and a positive interaction between the delivery agents, the transgenes and the target cells. The introduction of the therapeutic gene is primarily aimed at restoring ordinary functions or eliciting certain answers. A gene delivery agent is required to carry these therapeutic genes. The gene carrier's ability to reach a particular cell, especially the nucleus, affects gene therapy success (Thorne *et al*., 2018). The technique is performed by the vectors carrying therapeutic gene that can be classified into two vectors: viral and non-viral. Adenoviruses, retroviruses, and lentiviruses are the most frequently used delivery of viral vectors for gene therapies. While, non-viral vector examples are naked plasmids, liposomes, and polymers. Viral vectors are said to be a successful transfer scheme as they could provide efficient and particular transduction and expression of genes compared to the non-viral method (Husain *et al*., 2015). An important step in ensuring successful gene therapy is the creation of an efficient gene transfer scheme.

3. Viral gene delivery system

Viruses are tiny infectious particles (virions) that carry either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) as their genetic material. Their structure generally comprises of genes enclosed by a protein coat called capsid for use in attaching to the host cell and preventing the nuclease enzymes of the cell from viral destruction. Virus particles could not be produced during propagation. It must, therefore, insert its genetic materials and use the machinery of the host cell to obtain metabolic and biosynthetic products for transcription and replication (Giacca and Zacchigna, 2012). Viruses are pathogenic agents that need to be attenuated and manipulated before clinical trials are implemented. Viral vectors have been created and intended for this purpose from many distinct classes of viruses such as adenoviruses (Ad), adeno-associated viruses (AAV), retroviruses and lentiviruses. In addition, attention is also paid to other classes of viruses and the designation of hybrid viruses for gene transfer.

Viral gene delivery scheme is an experimental process that transfers genetic material through the use of a virus as a carrier. An infectious virus can be transformed into a non-infectious virus. They could bring genetic products to be transferred into the target cytoplasm and then into the nucleus without causing an infection that could damage the host as shown in Figure 1. The use of bacteria as a gene delivery agent in gene treatment represent more than 68% of all clinical studies for gene therapy (Nayerossadat *et al*., 2012). Adenovirus, retrovirus, and adeno-associated virus are the most commonly used viruses as shown in Table 1.

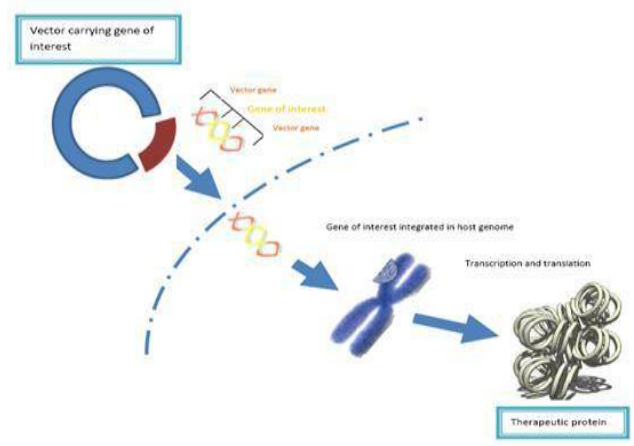

Figure 1: Basic steps of gene delivery

Table 1: The most commonly used viral vectors in gene therapy

Virus	Family	Nucleic acid	Enveloped / Non-enveloped	Integrated / Non-integrated	Target cells
Adenovirus	Adenoviridae	Double-stranded DNA	Non-enveloped	Non-integrated	Dividing and Non-dividing cells
Adeno-asscociated virus	Parvoviridae	Single-stranded DNA	Non-enveloped	Integrated	Dividing and Non-dividing cells
Retrovirus	Retroviridae	Single-stranded RNA	Enveloped	Integrated	Dividing cells
Lentivirus	Retroviridae	Single-stranded RNA	Enveloped	Integrated	Dividing and Non-dividing cells

Viral vectors can be divided into two categories: viral vectors that are integrated and non-integrated. The integration of viral vectors such as retroviruses, adeno-associated viruses and lentiviruses enables the transgene to be incorporated into the host genome. Non-integrating viruses such as adenovirus, on the contrary, are present in the nucleus but do not integrate DNA into the host. This expression of transgene is short-lived as the transgene is absent during cell division (Ibraheem *et al*., 2014).

