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Growing Promise of Oncolytic Virotherapy: Opportunities and Pitfalls of NDV In Cancer Therapy

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Abstract

Cancer remains one of the leading causes of death worldwide, largely due to the lack of effective therapeutic options for advanced stages of the disease. Over the past few decades, a variety of cancer treatment regimens have been explored. Among them, oncolytic virus therapy has emerged as an exciting and increasingly prominent field in cancer research. Several oncolytic viruses have been extensively studied, with Newcastle disease virus (NDV) standing out as a particularly promising agent for targeting cancer cells. The NDV exhibits selective cytotoxicity against tumour cells and is also capable of stimulating immune responses. Numerous strategies have been developed to employ NDV as a virotherapeutic agent, yielding variable outcomes. This paper reviews the various aspects of NDV virotherapy in human cancers, highlighting recent advancements and progress in clinical trials.

Keywords: *Newcastle Disease Virus, cancer, oncolytic, virotherapy*

The concept of using viruses in tumour therapy dates back to the early 1900s when observations were made of remissions of human cancers following natural viral infections with mumps, measles virus or influenza (Lindenmann *et al*.,1974). The first evidence for virotherapy was reported in 1912 by De Pace, who showed major tumour regression following rabies vaccination in cancer patients.

Previously, native viruses grown in embryonated chicken eggs and primary cell cultures were employed for oncolytic virotherapy. Later, genetically improved virus strains are used as oncolytic viruses (OV's) to promote therapeutic efficacy. In later stages, tumour destruction and tumour immune response are further enhanced by synthesizing "armed viruses", *viz.,* viruses cloned with cytokine genes, such as IL-2 or GM-CSF and toxin genes. (Lin *et al.,* 2023). Several DNA and RNA viruses, including vaccinia, adenovirus, measles, and Newcastle disease virus (NDV), are currently being used as OV's in advanced clinical trials. Among all those viruses, NDV emerged as one of the first oncolytic agents with promising properties that selectively destroy tumour cells in humans. This avian virus, since then, occupied a central place among other viral candidates as an anti-cancer agent. Regression of acute leukemia was reported after injecting

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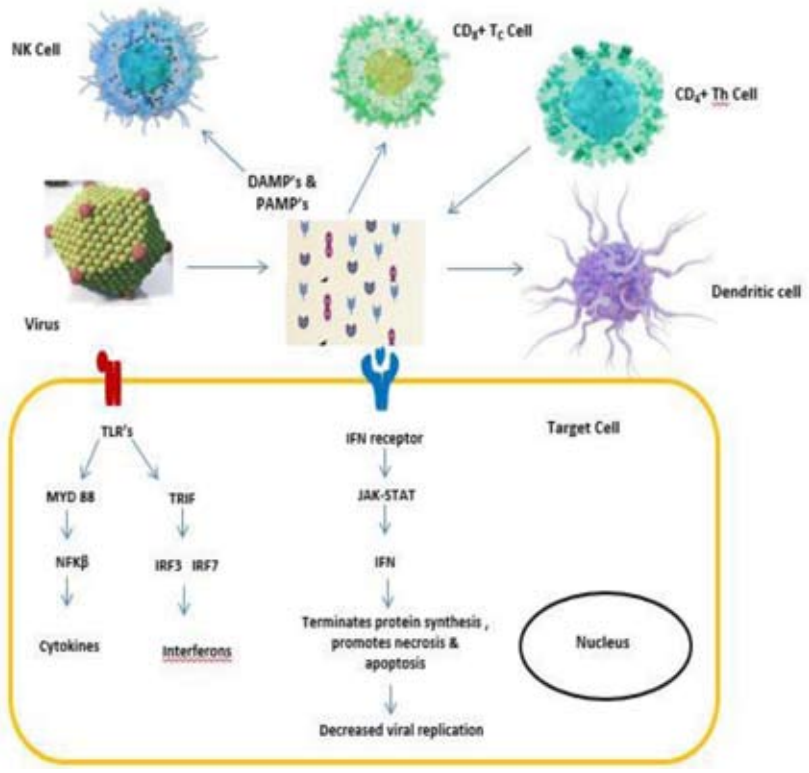

Fig. 1: Generalised overview of mechanism of Oncolytic virus

the patient repeatedly with Newcastle disease virus (Wheelock and Dingle, 1964). It is of interest to note that NDV infection in a farm led to a decline in the severity of a severe metastatic colon cancer in a Hungarian farmer. This report also suggests a correlation between tumours and NDV infection (Csatary, 1971).

