Viral Vectors: "Friends or Foes" in Gene Therapy

Muhammad Imran Qadir and Maria Tahir

Institute of Molecular Biology & Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Correspondence to: Muhammad Imran Qadir, mrimranqadir@hotmail.com

Additional material is published online only. To view please visit the journal online.

Cite this as: Qadir MI and Tahir M. Viral Vectors: "Friends or Foes" in Gene Therapy. Premier Journal of Science 2025;5:100045

DOI: https://doi.org/10.70389/PJS.100045

Received: 18 September 2024

Revised: 11 December 2024

Accepted: 11 December 2024

Published: 23 December 2024

Ethical approval: N/a

Consent: N/a

Funding: No industry funding

Conflicts of interest: N/a

Author contribution: Muhammad Imran Qadir and Maria Tahir – Conceptualization, Writing – original draft, review and editing

Guarantor: Muhammad Imran Qadir

Provenance and peer-review: Commissioned and externally peer-reviewed

Data availability statement: N/a

ABSTRACT

Viruses are usually reputed as highly damaging and are considered harmful particles; however, they may show beneficial effects, for example, in the case of viral vectors in gene therapy. Commonly used viral vectors include adenoviruses or lentiviruses. For a successful gene therapy experiment, an appropriate amount of a therapeutic gene must be administered to the intended tissue without considerable virulence. For a particular gene therapy practice, vectors should be of a distinctive nature that affects its fitness. The desired properties of viral vectors include, but are not limited to, stability, specificity, or low immunogenicity. The accurate realization of gene therapy is only possible by manipulating the current vectors in use or if specific targeted new vectors are developed. Viral vectors are also commonly used to deliver CRISPR/Cas9 because of their strong binding and high in vivo efficiency. However, these vectors pose several challenges including the risk of undesired gene mutations, insertional mutagenesis, off-target effects, carcinogenicity, immunogenic reactions, and limited transfection volumes.

Keywords: Viral vectors, Gene therapy, Oncolytic viruses, Adenovirus vectors, Immune response

Introduction

For successful gene therapy, an appropriate amount of a therapeutic gene must be administered to the target tissues. In particular gene therapy practice, vectors should be specific regarding their suitability for therapeutic action. The desired properties of viral vectors include, but are not limited to, stability, specificity, or low-immunogenicity gene therapy experiments are designed to change the infectious process of the virus. Therefore, the virus does not have a negative effect on human health, but it carries the therapeutic material inside it.[1]

Some gene transfer approaches are rooted in the transport of tumors certaining toxins or the bystander effect, which facilitates the conversion of pro-drugs into toxic substances.[2] Some new strategies for cancer gene transfer involve starting an immune response against tumor antigens, so the best practice demands some sort of midway form of gene transfer. Ultimately, oncolytic viruses do not contain transgenes, but they are genetically engineered and allow tumor-specific viral replication, leading to cell lysis and spreading to neighboring malignant cells. The currently used vectors integrate in an unplanned way. Integration is a mutagenic occurrence with a prospective of triggering many genes together with oncogenes.

Adenovirus vectors are greatly used in cancer gene therapy. They are very efficient and can enhance the gene expression duration. Adenovirus can be produced easily, and they can infect dividing and non-dividing cells. Adenoviral vectors are generally very stable and can be made by replication-competent adenovirus (RCA) without any contamination and can adjust the 7.5 kb transcript. The coxsackie and vitronectin alpha (v) beta (3) integrin receptors effectuate the adenovirus entry into humans through clathrin-coated vesicles, and when they enter the nucleus, they remain as extra chromosomal material. The E1 gene in adenovirus controls viral replication and expression of late genes. Transgenic adenoviral vectors are constructed by the replacement of E1A and E1B genes by a transgene.[3] These are called first-generation vectors. Due to the recombination and deletion of one gene, they cause RCA contamination, which leads to high toxicity. Second-generation vectors are made by mutation in the E2A or E3 regions. This improves the toxicity by decreasing RCA contamination.[4] The entry of adenovirus into the body causes intense immune and inflammatory responses. The innate response causes the release of cytokines such as interferon gamma and interleukins, which is then followed up by a specific neutralizing antibody or a T-cell response. Expressed viral genes and transgene are presented on MHC (the major histocompatibility complex) 1 and 2. The intense inflammatory reaction enhances tumor immune recognition and is responsible for the neutralization of immune-mediated vector response. The third-generation adenoviral vectors are constructed by the deletion of the E4 and E3 region preservation. The deletion of the E4 region reduces some immunogenicity, and the protein product made by E3 inhibits the transport of MHC to the surface of the cell, thus preventing immune recognition of adenovirus.[5] Gutless vectors with no viral gene have also been made to deal with immune response and RCA contamination. The gutless vectors require helper viruses because they are replication-deficient. They have a major advantage of being less immunogenic. Adenoviruses have high infection efficiency in dividing as well as non-dividing cells, so they are widely used for gene therapy. Coxsackie adenovirus receptors (CARs) are present in a number of tissues and cells, and CAR protein can express itself in a number of tissues, such as epithelial, endothelial, heart, and brain tissues. There are three main targets for gene therapy in cancer.[6] The first is to induce cytotoxicity of tumor cells via adenoviruses, the second is to promote and induce immunity for specific tumor cells, and the third is in tumor suppressor genes to repair defects. The major regulatory gene for cell death (apoptosis) is the Fas gene. This gene is very important for the sensitivity of tumors to

