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Oncolytic viruses: perspectives on clinical development

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Developing a live anti-cancer agent derived in most cases from human pathogens presents a unique set of challenges to clinical development versus those anticipated with standard chemotherapeutics and small molecules. The selection of therapeutic targets for oncolytic virus (OV) clinical development, as is true with the development of any agent for cancer therapy, requires careful consideration beyond preclinical and early clinical data, especially when multiple indications may initially appear equally promising. Further, the added complexity of the potential for infectious complications following OV therapy must be anticipated in order to efficiently and safely conduct clinical studies. As more OV enter the clinic, these issues will become increasingly important to successful OV drug development.

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Introduction

Unlike non-specific DNA poisons, monoclonal antibodies or even small molecule targeted therapies Oncolytic Viruses (OV) package multiple genetic effectors into a single agent [1]. As live biological agents designed to specifically target cancer, OV present both distinct advantages as well as unique challenges to clinical development. It is important to consider, as more OV constructs transition from the lab to the clinic, the complexities of OV product development, the lessons learned from OV agents that have been studied in human trials, and understand the fundamentals of drug development relevant to this growing field.

Preclinical studies and Phase 0 clinical trials

Mouse models are commonly used to test for toxicity and efficacy of novel therapeutics. However, in contrast to small molecule or protein therapeutics, mouse models are likely not predictive of humans with respect to OV activity (e.g. many OVs have evolved from human pathogens and do not infect murine tissue). One class of mouse models are syngeneic (implantation of murine tumors into immunocompentent mice) or transgenic models (orthotopic tumors spontaneously develop). Syngeneic models present the advantage of studying OVs in the context of an intact immune system (e.g. study impact of anti-viral and anti-tumor immunity) and the background normal tissue is derived from the same species as the tumor (a fair model for OV selectivity) (Table 1). However, several OV species (e.g. measles and vaccinia) do not or poorly infect mouse tissue which could lead to an underestimation of both anti-tumor activity and toxicity if studied only in syngeneic murine models [2,3]. Furthermore, some human versions of immunomodulatory transgenes expressed from OVs (e.g. GM-CSF) are not active in rodents [4], therefore contribution of these additional MOA cannot be studied in mice. In this instance, alternate species, for example, rabbits, can be considered [5]. In contrast, human-mouse xenograft models present the advantage of productive OV replication in tumors, however the contribution of anti-viral and anti-tumor immunity cannot be studied. The induction of anti-cancer immunity (OV as immunotherapy alone or in combination with other immunomodulatory agents) may well be a better reflection of OV activity than direct virus-mediated oncolysis.

Given the challenges of assessing OV mechanisms-of-action in preclinical models, neoadjuvant or 'window of opportunity' (Phase 0) studies should be considered [6•]. The 'window of opportunity' study consists of pre-surgical treatment of patients who are otherwise candidates for potentially curative intent resection of tumors (e.g. early stage breast, lung, bladder and colon cancer). By treating with low dose and/or intratumoral OV prior to surgery, significant tumor material can be harvested to facilitate the investigation of OV infection, gene expression, tumor lysis, and toxicity (as in preclinical models) as well as the study of anti-viral and anti-tumor immunity within the context of the definitive model — patients with cancer. If a Phase 0 trial is not feasible, assessment of OV mechanism-of-action should be included as endpoints in Phase 1 trials (e.g. demonstration of selective OV infection of tumors on biopsy analysis [7]). Based on the above issues, for OV drug development in particular, it may

Table 1

Considerations when choosing mouse models to study OV toxicity and efficacy

Mouse model	Advantages	Disadvantages
Syngeneic/ transgenic	• Intact immune system to allow for study of anti-viral and anti-tumor immunity • Tumor tissue derived from same species as normal tissue • Orthotopic models and transgenic models more reflective of human disease	• Some OVs do not infect murine cells • Some immunomodulatory transgenes are species specific (not active in rodents)
Xenograft	• Human tumor tissue more susceptible to many OV species	• Cannot study contribution (deleterious or beneficial) of adaptive immune response • Normal murine cells may not be susceptible to OV infection limiting assessment of off target toxicity

be advisable to transition to human studies as soon as the minimum safety and proof-of-concept studies are completed in animal models in order to better gauge both the true promise and limitations of OV therapeutic candidates.

Clinical development: considerations for clinical trial design

Inherent OV properties as well as design elements engineered into OV constructs (e.g. inherent tropism for specific tissues, tumor selective replication, or transgene expression targeting a limited subset of tumor types) will of course influence the initial direction of clinical development. For instance, ColoAd1 was the product of a bioselection process to identify OV characteristics optimal for use in colon cancer, thereby driving development toward colorectal carcinoma [8] while the adenovirus CG0070 replication is controlled by the E2F promoter making RB pathway defective tumors rationale targets [9]. In order to better exploit OV as vaccines, expression of tumor associated antigens will logically limit tumor choice as well (e.g. MAGE-A3 expressing tumors [10]).

In addition to these fundamental initial considerations, the process of selecting therapeutic candidates for OV clinical development, as with the development of any agent for cancer therapy, requires careful consideration beyond preclinical and early clinical data, especially when multiple therapeutic areas may appear equally promising. In order to anticipate downstream development issues optimally, map out the Phases 1–3 approval pathway as the program transitions from the lab to the clinic. Engaging clinical scientists as early as possible in this process is essential in order to provide disease specific advice and context. Once a list of candidate tumor types can be determined based on, for instance, preclinical evidence supporting virus replication, gene expression, and cell kill, the following must be well thought out and debated by the combined scientific and medical team:

1. **Patient population**
   a. *Medical need*: Consider the standard of care (SOC) and the level of activity that will be needed to displace the SOC for the candidate tumor. For example, if the SOC for the candidate tumor yields a 70% durable complete response (e.g. Bacillus Calmette–Guérin for treatment naïve carcinoma *in situ* of the bladder [11]), it may be advisable to either consider another target tumor (or different stage of the same tumor) or have a very well-founded rationale for how the agent is uniquely suited for just this niche and will improve upon the SOC in terms of efficacy or safety.
   b. *Early versus late-stage disease*: Late-stage tumors with limited treatment options are traditionally targeted for drug development due to, in some cases, the lack of a SOC and perceived lower bar for regulatory approval. Targeting late-stage patients comes at cost of less fit patients who may not support MOA (e.g. immunosuppressed patients may not respond to agent hypothesized to stimulate the immune system), live long enough to benefit from therapy (especially if response is delayed), or may poorly tolerate therapy (in particular with OV therapies that may lead to untoward toxicities in immunosuppressed, heavily pretreated patients). For example, T-Vec (Talimogene laherparepvec, HSV-GM-CSF; Amgen), the OV in most advanced clinical development has completed Phase 3 testing in patients with melanoma [12•]. The study met its primary endpoint of improvement in durable response rate versus treatment with GM-CSF protein [13••]. An exploratory subset analysis revealed a clear OS advantage found in treatment-naïve but not pre-treated melanoma [14]. Arguably the outcome of the T-Vec study may not have been as compelling had it included only pre-treated patients or end-stage patients exclusively.
2. **Treatment regimen**
   a. *Method of OV delivery*: What is the risk or added complexity of the required delivery mode for the selected tumor? For example, aside from polio which appears be the exception based on early results [15], OV approaches for brain tumors have generally demonstrated minimal activity at least in