Oncolytic viruses are natural or genetically modified viral species that selectively infect and kill neoplastic cells. Such an innate or exogenously conferred specificity has generated considerable interest around the possibility to employ oncolytic viruses as highly targeted agents that would mediate cancer cell-autonomous anticancer effects. Accumulating evidence, however, suggests that the therapeutic potential of oncolytic virotherapy is not a simple consequence of the cytopathic effect, but strongly relies on the induction of an endogenous immune response against transformed cells. In line with this notion, superior anticancer effects are being observed when oncolytic viruses are engineered to express (or co-administered with) immunostimulatory molecules. Although multiple studies have shown that oncolytic viruses are well tolerated by cancer patients, the full-blown therapeutic potential of oncolytic virotherapy, especially when implemented in the absence of immunostimulatory interventions, remains unclear. Here, we cover the latest advances in this active area of translational investigation, summarizing high-impact studies that have been published during the last 12 months and discussing clinical trials that have been initiated in the same period to assess the therapeutic potential of oncolytic virotherapy in oncological indications.

**Keywords**: adenovirus; ColoAd1; mesenchymal stem cells; MV-NIS; reolysin; talimogene laherparepvec

**Abbreviations**: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; HR, hazard ratio; HSV, herpes simplex virus; ICD, immunogenic cell death; IL, interleukin; MPS, mononuclear phagocytic system; MSC, mesenchymal stem cell; T-vec, talimogene laherparepvec; TLR, Toll-like receptor

---

**Introduction**

The term “oncolytic virus” is commonly employed to identify a non-pathogenic viral strain that selectively infects and kills neoplastic cells while leaving their normal counterparts virtually unaffected. Thus, oncolytic viruses not only display a preferential tropism for transformed over non-transformed tissues, in thus far being oncotropic, but also trigger the massive demise of infected cells. Such a cytotoxic activity can be natural and simply reflect the so-called cytopathic effect, i.e., the lethal outcome of a replicative viral infection. Alternatively, oncolytic viruses can mediate cytotoxic effects upon the expression of (endogenous or exogenous) gene products, irrespective of their ability to drive a productive infection. Although the possibility to harness the lytic potential of viruses against cancer has been theorized as early as at the beginning of the 20th century, it is only with the advent of modern genetic engineering technologies in the late 1990s that the interest in oncolytic virotherapy has crystallized. Since then, dozens of viruses have been tested for their natural oncolytic activity or genetically endowed with cancer-specific cytotoxic functions or immunostimulatory properties. A precise description of these viruses goes beyond the scope of this Trial Watch. For additional details on the viral species that have been harnessed so far for oncolytic virotherapy as well as on the advantages and pitfalls associated with their use please see Refs. 1, 5 and 11.

Specificity is a critical requirement for the safety of oncolytic virotherapy and multiple strategies have been developed throughout the past 2 decades to improve the oncotropism of naturally occurring viruses or endow otherwise unspecific viral strains with a highly-targeted lytic potential. Such a specificity can be obtained by conventional genetic engineering (1) at the transductional level, implying modifications of surface proteins...
that allow for the infection of cells bearing one (or a few) tumor-specific markers on their surface;13-17 (2) at the transcriptional level, based on the use of promoters that are active in neoplastic cells only to control the expression of essential viral genes;18-25 (3) at the post-transcriptional/translational level, either based on the insertion of microRNA-binding elements in non-coding regions of essential viral genes, allowing productive infections to develop only in tissues that do not express such microRNAs;26-35 or involving the cloning of genes that are absolutely required for the viral cycle downstream of internal ribosome entry sites that are inactive in selected tissues;33-35 (4) at the post-translational level, either based on “destabilization domains” that render essential viral proteins unstable in tissues that are not artificially or naturally exposed to a specific stabilizing agent,36-38 or based on viral protein precursors that can be processed only in cells expressing specific (cancer-associated) proteases;39 and (5) at a cell-wide level, harnessing the ability of attenuated viral strains to productively replicate in neoplastic cells bearing peculiar genetic or epigenetic defects, such as the hyperactivation of Harvey rat sarcoma viral oncogene homolog (HRAS) or signal transducer and activator of transcription 3 (STAT3) as well as the inactivation of p53.40-46 Among these strategies, the use of oxygen-dependent degradation domains (ODDs) stands out as a convenient approach to specifically direct the cytotoxicity of oncolytic viruses to solid tumors based on their limited oxygen supply.38

