Cell Host & Microbe
Minireview

# Viruses for Tumor Therapy

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Oncolytic virotherapy exploits live viruses with selective tropism for cancerous cells and tissues to treat cancer. As discussed here, the field has progressed considerably as a result of both the successes and failures of previous and on-going clinical trials for various cancers. These studies indicate that oncolytic viruses are remarkably safe and more efficacious when virus replication stimulates sustained antitumor immune responses. In the future, virotherapy should be combined with immunomodulatory reagents that target immune tolerance to established cancers.

## Introduction

The field of oncolytic virotherapy began as an observational science more than a century ago when it was noted that cancer regressions sometimes occurred spontaneously in patients following certain viral infections, (Kelly and Russell, 2007). These early anecdotes spawned a small number of clinical studies beginning in the 1940s using unmodified, and sometimes dangerous, test viruses. Although there were often glimmers of activity in these studies, the field of anticancer viral therapy languished for several decades, in part because of the early success of chemo and radiation therapies but also due to our limited understanding of the biology of these complex biological agents. The recombinant DNA revolution of the last 30 years has now provided the tools necessary to better understand, at the molecular level, how viruses attack and usurp host cell machinery. These advances coupled with those in the field of cancer biology have reignited interest in the use of replicating viruses as cancer therapeutics. Over the last two decades in particular, a variety of DNA and RNA viruses shown or engineered to be selective for cancer cells have transitioned from preclinical studies into early phase clinical testing and more recently into randomized clinical trials. The current status of ongoing clinical trials, and the candidate oncolytic viruses that are in various stages of development, have been summarized in great detail within many recent reviews, and the reader is encouraged to consult these for details regarding specific viruses and cancers under active clinical investigation today (for example, see Bourke et al., 2011; Donnelly et al., 2012, 2013; Eager and Nemunaitis, 2011; Russell et al., 2012; Patel and Kratzke, 2013; Sze et al., 2013; Vacchelli et al., 2013; Miest and Cattaneo, 2014). Our intent is to summarize some of the general trends currently emerging based on the clinical experiences to date, and to comment on the future prospects for oncolytic virotherapy assuming a more prominent role as a licensed modality that would join the current standard therapeutic trio of clinical oncology practice: i.e. surgery, chemotherapy and radiotherapy.

### *Oncolytic Viruses Target Cells with Malignantly Altered Signaling Pathways*

The startling recent advances in the sequencing of cancer patient genomes continue to re-enforce the notion that cancer is a complex, heterogeneous disease that defies treatment with agents that target only a single genetic mutation. As Bert Vogelstein noted in 2008, to make significant advances in cancer therapy, "the focus should shift from hunting for individual genes that cause certain cancers, to disrupting broader biological pathways that support cancer growth" (Hayden, 2008). We argue that oncolytic viruses are indeed just such agents, because they thrive in tumor cells where pathways are malignantly activated or disrupted and can exploit the deregulated metabolic processes that characterize cancerous transformation. However, because different oncolytic viruses likely benefit or even require specific alterations in host cell pathways, it has been difficult to identify individual molecular markers that predict specific antitumor efficacies for each oncolytic virus. While this remains an active area of research, the explanations for the precise tumor specificities of specific viruses vary widely from one virus/cell scenario to the next (Russell et al., 2012). Despite this, several overarching themes have become apparent to rationalize selective virus targeting of cancer cells. There is little doubt that the unbridled metabolism of tumor cells provides a selective niche for many viruses that benefit from dysregulated cell growth in general. Additionally, most, if not all, cancer cells during the transformation process undergo alterations that sacrifice elements of their potent cellular, innate antiviral response pathways. Thus, cancer cells in general become collectively susceptible to many more viruses than their parental nontransformed cellular counterparts and are often less responsive to the induction of the antiviral state by self-protective cytokines such as the type I and II interferons (IFNs) or tumor necrosis factor (TNF). There is a complex array of cellular defenses that have developed over evolution to combat virus infections, and, not surprisingly, each successful virus family has developed different strategies to overcome these collective antiviral responses, at least in their specific evolutionary hosts. Given the diversity of genetic alterations documented in cancer cells, it remains unlikely that a single "magic bullet" virus will ever be identified that would treat all cancers equally. Instead, viruses with differing cellular attack mechanisms will have to be matched with pathway-specific cancer cell defects.

