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# Viruses as Anticancer Drugs: A Detailed Review

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**Abstract:** *Viruses are nature's nanoparticles, a vast untapped bio-resource. Oncolytic viruses is a new class of anticancer drugs which have advantages of selective replication in tumor cells, delivery of multiple eukaryotic transgene payloads, induction of immunogenic cell death and promotion of antitumor immunity. It is a tolerable safety therapy. Four oncolytic virus have been approved for the treatment of cancer globally. Talimogenelaherparepvec(T-VEC)istheonlywidelyusedtherapy.T-VECisused for treatmentofrecurrentmelanoma.[1] Oncolytic viruses are mutated such that they can be used as anticancer drugs in cancer therapy. They attack on selective tumor cells and destroy them without harming non-cancerous cells. With the help of virus-engineering strategies they are developed specifically for neoplastic tissues. Noninvasive pharmacokinetic monitoring is facilitated by engineering marker genes into the viral genome. [2] Oncolytic viruses are a class of therapeutic agents which give anti-tumor action by either selective tumor killing or induction of systemic anti-tumor immunity. Specific mutated viruses has been developed as oncolytic agents. Mechanism of action is likely dependent on viral replication within transformed cells, induction of primary cell death, interaction with tumor cell antiviral elements and initiation of innate and adaptive anti-tumor immunity. [3]We are going to see a brief review on the following topic in this article.*

**Keywords:** *Virus ,Anticancer ,Therapy ,Immunity , Nanoparticle*

## I. INTRODUCTION

### A. History

In early beginning of 1900s, observations of viral infections causing tumor regression sparked interest in exploiting viruses for cancer treatment. [4] Initial experiments in between 1920-1950s, scientists tested various viruses including influenza and vaccinia against cancer cells in vitro and in animal models. [5] The first clinical trial held in between 1950-1960s, Oncolytic viruses were administered to cancer patients, showing promise but also limitations due to safety concerns and inconsistent results. [6] In between 1970-1980s, advances in genetic engineering enabled scientists to modify viruses to enhance their cancer selectivity and safety. In 1990s, Herpes Simplex Virus (HSV) was created. Researchers created HSV mutants with improved cancer killing properties leading to the development of talimogenelaherparepvec (T-VEC) approved by FDA in 2015. [7] Since 2000, researchers are exploring various mutated viruses including adenovirus, reovirus and coxsackievirus for their anticancer potential. Scientists are investigating combining oncolytic viruses with other cancer treatments such as immunotherapy and chemotherapy to enhance their effectiveness. [8]

### B. Advantages-

- 1) *Targeted therapy:* Viral vectors can be engineered to selectively target cancer cells, reducing toxicity to healthy cells. [9]
- 2) *Cancer cell lysis:* Oncolytic viruses can cause direct lysis of cancer cells, leading to tumor regression. [10]
- 3) *Immune system activation:* Viral infection can stimulate anti-tumor immunity, leading to long-term cancer control. [11]
- 4) *Low toxicity:* Viral vectors can be designed to have minimal side effects, reducing harm to healthy cells. [12]
- 5) *Potential for combination therapy:* Oncolytic viruses can be combined with other cancer treatments for enhanced effectiveness. [13]
- 6) *Tumor-specific replication:* Some viruses can replicate selectively in cancer cells, amplifying anti-tumor effects. [14]
- 7) *Systemic delivery:* Viral vectors can be administered systemically reaching distant tumor sites. [15]
- 8) *Potential for personalized medicine:* Viral vectors can be tailored to individual patients of specific cancer types and genetic profiles. [16]

### C. Disadvantages

- 1) *Cost effective:* Viral cancer therapies may be more cost effective than traditional treatments.
- 2) *Viral resistance:* Cancer cells may develop resistance to the viral vector, reducing its anti-tumor effect.
- 3) *Tumor heterogeneity:* Viral vectors may not effectively target all cancer cells within a tumor.
- 4) *Delivery challenges:* Delivering viral vectors to distant tumor sites can be difficult.
- 5) *Scalability:* Large scale production of viral vectors can be challenging.