In addition, genetic engineering has been largely employed to endow oncolytic viruses with (at least hypothetically) desirable features, including (but not limited to) an increased cytotoxic potential and a superior ability to drive cell-mediated immune responses.5,6,7 Thus, the viral genome has been integrated with sequences coding for (1) enzymes that convert non-toxic prodrugs into a lethal cytotoxic agent;46-50 (2) proteins that (at least on theoretical grounds) mediate tumor-specific lethal effects;56-58 or (3) short-hairpin RNAs targeting proteins that are necessary for the survival of neoplastic cells, such as survivin.59-61 All these approaches have been shown to improve the cytotoxic potential of oncolytic virotherapy, hence ameliorating its therapeutic profile (at least to some extent) in experimental settings.

Accumulating evidence indicates indeed that the antineoplastic effects of oncolytic virotherapy do not simply originate from cancer cell-autonomous mechanisms but involve the (re)activation of tumor-specific immune responses.62-70 Thus, the administration of oncolytic viruses to cancer patients has been associated with the insurgence of cellular as well as humoral antitumor immune responses of potential therapeutic value.71-74 Moreover, the clinical activity of oncolytic viruses seems to benefit from some extent of initial immunosuppression (which facilitates viral spread, see below) followed by the administration of immunostimulatory molecules (which exacerbate antitumor immunity).1,5 In line with this notion, oncolytic viruses have also been engineered to express (1) tumor-associated antigens (generating so-called oncolytic vaccines);75-79 (2) co-stimulatory molecules, such as CD40 ligand (CD40L) and CD80;80-84 (3) immunostimulatory cytokines, including interleukin (IL)-2,85-87 IL-12,88-95 IL-15,96-101 IL-23,102 IL-24,103-106 and granulocyte macrophage colony-stimulating factor (GM-CSF);73,89,107-113 or (4) chemokines, such as chemokine (C-C motif) ligand 7 (CCL7)114 and CCL19.115

The clinical profile of oncolytic virotherapy employed as a standalone therapeutic intervention is generally limited, for several reasons.1,5,116 These include (but may be not limited to): (1) the heterogeneous and relatively incomplete diffusion of oncolytic viruses within neoplastic lesions,117-119 (2) the equilibrium that is generally established between oncolytic viruses and continuously proliferating, non-infected cancer cells, which eventually shifts in favor of the latter owing to the insurgence of an antiviral immune response (at least in immunocompetent individuals);120-128 (3) the propensity of malignant cells to become resistant to oncolytic virotherapy,121,126,130-132 presumably reflecting their genomic instability;133,134 (4) the elevated diffusion among the population of viral species that are employed to create therapeutic strains, resulting in a significant fraction of individuals who are insensitive to some oncolytic viruses owing to neutralizing humoral immunity;135,136 (5) the elevated sensitivity of some oncolytic viruses to the complement system;137,138 (6) the sequestration of intravenously administered oncolytic viruses by the mononuclear phagocytic system (MPS) of the liver and spleen,139,140 limiting the availability of viral particles at the tumor site and (at least in some cases) causing driving serious, dose-limiting toxicities;141-145 and (7) the threats that are intrinsically associated with the use of replicating viral particles in cancer patients, who are particularly weak and often immunodepressed.144-150

Consistent efforts have been dedicated at the development of strategies that would circumvent (at least in part) these issues. For instance, several oncolytic viruses have been genetically manipulated to express endogenous (or co-administered with exogenous) inhibitors of angiogenesis.151-154 This approach may exert a dual benefit in that the inhibition of cancer-associated angiogenesis not only mediates direct antineoplastic effects,155,156 but also causes a normalization of the tumor vasculature that improves the delivery/penetration of therapeutic agents, including oncolytic viruses themselves.157,159 Along similar lines, tumor-infiltrating cells including macrophages,160-165 myeloid-derived suppressor cells,166-164 and mesenchymal stem cells (MSCs) have been harnessed as vehicles to selectively deliver oncolytic viruses to neoplastic lesions while shielding them from neutralizing antibodies and protecting them from sequestration by the MPS.166-170 Finally, several laboratories worldwide have demonstrated that the therapeutic profile of oncolytic virotherapy can be remarkably boosted by the co-administration of several chemotherapeutics, including (but not limited to) gemcitabine (an immunostimulatory nucleoside analog),171-173 paclitaxel (a microtubular inhibitor),174-178 temozolomide and cyclophosphamide (two alkylating agents),2,177,179 sunitinib (a relatively unspecific tyrosine kinase inhibitor)180-182 cisplatin (a non-immunogenic DNA-damaging agent),183-186 various histone deacetylase inhibitors,187 and 13-cis retinoic acid (a retinoid employed for the treatment of high risk neuroblastoma).188,189

