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Scoping the Utility of Lentiviruses as an Aid in Oncologic Treatment and Vaccine Development: A Narrative Review

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Abstract

Lentiviruses have emerged as the "go-to" when it comes to viral vectors. Their capacity to effectively introduce therapeutic genes into specific cells, such as cancer cells, is extremely promising. The review also looks at the use of lentiviruses in the creation of innovative vaccines. Researchers hope to trigger a strong immune response against cancer cells by encoding tumour-associated antigens or immune stimulatory chemicals into the viral vector. The possible benefits and difficulties of using lentiviruses in various fields are carefully evaluated. They have a high capacity to deliver large antigens and have low anti-vector immunity, making them an attractive choice for immunizations targeting various cancers and infectious diseases. Ultimately, the study clarifies future approaches and existing research endeavours aimed at maximising lentiviral vectors' potential for cancer medicines and vaccines. [*Bangladesh Journal of Infectious Diseases, December 2024;11(2):152-159*]

Keywords: Cancer treatment; immunotherapy; vaccine; lentivirus; viral vector therapy

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Introduction

Cancer is a category of disorders characterised by abnormal cell proliferation with the ability to infiltrate or migrate to other regions of the body[1]. This differs from benign tumours, which do not spread. One is every sixth death is due to cancer. Humans are affected by about 100 different forms of cancer. There are a lot of treatment options when it comes to cancer[2,3]. Patients are usually offered either chemotherapy, surgery, radiation therapy, immunotherapy, palliative care, laser therapy or alternative medicine[1]. Cancer cells continue to proliferate unless one of four things happens: (A) the malignant mass is surgically removed; (B) chemotherapy or another sort of cancer-specific medicine, such as hormone treatment is used; (C) radiation therapy is used; or (D) the cancer cells shrink and die on their own. This last occurrence, albeit exceedingly rare, can occur with some melanomas or kidney malignancies[4].

There have been a lot of difficulties in treating cancer. The majority of them are very painful and hard for the human body to handle, yet the therapies provided these days are only 25% to 50% effective[5]. Chemotherapy, for example, is known to cause immunosuppression, alopecia (hair loss), peripheral

neuropathy and anaemia[6]. Going for surgery, on the other hand, has the risk of infection and pain, and even after that, the cancer may remain in the body until proliferation. Gene therapy displays a recent and remarkable option for treating cancer in upcoming years. Because gene therapy may target and change particular genes that are important for the genesis and progression of cancer, it is a potential strategy for treating the disease. Introducing genetic material into cells to change their behaviour or function is known as gene therapy. Gene therapy may be made to specifically target cancer cells, minimising harm to healthy cells and lowering side effects, in contrast to conventional chemotherapy and radiation therapy, which indiscriminately target fast-proliferating cells. This may be accomplished in several ways, including the direct insertion of genetic material into cells and the use of viral or non-viral vectors. Therapeutic genes, such as tumour suppressor genes, suicide genes, or genes that boost the immune system's ability to combat cancer cells, can be introduced via these techniques[7–11]. The ability to use gene therapy for personalised treatment is one of its greatest advantages. Gene therapy may be customised to each patient's tumour by focusing on certain genetic abnormalities or variations, which increases the chance of a good treatment outcome. Moreover, gene therapy can be used in conjunction with immunotherapy or chemotherapy to increase the efficacy of other cancer therapies[12–15]

Intending to strengthen the immune system's response to tumours and specifically target cancer stem cells (CSCs), stem cell-based treatments and vaccines have become more viable approaches to the treatment of cancer. A subset of cells found within tumours known as cancer stem cells (CSCs) have the stem cell qualities of quiescence, differentiation, self-renewal, and the capacity to replicate the parent tumour when transplanted into a host[16]. Due to CSCs' role in metastasis and treatment resistance, there is a negative correlation between them and favourable clinical outcomes. Cancer research has shifted its attention to specifically targeting CSCs since doing so may be one of the most effective therapies[17]. With the ability to develop into numerous cell types, stem cells are used in stem cell-based treatments to replace or repair damaged tissues. Several therapy approaches have been investigated for cancer, such as the application of mesenchymal stem cells (MSCs) to alter the tumour microenvironment and stimulate the immune system against the tumour[18]. The goal of cancer vaccines is to prime the immune system to identify and combat cancerous cells. Pancreatic cancer T cell stimulation has been achieved by the development of customised RNA neoantigen vaccines[19]. Tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) are examples of particular tumour antigens that can be targeted by cancer vaccines. They can also be created to improve the immune system's reaction to current cancer therapies[20]. Recent developments in lipid-mRNA nanoparticles have been investigated as a cancer immunotherapy treatment option, with the potential to enhance the delivery and effectiveness of cancer vaccines[21]. Apart from these methods, contemporary research has emphasised the possibility of focusing on the gut microbiota in the identification and management of colorectal cancer, in addition to the function of the gut microbiota in the initiation and advancement of cancer[22].