- 6) *Regulatory hurdles*: Strict regulations govern the development and approval of viral anticancer drugs.
- 7) *Public perception*: Concerns about using viruses as drugs may affect public acceptance.
- 8) *Potential for mutation*: Viral vectors can mutate, potentially leading to unintended consequences. [17]

**D. Ideal characteristics-**

- 1) *Tumor specificity*: Selectively target and infect cancer cells, sparing healthy cells.
- 2) *High replication efficiency*: Efficiently replicate within cancer cells, amplifying antitumor effects.
- 3) *Strong immunostimulation*: Stimulate a robust antitumor immune response.
- 4) *Low toxicity*: Minimize harm to healthy cells and tissues.
- 5) *Stability and consistency*: Maintain potency and consistency throughout production and storage.
- 6) *Flexibility*: Can be engineered to express various therapeutic genes or proteins.
- 7) *Resistance to neutralization*: Resist neutralization by the immune system.
- 8) *Genetic stability*: Maintain genetic stability throughout replication and transmission.
- 9) *Ability to target cancer stem cells*
- 10) *Cost effective*: Offer a cost-effective treatment option.
- 11) *Non-pathogenic*: Do not cause disease in healthy individuals. [18]

**E. Importance**

Viruses have been harnessed as a novel class of anticancer agents, leveraging their inherent ability to selectively infect and kill cancer cells while sparing healthy tissues. [19] This innovative approach known as oncolytic therapy has gained significant attention in recent years due to its potential to overcome the limitations of traditional cancer treatments. [10] By exploiting the unique characteristics of viruses such as their ability to target specific cell types and stimulate antitumor immunity, researchers have developed a range of viral vectors with potent anticancer activity. [11]

**II. MECHANISM ACTION**

Viral anticancer drugs work through various mechanisms, including:

**A. Selective Infection**

Viruses selectively infect cancer cells, sparing healthy tissues

**B. Immune Stimulation**

Viruses stimulate antitumor immunity enhancing cancer cell killing

**C. Cancer cell lysis**

Viruses cause direct lysis of cancer cells, reducing tumor burden.

**D. Antitumor Immune Response**

The released tumor antigens stimulate an immune response against cancer.

**E. Tumor Microenvironment Modulation**

Oncolytic viruses can alter the tumor microenvironment making it more conducive to immune attack.

**F. Direct Cell Killing**

Some oncolytic viruses can directly kill cancer cells through apoptosis or necrosis.

**G. Anti-Angiogenic Effects**

Some oncolytic viruses can inhibit tumor angiogenesis reducing blood supply to tumor.

**H. Immunogenic Cell Death**

Oncolytic viruses can induce immunogenic cell death enhancing antitumor immunity. [10,11,19]

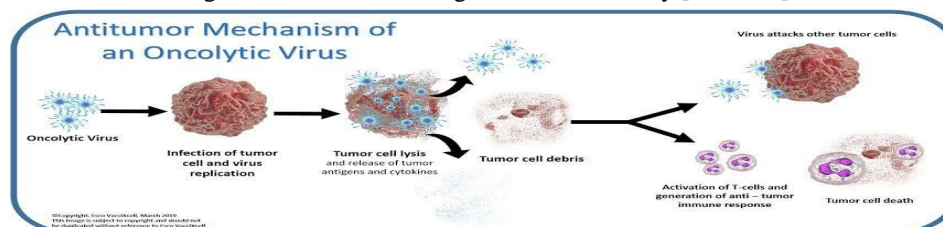


Fig.1

### III. FUTURE DIRECTIONS

#### A. Combination Therapies

Combining viral anticancer drugs with other treatments to enhance efficacy.

#### B. Personalized Medicine

Tailoring viral vectors to individual patients' specific cancer types and genetic profiles.

#### C. Overcoming Resistance

Developing strategies to overcome viral resistance and ensure long-term efficacy. [10,11,19]

### IV. TYPES

#### A. Herpes Simplex Virus (HSV)

Engineered to selectively infect and kill cancer cells, while sparing healthy tissues.

#### B. Adenovirus (Ad)

Modified to target specific cancer cells and stimulate anti-tumor immunity.

#### C. Reovirus (Reo)

Naturally infects and kills cancer cells, with minimal harm to healthy cells.

#### D. Vaccinia Virus (VV)

Used as a vector to deliver therapeutic genes to cancer cells.

#### E. Newcastle Disease Virus (NDV)

Stimulate anti-tumor immunity and selectively kill cancer cells.

#### F. Measles Virus (MV)

Engineered to target and kill cancer cells with potential for combination therapies.

#### G. Vesicular Stomatitis Virus (VSV)

Rapidly replicates in and kills cancer cells with minimal harm to healthy cells.

#### H. Maraba Virus (MV)

A rhabdovirus with potential for cancer treatment due to its ability to selectively infect and kill cancer cells.

#### I. Seneca Valley Virus (SVV)

Demonstrates anti-tumor activity and potential for combination therapies.

#### J. Coxsackievirus (CVB)

Shows promise as an oncolytic virus, selectively infecting and killing cancer cells. [19,20,21]

### V. APPLICATIONS

#### A. Oncolytic Virotherapy

Viruses selectively infect and kill cancer cells, reducing tumor burden.