Taken together, these findings indicate that oncolytic viruses can mediate therapeutically relevant anticancer effects in vivo. In line with this notion, clinical trials performed throughout the
2 past decades demonstrated that oncolytic virotherapy can be safely implemented in cancer patients and can exert substantial antineoplastic activity, at least in a fraction of individuals.

As it stands, no oncolytic virus is currently licensed by the US Food and Drug Administration and the European Medicines Agency for use in cancer patients (sources http://www.fda.gov/Drugs/default.htm and http://www.ema.europa.eu). Along similar lines, in spite of promising preclinical results,190-194 oncolytic virotherapy has not yet been approved as part of veterinary protocols in the US and Europe. Conversely, the Chinese State Food and Drug Administration approved a recombinant adenovirus (H101, commercialized under the name of Oncorine®) for use together with chemotherapy in refractory head and neck cancer patients as early as in November 2005.195-197

One year ago, in the May issue of OncolImmunology, we presented the scientific background to the use of oncolytic viruses in oncological indications and discussed recent clinical trials evaluating the safety and efficacy of this immunotherapeutic regimen.198 Along the lines of our monthly Trial Watch series,199-201 here we summarize the latest developments in oncolytic virotherapy.

Literature Update

Since the submission of our previous Trial Watch on this topic (March 2013),198 no less than 11 studies dealing with clinical aspects of oncolytic virotherapy have been published in peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed). Four of these studies tested a serotype-chimeric, infectivity-enhanced, conditionally-replicative adenovirus initially developed to specifically infect and kill ovarian cancer cells,202,203 either in its pristine configuration (Ad5/3-Delta24)204 or as a 2nd generation variant further modified to express GM-CSF (CGTG-102).72,73,205 Kim and colleagues investigated the feasibility and efficacy of intraperitoneally administered Ad5/3-Delta24 in 10 recurrent ovarian cancer patients. Nine patients completed the therapeutic protocol and only manageable Grade I/II side effects were recorded. In spite of the development of neutralizing immunity in all individuals, 6 out of 8 patients that could be evaluated for response experienced disease stabilization.204 Kanerva and coworkers tested multiple immunological and clinicopathological parameters in 115 cancer patients treated with CGTG-102, either as a single injection, either in a serial manner (3 injections over 10 wks), or in the context of a switch protocol involving the administration of viruses with modified capsid proteins to avoid neutralizing immunity. A good safety profile was recorded. Moreover, the serial regimen was associated with the induction of anticancer immune responses, with indirect indications of the mobilization of tumor-specific T cells to neoplastic lesions,164,206,207 as well as with an improved overall survival (as compared with the single injection-based protocol).73 Liikanen and collaborators assessed the clinical profile of CGTG-102 in combination with metronomic temozolomide and/or cyclophosphamide in 17 individuals affected by chemotherapy-refractory neoplasms. This chemoimmunotherapeutic regimen was well tolerated by all patients and elicited several signs of immunogenic cell death (ICD) in neoplastic cells, including the activation of autophagy and the release of high mobility group box 1 (HMGB1).208-214 This was paralleled not only by the release of pro-inflammatory cytokines but also by the activation of tumor-specific immune responses, which were observed in 10 out of 15 patients. Clinical effects were evident in 67% of patients treated with CGTG-102 plus temozolomide and/or cyclophosphamide and these individuals exhibited a trend for improved survival as compared with subjects receiving CGTG-102 only.72 Bramante et al. tested the clinical profile of CGTG-102 in 15 patients with treatment-refractory soft tissue (13/15) or primary bone (2/15) sarcoma. Of 12 patients who could be assessed for clinical outcome, 2 exhibited an objective (though minor) response, 6 stable disease, and 4 progressive disease. Median overall survival was 170 d, and 1 patient was still alive when the paper was published, approx. four years after oncolytic virotherapy.205