chemotherapeutics and tumor development. The expression level of the Fas gene is very low in the tumor cells as compared to other cells and this low expression level is the major barrier for ovarian cancer gene therapy. Shuttle vectors were constructed containing Fas gene, human telomerase reverse transcriptase promoter, TSTA (two-step transcriptional amplification), and then packaged into adenovirus. YδT-mediated cell killing in combination with the Fas gene is used.[7] A total of 35 BALB/c mice were taken and divided into five groups, and xenografts of which were used to treat ovarian cancer. The mice were treated with PBS, YδT cells, Fas-expressing adenoviruses, taxol, Fas-expressing adenovirus and YδT cell. The result indicates that mice treated with YδT cells and adenoviruses are safe and effective for ovarian cancer treatment. There are no clinical implications of adenovirus-mediated gene therapy for ovarian cancer because the quick development of immune response against vectors and the poor virus uptake and gene expression due to the lack of CARs in primary tumor tissues.[8]

How Viruses are Manipulated to Work as Carriers or Vectors

The viral life cycle is divided into two phases: infection phase and replication phase (Figure 1). In the first phase, the virus deactivates the host defense mechanisms, recognizes the target cell, and finally enters into the cell and introduces its genome in it. In the second phase, the viral genes are replicated, and structural genes are expressed to produce viral structural components. Then, the viral genome along with viral structural components are gathered at a certain point and released from the cell.[9]

