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Review

Oncolytic Viruses: Therapeutics With an Identity Crisis

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ABSTRACT

Oncolytic viruses (OV) are replicating viral therapeutics for the treatment of cancer and have been in laboratory development for about twenty years. Recently, the FDA approved Imlygic, a herpes virus based therapeutic for the treatment of melanoma and thus OVs have entered a new era where they are a weapon in the armament of the oncologist. OVs are unique therapeutics with multiple mechanisms of therapeutic activity. The exact path for their development and eventual uptake by pharmaceutical companies is somewhat clouded by an uncertain identity. Are they vaccines, tumour lysing therapeutics, inducers of innate immunity, gene therapy vectors, anti-vascular agents or all of the above? Should they be developed as stand-alone loco-regional therapeutics, systemically delivered tumour hunters or immune modulators best tested as combination therapeutics? We summarize data here supporting the idea, depending upon the virus, that OVs can be any or all of these things. Pursuing a "one-size fits all" approach is counter-productive to their clinical development and instead as a field we should build on the strengths of individual virus platforms.

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1. Breaking Through the Oncolytic Virus Glass Ceiling

There is a great deal of intellectual appeal in the concept of oncolytic viruses (OVs) as programmable biological machines that target, replicate in and ultimately destroy cancer cells. OVs have been under development in academic laboratories around the world for in excess of 20 years but like any new therapeutic idea, OVs have faced an uphill battle in achieving clinical validation and ultimately commercial acceptance. Only recently has the herpes virus based therapeutic, *Imlygic* (talimogene laherparepvec, Amgen), broken through the "glass ceiling" and emerged as an FDA and EMEA approved treatment for advanced melanoma. This has led to a virtual stampede (by OV standards) of small biotechnology companies vying to produce the next "*Imylgic*", at last count in excess of twenty burgeoning companies. According to

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BioCentury (Cuickner-Meisner, 2016) there currently are two OVs in phase III trials, nine in phase II, at least eight in phase I development and the number will increase by the end of the year.

2. Oncolytic Viruses Have Arrived: But What Are They? What Do They Do?

OVs are multi-mechanistic therapeutics but their versatility has left them suffering from an identity crisis - are they *in situ* vaccines, systemically administered cancer killers, potent oncolytic vaccines, anti-vascular agents, gene therapy vectors, or loco-regional adjuvants that stimulate innate immune reactions? The reality is OVs can be any or all of these things depending upon the virus platform under consideration and the clinical indication (Leveille et al., 2011; Breitbach et al., 2013; Melcher et al., 2011; Russell et al., 2012; Kelly and Russell, 2007; Russell et al., 2014; Kirn and Thorne, 2009; Kaufman et al., 2015; Lichty et al., 2014). With our advanced understanding of the molecular biology of cancers and virus:host interactions we are positioned to rapidly create tailored therapeutics with multiple mechanisms of action. Let's first consider OVs as loco-regional *in situ* vaccines.

3. Imlygic: The Case for an Oncolytic Virus In Situ Vaccine

Since the insightful development of Coley's toxin over a century ago, there have been numerous strategies developed to stimulate a cancer patient's immune response against their own tumour (Pierce et al., 2015; van der Burg et al., 2016). Much like Coley's toxin, these strategies provided provocative responses in small trials of select patients but for the most part, failed when tested more widely. These "*adjuvant and vaccine*" therapies were designed to drive immune responses against so-called tumour antigens including cancer testis antigens, over-expressed tissue specific proteins, aberrant post-translational modifications and neoepitopes created during malignant evolution (Rosenberg et al., 2004). The reasons for these frustrating failures were revealed by fundamental research into the signaling pathways that regulate our immune systems. We are genetically programmed to rapidly mount immune responses to invading pathogens but at the same time, just as quickly dampen immune responses to avoid acute cytokine storm toxicity and autoimmunity. These homeostatic mechanisms are controlled in large part by integrated *immune checkpoint* networks and in the tumour microenvironment, these critical regulatory pathways are usurped providing malignant cells with an immunosuppressive cloak (Pardoll, 2012). Given that therapeutics have now been approved that block this negative feedback loop, there is a renewed interest in *in situ* vaccines and other approaches that may show enhanced activity upon combination with *immune checkpoint inhibitors* (ICIs). For instance, so-called "*viral mimetics*" like imiquimod (Vasilakos and Tomai, 2013) and "*sting agonists*" are in development (Deng et al., 2014; Fu et al., 2015; Wang et al., 2016) in an attempt to re-polarize the tumour microenvironment making it immunologically responsive and like Coley's toxin, facilitating an environment conducive to creating an *in situ* vaccine.