Recent years have seen a significant amount of research focused on cancer, vaccinations, and gene therapy, with viral vectors being essential to these areas of study. The purpose of viral vectors is to introduce genetic material into cells so that vaccinations or therapeutic genes can be expressed. Because of their special characteristics, lentiviruses have become one of these vectors' most promising tools. Naturally occurring viruses that have been altered to deliver vaccinations or therapeutic genes are the source of viral vectors. Gene therapy has made use of them to transfer genetic information to specific cells, changing their function or swapping out malfunctioning genes.

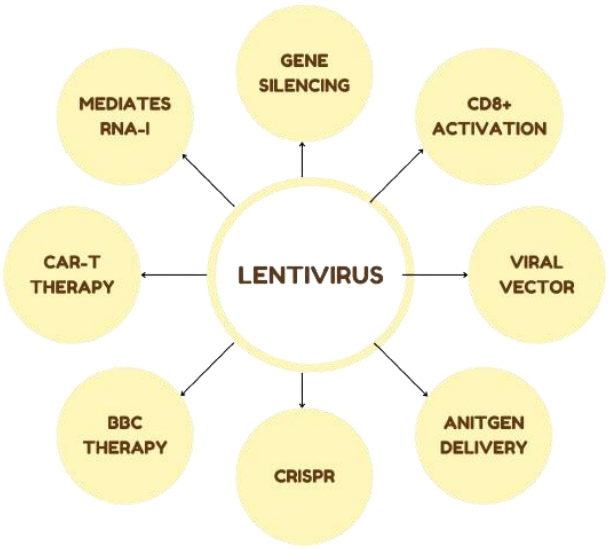

Figure I: Utilities of a Lentivirus

Viral vectors are employed in vaccine development to generate antigens that elicit an immunological response from the body that defends against infections[23]. Lentiviruses, such as HIV, are a kind of retrovirus that may insert its genetic material into the host cell's DNA. They can express genes for a long time thanks to this characteristic, which has been

used in gene therapy for many purposes, including cancer research. Lentiviruses have an advantage over other viral vectors like adenoviruses in that they can transduce both dividing and non-dividing cells[24]. Gene therapy has made use of lentiviruses to target particular cell types, such as immune cells, and to transfer therapeutic genes to cure hereditary diseases. Lentiviruses have been utilised in cancer research to express immune checkpoint inhibitors or transfer genes that prevent tumour development, strengthening the body's defences against cancerous cells[24].

Lentivirus in Cancer Treatment

In the realm of gene therapy, lentiviral vectors have emerged as a key player, especially in the treatment of cancer. These vectors, which are derived from HIV, have been refined to effectively alter eukaryotic cells for use in clinical and research settings. The use of third-generation, self-inactivating lentiviral vectors in clinical trials has been made possible, especially when it comes to introducing genes into hematopoietic stem cells to treat hemoglobinopathies and primary immunodeficiencies[25].

Engineering T cells to express chimeric antigen receptors (CARs) or cloned T-cell receptors is one of the most important uses of lentiviral vectors in cancer therapy. The first genetically altered cellular treatment employing lentiviral vectors was approved by regulators as a result of this strategy's outstanding performance in treating B-cell malignancies[25]. Additionally, antigens have been delivered to dendritic cells using lentiviral vectors, both in vivo and in vitro, to stimulate humoral responses and cellular immunity against a variety of infectious illnesses and cancers[26]. Because of this property, lentiviral vectors are a great option for vaccinations aimed at different types of cancer. Clinical experiments have proven the safety and effectiveness of lentiviral vectors; the first gene therapy trials for advanced leukaemia that used lentiviral vectors were successful. Additionally, lentiviral vectors have demonstrated potential in treating β-thalassemia, X-linked adrenoleukodystrophy, and HIV[27].