Different research groups investigated the clinical profile of Pexa-Vec (formerly known as JX-594), an oncolytic vaccinia virus engineered to selectively replicate in cells with alterations of the RAS pathway and to express GM-CSF.199,215-217 Kim and colleagues reported that the administration of Pexa-Vecto 3 patients with diverse tumors (in the context of a Phase I clinical trial) resulted in the insurgence of a cancer cell-specific, antibody-mediated, complement-dependent cytotoxic response, whose intensity positively correlated with overall survival.71 Breitbach and collaborators studied the effects of Pexa-Vec on the tumor vasculature in patients with treatment-refractory, histologically confirmed advanced/metastatic solid tumors (n = 18, from a Phase I clinical trial, NCT00625456) as well as in subjects with hepatic neoplasms of hepatocellular (n = 15) or colorectal (n = 1) origin (from Phase II clinical trials, NCT00554372 and NCT01171651). These authors demonstrated that Pexa-Vec infects not only neoplastic cells but also the tumor-associated (but not the normal) vasculature, resulting in its destruction and hence mediating antineoplastic effects.195

Markert and colleagues conducted a Phase I clinical trial to test the effects of the stereotactic intratumoral administration of G207, a conditionally replicating herpes simplex virus (HSV) Type 1 variant,218-220 in 9 glioblastoma patients allocated to receive a single 5 Gy dose of radiation 24 h later. Oncolytic virotherapy was well tolerated and 6 out of 9 patients exhibited stable disease or a partial response at least at one evaluation time point.221 Interestingly, interim overall survival data from a Phase III study comparing subcutaneous GM-CSF with intratumoral talimogene laherparepvec (T-vec), an oncolytic HSV variant manipulated to express GM-CSF,252,253 in over 400 patients with unresected Stage IIIB, IIIC or IV melanoma (NCT00769704) have been released by Amgen at the 2013 meeting of the American Society of Clinical Oncology (ASCO), which was held in Chicago last June. In this setting, 26% of patients receiving T-vec developed serious adverse effects, including cellulitis and pyrexia, as compared with 13% of patients receiving GM-CSF. At a predetermined interim analysis, median overall survival among T-vec- and GM-CSF-treated patients was 23.3 and 19.9
mo, respectively (HR = 0.79, 95% CI 0.61–1.02; \( P = 0.0746 \)). According to Amgen representatives, such a difference, which was slightly below the threshold for statistical significance, was “pronounced” in the subset of patients with Stage IIIIB, IIIC or IV disease (HR = 0.56, 95% CI, 0.38-0.81) or who received T-vec as first-line treatment (HR = 0.49, 95% CI, 0.33-0.74), each comprising approximately 50% of the study population” (source http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1877950). Thus, although NCT00769704 met its primary endpoint of durable response rate, defined as the rate of complete or partial response lasting continuously for at least 6 mo (source http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1798143), the actual clinical benefits of T-vec remains to be elucidated.

Morris and colleagues tested the clinical profile of percutaneously administered Reolysin\textsuperscript{6}, a wild-type reovirus (serotype 3 Dearing),\textsuperscript{225} in 19 patients with accessible solid tumors who failed to improve on standard therapeutic approaches. Common toxicities included Grade 1/2 local erythema and transient flu-like symptoms. Moreover, objective responses were recorded in 7/19 (37%) patients, with 1 individual exhibiting a complete response, 2 a partial response, and 4 stable disease.\textsuperscript{226}

During the last 13 mo a few immunological and clinicopathological parameters have been suggested to have a prognostic or predictive value in patients treated with oncolytic virotherapy. Such parameters include polymorphisms in the gene coding for Fc fragment of IgG, low affinity IIIa, receptor (FCGR3A), perhaps because of their influence on natural killer (NK) cell antibody-dependent cellular cytotoxicity,\textsuperscript{116,227} as well as a hypointense tumor core in T2-weighted magnetic resonance imaging, perhaps indicating ongoing coagulative necrosis.\textsuperscript{228,229} Moreover, Koski and colleagues demonstrated that \(^{18}\text{F}\)-fluorodeoxyglucose positron emission tomography (\(^{18}\text{F}-\text{FDG PET}\) and computed tomography (CT) are equally reliable means to predict the long-term survival of cancer patients on oncolytic virotherapy.\textsuperscript{230} These studies may have significant implications for oncolytic viruses to become a clinical reality, as they may allow for the identification of patients who are most likely to obtain actual benefits from therapy.