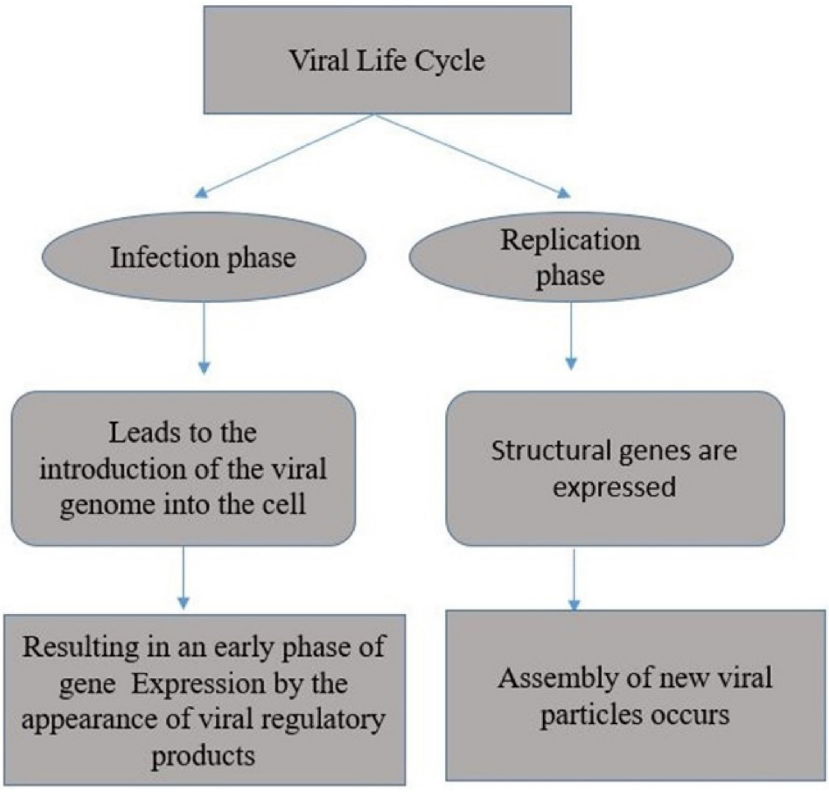

Fig 1 | The flow chart of the viral life cycle

In a gene therapy experiment, viral particles are modified in such a way that they carry the gene of interest in place of their genome; they enclose a modified genome. Transduction is the type of contagion that presents a new genetic material into the cells using vectors. Mostly, it is an unsuccessful or non-replicative and dead-end type. Structurally, the genome of a virus consists of cis-acting gene regulatory sequences and genes. Mostly, cis-acting sequences plot the exterior of the viral coding sequences even though some overlap exists there. To design the recombinant viral vectors, this property of segregation (spatial) of genes and cis-acting sequences sideways with the viral genome is used. To manipulate a vector, both the coding genes and cis-acting sequences are unglued into different nucleic acid molecules to ensure that they will not reconstitute. Their reconstitution might result in productive viral particles by recombination.

The helpful gene of interest accompanying viral cis-acting sequences can then be entered into the same cell to introduce new genetic information to the target cells. An important factor in improving the efficiency and biosafety of a vector system is to maintain the separation of viral genes and cis-acting sequences during their assembly.

The described process of genetic engineering offers a limitation by the grade of the structural intricacy of that viral genome. Cis-interactions between the genome and their translational products are not there in a fix-up vector. These deficient vector particles are incapable of gene transfer, and sometimes also interfere with the transduction of vector particles (naturally full of life). Duplicating these processes has proven to be a great challenge in an in vitro assembly system that would if successful, upsurge the biosafety of viral vectors.

There are diverse natures of viral vectors (Figure 2), and the most common ones are adenoviruses, which are extensively used. Some other viruses that are less widely used are the adeno-associated viral vector, herpes simplex virus 1, lentiviruses, retrovirus, baculovirus, and vaccinia virus as recorded below in Table 1.[10–13]

Role of Viral Vectors as Friends

Initially, gene therapy was considered an approach to treat patients with inherited diseases (like cystic fibrosis or Huntington's disease). Later, the potential has grown, for most of all gene-therapy medical trials were for cancer. A number of unalike proposed actions for cancer gene therapy have evolved that specifically exploit replication-defective viral vectors to deliver anti-angiogenic traits, some tumor-suppressor genes, or the genes that turn on pro-drug such as HSV-1 thymidine kinase and genes that trigger immune response. The inherent potential of virus particles has been reduced to make a replica and lyse the cells in another practice of cancer gene therapy. Viruses have advanced to increase

DOI: https://doi.org/10.70389/PJS.100045 | Premier Journal of Science 2025;5:100045