Mechanisms of OV action

Therapeutic efficacy of oncolytic viruses depends on two prime characteristics, *viz.,* inducing antitumour immunity and their ability to kill virus infected cells selectively (Fig. 1). Virus infected tumour cells release cellular debris and viral antigens into the tumour microenvironment, stimulating immune responses when they are lysed (Wang *et al.,* 2022).

Several factors drive tumour selectivity in oncolytic virus therapy. The primary factor is virus-specific entry via receptor-mediated mechanisms, as tumour cells often overexpress virus-specific receptors. Exploiting these receptors enhances tumour selectivity. Secondly, tumour cells replicate rapidly together with high metabolic activity, facilitating viral replication more efficiently than in non-cancerous cells. Additionally, tumour-driven mutations further enhance viral replication selectivity (Aghi *et al.,* 2008). Thirdly, many tumour cells have deficient type I interferon signalling, a key antiviral defence, allowing preferential viral replication (Lin *et al.,* 2023).

Viral replication within the tumour microenvironment activates immune mechanisms, which help limit viral spread. Moreover, immune suppression within the tumour may be countered by the release of molecules like damage associated molecular patterns (DAMP's) from dying cells, and tumour antigens. The success of oncolytic virotherapy depends on factors such as the incorporation of immune-stimulatory transgenes into the virus and the patient's pre-existing antiviral and antitumour immunity.

Criteria for selection of oncolytic viruses for the treatment of tumours

For effective utilisation of oncolytic viruses in therapy, these viruses should meet stringent criteria so that both safety and efficacy are ensured.

***Safety*:** Designing a safe oncolytic virus requires careful consideration of specific criteria. The criteria include type of cancer, risk of reacquiring virulence, possibility of transmission to healthy individuals, unintended side effects and pre-existing immunity. Employing non-human viruses in treating cancers can help reduce these risk factors (Tayeb *et al*., 2015).

***Efficacy*:** The efficacy of viruses used as oncolytic agents can be improved by optimising delivery strategies and overcoming the host's antiviral

immune response. Antiviral response can be evaded by administering different viral serotypes during the treatment cycle, and polymer coating (modification of amino groups by mixing viral particles with polymers such as poly [N-(2-hydroxypropyl)methacrylamide] (Phpma) bearing reactive 4-nitrophenyl esters on pendent diglycyl side chains) so that antibody cannot recognize the virus particle and use of cellular vehicles (Moaven *et al*., 2021).

Morphology of Newcastle Disease Virus

Newcastle disease virus (NDV) causes Newcastle disease (ND), a severe illness in chickens and other birds (Miller and Koch, 2013). Virions are pleomorphic, but mostly spherical with size just more than 100 nm. The virion is enveloped with a lipid membrane derived from the host cell's plasma membrane. The envelope is covered by two glycoproteins—the Haemagglutinin- Neuraminidase (HN) and the fusion (F) protein. Just below the envelope is the matrix (M) protein, a non-glycosylated protein. The core of the virion consists of a nucleocapsid with herringbone morphology. Genome of Paramyxoviruses is a single-stranded RNA (15,186 to 15,198 nucleotides (nt) in length) and replicon complex proteins—the nucleocapsid (N), the phosphoprotein (P) and the large polymerase protein (L) (Samal, 2011).

Immunobiology of NDV

Most of the single stranded RNA viruses involve formation of double-stranded RNA (dsRNA) intermediates during replication. This dsRNA intermediate, a foreign structure, triggers a key cellular immune mechanism driven by type I interferons, such as IFN-α and IFN-β. The interferon system is often impaired by mutations in tumour cells, enabling uncontrolled proliferation and resistance to apoptosis (Fenton *et al*., 2021). Mutations in tumour cells of non-permissive hosts make them relatively more permissive for replication of RNA viruses such as NDV.

The identified mechanisms that explain replication of oncolytic virus in tumours and induction of oncolysis in non-permissive hosts include: (i) defects in antiviral signalling pathways, (ii) impaired type I IFN signalling, (iii) dysfunctional apoptotic pathways, and (iv) activation of Ras signalling and Rac1 protein expression (Kaufman *et al.,* 2015).

Infection of susceptible cells with NDV involves regular steps that occur during virus replication *viz.,* attachment of virus to host cell receptors, fusion of viral membrane to cell membrane, transcription and translation of virus-specific genes and synthesis of new virions. Though normal cells in non-permissive hosts do not allow viruses to synthesize viral genes, NDV is an exception, where nearly all tested human/murine tumour cells and transformed cells infected with NDV proceeded to the next step, thus allowing virus replication selectively in tumours. NDV replicates 10,000 times rapidly in tumour cells than in normal healthy cells (Lam *et al.,* 2011).