Among recent (i.e., published during the last 13 mo) preclinical studies investigating the safety and efficacy of oncolytic virotherapy in experimental settings we found of particular interest the work of (1) Beug and collaborators, from the Children’s Hospital of Eastern Ontario Research Institute (Ottawa, Canada), who demonstrated that the therapeutic potential of SMAC mimetics is dramatically exacerbated by oncolytic viruses, as well as by Toll-like receptor (TLR) agonists, owing to their ability to stimulate the production of interferon \(\beta\) (IFNB), tumor necrosis factor \(\alpha\) (TNF\(\alpha\)), and tumor necrosis factor (ligand) superfamily, member 10 (TNFSF10, best known as TRAIL),\textsuperscript{231-236} (2) Zamarin and colleagues, from the Sloan Kettering Institute for Cancer Research (New York, NY, US), who proved that the intratumoral administration of oncolytic viruses can elicit tumor-specific immune reactions in distant, non-injected lesions, and that such an effect synergize with the systemic delivery of cytotoxic T lymphocyte-associated protein 4 (CTLA4)-blocking antibodies to achieve a superior antineoplastic activity,\textsuperscript{237-240} and (3) Castleton et al., from the University College London (London, United Kingdom), who provided robust evidence in support of the notion that MSCs can be efficiently employed to deliver oncolytic viruses to neoplastic lesions even in the presence of high-titer neutralizing antibodies;\textsuperscript{241} (4) Carew and coworkers, from the University of Texas Health Science Center (San Antonio, TX, US), who demonstrated that (at least some) oncolytic viruses promote the demise of transformed cells upon the establishment of endoplasmic reticulum stress, which is currently viewed as an absolute requirement for cell death to be perceived as immunogenic.\textsuperscript{208,209,241} and (5) Donnelly and colleagues, from the Leeds Institute of Cancer and Pathology (Leeds, UK), who proved that the therapeutic activity of (at least some) oncolytic viruses is significantly enhanced in animals immunized against the same viruses and pre-administered with GM-CSF, but not IL-2 or granulocyte colony-stimulating factor (G-CSF).\textsuperscript{242} This latter study has profound repercussions for the implementation of oncolytic virotherapy in patients who may be endowed with neutralizing immunity as a result of previous exposure to naturally occurring viruses.

### Update on Ongoing Clinical Trials

When this Trial Watch was being prepared (March 2014), official sources listed no less than 16 clinical trials launched after March 1st, 2013 that would evaluate the efficacy and safety of oncolytic virotherapy in oncological indications (source http://www.clinicaltrials.gov).

In particular, (1) ColoAd1, a chimeric oncolytic virus developed by directed evolution,\textsuperscript{243,244} is being tested as a standalone therapeutic intervention in patients with resectable colorectal carcinoma (NCT02053220), platinum-resistant ovarian carcinoma (NCT02028117) or various neoplasms of epithelial origin (NCT02028442); (2) the safety and efficacy of MV-NIS, a strain of measles virus genetically engineered to express human solute carrier family 5, member 5 (SCL5A5, best known as sodium/iodide symporter),\textsuperscript{245-248} are being evaluated in ovarian cancer patients, receiving MV-NIS-loaded MSCs i.p. (NCT02068794), as well as in subjects with head and neck squamous cell carcinoma, who are treated with MV-NIS i.t. (NCT01846091); (3) the intratumoral or intravenous administration of VCN-01, a replication-competent adenovirus expressing human sperm adhesion molecule 1 (SPAM1, best known as PH20 hyaluronidase),\textsuperscript{249} is being assessed in individuals affected by advanced pancreatic cancer (NCT02045589) or other solid neoplasms (NCT02045602), respectively; (4) the biodistribution and shedding of intratumorally administered T-vec are being evaluated in melanoma patients (NCT02014441); (5) the safety and efficacy of Toca 511, an amphotropic replication-competent retrovirus genetically modified to express cytosine deaminase,\textsuperscript{250-252} given as a standalone therapeutic intervention are being assessed in patients undergoing surgery for recurrent brain tumors (NCT01985256); (6) a naturally occurring variant of coxsackievirus, namely, coxsackievirus
A21,235-256 is being evaluated as a single agent for the systemic treatment of residual metastatic disease in subjects with NSCLC, melanoma, bladder carcinoma, and castration-resistant prostate cancer257 (NCT02043665); (7) the intravesical instillation of CG0070, a conditionally replicating oncolytic adenovirus genetically modified to express GM-CSF,108,258 is being investigated as a standalone therapeutic intervention in bladder carcinoma patients who failed Bacillus Calmette-Guérin (BCG)-based immunotherapy259,260 (NCT00109655); (8) the clinical profile of ICOVIR-5 and DNX2401, 2 oncolytic adenoviruses engineered to replicate only in cells exhibiting alterations of the retinoblastoma 1 (RB1) signaling pathway,261-266 is being assessed in subjects with advanced melanoma (NCT01864759) or other solid tumors (NCT01844661), in both scenarios as a standalone therapeutic intervention, as well as in patients with recurrent glioblastoma (in the context of temozolomide-based chemotherapy) (NCT01956734); (9) HSV-1716, a γ34.5-deficient variant of HSV,267-270 is being tested in combination with dexamethasone and surgery (NCT02031965); and (10) Pexa-Vec is being tested as a single therapeutic intervention in ovarian carcinoma patients (NCT02017678) (Table 1).