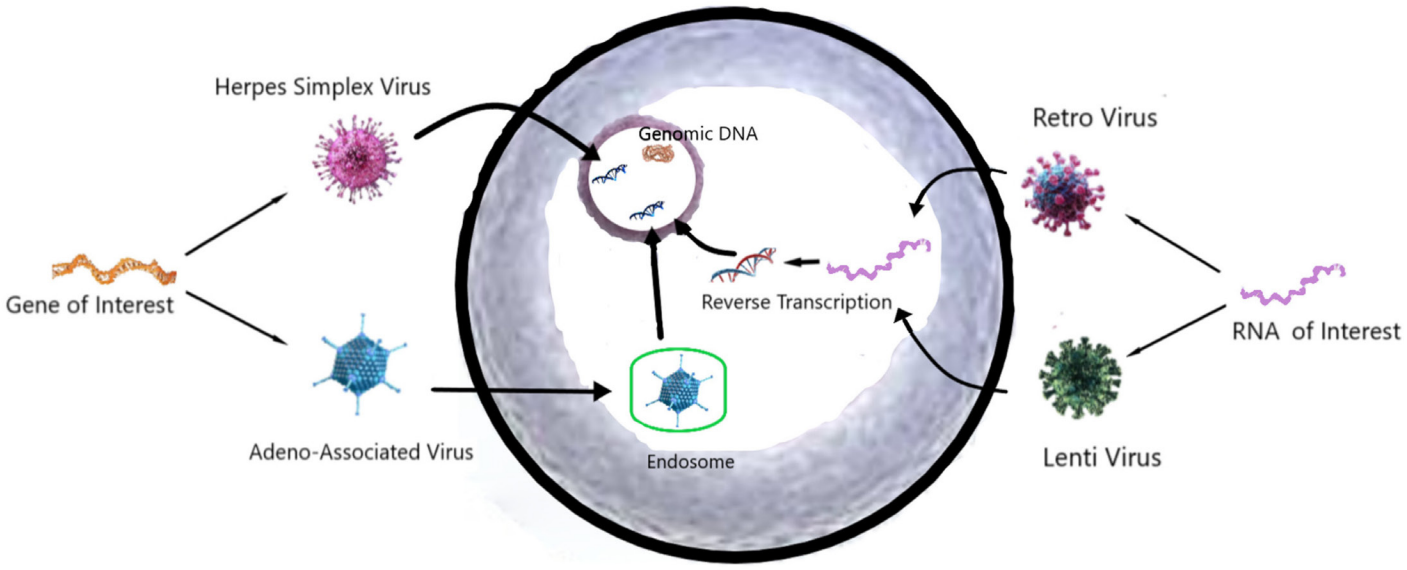

Fig 2 | Practicing different viral vectors for gene therapy

Table 1 | Different Types of Viral Vectors

Vectors	Genetic Material	Main Class	Capacity	Examples	Availability	Advantages	Drawbacks
Adenovirus	dsDNA	Enveloped	30 kb[a]	Ad5-D24, CG870, Ad5-CD/TKrep. recombinant H103, gutless adenovirus, and OBP-301	ONYX-015	Significantly efficient in transduction to many tissues	Capsid mediates inflammatory response
Adeno-associated viral vector	ssDNA	Enveloped	‹5 kb	Adeno-associated; parvovirus	–	No Inflammatory response; non-pathogenic	Less packaging capacity
Herpes simplex virus 1	dsDNA	Enveloped	150 kb	Herpetic viruses; herpes simplex 1 and TVEC	–	Large capacity to package	Inflammatory response; the transient gene expresses other than neuron
Lentiviruses	RNA	Non-enveloped	8 kb	HIV-1, HIV-2, simian IV, and feline IV	–	Gene transfer in most tissues is persistent	Might induce oncogenesis
Retrovirus	RNA	Non-enveloped	8 kb	Moloney murine leukemia virus (MLV	–	Gene transfer in dividing cells is persistent	Might induce oncogenesis in some practices, transduces only dividing cells
Baculovirus	Double-stranded circular DNA	Enveloped	130 kb	***Autographa californica*** multiple nucleopolyhedrovirus (AcMNPV)	BacVector 1000 series)		Unstable in expression, infects non-dividing cells
Vaccinia virus	Double-stranded linear DNA	Enveloped	190 kb	Modified vaccinia Ankara (MVA) and NYVAC	–	Expression transient due to an immune response; replicates in cytoplasm	Infects non dividing cells

[a]Helper dependent.

their feasibility of replication by inducing changes in cellular metabolism and imitate the changes that are gained by transformed cells such as arresting p53. Approximately 66.5% gene therapy trials have been intended for dealing with cancer.[14]

Nowadays, a number of selectively replicating viruses have emerged that lack the genes responsible for making copies in normal cells and mutant viruses are generated that can only replicate in target tumor cells in which missing function is supplied to gain safe tumor-specific replication. Mostly, oncolytic viruses have been engineered from adenovirus, and Herpes simplex viruses are also being tested in trials. These oncolytic viruses will be potent implements for the therapy of solid tumors. The handling of metastases will be a more daunting trial, and "virus therapy" probably becoming a feasible substitute conduct for some types of cancer in the subsequent few ages.[9,15] Some noticeable benefits of different viral vectors are listed below in Table 2.