*Oncolysis and immunogenic cell death***:**

Immunogenic cell death (ICD) is a key paradigm in OV-mediated immunotherapy, transforming the way cancer treatment leverages the immune system. (Kroemer *et al*., 2013). ICD is a regulated cell death whose induction is sufficient to generate an adaptive immune reaction against the antigens of the deceased cell in an immunocompetent host. Since induction of ICD is feasible with conventional cytotoxic agents, it is also a promising approach towards the immunotherapy of cancer (Rodrigues *et al*., 2022).

The NDV-induced ICD in tumour cells is characterized by several key processes. The viral infection triggers endoplasmic reticulum stress, leading to the pathways that enhance the release of DAMPs, such as calreticulin exposure and ATP secretion. This stress response plays a crucial role in priming the immune system. Newcastle disease also promotes programmed cell death in a manner that enhances antigen presentation and immune activation. The apoptotic tumour cells release High mobility group box-1 (HMGb1) protein and other signals that stimulate dendritic cells and T-cell responses (Rodrigues *et al*., 2022). In addition to apoptosis, NDV infection can cause necrotic cell death, further amplifying inflammation and immune recruitment through the passive release of antigens associated with tumours and DAMPs. NDV-induced autophagy supports ICD by sustaining ATP release, maintaining intracellular antigen processing, and improves the microenvironment of the tumour to favour immune activation (Ye *et al*., 2018).

It was shown that virotherapy with NDV in an orthotopic murine glioma model, induces ICD with release of several key molecules such as calreticulin, HSP and HMGb1. These ICD-associated signals initiate a robust anti-tumour immune response, leading to the activation of tumour-specific T cells followed by T cell memory that is also tumour specific (Koks *et al.,* 2015).

Haemagglutinin-neuraminidase (HN) protein was identified as a key factor in activating innate immune responses. Notably, HN is recognised by the pattern recognition receptor (PRR), Nkp46, on murine natural killer (NK) cells and enhances NK cell activity. NDV also activates monocytes and macrophages, contributing to its tumouricidal effects through multiple immune mechanisms such as TRAIL- mediated cytotoxicity (TNF-related apoptosis-inducing ligand) and nitric oxide (NO) production (Schirrmacher *et al*., 2022).

It is notable that systems biology was employed to study the behaviour of NDV on dendritic cells (DCs) in humans. An avian virus, Newcastle disease virus, has been used as a reference strain to understand the

unrestricted cellular response of human DCs. Unlike some human-adapted viruses that have evolved immune evasion mechanisms, NDV triggers a strong, uninhibited immune response in human DCs. NDV induces an antiviral state in human DC's and is associated with their polarization toward a type 1 DC (DC1) phenotype. This polarization is crucial for shaping an effective anti-tumour immune response. NDV infection drives DC1 polarization, favouring the production of IL-12, which is essential for inducing Th1 responses (Schirrmacher *et al*., 2022). Th1 cells secrete IFN-γ, supporting CD8+ T cell activation and cytotoxicity. HN receptors on the tumour cells infected with oncolytic viruses are shown to enhance the interaction of these cells with CD4+ Th1 and CD8+ Tc cells. By integrating these mechanisms, NDV fosters a robust DC1-driven Th1 response and T cell-mediated tumour destruction, reinforcing its potential as a powerful oncolytic immunotherapy (Zhao *et al*., 2021).

In vivo anti-tumour effects

Mesogenic attenuated strain of NDV, PV701, has demonstrated potent anti-tumour effects in preclinical models. PV701 strain injected directly into the tumour and into the peritoneal cavity led to complete and long-lasting tumour regression in thymic mice implanted with xenografts of human fibrosarcoma and neuroblastoma. This suggests strong oncolytic activity and immune-mediated tumour clearance.

The velogenic NDV strain, *Italien,* induced syncytium formation in the tumour cells upon direct administration into the tumour. This fusion promotes extensive cell death, enhancing the virus's oncolytic effect and facilitating viral spread within the tumour. Athymic (immunodeficient) mice treated with recombinant NDV, despite lacking functional T cells, experienced extended survival, indicating the ability of virus to directly lyse tumour cells independent of adaptive immunity. NDV treatment also mitigated cancer-associated cachexia, reducing weight loss in tumour-bearing mice (Pei *et al*., 2024).

