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Pexa-Vec double agent engineered vaccinia: oncolytic and active immunotherapeutic

Caroline J Breitbach[1], Kelley Parato[2], James Burke[1], Tae-Ho Hwang[3,4], John C Bell[2] and David H Kirn[1]

Oncolytic immunotherapies (OI) selectively infect, amplify within and destroy cancer cells, thereby representing a novel class of anti-cancer therapy. In addition to this primary mechanism-of-action (MOA), OI based on vaccinia have been shown to selectively target tumor-associated vasculature, triggering an acute reduction in tumor perfusion. This review focuses on a third complementary MOA for this product class: the induction of active immunotherapy. While the active immunotherapy approach has been validated by recent product approvals, the field is still faced with significant challenges. Tumors have evolved diverse mechanisms to hide from immune-mediated destruction. Here we hypothesize that oncolytic immunotherapy replication within tumors may tip the immune balance to allow for the effective induction and execution of adaptive anti-tumor immunity, resulting in long-term tumor control following OI clearance. This immune activation against the cancer can be augmented through OI 'arming' for the expression of immunostimulatory transgene products from the virus genome. With the first vaccinia OI (Pexa-Vec, thymidine kinase-inactivated vaccinia expressing Granulocyte-colony stimulating factor [GM-CSF]) now in advanced-stage clinical trials, it has become more important than ever to understand the complimentary MOA that contributes to tumor destruction and control in patients.

Addresses
[1] SillaJen Biotherapeutics, 450 Sansome St, Suite 650, San Francisco, CA 94111, United States
[2] Ottawa Hospital Research Institute, 501 Smyth Road, Box 926, Ottawa, ON K1H 8L6, Canada
[3] SillaJen Inc., South Korea
[4] Medical Research Institute, Pusan National University, 1-10 Ami-Dong, Seo-Gu, Busan 602-739, South Korea

Corresponding author: Breitbach, Caroline J (cbreitbach@sillajen.com)

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An introduction to Pexa-Vec oncolytic immunotherapy

Therapeutic oncolytic immunotherapies (OI) constitute a class of cancer-targeted products that have unique mechanisms-of-action (MOA) compared with approved cancer therapeutics. OI are replication-competent viruses designed for selective replication and amplification within tumor cells [1,2]. These agents can also stimulate anti-cancer immunity directly (active immunotherapy), presumably through induction of intratumoral immune danger signals coupled with release of tumor antigens (discussed in more detail below). Numerous biological properties of vaccinia and other poxviruses have been proposed as optimal for their development as oncolytic and immunostimulatory agents for cancer [3•,4–9]. First, their potency is high relative to other virus species due to their rapid replication, cell lysis and motile spread; the rate of viral spread is a critical factor in determining oncolytic virus efficacy [10]. In addition, poxviruses have extremely broad tumor tissue infectivity [11]. Poxviruses are also highly efficient at spreading through the blood to distant tumors (including metastases) within a host, while maintaining resistance to neutralization within the blood stream. The result is that systemic delivery and spread between tumors is highly efficient with vaccinia [11–13]. Finally, the relatively large transgene expressing capacity (25–50 kB) allows the expression of multiple therapeutic and monitoring transgenes [3•,14]. Indeed, vaccinia has been explored clinically as a tumor-antigen delivery vector for cancer vaccination against a variety of cancer types including melanoma, cervical cancer, renal cell carcinoma, colorectal cancer, prostate cancer, and non-small cell lung cancer [15] (reviewed extensively in [16]).

Pexa-Vec (pexastimogene devacirepvec, JX-594) is an oncolytic immunotherapy (OI) based on the Wyeth vaccinia vaccine strain which has been engineered for viral thymidine kinase (TK) gene inactivation, and expression of the human granulocyte-monocyte colony stimulating factor (hGM-CSF) and β-galactosidase (β-gal) transgenes under control of the synthetic early-late and p7.5 promoters, respectively [12,17]. Administration of GM-CSF protein has long been used in patients to stimulate white blood cell (WBC) counts and has a long track record in cancer vaccination via expression in tumor cells or by viral vector delivery [18–20]. GM-CSF expression and subsequent induction of GM-CSF responsive WBC subsets has been detected in patients treated with Pexa-Vec by intravenous or intratumoral injection [21,22•,23]. Over 300 patients with advanced cancer have been treated with Pexa-Vec to date on Phase 1, 2 and 2b clinical trials ([21,22•,24–26]