The following clinical studies discussed in our previous Trial Watch dealing with oncolytic virotherapy28 have changed status during the last 12 mo. NCT00602277, NCT00805376, NCT00861627, NCT00984464, NCT00998192, NCT01240538, NCT01387555, NCT01394939, NCT01469611, NCT01533194, NCT01598129, and NCT0163628 are now listed as “Active, not recruiting”; NCT01017601, NCT01274624, and NCT01438112 now appear as “Recruiting”; NCT00651157, NCT01227551, and NCT01048892 are now indicated as “Completed”; NCT01437280 has been “Terminated”; and the status of NCT00753038 and NCT01443260 is now “Unknown” (source http://www.clinicaltrials.gov). In the context of NCT00651157, a Phase II study testing Reolysin® as a standalone therapeutic intervention in Stage IV melanoma patients,225 serious adverse effects developed in a significant proportion of patients (50%) and no clinical activity was recorded (source http://clinicaltrials.gov/ct2/show/results/NCT00651157?term=NCT00651157&rank=1). Although both these trials have been completed, results are available neither for NCT01048892, a Phase I trial testing the Seneca Valley virus in A21,235-256 is being evaluated as a single agent for the systemic treatment of residual metastatic disease in subjects with NSCLC, melanoma, bladder carcinoma, and castration-resistant prostate cancer257 (NCT02043665); (7) the intravesical instillation of CG0070, a conditionally replicating oncolytic adenovirus genetically modified to express GM-CSF,108,258 is being investigated as a standalone therapeutic intervention in bladder carcinoma patients who failed Bacillus Calmette-Guérin (BCG)-based immunotherapy259,260 (NCT00109655); (8) the clinical profile of ICOVIR-5 and DNX2401, 2 oncolytic adenoviruses engineered to replicate only in cells exhibiting alterations of the retinoblastoma 1 (RB1) signaling pathway,261-266 is being assessed in subjects with advanced melanoma (NCT01864759) or other solid tumors (NCT01844661), in both scenarios as a standalone therapeutic intervention, as well as in patients with recurrent glioblastoma (in the context of temozolomide-based chemotherapy) (NCT01956734); (9) HSV-1716, a γ34.5-deficient variant of HSV,267-270 is being tested in combination with dexamethasone and surgery (NCT02031965); and (10) Pexa-Vec is being tested as a single therapeutic intervention in ovarian carcinoma patients (NCT02017678) (Table 1).