3.1. Adenoviral vector

An adenoviral vector is derived from an adenovirus (Adv) consisting of a linear, double-stranded DNA in its size of 36 kb genome. For approximately 50 viral proteins, the Adv genome encodes 11 of which are structured and used to produce virions (Vannucci *et al*., 2013). Adv infection is primarily mediated by binding the fiber knob area to the target host cell's Coxsackie-Adv Receptor (CAR). Virus integration with the host cell proteins is facilitated by the interaction of Arg–Gly–Asp (RGD) penton-base and αvβ cellular integrins via endocytosis of the virus particle via clathrin-coated pits (Anselmo and Mitragotri, 2014). Once the virus is disassembled in the endosome, it will transport the viral DNA into the nucleus and express transgenes. There are two types of Ad vector used to supply genetic products like a car. First, the Replication-Competent Ad (RCA) vectors are complemented by the virus genome's early region 1 (E1) with a transgene expression cassette frequently found in the E3 region (Kovesdi and Hedley, 2010). The second type of ad vectors is replication-defective, generally due to partial or complete removal of the region E1 and the cassette of transgenic expression inserted in that region E1 or E3. Because of their high safety profile, these Replication-Defective Ad (RDA) vectors were used the most (Suzuki *et al*., 2015). The use of Adv is heavily based on these characteristics (i) the capacity of this virus to transduce non-dividing cells, (ii) first-generation (E1/E3-deleted) Adv which can take up to 8-10 kb in transgenic cassettes, and (iii) Adv is discovered to be in an episomal shape as an Adv is a non-integrating vector (Lee *et al*., 2017).

The primary benefit of frequently used adenoviral vectors is that in both dividing and non-dividing cells, high-efficiency infection means that it can be used to pass genes into the wide spectrum of tissues. Adv can also cargo large transgene (up to 38 kb), however, one of the disadvantages is the fact that it is a non-integrating viral vector where its genome stays in the nucleus as transgene expression like an episomal component (Lee *et al*., 2017). Ad viruses have spread extensively, with about 80% of healthy individuals nowadays developing antibodies against one or more of the accessible Adv serotypes (Amer, 2014). Adv proteins' elevated immunogenicity limits the amount of administration of vectors in the same individual. Activating the system supplement, innate immunity, and pre-existing immunity increases the danger of anaphylactic shock. The danger is proportional to the number of administrations, generally following the third inoculum (Saxena *et al*., 2013). New insights have started to overcome the pre-existing Ad immunity by enhancing the effectiveness of the therapeutic approach based on Adv. These methods include generating chemically altered Adv serotype 5 capsids; generating chimeric Adv; replacing Adv serotype-5 derived vaccine with alternative Adv serotypes (human or non-human origin); and Adv serotype-5 genome modification method that preserves the initial Adv serotype-5 capsids. The procedures will indirectly enhance the effectiveness of the Adv and minimize the impact of pre-existing Adv immunity (Fausther-Bovendo and Kobinger, 2014).

3.2. Adeno-associated virus vector

Adeno-associated virus (AAV) is a virus of the genus dependovirus, small size of less than 5 kb, single-stranded DNA viruses (Naso *et al*., 2017). AAV includes only two open reading frames that are the replicas needed for non-structural proteins such as replication of the viral genome and cap encoding structural proteins. The uniqueness of this virus is that it generally does not cause any infection without a genotoxic agent such as adenovirus or herpes simplex virus being co-infected (Weitzman and Linden, 2011). AAV derived vectors could transduce a wide range of cancer cell lines and primary cells in oncology applications. This vector is also capable of transmitting dominant therapeutic genes (anti-angiogenesis gene and suicide gene) as well as the gene encoding for lower nucleic acids such as shRNAs and siRNAs (Santiago-Ortiz and Schaffer, 2016; and Zamberi *et al*., 2016).