and unpublished data). In a Phase 1 trial of intratumoral injection into liver tumors, Pexa-Vec was well-tolerated and associated with virus replication, expression of biologically active GM-CSF and tumor necrosis [21]. In a subsequent Phase 1 trial of intravenous administration, Pexa-Vec was detected in a dose-related fashion both by immunohistochemistry and quantitative polymerase chain reaction (Q-PCR) in tumor biopsy samples collected one week following infusion [22•]. Intravenous Pexa-Vec treatment was well-tolerated, with transient mild to moderate flu-like symptoms being the most common adverse events [21,22•]. Anti-tumor effects were observed in advanced cancer patients on these early-phase clinical trials [17,21,22•,27,28]. A randomized Phase 2 dose-ranging study in patients with advanced hepatocellular carcinoma (HCC; primary liver cancer) ($n = 30$) demonstrated that intratumoral Pexa-Vec injection was well-tolerated. Further, overall survival was significantly longer in the high-dose arm compared with the low-dose arm (median 14.1 months versus 6.7 months, hazard ratio 0.39; p-value 0.020) [24]. In contrast, a Phase 2b clinical trial in HCC patients who failed sorafenib therapy ($n = 120$) was recently completed and did not achieve the primary endpoint of prolonging overall survival in Pexa-Vec treated patients when compared to patients treated with best supportive care in this last-line, poor prognosis patient population. A Phase 3 study of Pexa-Vec in first-line HCC patients is planned.

Challenges with current active immunotherapy approaches: hurdles to overcome

Despite recent product approvals, hurdles remain for active immunotherapy as a field. Spontaneous, naturally-occurring cancers co-evolve with the host immune system. The immune system selects for the outgrowth of tumor cells that have low antigenicity. In addition, a micro-environment is selected for that is conducive to immune evasion and active immune suppression. At the same time, the immune system is also shaped by the tumor. The repertoire of potentially tumor-reactive T cell clones is often tolerized or anergized against tumor antigens. As a result, potentially responsive clones that could be activated, even in the absence of such immune suppressive mechanisms, are functionally inert. Thus, an 'awakening' intervention is required [29]. The mechanisms of T cell tolerance induction are beginning to be understood, and both central and peripheral tolerance are involved. Central tolerance involves the shaping of the immune repertoire to avoid self-recognition by pre-deletion of T cell progenitors that are autoreactive, thus restricting the number of potentially tumor-reactive naïve T cells. In addition, powerful peripheral tolerance mechanisms are in play to prevent the erroneous activation of potentially autoreactive T cell clones [30,31]. These blockades in the tumor microenvironment (reviewed extensively in [32]) include the following: (1) low expression of costimulatory molecules and/or major histocompatibility complex (MHC) on tumor cells; (2) enhanced expression of T cell inhibitory molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed Death-1 (PD-1); (3) production of soluble immune suppressive factors such as indoleamine 2,3-dioxygenase (IDO), transforming growth factor-β (TGF-β), interleukin 10 (IL-10), vascular endothelial growth factor (VEGF); (4) regulatory T cells (T_{reg}); and (5) myeloid-derived suppressor cells (MDSC). A large portion of the responsibility for maintaining peripheral tolerance rests on dendritic cells (DCs) and their ongoing sampling of self-antigen. Hypothetically, any intervention that reverses or overcomes any of these immunosuppressive forces would favor recruitment of effector cells and would facilitate elicitation of their effector function. In fact, investigators have attempted to prime and recruit tumor-reactive cytotoxic T lymphocytes (CTL) by inducing local inflammation using various Toll-like receptor (TLR) ligands including lipopolysaccharide (LPS), CpG DNA, or imiquimod, achieving signs of tumor regression [33–36]. While promising, systemic application of such potent inflammatory agents is not feasible, and such approaches are thus limited to cancers that are amenable to local injection. If such inflammation could be delivered systemically, and then amplified locally in tumors selectively, this therapeutic approach would be potentially viable.

Thus, efforts to mount immune responses without modifying the potent immune suppression within the tumor microenvironment are largely inadequate. In addition, classical cancer vaccines are limited by the relevant tumor antigen(s) choice, penetrance, and potential for mutation or evolved loss of expression. Generation of potent systemic anti-tumor immunity does not necessarily translate into tumor infiltration and effective activity of primed $CD8^+$ T cells [37]. Even transplantation of highly expanded and activated tumor-reactive tumor infiltrating lymphocytes (TILs) are met with the challenges of tumor infiltration and immune suppressive forces within the tumor, as well as host homeostatic mechanisms that curtail the longevity and further expansion of adoptively transferred T cells. For maximal efficacy, an immunotherapeutic approach should *prime* endogenous tumor antigen-reactive T cells, concomitantly *recruit* tumor antigen-reactive T cells into the tumor, and finally *reverse* the immunosuppressive tumor milieu. An immunotherapeutic strategy that exhibits these effects, in combination with a therapy that *debulks* tumors without immunosuppression, should maximize clinical benefit.