Table 2 | Advantages of Viral Vectors

Sr. No.	Type of Viral Vector	Advantages	References
1	Adenovirus	Make certain high sort of transgene expression	16,17 18,19 20–22
		Convenient as oncolytic (the virus that infects and kills cancer cells) vector	
		Carry up to 8 Kbp heterologous DNA	
		To undergo transduction in non-dividing and dividing cells	
		Vectors developed at high titers (1010 number of plaque-forming units/ml)	
2	Adeno-associated viral vector	To undergo transduction in non-dividing and dividing cells	23–25
		Low immunogenic	
		Potential site-specific integration	
		Wide cellular tropism	
		Parental virus apathogenic	
3	Herpes simplex virus 1	Natural tropism for neuronal (HSV vectors)	26–28
		Wide cellular tropism	
		Can package 50 Kbp heterologous DNA	
		Convenient as oncolytic (virus that infects and kills cancer cells) vector	
		Vectors developed at high titers (1010 number of plaque-forming units/ml)	
4	Retrovirus	Viral vector genome integrates into host cell genome, more or less unplanned	29–33
		Wide cellular tropism	
		Can accommodate up to 8 Kbp heterologous DNA	
		Manufacturing fairly simple	
		Low immunogenic	
		Vector particles produced at high titers such as 106–108 pfu/ml	
		No or negligible pre-existing immunity	
5	Lentiviruses	Transduction in dividing and non-dividing cells	34,35,20,36,37
		Viral vector genome incorporates into host cell genome	
		Availability of integration-defective vectors	
		Extended expression of the transgene	
		Can package up to 9 Kbp heterologous DNA	
6	Poxvirus	Accommodate up to 30 Kbp heterologous DNA	38,39
		Transgene insertion can be at multiple sites	
		Specifically appropriate as weakened recombinant vaccine	
		Convenient as the oncolytic vectors	
		Level of pre-existing invulnerability is low	

Role of Viral Vectors as Foes

Viruses show a beneficial role in some cases, but are being reputed highly detrimental and are considered negative particles. Some of the problems with vectors that are noticed while transferring genes to target cells include (a) toxicity produced because viral vectors are recognized as foreign materials, (b) immune responses of the cell directed in opposition to the cells that are transduced, and (c) the humoral immune response.

To reduce humoral insusceptibility heading for a counter to the viral vector particle, one should make the obligatory repetitive administration of the vector because it is observed generally when the special effects of gene relocation are for a small period. It is considered that there is a theoretical possibility of the formation of harmful antibody-vector complexes, even by constructing a purified vector, the danger of tempting an immune response to the gene product is observed by the receiver's immune response.

One weak point of gene therapy is that several immunological defense systems are switched on against the viral vectors that are used to attack all wild-type infections. In addition, new products of transgene might be recognized as an outsider. The group of viral vectors that is most immunogenic of all the viral vectors is the adenovirus vector, and the largest hurdle is to control this immunogenicity that is faced by researchers using these vectors.[10] An additional daunting task is the challenge to fix up vectors that can fit into preprogrammed locations inside the genome. This would evade arbitrary integration into actually detrimental locations that might end in harmful actions, as some noticeable drawbacks of different viral vectors are listed below in Table 3.

DOI: https://doi.org/10.70389/PJS.100045 | Premier Journal of Science 2025;5:100045

Table 3 | Disadvantages of Viral Vectors

Sr. No.	Type of Viral Vector	Disadvantages	References
1	Adenovirus	Transient appearance of the transgene	16, 17 22 18,20,40,21
		Highly capable of producing immune response	
		The vector genome does not incorporate into the host cell genome	
		High levels of pre-existing immunity	
2	Adeno-associated viral vector	Less packaging capacity, up to 5 Kbp heterologous DNA	23–25
		High vector titers hard to attain	
		Need co-infection by helper virus	
3	Herpes simplex virus 1	Probable leftover cytotoxicity	26–28
		The vector genome does not incorporate into the host cell genome	
		Transient expression of the transgene or B lymphoid cells (EBV vectors)	
		High levels of pre-existing immunity	
		Danger of recombination with latently herpes simplex virus-infected cells	
4	Retrovirus	Transduce only copying cells	29–33
		Cellular targeting problematic to attain	
		Inappropriate for non-replicating cells	
		Unsystematic integration of the retroviral genome	
		Low stability	
		High risk of insertional mutagenesis	
5	Lentiviruses	Insertional mutagenesis is conceivable	34, 35,20,36,37
		Existence of regulatory proteins in the packaging construct	
		Temporary expression of the transgene with integration-defective vector	
6	Poxvirus	Possibly cytotoxic	38,39
		Generation of recombinants is problematical	
		Transient expression of the transgene	
		Exceedingly adept at producing immune response	
		Heterologous promoters difficult to use	