The following clinical studies discussed in our previous Trial Watch dealing with oncolytic virotherapy28 have changed status during the last 12 mo. NCT00602277, NCT00805376, NCT00861627, NCT00984464, NCT00998192, NCT01240538, NCT01387555, NCT01394939, NCT01469611, NCT01533194, NCT01598129, and NCT0163628 are now listed as “Active, not recruiting”; NCT01017601, NCT01274624, and NCT01438112 now appear as “Recruiting”; NCT00651157, NCT01227551, and NCT01048892 are now indicated as “Completed”; NCT01437280 has been “Terminated”; and the status of NCT00753038 and NCT01443260 is now “Unknown” (source http://www.clinicaltrials.gov). In the context of NCT00651157, a Phase II study testing Reolysin® as a standalone therapeutic intervention in Stage IV melanoma patients,225 serious adverse effects developed in a significant proportion of patients (50%) and no clinical activity was recorded (source http://clinicaltrials.gov/ct2/show/results/NCT00651157?term=NCT00651157&rank=1). Although both these trials have been completed, results are available neither for NCT01048892, a Phase I trial testing the Seneca Valley virus in

| Virus        | Indication(s)             | Phase | Status                        | Route          | Notes                                      | Ref.               |
|--------------|---------------------------|-------|-------------------------------|----------------|--------------------------------------------|--------------------|
| CG0070       | Bladder carcinoma        | I     | n.a.                          | Intravesical   | As a single agent                          | NCT00109655       |
| ColoAd1      | Colorectal carcinoma      | I     | Recruiting                    | i.t. or i.v.   | As a single agent                          | NCT02053220       |
|              | Ovarian carcinoma         | I/II  | Not yet recruiting            | i.p.           | As a single agent                          | NCT02028117       |
|              | Solid tumors              | I/II  | Recruiting                    | i.v.           | As a single agent                          | NCT02028442       |
| CVA21        | Solid tumors              | I     | Not yet recruiting            | i.v.           | As a single agent                          | NCT02043665       |
| DNX2401      | Glioblastoma              | I     | Recruiting                    | i.t.           | Combined with temozolomide and/or surgery  | NCT01956734       |
| HSV-1716     | Glioma                    | I     | Recruiting                    | Into the tumor resection cavity | Combined with dexamethasone and surgery | NCT02031965       |
| ICOVIR-5     | Melanoma                  | I     | Recruiting                    | i.v.           | As a single agent                          | NCT01864759       |
|              | Solid tumors              | I/II  | Recruiting                    | i.p. (via MSCs)| As a single agent                          | NCT01844661       |
| MV-NIS       | HNSCC                     | I     | Recruiting                    | i.t.           | As a single agent                          | NCT01846091       |
|              | Ovarian carcinoma         | I/II  | Not yet recruiting            | i.p. (via MSCs)| As a single agent                          | NCT02068794       |
| Pexa-Vec     | Ovarian carcinoma         | II    | Not recruiting                | i.v.           | As a single agent                          | NCT02017678       |
| T-vec        | Melanoma                  | II    | Not yet recruiting            | i.t.           | As a single agent                          | NCT02014441       |
| Toca 511     | Brain tumors              | I     | Recruiting                    | i.t.           | Combined with 5-FC                          | NCT01985256       |
| VCN-01       | Pancreatic cancer         | I     | Recruiting                    | i.t.           | Combined with gemcitabine                  | NCT02045589       |
|              | Solid tumors              | I     | Recruiting                    | i.v.           | Combined with gemcitabine                  | NCT02045602       |

Abbreviations: 5-FC, 5-fluorocytosine; CVA21, coxsackievirus A21; i.a., intra arteriam; i.p., intra peritoneum; i.t., intra tumorem; i.v., intra venam; HNSCC, head and neck squamous cell carcinoma; MSC, mesenchymal stem cell; n.a., not available; T-vec, talimogene laherparepvec. *Between 2013, March 1st and the date of submission.
Combination with metronomic cyclophosphamide in patients with neuroendocrine tumors, nor for NCT01227751,271-272 a Phase II study testing cossackevirus A21 as a standalone therapeutic intervention in patients with advanced melanoma,273-275 NCT01437280, a Phase I trial testing the safety and efficacy of a GM-CSF-encoding oncolytic adenovirus (CGTG-102) in patients with advanced tumors has been terminated prior to enrollment for undisclosed reasons.73,205

