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Editorial Article Open Acess

# Oncolytic Virotherapy: A Brief Overview

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## Editorial

Oncolytic virotherapy is the use of viruses to target a tumor for infection and lysis while leaving healthy cells uninfected. The history of viral oncology dates back to the turn of the 20th century when clinicians observed spontaneous regression of tumors after vaccination with attenuated viruses [1]. Experiments were done in the 1950s using Picornaviruses but soon fell out of favour to chemotherapies and radiation. Further studies into the efficacy of viral oncolytic therapy took place throughout the second half 20th century but didn't begin in earnest until the last two decades. The first viral candidates introduced as possible oncolytic agents were herpes simplex II [2-4] and members of the adenovirus family. Current strategies in viral oncolytics are based on research pioneered in these two viral families and now include viruses from Poxviridae, Picornaviridae, and Rhabdoviridae [2].

Current investigational treatments of cancer using viral oncolytics relies on a comprehensive library of viruses to maximize applicability and target different types of cancers while simultaneously circumnavigating the issue of acquired viral-immunity [5,6]. Current approaches for engineering candidate viruses to be used as oncolytic agent are threefold. First, ablation of genes responsible for replication usually serves as a backbone for further generated viruses. The second approach involves ablation of immunoregulatory genes that viruses use to suppress host immune response. Finally, some viruses feature the inclusion of non-viral immunoregulatory genes to further stimulate host innate and adaptive immune response [7].

To restrict viral tropism, genes responsible for normal viral replication are targeted for ablation. The most common target for this is the thymidine kinase genes, as the normal cellular levels are usually low. The inverse is true in cancer cells [8,9]. This selectivity, in the case of the thymidine knockouts, is present because normal cells that are not undergoing rapid division will not have an excess of thymidine or thymidine kinase and will therefore hinder viral replication long enough for the host to defend itself against infection [10]. Cancer cells, which are always mitotic, more often than not have an excess of thymidine which the virus can use to successfully replicate its genome [8]. Current research using thymidine kinase knock-outs for Herpesvirus, Adenovirus, Picornaviruses, and *Tanapox virus* is ongoing and showing various degrees of success [8,11].

To further restrict tissue tropism and limit infection of healthy cells, additional genes have been targeted for ablation. Large DNA viruses usually encode multiple genes which are responsible for down regulating host immune response to infection [12]. These same pathways also are part of pathways implicated in oncogenesis. Because of this, tumor cells often have disregulation of genes comprising the NF-kB pathway. This allows for corresponding genes to be targeted for ablation in candidate virus, such as E1 in adenovirus [13]. Another target for knock-out is the ICP47 in herpes simplex viruses, which blocks the viral peptides from interacting with MHC I [4]. A final example of a target for ablation is genes that regulate TNF-alpha production. *Tanapox virus* contains a gene, 2L, which has been shown to down regulate TNF-alpha function in healthy cells. Current research is being done to determine the efficacy of this knock-out in colorectal cancer models both *in vitro* and *in vivo* [8].

In addition to the various knock-outs of viral genes, immunostimulatory transgenes have also been experimentally inserted into the viral genome. These genes function to induce production of chemokines and cytokines to stimulate the immune system and increase its ability to identify and destroy cancer cells [7]. Cytokine-chemokine mediated tumor regression works through a variety of mechanisms. Infiltration of the tumor is one result of cytokine/chemokine production, which draws immune cells to the tumor microenvironment where they can assert their effects through direct interaction of cancer cells. Differentiation of immune cells occurs as a result of certain stimulatory genes, such as GMCSF seen in *Tanapox virus* and Herpes simplex virus models, to prompt phagocytic and cytotoxic activities [6-8]. Once localization and infiltration of the tumor have occurred, additional signaling mechanisms may be activated to work synergistically toward tumor reduction. Additionally, activation of surface Toll-Like Receptors (TLR), specifically TLR5, by transgenic bacterial flagellin component C (FliC) can induce intracellular cascades that result in activation site inflammation [8].

The current treatment paradigm, using radiation, surgery and chemotherapeutics has shown to be both expensive financially and physically, and sometimes without desired results [14]. Because of this alternatives need to be explored. Past and current research in viral onoclytics has and continues to show them as viable candidates for treatment for a multitude of different cancers. Viral oncolytic therapy shows great promise as a powerful tool for clinicians in the treatment of tumors [2].

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