Research on orthotopic glioma in immune-competent syngeneic mice demonstrated that intra-tumoural virotherapy with NDV induces immunogenic cell death (ICD), leading to long-term survival. An active and functional adaptive immune system provides protective immunity, highlighting the role of CD8+ cytotoxic T lymphocytes (CTLs) in tumour regression, directly targeting and eliminating glioma cells (Lemos de Matos *et al*., 2020). The immune response was tumour antigen-specific, preventing the metastatic outgrowth and ensuring systemic protection beyond the primary tumour site.

The NDV can replicate in tumour cells that have stopped proliferating, including tumour vaccine cells irradiated with X-rays. Because its replication occurs in the cytoplasm and is independent of cell proliferation, oncolytic NDV may target tumour stem cells and dormant tumour cells, which are often resistant to chemotherapy and radiotherapy. Additionally, NDV can replicate in apoptosis-resistant, hypoxic, and interferon-resistant tumour cells (Fournier *et al.,* 2012).

Anti-fibrotic activity

Fibrosis of liver is a serious global health issue, contributing to significant morbidity and mortality (Younossi *et al*., 2023). Hepatic stellate cells are central to the development of liver fibrosis, as they transition from a quiescent state to activated, fibrogenic myofibroblasts in response to liver injury. Once activated, these cells produce excess collagen and extracellular matrix proteins, driving the scarring and structural distortion characteristic of fibrotic liver disease (Tsuchida and Friedman, 2017).

NDV has shown potential in reversing liver fibrosis in mice. When injected into fibrotic livers, NDV replication was observed in both murine primary hepatic stellate cells (HeSCs) and LX-2 cell line, as confirmed by co-localization with alpha-smooth muscle actin (α-SMA), a marker of activated HeSCs. NDV infection led to a reduction in collagen fibril production and matrix metalloproteinase (MMP) levels, indicating a decrease in extracellular matrix deposition. Furthermore, viral replication in HeSCs triggered apoptosis, effectively eliminating these fibrosis-driving cells. These findings suggest NDV as a potential antifibrotic agent by selectively targeting activated HeSCs. (Li *et al.,* 2009). Given the critical role of liver fibrosis in advancement to liver cellular carcinoma, these findings have significant clinical implications.

NDV-based approaches in cancer therapy

The research on the application of NDV in tumour treatment has progressed to clinical trials, including phases I, II, and III. NDV is employed as an agent for cancer therapy in three different methods: (1) Injection of infectious virions alone, (2) Injection of NDV-infected cancerous cells that are intact, (3) Injection of the protein lysate of NDV-infected tumour cells, and (4) Combined use.

The attenuated oncolytic NDV vaccine strains MTH-68/H and PV701 were previously explored as whole-virus therapy for cancer treatment. Inhalation of 4,000 infectious units per day, for 6 months weekly twice, was associated with a reduction in symptoms associated with human high-grade glioma and improved survival rates (Csatary *et al.,* 1993; 2004).

The autologous live cell tumour vaccine ATV-NDV was developed by modifying tumour cells through infection with the less virulent NDV strain, such as Ulster, along with γ-irradiation (Schirrmacher *et al*., 1998). This approach ensures that the tumour cells remain immunogenic while losing their ability to proliferate. Ulster strain follows an

abortive monocyclic replication cycle in cancer cells, meaning the virus replicates only once, producing non-infectious progeny. This controlled proliferation leads to tumour cell apoptosis while preventing further viral spread.

Cassel *et al.* (1977) developed another direction based on oncolysates derived from a melanoma infected with an oncolytic NDV strain, *73-T,* which was evaluated for anti-tumour immune responses (Shalhout *et al*., 2023). The key finding was that viral oncolysates enhanced anti-tumour immunity by combining the benefits of post-oncolytic immune responses with targeted tumour-specific immunization.

Another strategy for enhancement involved increasing T-cell co-stimulatory signals. This was achieved by attaching NDV-specific single-chain antibodies with dual specificity (bispecific antibody fusion proteins) to ATV-NDV. An example is the bsHN-CD28 antibody, which targets both the NDV hemagglutinin-neuraminidase (HN) and the T-cell co-stimulatory receptor CD28 (Schirrmacher *et al*., 2015). In a Phase I trial, 14 colorectal cancer patients with late-stage disease, ineligible for curative surgery, were treated with ATV-NDV-bsHN-CD28. No severe adverse events were reported. All patients exhibited an immune response, with tumour-reactive MTC's detected at least once over five vaccinations. A dose-response relationship was observed with the co-stimulatory molecule attached to the vaccine. Notably, four patients experienced a partial response, with metastatic tumours decreasing by more than 30% according to RECIST criteria.