Recombinant AAV (rAAV) is formed between two reversed terminal repeats (ITRs) by inserting a therapeutic gene. Because AAV is a model deficient in replication, it requires to be co-transfected for viral replication with other helper bacteria (adenovirus or herpes simplex). Since most inner coding sequences have been removed, AAV becomes faulty in replication and therefore needs to be co-transfected with help viruses (Giacca and Zacchigna, 2012). If the helper virus is present, with the assistance of the helper virus, AAV can undergo replication and provide an efficient infection (Chan *et al*., 2017). Briefly, rAAV is built by removing replacing

both Rep and Cap genes with the cassette of transgenic expression. RAAV was chosen to transfer a small-scale therapeutic gene because of the small-scale genome of AAV (Mali, 2013). For AAV to transfer larger genes (larger than 4.7 kb), transgene concatemerization post-transduction that was maintained in two distinct AAV constructs by trans-splicing or homologous recombination of two transgene sequences (Colella *et al*., 2018).

Numerous studies have tried to use AAV as an agent for the delivery of genetic material. Because recombinant AAVs can be readily grown in a laboratory and its safety profile, the primary reason for AAV vector is a decision for gene therapy strategy. For example, Weng and collageous focus on the impact of adeno-associated virus (AAV)-mediated survivor mutant Cys84Ala on the development of gastric cancer where it is concluded that chemotherapy treatment could be a promising antitumor agent for gastric cancer (Weng *et al*., 2013). Yuan *et al*. concluded that there is a notable potential for AAV vectors co-expressing IL-24 and apoptin in cancer gene therapy (Yuan *et al*., 2013; and Ismail *et al*., 2016).

AAV vectors are a common candidate for various studies due to its unique features such as low immunogenicity, integration site-specificity and the capacity of this virus to transduce in dividing and quiescent cells *in vivo* and *in vitro* research (Shin *et al*., 2012). Nothing is ideal' is undoubtedly the precise way to look at this vector because even this virus has some benefits, but in a particular manner it still lacks. A co-infection helper virus is required to make this vector more efficient. For some *in vitro* research, AAV is also said to be "too slow," as it requires an additional step to convert the single-stranded AAV DNA into double-stranded DNA before gene expression can begin. Not only is it very difficult to achieve a high vector titer of AAV, but this can be overcome by the method of purification of the heparin column, which is said to elevate the viral titer and produce a cleaner preparation of the viral yield than centrifugation by a method of gradient cesium chloride or other methods of purification (Clément and Grieger, 2016).