4. Heating Up Immunologically Cold Tumours With an Oncolytic Virus

As discussed our immune systems have evolved elaborate mechanisms to react against invading pathogens and rapidly mount immune responses to eliminate the pathogen and in some instances, the cells they infect. OVs are natural pathogens that have been selected or designed to specifically infect and destroy cancer cells. Tumour cell infection by an OV leads to an inflammatory response with localized production of cytokines that favour the elaboration of an immune response (Breitbach et al., 2007; Worschech et al., 2009). At the same time, it is thought that virus mediated tumour lysis leads to the liberation of tumour associated antigens and/or mutant proteins that have arisen during tumour evolution. Indeed Woller and colleagues have shown in a mouse tumour model that oncolytic adenovirus tumour therapy stimulates therapeutically beneficial immune responses against mutanome peptides (Woller et al., 2015).

Imlygic has provided the first convincing human data supporting the idea that direct tumour lysis by a replicating virus can locally stimulate sufficient anti-tumour immune responses to provide systemic, long lasting, cancer killing immune responses in advanced cancer patients (Senzer et al., 2009; Kaufman et al., 2010; Andtbacka et al., 2015). This product was administered multiple times *via* direct intratumoral injection and, in the OPTiM pivotal phase III trial as a mono-therapy, generated durable responses in over 16% of patients (Andtbacka et al., 2015). At the time of FDA approval, Imlygic was shown to have improved overall survival *versus* treatment with GM-CSF ($p = 0.049$, Hazard Ratio $= 0.79$). In earlier phase I and II studies, Imlygic therapy was shown to increase T cell infiltration into tumours and generate a systemic immune response against tumour associated antigens like MART1 (Kaufman et al., 2010).

5. Timing is Everything! – Making a Good Therapeutic Great!

In a follow-up retrospective analysis of the OPTiM trial, Imlygic was found to generate complete responses in 17% of advanced cancer patients thus providing the oncologist with a new monotherapy treatment option for melanoma patients. However the better news is that Imlygic arrived on the scene coincident with the tremendous clinical excitement surrounding the approval of antibodies targeting immune checkpoint molecules (*e.g.* Yervoy [Bristol-Meyers Squibb] directed against CTLA4 and Keytruda [Merck], Opdivo [Bristol-Meyers Squibb] against PD1). As mentioned above, these immune checkpoint inhibitor antibodies interrupt negative feedback systems within the tumour bed effectively "taking the brakes off" pre-existing anti-tumour immune responses (Pardoll, 2012) and can create durable responses that are on a trajectory for cure as monotherapies in as many as 20% of patients (Topalian et al., 2012) (depending upon the indication). For the remaining 80% of patients it appears that a lack of anti-tumour immune responses or other immune suppressive aspects of the tumour microenvironment still need to be corrected before immune checkpoint inhibitors (ICIs) can provide benefit. Infection of tumours by an OV triggers induction of anti-tumour immunity and recruitment of T cells to tumours; addition of the ICI ensures those T cells remain active (Fig. 1).

Indeed, Imlygic seems to be a perfect complement to ICIs and as predicted, in ongoing phase I studies Imlygic used in combination with Yervoy significantly increases durable response rates in melanoma patients over what would be expected from either agent alone, perhaps providing benefit in as many as 50% of patients treated including many with significant tumour burden (Puzanov et al., 2016). The anti-PD1 immune checkpoint inhibitor Keytruda is also being studied in combination with Imlygic in patients with melanoma and head and neck cancer (NCT02263508, NCT02626000). Thus Imlygic continues to provide clinical evidence for the "*in situ vaccine*" paradigm for oncolytic viruses demonstrating that virus oncolysis, even in a limited number of tumours, can generate systemic anti-tumour immunity. These early clinical results are encouraging but they also raise a number of questions. Why do only a minority of patients experience complete response on Imlygic monotherapy even though direct injection of tumours should be the optimal way to deliver a maximum dose of virus to the tumour bed? Are the majority of tumours injected by this route only marginally infectable? Could a more potent OV have more profound tumour lytic and *in situ* vaccine effect? Can outcomes be improved with optimized Imlygic dosing strategies? Are uninfected tumours in the majority of patients resistant to the systemic immunity that local Imlygic therapy initiates? Will other tumour indications beside melanoma respond systemically after locoregional virus therapy?