Another approach to enhancement involved combining viral oncolysate (VOL) from ATV-NDV with DC's. At the Immunological and Oncological Center (IOZK) in Cologne, Germany, VOL-pulsed DCs were developed to enhance the de novo generation of tumour-associated antigen (TAA)-specific T cells from naïve T cells. In 2015, IOZK was officially authorized to administer this Advanced Therapeutic Medicinal Product (ATMP) to individual cancer patients.

Investigation on mice with induced cervical tumors treated with NDV, Doxorubicin and a combination of both revealed that NDV could boost the antitumor effects of Doxorubicin. The study found that the combined therapy group had significantly better survival rates and slower tumor growth than groups receiving only one treatment or none. This combination also triggered stronger antitumor immune responses, as seen by increased levels of Th1 cytokines (such as TNF-α, IL-12, and IFN-γ) and markers of tumor cell destruction, while decreasing pro-tumor Th2 cytokines (like TGF-β and IL-4).

Recent clinical advances have highlighted the promise of NDV as an oncolytic agent in cancer therapy. In a 2024–2025 clinical trial, a genetically engineered NDV expressing the porcine α1,3GT gene (NDV-GT) was administered intravenously to 20 patients with relapsed or refractory metastatic cancers. The study reported a disease control rate of 90%, with durable clinical responses and no serious adverse events observed. Notably, there was no development of clinically functional neutralizing antibodies, underscoring the favorable safety and immunogenicity profile of NDV-GT. This trial (Chinese Clinical Trial Registry: ChiCTR2000031980) underscores the ongoing progress in the clinical application of NDV, especially as a platform for combination therapies, and demonstrates its potential as a safe and effective oncolytic virus for advanced malignancies (Zhong *et al.,* 2025).

Other oncolytic viruses in development

A wide range of viruses have been explored as oncolytic agents due to their ability to selectively infect and destroy cancer cells. Among the most prominent examples are herpes simplex virus (HSV), with HSV-1-based therapies already approved for melanoma and under investigation for brain tumors, and adenoviruses, many of which are genetically engineered for tumor selectivity and have advanced to clinical trials for various malignancies (Yang *et al*., 2021). Vaccinia virus, previously used for smallpox vaccination, is now engineered for oncolytic activity and immune stimulation, while Reovirus naturally targets tumor cells with activated Ras pathways and has advanced in clinical evaluations, including as "Reolysin". Other viruses in clinical and preclinical development include Coxsackievirus A21 for melanoma and bladder cancer, Vesicular stomatitis virus (VSV), which demonstrates potent activity against tumors with defective interferon responses, and modified Polioviruses for neuronal-derived tumors (Cook and Chauhan, 2020). Parvoviruses, Measles virus vaccine strains re-targeted to specific cancer antigens, and Newcastle Disease Virus (NDV) also show promise in diverse oncological settings. Additional notable viruses under investigation include Myxoma virus, Maraba virus, various Poxviruses, Seneca Valley virus, and Echoviruses. Collectively, these viruses exemplify the rapidly evolving field of oncolytic virotherapy and hold significant potential for the targeted treatment of numerous cancers.

Repeated NDV vaccinations can trigger neutralizing antibodies that may reduce the antitumour effectiveness of NDV-based therapies. Additionally, the tumour extracellular matrix can hinder the spread of viral particles and immune cells, while the immunosuppressive tumour microenvironment can further limit vaccine efficacy. Low immunogenicity in some tumours also presents a significant challenge in generating strong tumour-specific immune responses. Addressing these barriers is essential in enhancing the therapeutic potential of virotherapy for advanced cancers.

Conclusion

NDV, an avian RNA virus, offers valuable insights for cancer therapy. It meets key criteria for a promising therapeutic agent in humans, including a strong safety profile, minimal side effects compared to chemotherapy or radiotherapy, multiple anti-tumour mechanisms, robust type I IFN response, and broad immune stimulatory effects. Humans and mice, though considered as non-permissive hosts, allows NDV to replicate selectively in tumour cells, inducing oncolysis. Continued research and clinical application of NDV hold significant potential for advancing cancer therapy.

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The work presented in this review includes information gathered from contributions of many scientists and clinicians in the investigations on the potential of NDV as anticancer immunotherapeutic agent. Their names can be obtained from the list of the quoted references.

Conflicts of interest

The author reports no conflicts of interest.

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