Emerging Trends and Technologies

The clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 system is a gene-editing technology. Viral vectors such as LV and AAV are commonly used to deliver CRISPR/Cas9 because of their strong binding and high in vivo efficiency. However, these vectors pose several challenges including the risk of undesired gene mutations, insertional mutagenesis, off-target effects, carcinogenicity, immunogenic reactions, and limited transfection volumes.[41]

Conclusions

In clinical practices of gene therapy, the vectors have and will continue to make major contributions. A lot of distinct viral vectors are there to be discovered and utilized yet. They will probably complement the current collection of resources available for this purpose. For all the gene therapy practices, no solitary viral vector system is promising to be optimum. In a specific length of time, trajectories should express a beneficial amount of transgene produced with the looked-for parameter. In the near future, though, we are hopeful to see gene therapy advancement to a great extent, the accurate realization of gene therapy is only possible by manipulating the current vectors, or new vectors should be developed of the desired premises. Even though the prevailing viral vector systems have been adequate enough to gain some clinical achievements, many scientific experiments have persisted in disclosing a number of administration and transport challenges.

References

1 Kay MA, Glorioso JC, Naldini L. Viral vectors for gene therapy: The art of turning infectious agents into vehicles of therapeutics. Nat Med. 2001;7(1):33–40.
2 Aghi M, Hochberg F, Breakefield XO. Prodrug activation enzymes in cancer gene therapy. J Gene Med. 2000;2(3):148–64.
3 Chen K, Liu MX, Mak CS-L, Yung MM-H, Leung TH-Y, Xu D, et al. Methylation-associated silencing of miR-193a-3p promotes ovarian cancer aggressiveness by targeting GRB7 and MAPK/ERK pathways. Theranostics. 2018;8(2):423.
4 Curry E, Zeller C, Masrour N, Patten D, Gallon J, Wilhelm-Benartzi CS, et al. Genes predisposed to DNA hypermethylation during acquired resistance to chemotherapy are identified in ovarian tumors by bivalent chromatin domains at initial diagnosis. Cancer Res. Doi:2018:canres. 1650.2017.
5 Russell W. Adenovirus Gene Therapy for Ovarian Cancer. Oxford University Press. 2002.
6 Bellone S, Buza N, Choi J, Zammataro L, Gay L, Elvin JA, et al. Exceptional response to pembrolizumab in a metastatic, chemotherapy/radiation resistant ovarian cancer patient harboring a CD274/PD-L1-genetic rearrangement. Clin Cancer Res. Doi:2018:clincanres. 1805.2017.
7 Van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HW, Hermans RH, et al. Hyperthermic

intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230–40.
8 Li YQ, Yin JY, Liu ZQ, Li XP. Copper efflux transporters ATP7A and ATP7B: Novel biomarkers for platinum drug resistance and targets for therapy. IUBMB Life. 2018;70(3):183–91.
9 Vannucci L, Lai M, Chiuppesi F, Ceccherini-Nelli L, Pistello M. Viral vectors: A look back and ahead on gene transfer technology. New Microbiol. 2013;36(1):1–22.
10 Thomas CE, Ehrhardt A, Kay MA. Progress and problems with the use of viral vectors for gene therapy. Nat Rev Genet. 2003;4(5):346–58.
11 Airenne KJ, Hu Y-C, Kost TA, Smith RH, Kotin RM, Ono C, et al. Baculovirus: An insect-derived vector for diverse gene transfer applications. Mol Therapy. 2013;21(4):739–49.
12 Kresina TF. An Introduction to Molecular Medicine and Gene Therapy. Wiley Online Library. 2001.
13 Stanbridge LJ, Dussupt V, Maitland NJ. Baculoviruses as vectors for gene therapy against human prostate cancer. BioMed Res Int. 2003;2003(2):79–91.
14 Edelstein ML, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2007—An update. J Gene Med. 2007;9(10):833–42.
15 Kotterman MA, Chalberg TW, Schaffer DV. Viral vectors for gene therapy: Translational and clinical outlook. Annu Rev Biomed Eng. 2015;17(1):63–89.
16 Davison AJ, Benkő M, Harrach B. Genetic content and evolution of adenoviruses. J Gen Virol. 2003;84(11):2895–908.
17 Campos SK, Barry MA. Current advances and future challenges in Adenoviral vector biology and targeting. Curr Gene Ther. 2007;7(3):189.
18 Graham FL, Prevec L. Methods for construction of adenovirus vectors. Mol Biotechnol. 1995;3(3):207–20.
19 Raper SE, Chirmule N, Lee FS, Wivel NA, Bagg A, Gao G-p, et al. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. Mol Genet Metabol. 2003;80(1):148–58.
20 Howarth JL, Lee YB, Uney JB. Using viral vectors as gene transfer tools (Cell Biology and Toxicology Special Issue: ETCS-UK 1 day meeting on genetic manipulation of cells). Cell Biol Toxicol. 2010;26(1):1–20.
21 Castro M, Xiong W, Puntel M, Farrokhi C, Kroeger K, Pechnick R, et al. Safety profile of gutless adenovirus vectors delivered into the normal brain parenchyma: Implications for a Glioma Phase I Clinical Trial. Hum Gene Therapy Methods. 2012; 23(4):271–84.
22 Wang L, Qi X, Shen R, Sun Y, Tuveson DA. An shRNA silencing a non-toxic transgene reduces nutrient consumption and increases production of adenoviral vectors in a novel packaging cell. J Cell Physiol. 2009;219(2):365–71.
23 Glauser DL, Ackermann M, Saydam O, Fraefel C. Chimeric herpes simplex virus/adeno-associated virus amplicon vectors. Curr Gene Ther. 2006;6(3):315–24.
24 Grieger JC, Samulski RJ. Adeno-associated virus vectorology, manufacturing, and clinical applications. Methods Enzymol. 2012;507:229–54.
25 Clément N, Knop DR, Byrne BJ. Large-scale adeno-associated viral vector production using a herpesvirus-based system enables manufacturing for clinical studies. Hum Gene Ther. 2009;20(8):796–806.
26 De Silva S, Bowers WJ. Herpes virus amplicon vectors. Viruses. 2009;1(3):594–629.
27 Marconi P, Argnani R, Epstein AL, Manservigi R. HSV as a vector in vaccine development and gene therapy. Hum Vaccin. 2008;4(2):91–105.
28 Manservigi R, Argnani R, Marconi P. HSV recombinant vectors for gene therapy. Open Virol J. 2010;4:123.
29 Hacein-Bey-Abina S, Garrigue A, Wang GP, Soulier J, Lim A, Morillon E, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest. 2008;118(9):3132.
30 Wu X, Burgess S. Integration target site selection for retroviruses and transposable elements. Cell Mol Life Sci CMLS. 2004;61 (19–20):2588–96.
31 Yamashita M, Emerman M. Retroviral infection of non-dividing cells: Old and new perspectives. Virology. 2006;344(1): 88–93.
32 Suzuki Y, Craigie R. The road to chromatin—Nuclear entry of retroviruses. Nat Rev Microbiol. 2007;5(3):187–96.
33 Urban JH, Merten CA. Retroviral display in gene therapy, protein engineering, and vaccine development. ACS Chem Biol. 2010;6(1):61–74.
34 Dropulić B. Lentiviral vectors: Their molecular design, safety, and use in laboratory and preclinical research. Hum Gene Ther. 2011;22(6):649–57.
35 Mátrai J, Chuah MK, VandenDriessche T. Recent advances in lentiviral vector development and applications. Mol Ther. 2010;18(3):477–90.
36 Toshie S, Michael AB, Yasuhiro I. Lentiviral vectors: Basic to translational. Biochem J. 2012;443(3):603–18.
37 Burnett JC, Zaia JA, Rossi JJ. Creating genetic resistance to HIV. Curr Opin Immunol. 2012;24(5):625–32.
38 Gomez CE, Najera JL, Krupa M, Perdiguero B, Esteban M. MVA and NYVAC as vaccines against emergent infectious diseases and cancer. Curr Gene Ther. 2011;11(3):189–217.
39 Kim JW, Gulley JL. Poxviral vectors for cancer immunotherapy. Exp Opin Biol Ther. 2012;12(4):463–78.
40 Kaufmann JK, Nettelbeck DM. Virus chimeras for gene therapy, vaccination, and oncolysis: Adenoviruses and beyond. Trends Mol Med. 2012;18(7):365–76.
41 Kim M, Hwang Y, Lim S, Jang HK, Kim HO. Advances in nanoparticles as non-viral vectors for efficient delivery of CRISPR/Cas9. Pharmaceutics. 2024;16(9):1197.