3.3. Retroviral vector

Retroviral vector is a positive-sense RNA virus with a DNA intermediate diploid, enveloped, single-stranded. A retrovirus originating from the species Moloney Murine Leukemia Virus (MMLV) is the most widely used delivery system for both somatic and germline gene therapies. The genome of retrovirus is about 7-11 kb in size and could contain approximately 7-8 kb of gene inserts (Nayerossadat *et al*., 2012). It carries a gene that encodes for a reverse transcriptase that is accountable for converting RNA into intermediate DNA due to the reality that retrovirus is an RNA virus. This intermediate DNA would then be incorporated into the host genome, allowing a full virion to be produced by the host cell machinery (Robbins and Ghivizzani, 1998). Retroviral vectors composed of four significant genes (gag, pol, pro, env) compared to lentiviruses, primarily used in clinical trials such as oncoretroviruses. Simple oncoretroviruses have two long terminal repeats (LTRs) that include the retroviral genes that also have the primary binding site (PBS), the polypurine tract (PPT) and the packaging signal (CIS) recognized as the cis-acting elements. On the other side, genes (gag, pol, pro, env) encoding for viral proteins present the trans-acting components. At each LTR, integrase attachment site (att) enables the viral genome to be integrated into the host genome (Chira *et al*., 2015). Gene delivery via a retroviral vector is accomplished through the interaction between the viral envelope and the cellular receptors inserted in the membrane at the entrance to the host cell (Vannucci *et al*., 2013). Combining the protein envelope with viral particles provides the virus a consent to bind to the target cell that is receptor positive. The first stage of infection is nucleus internalization initiated by virus and cell membrane fusion (Yi *et al*., 2011). This is done by binding the glycoprotein envelope (Env) to the cell receptor and the fuses virus. Env protein releases into the host cytoplasm the viral nucleus. Once the viral nucleus enters the cytoplasm, the gene sequence would then be incorporated into the genome to allow transgenic expression using machinery for transcription and translation in the host cells. According to a study conducted by Vargas and colleagues, retroviruses are said to only transfer genetic material to divide cells, which is why there are numbers of processes that take retroviruses, particularly for *ex vivo* (Vargas *et al*., 2016). The characteristic of retroviruses is that it focuses only on actively dividing cells, thus keeping the normal cells secure indirectly. Indeed, retrovirus targets only the tumor, which nearly all tumors contain G0-phase non-dividing cells, known as the tumor cell cycle's resting phase (Fan *et al*., 2018).

Retroviruses as a gene delivery agent show a number of benefits where they could be integrated into the host cell genome and produce a continuous expression of transgenes, for instance in the 2011 research, using a retroviral vector carrying a pro-apoptotic gene (VP3 gene) to cause cell death in mice challenged by CT26 cancer cells, as the transgene was successfully inserted into CT26 cancer cells (Nik-Mohd-Afizan *et al*., 2011). Most importantly, against this specific vector there is low or almost no pre-existing immunity (Vannucci *et al*., 2013).

That is not all, the retroviral system has the ability to create stable cell lines capable of producing higher numbers of recombinant viral particles compared to other vector systems that have to depend on multiple cycles of transfection and the requirement to remove a large quantity of plasmid DNA from the preparation stage just before it is used in clinical trials. This viral vector model could also generate genetically homogeneous vectors from cells that perform embedded vector copies as opposed to transfection-based vectors that are said to generate a large quantity of mutated and rearranged sequences of the vector genome (Miller, 2014). In addition to the benefits, there are several disadvantages to the virus scheme. One of these is that this particular virus can only effectively transduce to specific kind of cells in order to reproduce. Compared to the AAV viral vector, the relative frailty of this virus as a vector makes storage at –70 °C a must for maintaining this virus ' healthy activity. One of the disadvantages of being a gene material delivery agent is also the random integration of the viral vector. Random integration of this virus can be more clearly grasped through a previous study that disclosed the retroviral integration mechanism (Kvaratskhelia *et al*., 2014). Retroviruses vary in their chromatin-associated characteristics preferences and these viruses are a bit chosen when it comes to the integration site choice as they prefer specific nucleotide sequences at that specific insertion point. Retroviruses, particularly the insertion site targeting species Moloney MMLV, are driven by integrase-interacting host factors such as retrovirus BET proteins and lentivirus LEDGF / p75 chaining viral intasomes to chromatin. Based on the research, two significant players are discovered to be involved in selecting a retrovirus integration site. These players are the protein and cognate cellular binding partners of retroviral integrase (IN) (DeRijck *et al*., 2013).