#### B. Gene Therapy

Viruses deliver therapeutic genes to cancer cells, promoting anti-tumor effects.

#### C. Immunotherapy

Viruses stimulate anti-tumor immunity, enhancing cancer cell killing.

#### D. Combination Therapies

Viruses are combined with other cancer treatments, such as chemotherapy or radiation, to enhance efficacy.

#### E. Targeted Therapy

Viruses selectively target specific cancer cells or pathways, reducing harm to healthy cells.

#### F. Cancer Stem Cell Therapy

Viruses target and eliminate cancer stem cells, reducing recurrence risk.

#### G. Lymphoma Therapy

Viruses show promise in treating lymphoma, a type of blood cancer. [20]

#### H. Solid Tumor Treatment

Viruses are being explored for treating solid tumors, such as breast, lung and colorectal cancer.

#### I. Pediatric Cancer Treatment

Viruses offer potential for treating childhood cancers such as neuroblastoma and rhabdomyosarcoma. [21]

*J. Personalized Medicine*

Viruses can be tailored to individual patients with specific cancer types and genetic profiles.

## VI. DRUGS ELECTION CRITERIA

*A. Tumor Specificity*

Selectively targets and kills cancer cells, sparing healthy tissues.

*B. Oncolytic Potency*

Effectively kills cancer cells through oncolysis.

*C. Immune Stimulation*

Stimulates anti-tumor immunity, enhancing cancer cell killing.

*D. Cancer Stem Cell Targeting*

Targets and eliminates cancer stem cells, reducing recurrence risk.

*E. Safety Profile :*

Demonstrates minimal toxicity and side effects.

*F. Delivery Efficiency*

Can be efficiently delivered to tumor sites.

*G. Genetic Stability*

Maintains genetic stability throughout replication and transmission.

*H. Scalability*

Can be produced in large quantities for clinical use.

*I. Synergy With Other Therapies*

Enhances effectiveness when combined with other cancer treatments.

*J. Regulatory Approval*

Meets regulatory requirements for clinical use. [22]

## VII. COMPOSITION

*A. Genome*

Consists of genetic material (DNA/RNA) encoding viral proteins.

*B. Capsid*

Protein shells surrounding the genome, providing structural support.

*C. Envelope*

Lipid membranes surrounding the capsid.

*D. Viral proteins*

Perform various functions, such as replication, transcription and immune evasion.

*E. Transgenes*

Additional genetic material inserted into the viral genome for therapeutic purpose.

*F. Promoters*

Regulatory elements controlling transgene expression.

*G. Oncolytic genes*

Genes encoding proteins that selectively kill cancer cells.

*H. Immunostimulatory genes*

Proteins recognized by the immune system as tumor specific.

*I. Conditionally replicative elements*

Elements allowing viral replication only in cancer cells.

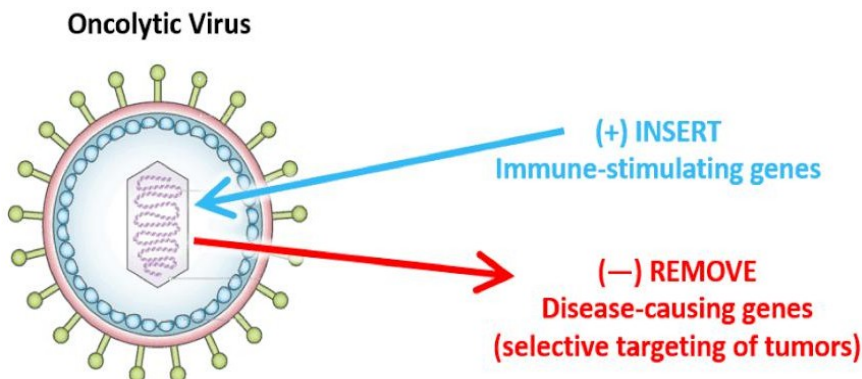


Fig. 2

## VIII. MANUFACTURING

### A. Cell Culture Based Production

Growing cells in bioreactors and infecting them with virus.

### B. Viral Vector Production

Using plasmids or other vectors to produce the virus in cells.

### C. Baculovirus Based Production

Using baculovirus to produce virus in insect cells.

### D. Adenovirus Based Production

Using adenovirus to produce virus in human cells.

### E. Herpesvirus Based Production

Using herpesvirus to produce virus in human cells.

### F. Virus like particle (VLP) production

Producing VLPs that mimic the virus but lack genetic material.

### G. Microbial Fermentation

Using microorganisms like bacteria or yeast to produce virus.