Cancer Gene Therapy

Lentiviruses have been utilised in gene therapy to shut specific genes in cancer cells. For instance, in human bladder cancer cells, a study employed a lentivirus to silence the centromere protein U (CENPU) gene. This resulted in decreased cell proliferation, cell cycle arrest, and increased apoptosis[28]. Another research reduced cell proliferation changed the distribution of the cell cycle, and improved cisplatin-stimulated apoptosis in esophageal cancer cells by using a lentivirus to knock down histone deacetylase 1 (HDAC1)[29]. Lentiviral vectors are effective in transducing human tumour cells in a variety of cell lines and tumour types, indicating their potential use in cancer gene therapy[30].

It has been demonstrated that lentivirus-mediated RNA interference (RNAi) may inhibit the development of breast and pancreatic cancer cells, respectively, by targeting certain genes such as the proliferation-inducing ligand (APRIL) and the insulin-like growth factor 1 receptor (IGF-1R)[31,32]. Moreover, the creation of lentiviral vectors that have specific tropism for cancer cells that overexpress certain receptors, such as HER2, offers a novel retargeting mechanism for lentivirus vectors, improving their specificity and possible therapeutic effect[33]. Using lentivirus-mediated gene therapy to decrease survivin in BALB/c nude mice with oral squamous cell cancer was the subject of one of the clinical trials. The research demonstrated that lentivirus-mediated RNA interference (RNAi) decreased survivin expression, which in turn caused KB cells to grow less rapidly and undergo more apoptosis[34].

Cancer Immunotherapy

Lentiviruses have been utilised in immunotherapy to alter the immune system's response to malignancy. Programmed death receptor ligand 1 (PD-L1) in pancreatic cancer cells was silenced by a lentivirus in research that enhanced the in vitro and in vivo therapeutic effects of dendritic cell immunisation[35]. In a different research, endometrial cancer cells were engineered to overexpress the steroid receptor-associated and regulated protein (SRARP) by lentivirus. This altered progesterone receptor signalling and had an impact on cell invasion, migration, and proliferation[36]. Moreover, lentiviruses have been utilised to investigate the function of certain genes in cancer resistance. For instance, research that employed a lentivirus to decrease the ESR1 gene in estrogen-receptor-positive breast cancer cells resulted in the patient-derived xenograft model tumour growth reduction[37].

The creation of replication-competent lentivirus assays for lentiviral vectors that target dendritic cells is one of the most prominent uses of lentiviral vectors in cancer immunotherapy. This strategy targets dendritic cells, which are essential for both

starting and modifying immune responses, which has been shown to increase the effectiveness of cancer vaccinations[38]. Moreover, therapeutic genes have been delivered to T cell products utilised in cancer immunotherapy by the use of lentiviral vectors in clinical studies.

The objective of these studies has been to enhance the safety and effectiveness of T cell-based treatments, which have demonstrated potential in the treatment of several forms of cancer[39]. Bacteria-based cancer therapeutics (BBCT) have also been developed using lentiviral vectors. These therapies work by allowing bacteria to grow and multiply inside the tumour microenvironment, therefore inducing antitumor immune responses. As a substitute for conventional cancer treatments like radiation and chemotherapy, which frequently have negative effects on non-cancerous cells, BCT has demonstrated promise[40].

Lentivirus in Vaccine Development

Because lentiviral vectors may elicit strong and enduring immune responses, they have become an important tool in the generation of vaccines. When it comes to transducing dendritic cells—which are essential for triggering adaptive immunity—these vectors perform very well in such cases. Lentiviral vectors have an advantage over conventional peptide/adjuvant immunisation techniques because they can effectively transduce dendritic cells in vivo, eliciting potent cytotoxic T lymphocyte responses[41].