### *Delivery Issues: In vivo, In situ, Ex vivo, or FedEx?*

Oncolytic viruses are quite unique as cancer therapeutics, since they are capable of productive replication within the tumor bed and have the potential to "self-amplify," thus spreading

**Table 1. Clinical Trials of Oncolytic Viruses**

| Virus Family | Examples | Genetic Modifications | Target Cancers | Clinical Trial Sponsor |
|---|---|---|---|---|
| Adenovirus | Oncorine (H101) | Ad-E1b$^-$ | Liver, lung, head/neck, pancreas | Shanghai Sunway (approved in China) |
| | CGTG-102 | Ad-GMCSF$^+$ | Solid tumors | Oncos |
| | DNX-2401 | Ad-d24RGD | Brain | DNAtrix/Erasmus Medical Center |
| | ICOVIR-5 | Ad-DM-E2F-K-d24RGD | Melanoma | Institut Catala d'Oncologia |
| | CG0070 | Ad-GMCSF$^+$ | Bladder | Cold Genesys |
| | Colo Ad1 | Ad3:Ad11p hybrid | Metastatic solid tumors | PsiOxus |
| Herpesvirus | T-VEC | HSV1-ICP34.5$^-$/4$^-$GMCSF$^+$ | Melanoma | Amgen/BioVex (completed Phase III) |
| | Seprehvir | HSV1716-ICP34.5$^-$ | Lung, various solid tumors | Virttu Biologics and Children's Hospital |
| | G207 | HSV1-ICP34.5$^-$/6$^-$ | Brain | MediGene |
| | HF10 | HSV-HF strain | Head/neck, skin, breast, melanoma | Takara Bio |
| Poxvirus | Pexa-Vec/JX594 | Vaccinia Wyeth TK$^-$/GMCSF$^+$ | Liver, colorectal, head/neck, others | Jennerex (multiple trials) |
| | GL-ONC1 | Vaccinia Lister-GFP$^+$ F14.5L$^-$/TK$^-$/A56R$^-$ | Peritoneal cavity, head/neck, others | GeneLux (multiple trials) |
| Paramyxovirus | Measles virus | MV-NIS$^+$, MV-CEA$^+$ | Ovarian, peritoneal, myeloma, others | Mayo Clinic/NCI (multiple trials) |
| | Newcastle disease virus | Natural isolate (HUJ) | Glioblastoma multiforme, neuroblastoma, sarcomas | Hadassah Medical Organization |
| Reovirus | Reolysin | Reovirus-serotype 3 | Diverse cancers | Oncolytics Biotech Inc (multiple trials) |
| Rhabdovirus | Vesicular somatitis virus | VSV-IFNb$^+$ | Hepatocellular carcinoma | Mayo Clinic |
| | Maraba virus | MAGE A3$^+$/Matrix glycoprotein mutations | Lung, colon, melanoma | NCIC Clinical Trials Group |
| Picornavirus | CAVATAK | Coxsackievirus-A21 | Melanoma | Viralytics (multiple trials) |
| | PVS-RIPO | Polio:Rhino virus chimera | Glioblastoma | Duke University |
| | Seneca Valley V. | Natural isolate (NTX-010) | Neuroendocrine tumors | Children's Oncology Group |
| Parvovirus | H-1 PV | Natural isolate | Glioblastoma | Heidelberg University Hospital |

within and between tumors. This property allows them to be administered in multiple different ways to the patient, including systemic infusion, intratumoral injections, and/or combinations thereof. For localized cancers, for instance, those contained within the skull, it may be appropriate to use strategies like convection-enhanced delivery, which uses a surgically implanted catheter to focus the virus payload in the local vicinity of the brain tumors. Similarly, in diseases like hepatocellular carcinoma, where the standard of care includes locoregional therapy through direct injections or radio frequency ablation, intratumoral virus administration is easily implemented. For patients with metastatic disease, it seems reasonable to propose that intravascular infusion would be the preferred route, as it potentially provides access to all vascularized tumor sites within the body. However, if virus-induced acquired antitumor immunity is in fact the end goal, the blanket infection of every available cancer cell in situ may not be necessary. For example, the recent Amgen melanoma trial (see Table 1) is a clear example where the effective treatment of metastatic disease was accomplished through direct peripheral tumor injections. In this case, the induction of systemic antitumor immunity in therapy responders was accomplished by the direct infection of only a limited subset of tumor lesions manifested by the patient.

In contrast to treating cancer in situ, one particular subset of virotherapy is to target and eliminate potential cancer cells that can contaminate self-transplant tissues or cells ex vivo, prior to tissue engraftment into the patient. This ex vivo purging strategy offers the prospects of delivering oncolytic virus to all of the potential cancer cells within a given patient transplant sample (for example, in order to eliminate even low levels of cancer stem cells that might reside within an autologous hematopoietic stem cell transplant specimen) (Rahman et al., 2010).

Another virus delivery strategy that has received a great deal of attention but has not yet been exploited in oncolytic virotherapy clinical trials involves using patient cells as virus carriers. This delivery mechanism uses cells, particularly immune cells that exhibit a natural predilection to migrate to tumor sites within the body, as cellular carriers that can be infected with therapeutic virus ex vivo, then infused back into the patient with the hope that they will deliver live oncolytic virus to distant