### H. Insect Cell Based Production

Using insect cells to produce virus.

### I. Mammalian Cell Based Production

Using mammalian cells to produce virus.

### J. Closed System Production

Using closed systems to produce virus minimizing contamination risk.

## IX. MAKING OF MODIFIED VIRUS

### A. Vector Construction

Creation of the viral vector including insertion of therapeutic genes.

### B. Cell Line Development

Establishment of a cell line for virus production ensuring consistency and scalability.

### C. Virus Production

Large scale production of the viral vector using cell culture or other methods.

### D. Purification

Removal of impurities and contaminants from the viral vector ensuring safety and efficacy.

### E. Concentration And Formulation

Concentration and formulation of the viral vector into a final product.

### F. Quality Control

Rigorous testing for purity, potency and safety.

### G. Fill And Finish

Filling and packaging the final product for distribution.

#### H. Regulatory Compliance

Adherence to regulatory guidelines and standards throughout the process.

### X. EVALUATION

#### A. In-Vitro Cytotoxicity Assays

Assessing virus-mediated killing of cancer cells in culture.

#### B. In-Vivo Tumor Models

Evaluating virus efficacy in animal models of cancer.

#### C. Apoptosis Assays

Measuring virus-induced programmed cell death in cancer cells.

#### D. Cell Proliferation Assays

Assessing virus impact on cancer cell growth and division.

#### E. Immune Response Evaluation

Measuring virus-stimulated immune responses against cancer cells.

#### F. Biodistribution Studies

Tracking virus distribution and accumulation in tumors and healthy tissues.

#### G. Toxicity and Safety Assessments

Evaluating virus side effects and safety in preclinical and clinical trials.

#### H. Efficacy Assessments in Combination Therapies

Evaluating virus efficacy in combination with other treatments.

#### I. Pharmacokinetic and Pharmacodynamic Studies

Assessing virus absorption, distribution, metabolism, and excretion.

#### J. Clinical Trials

Evaluating virus safety and efficacy in human cancer patients.

### XI. RESULT AND DISCUSSION

The purpose of clinical studies examining mutant viruses as anticancer medicines is to assess the safety and efficacy of these agents in identifying and eliminating cancer cells. For the purpose of figuring out how to include new therapies into conventional cancer treatments, these trials are essential.

#### A. Talimogene Laherparepvec (T-Vec)

The treatment of melanoma with this genetically altered herpes simplex virus is authorized. T-VEC showed a 16% overall response rate in patients with unresectable melanoma in a key trial that was published in the Journal of Clinical Oncology; some patients even experienced complete responses (Andtbacka et al., 2015).

#### B. Oncovex GM-CSF

This modified herpes simplex virus, an additional oncolytic virus, has demonstrated potential in melanoma clinical trials, resulting in immune activation and tumor shrinkage (Cohen et al., 2015). Reovirus, or Reolysin: Numerous malignancies, including head and neck tumors, have been studied in relation to this naturally occurring virus. Reolysin has been shown to increase the effectiveness of chemotherapy and improve patient outcomes, according to a study published in Clinical Cancer Research (Gerritsen et al., 2014). [23]

#### C. Efficacy Outcomes

A lot of studies show improvements in survival rates and tumor shrinking. For instance, approximately 16% of patients in the T-VEC studies had lasting responses, and some of them had complete responses (Andtbacka et al., 2015). [24]

#### D. Safety Profile

These modified viruses are typically considered safe. The majority of side effects, such as flu-like symptoms, are mild to moderate. The rarity of serious adverse events is positive for current and upcoming research.

**E. Combination Therapies**

Oncolytic virus trials are also investigating the use of these drugs in conjunction with immune checkpoint inhibitors and other treatments. According to preliminary findings, these combinations may strengthen therapeutic benefits and improve patient outcomes (Cheng et al., 2020).

**F. Regulatory Acceptance and Upcoming Trials**

Some treatments, like T-VEC, have received regulatory approval as a result of the positive results of early trials. New mutant viruses and their potential in combination therapy are still being investigated by ongoing research. [25]

Clinical investigations show that mutant viruses offer a great deal of promise as anticancer medications, giving patients with a variety of tumors hope. To maximize their utilization and broaden their uses in oncology, ongoing research is crucial.