The promise of lentiviral vectors in immunotherapy is highlighted by their ability to produce sustained gene expression in dendritic cells, which may activate cytotoxic T lymphocytes without the aid of CD4+ T-cells or exogenous cytokines[42]. Lentiviral vectors are perfect for addressing a range of infectious illnesses and malignancies since their usage in vaccinations has demonstrated potential in eliciting humoral and cellular immune responses[26]. Nonintegrative lentiviral vectors can provide protective antiviral immunity after just one dose, and they were created to solve safety issues such as insertional mutagenesis[43].

Certain promoter-containing lentivirus vectors can affect both the immune response and the duration of expression; some vectors induce immunological activation, while others result in long-term transgene expression[44]. The low inflammatory qualities and absence of pre-existing immunity in humans of lentiviral vectors have been identified as desirable characteristics for vaccine production, particularly mucosal vaccination strategies[45,46]. A viable vaccination approach against pulmonary illnesses such as TB has been demonstrated by the successful induction of certain CD8+ T-cell responses in the lung by the use of lentiviral vectors administered intratracheally[47]. HIV vaccination methods may take a new turn thanks to the potential of conditionally infectious and replicating lentiviral vectors to elicit HIV-specific T and B cell responses[48]. Lentiviral vectors have demonstrated a greater capacity for in vivo transduction of dendritic cells in comparison to adenoviral vectors, resulting in the production of endogenous antigens and strong protection against a range of infectious diseases[49].

Vaccines based on lentiviruses offer a viable avenue for cancer immunotherapy. These vaccines increase the capacity of cells to fight cancer by introducing therapeutic genes into them via lentiviruses, a kind of retrovirus. Leukaemia cell-derived exosomes (LEXs) can be utilised to promote anti-leukaemia immunity by downregulating PD-L1 expression by lentivirus-mediated PD-L1 shRNA. This is an example of a lentivirus-based vaccination. It has been demonstrated that this strategy improves T-cell activation and dendritic cell (DC) maturation, which increases T-cell proliferation, Th1 cytokine production, and antigen-specific cytotoxic lymphocyte (CTL) response[50].

The mesothelin (MSLN) protein is a possible target in the context of pancreatic cancer, which is another use for lentivirus-based vaccinations. Researchers have shown that MSLN promotes the formation of pancreatic cancer within the peritoneal cavity by deleting MSLN from the KLM-1 pancreatic cancer cell line using CRISPR-Cas9 gene editing. When MSLN expression was restored in MSLN cells via lentivirus transduction, intraperitoneal growth was shown to be restored by full-length MSLN but not by a Y318A mutant[51]. The use of lentivirus-based vaccines in dendritic cell (DC) immunotherapy has also been studied. Dendritic cells can be utilised as cellular vaccines in cancer immunotherapy and are essential for controlling the adaptive immune response.

The expression of particular SAM domain and HD domain-containing protein 1 (SAMHD1) by dendritic cells limits the ability of these cells to successfully infect other cells. To get over this restriction, scientists have created an enhanced helper vector that can be used to produce large titres of lentiviral particles carrying Vpx that can effectively infect human dendritic and monocyte cells[52].

Table 1: Advantages of Different Approaches

Application	Description	Advantages	Examples
Cancer Gene Therapy	Silence specific genes or deliver therapeutic genes to inhibit cancer cell growth	Effective in transducing human tumor cells	- Silencing CENPU gene in bladder cancer for decreased proliferation
Cancer Immunotherapy	Modify immune system response to target cancer	Improves effectiveness of T cell-based treatments	- Silencing PD-L1 in pancreatic cancer to enhance immune response
Vaccine Development	Elicit strong and long-lasting immune responses	Effective in transducing dendritic cells, crucial for immune response	- Lentivirus-based vaccines against Leukemia and Pancreatic cancer

Discussion

In the future, lentivirus-based gene therapy and immunotherapy may be used to treat cancer. Gene therapy includes several approaches, including immunotherapy, suicide gene therapy, oncogene inhibition, tumour suppressor gene activation, and antiangiogenic gene therapy, which entails inserting therapeutic genes into cancer cells to either kill the cells or slow down their development[53]. Because lentivirus vectors can transduce both proliferating and non-dividing cells, a wider range of therapeutic applications are made possible, making them very helpful for gene therapy[54]. Conversely, immunotherapy primes the body's ability to identify and combat cancerous cells. Immune checkpoint inhibitors are a kind of immunotherapy that has demonstrated remarkable outcomes in the treatment of many malignancies and has garnered interest due to their distinct benefits and auspicious future[55].