3.4. Lentiviral vector

There have been many studies on the use of lentivirus for transgenic delivery over the previous few years. More preferred than any other viral vectors are this specific virus. Lentivirus is a retrovirus subfamily that could carry up to 8 kb of a series of genes. This virus has been a decision because it has some favorable characteristics, such as its ability to infect both dividing and non-dividing cells (Escors and Breckpot, 2010). This characteristic is peculiar distinct to only lentiviruses compared to retroviruses, which it transduces only dividing cells. This virus also has a promising, safer insertion profile. For instance, HIV has been modified into a gene delivery vector of the famous lentiviruses (Sakuma *et al*., 2012). Researchers have succeeded in removing several infectious regions and replacing these regions with other genes from viruses such as cytomegaloviruses (Hu *et al*., 2009). These engineered viruses could target a wide range of cell types such as quiescent and those cells that are difficult to translate such as hematopoietic precursors, neurons, lymphoid cells, and macrophages (Dropulić, 2011; and Yahaya *et al*., 2019). Researchers have also succeeded in creating lentiviruses that lack of integration and it would not incorporate this altered virus into the host genome. Such lentiviruses have several exciting features that make them safer and have more variable specificities for either a particular cell or all cells. In addition, it also has productive transduction that is said to have low antiviral immunity and low genotoxicity owing to insertional mutagenesis for both dividing and non-dividing cells. There are currently approximately 114 clinical protocols that have been recorded using lentiviruses to act on illnesses that include cancer. This figure reflects about 21% of all procedures for retroviral gene treatment, showing the widespread use of this vector as a car for therapeutic transportation (Vargas *et al*., 2016).

In order to incorporate into the host, lentiviruses that maintain their gag gene in a non-functional state and the accessory vpr protein encoded in their genome do not involve nuclear membrane deterioration. Both integrase and matrix proteins contain nuclear localization signal sequences. Similar to the reactive element (RRE), which is mediated by the protein by viral ARN nuclear export. These proteins are capable of interacting with the host cell's nucleus import mechanism that allows the pre-integration complex to be actively transported via nucleopores (Kamimura *et al*., 2011). This intriguing lentivirus potential allows this virus to transfect cells that are not divided. Indirectly, gene transfer vectors, peculiarly neurons, became the most appropriate. The cassette of transgene expression would substitute the viral gene; basically, the viral genes are given by the structure of the first-generation aid. While, the second generation of aid building was created by removing all the accessory genes that are primarily accountable for pathogenicity but are not essential for gene transfer. These accessory genes are removed from the structure of the helper (Chira *et al*., 2015). The third generation of this vector building is produced by supplying a regulatory Rev protein from a separate construct of rev building and gag-pol construction, then co-transfecting these two constructs to generate vector particles. This generation vector particle has a splendid benefit in reducing the danger of constructing the helper with the viral vector, resulting in constructing the helper with low replication-competent vector particles with the viral vector titers (Hu and Pathak, 2000). The next step to reduce the threat of replication-competent vectors is said to be a stably transformed packaging cell line. Researchers have gained so much attention from the backbone

of the lentivirus vector as a manner to enhance gene delivery safety and effectiveness. The first step is to raise a lentivirus 'security profile by removing the 3' LTRtobe SIN (self-inactivating) vector U3 region (Zufferey *et al*., 1998). This implies that the transduction of the lentivirus ' viral transcription capacity is lost, minimizing the promoter interference and reducing the danger of activating neighboring genes at the integration site. The next step is to include insulators where genomic DNA sequences are capable of hindering the interaction between vector integration and neighboring genomic regulatory sequences. Moreover, the chromosomal position effect also inhibits transgene silencing. For instance, the chicken hypersensitivity site 4 isolator (cHS4) (the standard used for multiple studies to improve transgenic expression). This cHS4 insulator improves the lentiviral vector with other kinds of insulators such as the locus control region compared to the lentivirus vector. Recent progress in the gene therapy sector has altered the cHS4 insulator by fusing the insulator to the scaffold attachment region (SAR) element, which has been shown to enhance the viral vector and the lentivirus vector transgene expression (Uchida *et al*., 2013). Some other kinds of genomic insulators have been recognized and proved as a key component to be included in the lentivirus vector rather than cHS4. This progression is said to enhance the effectiveness of lentivirus transduction and reduce the oncogenic potential of the virus.