**XII. MARKETED EXAMPLES**

Brandname	Virusname	Mfg. company	Cost (per treatment)	Region of use	Indication
Imlygic	Talimogenelaherp arepvec	Amgen Inc.(USA)	\$65000	USA	Melanoma
Oncorin	Adenovirus based	Shanghai Sunway Biotech Co. Ltd.(China)	\$45000	China	Headandneck cancer
Reolysin	Reovirusbased	Oncolytics Biotech Inc.(Canada)	\$30000	Canada	Ovarian
Rigvir	Picornavirus based	Latvian Biomedical Research and study centre(Latvia)	\$20000	Latvia and Georgia	Melanoma
Theravir (G47A)	Herpesvirus based	Takara Bio Inc.(Japan)	\$10000	Japan	Glioblastoma
CavatakA21	Coxsackievirus based	ViralyticsLtd.(Aus tralia)	\$20000	Australia	Melanoma
Vaxinia (JX-594)	Poxvirusbased	Jennerex Biotherapeutics Inc.(South Korea)	\$30000	Southkorea	Livercancer

Table 1

**XIII. CHALLENGES AND LIMITATIONS**

There are a number of difficulties and restrictions associated with using mutant viruses as anticancer medications. Here are some important things to think about:

**A. Safety Concerns**

- 1) **Toxicity:** Oncolytic viruses carry the potential to damage normal, healthy cells, which could result in unforeseen side effects.
- 2) **Immune Response:** The virus may be neutralized before it has a chance to infect cancer cells if the immune system perceives the viral therapy as alien and launches a strong defense.

**B. Efficacy**

- 1) **Tumor Heterogeneity:** Tumors can exhibit a variety of features due to their heterogeneity. Because of this variety, it may be challenging for a single viral therapy to eradicate every cancer cell present in a tumor.

2) Resistance: Overtime, cancer cells may become resistant to viral infection or replication, which would decrease the treatment's efficacy.

#### C. Delivery Challenges

1) *Targeting Tumors*: It can be difficult to effectively transport the virus to the tumor site, particularly if it is deep-seated or located in a complicated anatomical region.

2) *Viral Spread*: Maximizing the effectiveness of treatment requires that the virus spread efficiently within the tumor and reaches every cancer cell. [26]

#### D. Regulatory and Ethical Concerns

1) *Permission Procedure*: Creating and receiving regulatory permission for viral treatments can be a drawn-out procedure that necessitates substantial preclinical and clinical research.

2) *Ethical Concerns*: Research and development may be complicated by ethical concerns about the use of genetically modified organisms in humans.

#### E. Cost and Accessibility:

1) *High Costs*: The creation, study, and manufacturing of oncolytic viruses can be costly, which may restrict patient accessibility.

2) *Limited Availability*: There are currently approved viral therapies for a small number of malignancies, and further research is required to increase the number of tumors that can be treated.

In conclusion, although mutant viruses have great potential as anticancer medications, there are a number of issues and restrictions that must be resolved to guarantee their safe and efficient application in clinical settings. [27]

## XIV. ADVANCES

Future developments for employing mutant viruses as anticancer medications are very encouraging and center on a number of important areas, including:

#### A. Genetic Engineering

To improve the selectivity and effectiveness of oncolytic viruses, scientists are investigating cutting-edge genetic editing methods. One example of this is creating viruses with precise targeting capabilities that spare healthy cells.

#### B. Personalized Health Care

The focus of future therapeutics may be on customizing viral therapies to the tumor characteristics of specific patients. Viral therapies that are specifically tailored to the genetic and molecular characteristics of a patient's cancer can be developed for more successful treatment.

#### C. Improved Distribution Method

It is essential to develop more effective delivery strategies to guarantee that the viruses successfully infect their intended tumors. This could entail enhancing the diffusion and uptake of viral treatments through the use of nanoparticles or other cutting-edge methods. [28]

#### D. Comprehending The Immune Reaction

Finding out how the immune system engages with oncolytic viruses can help develop tactics that maximize positive effects while boosting the immune system's defenses against malignancies. This may contribute to optimizing the therapeutic advantages of viral treatments.

#### E. Regulatory Advancements

As the field develops, regulatory frameworks may advance in a way that expedites the approval of potential viral medicines, giving patients speedier access. In summary, the development of mutant viruses as anticancer medications will revolve around enhancing their efficacy, safety, and availability via creative research and combination approaches. In the upcoming years, this may result in cancer patients receiving more potent treatments. [29]

## XV. CONCLUSION

Utilizing certain viruses' innate capacity to specifically infect and destroy cancer cells while inducing an immune response, mutated viruses as anticancer medications provide a novel approach to the treatment of cancer. Treatments that are more precise and efficient are coming from the continuous research in genetic engineering, combination therapy, and customized medicine. These treatments appear to have a good chance of becoming commonplace choices for cancer patients as long as clinical trials proceed. In summary, the future of mutated viruses in cancer therapy is bright, with ongoing advancements likely to yield significant breakthroughs in the fight against cancer. [30]

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