Immunotherapy can improve treatment effectiveness and lower toxicity when used with targeted therapies like chemotherapy and anti-PD-1/PD-L1 drugs[56]. Combining immunotherapy with lentivirus-based gene therapy can be utilised in the treatment of cancer. For instance, immunotherapy can be used to specifically target and destroy cancer cells, while gene therapy can be used to strengthen the immune system's response to cancer cells. This combination may result in more individualised and efficient cancer therapies. Nonetheless, there remain obstacles to be addressed in the development of immunotherapy and lentivirus-based gene therapy for the treatment of cancer. These include unintentional changes, off-target consequences, and ethical issues with germline editing[57]. Researchers are investigating novel approaches for anticipating and minimising off-target effects, including better nucleases, optimised delivery strategies, and enhanced bioinformatics tools. Points to relevant

The use of lentivirus in vaccine production appears to have a bright future, especially when considering HIV and other infectious illnesses. The capacity of lentivirus, a kind of retrovirus, to integrate its genome into the host DNA and so provide long-lasting immunity, has drawn attention as it may have vaccine development potential. Nevertheless, attenuated lentiviruses' safety issues have impeded their progress as potential vaccines. The creation of a unique self-replicating chimeric lentivirus-like particle, which combines the advantages of a live attenuated virus vaccination with none of the inherent safety risks of attenuated lentiviruses, is one way to solve these safety problems[58]. This proposed chimeric viral vaccine might expose people naturally to a particle resembling a lentivirus, perhaps providing strong protection against HIV infection. This paragraph is ok.

The discovery of mRNA vaccines in the context of HIV has prompted more investigation into the application of mRNA vaccines in HIV, intending to develop a preventive and therapeutic therapy[59]. Global health continues to place a high premium on the discovery of a safe and effective HIV vaccine, notwithstanding the encouraging outcomes that mRNA vaccines have produced. Apart from HIV, lentivirus may find use in the creation of vaccines against other infectious disorders, such as contagious caprine pleuropneumonia (CCPP) caused by Mycoplasma capricolum subspecies capripneumoniae (MCCP)[60]. To potentially revolutionise immunisation against CCPP, novel candidate antigens such as capsular polysaccharides,

proteins, enzymes, and genes are being assessed for possible use as vaccines against MCCP. The reviewed study highlights the noteworthy possibilities of lentiviral vectors in the fields of vaccine development and oncologic therapy. It has been demonstrated that lentiviral vectors are effective gene delivery agents that can alter dividing as well as non-dividing cells, such as dendritic cells, which are essential for inducing immunological responses. Lentiviral vectors are clinically useful in gene therapy applications, namely in the repair of hemoglobinopathies and primary immunodeficiencies, as well as in the development of CAR T-cell treatments for the treatment of cancer.

These treatments have been approved by the government and have treated B-cell cancers very well. Moreover, lentiviral vectors have been effectively used in the creation of vaccines, especially when it comes to eliciting potent cytotoxic T lymphocyte responses in vivo, which outperforms alternative immunisation approaches in terms of the strength and duration of the CTL response. A major development for immunotherapeutic approaches has been the capacity of lentiviral vectors to effectively transduce human monocyte-derived dendritic cells and activate antigen-specific cytotoxic T lymphocytes. The study also emphasises how lentiviral vectors may be directly administered in vivo to provide antigen-specific immunisation, which might streamline the vaccination procedure and save expenses. The selectivity, safety, and effectiveness of lentiviral vectors can be further improved by limiting transgene expression and targeting the vectors to particular cell types.

Conclusion

In conclusion, the available research supports the use of lentiviral vectors in cancer therapy and vaccine development. The increasing body of research demonstrating that lentiviral vectors are a flexible and potent weapon in the battle against infectious illnesses and cancer is bolstered by developments in vector design, safety, and delivery techniques. It is expected that lentiviral vector-based medicines will become more prevalent in clinical applications as research develops.

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The author has no relevant conflicts of interest to declare.

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Contribution to authors
The author has searched the literature, manuscript writing, reviewed and approved the final manuscript.

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