Currently, numbers of research have used lentiviruses as a vehicle for gene transfer. Jubayer *et al*. (2016) recently used lentivirus to deliver HSV-Tk suicide gene to healthy, immunocompetent rats ' brains. The goal was to assess the toxicity impact when the HSV-Tk suicide gene was delivered to normal brain cells. The results of this research were noteworthy as it demonstrates that the translation of this HSV-therapy lentivirus-mediated suicide gene does not damage the normal brain cells. This observation is highly relevant to the efficacy of this particular vector to be used as a therapy for patients with brain tumors in clinical trials (Hossain *et al*., 2016).

In addition, the capacity to transfect non-dividing cells and those cells that are difficult to transduce. This virus can also incorporate in an integration-defective form into the host cell genome. Despite the benefits celebrated by this virus, it also has some disadvantages. One of these is the viral's damaging probability of transforming it into pathogenic HIV infection, especially in people immunized. This is due, though, to the insertion mutagenesis; even in patients with HIV infection, this phenomenon has not yet been noted. The chance of the patient becoming infected with HIV is another possible issue with the use of the lentiviruses. This could result in the vector mobilization that this wild-type virus could behave like a virus of help. This help virus will cause this disease to spread to other tissues in the body or even to others (Ruzila *et al*., 2010). Creating the vectors that contain "suicide" genes that would activate and kill cells that have the genomes of the vectors in a certain condition would be one of the ways to address this issue (Merten *et al*., 2016). Lentiviruses also could cause a tumor formation, but the danger was significantly smaller than the retroviral vectors. This is basically because lentivirus integration sites are far from cellular promoters accommodating sites (Ura *et al*., 2014).

4. Conclusion

The increasing number of patients with cancer is calling for a solution globally. Gene therapy has been viewed as a prospective strategy for treating multiple diseases, including cancer that is not curable. An issue continues the discussion on the "ideal" technique of transferring therapeutic genes. A broad range of gene transfer technologies have been created over all these years, but still, all transfer technologies have constraints in clinical applications and there are no delivery systems that could be implemented *in vitro* and *in vivo* in all cell types without any limitations or side effects. Viral vectors and hybrid viral vectors are said to be a promising transferring mechanism based on research conducted over the previous three centuries as it could provide efficient and specific transduction and expression of genes. To date, adenovirus, adeno-associated virus, retrovirus, adenovirus lentivirus and adenovirus hybrid virus vectors, adeno-associated virus, and retrovirus are among the most widely used vector gene transfer. Each vector has its distinctive benefits, and the exploitation of these benefits could boost the capacity for genetic material delivery.

Future Recommendation

All of these viral delivery vectors that have been established could be improvised to (i) reduce toxicity and adverse side effects to non-cancerous cells, (ii) develop a delivery agent with no or less immunogenicity, and (iii) transmit genes to the desired cell with the precise quantity. In addition, gene vectors could be generated in mass with gradual progress in molecular studies and could be commercially accessible. These vectors ' accessibility will make gene therapy easy to use as a treatment for most patients with cancer. This will alter the future of treatment for cancer from widespread, traditional approaches to a more particular and efficient

remedy. With elevated cure rates and less toxicity, this current therapy envisages being rapidly, particular, affordable.

Acknowledgment

This study was funded by Universiti Putra Malaysia through the GP-IPS grant number 9524700.

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Cite this article as: Nurliyana Mohd Yusof, Natasha Nur Afiqah Mohamed Noor Fuadi, Mohd Azuraidi Osman, Mohd Azmi Mohd Lila and Nik Mohd Afizan Nik Abd Rahman (2020). Viruses, the vehicle for cancer gene therapy: A Review. *African Journal of Biological Sciences.* 2(3), 10-19.