Concluding Remarks

As discussed in this Trial Watch, oncolytic virotherapy has been shown to mediate robust, therapeutically relevant antineoplastic effects in both preclinical and clinical scenarios. It is now evident that such a therapeutic activity is not a mere consequence of the cytotoxic effect, but rather involves the induction of a tumor-specific immune response. Oncolytic viruses appear indeed to specifically kill transformed cells, hence releasing elevated amounts of tumor-associated antigens, and deliver to the immune system robust stimulatory signals, de facto acting as therapeutic anticancer vaccines.64 The elevated immunogenic potential of oncolytic virotherapy presumably reflects the ability of viral components to act as microbe-associated molecular patterns, hence activating multiple pattern recognition receptors,73-279 as well as to promote the emission of danger-associated molecular patterns.59,208,241,280 In line with this notion, oncolytic viruses have already been shown to improve the efficacy of multiple immunotherapeutic interventions against cancer, including peptide- as well as DNA-based vaccines.75,77,281 Conversely, a large panel of immunostimulatory agents including multiple TLR agonists299,282 and ICD inducers74,283-286 appears to boost the antineoplastic activity of oncolytic virotherapy. We believe that precisely scheduled combinatorial regimens that initially allow for the replication and dissemination of viral particles thought neoplastic lesions, and then boost the ability of oncolytic viruses to induce tumor-specific immune responses may mediate optimal antineoplastic effects. Future will tell which, if any, of the immunonchemotherapeutic regimens that may be devised287 is best suited for this purpose.

Disclosure of Potential Conflicts of Interest

P.E., J.M.L., and X.P. are full-time employees of Transgene; L.Z. is part of the Board of Directors of Transgene.

Acknowledgments

Authors are supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR); Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; AXA Chair for Longevity Research; Institut National du Cancer (INCa); Fondation Bettencourt-Schuller; Fondation de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the LabEx Immuno-Oncology; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPP); and the Paris Alliance of Cancer Research Institutes (PACRI).

References

1. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol 2012; 30:658-70; PMID:22781695; http://dx.doi.org/10.1038/nbt.2287
2. Griffith TS, Kawakita M, Tian J, Ritchey J, Tarraglia J, Sehgal I, Thompson TC, Zhao W, Ratliff TL. Inhibition of murine prostate tumor growth and activation of immunoregulatory cells with recombinant canarypox viruses. J Natl Cancer Inst 2001; 93:998-1007; PMID:11438565; http://dx.doi.org/10.1093/jnci/93.13.998
3. Mukela AR, Marttilainen H, White DJ, Ruolalhti E, Oker-Blom C. Enhanced baculovirus-mediated transduction of human cancer cells by tumor-homing peptides. J Virol 2006; 80:6603-11; PMID:16775347; http://dx.doi.org/10.1128/JVI.00528-06
4. Singh P, Destino G, Schneemann A, Manchester M. Canine parvovirus-like particles, a novel nanomaterial for tumor targeting. J Nanobiotechnology 2013; 11:21; http://dx.doi.org/10.1186/1477-3155-11-21
5. Stanford MM, Bell JC, Vaha-Koskela MJ. Novel oncolytic viruses: riding high on the next wave? Cytokine Growth Factor Rev 2010; 21:177-83; PMID:20219409; http://dx.doi.org/10.1016/j.cytofgr.2010.02.012
6. Quetglas JJ, John LB, Kershaw MH, Alvarez-Villaña L, Melero I, Darcy PK, Smerdou C. Virotherapy, gene transfer and immunostimulatory monocular antibodies. Onc Immunol 2012; 1:1344-54; PMID:22324397; http://dx.doi.org/10.4102/oic.v1i1.21679
7. Hemminki A, Oksanen M, Meisala-Sokkeli M. Oncolytic virotherapy trials—literate. Clin Cancer Res 2013; 19:4941-2; PMID:23946419; http://dx.doi.org/10.1158/1078-0432.CCR-13-1471
8. Walker W, Schlag PM. Current status of gene therapy for cancer. Curr Opin Oncol 2013; 25:659-64; PMID:24100345; http://dx.doi.org/10.1097/CCO.0b013e32834a0004
9. Donnelly O, Harrington K, Melcher A, Pandha H. Live viruses to treat cancer. J R Soc Med 2013; 106:310-4; PMID:23824333; http://dx.doi.org/10.1177/1477780013491496
10. Ayala-Breton C, Barber GN, Russell SJ, Peng KW. Retargeting vascular stromatosis virus using measles virus envelope glycoproteins. Hum Gene Ther 2012; 23:484-91; PMID:22176355; http://dx.doi.org/10.1089/hum.2011.146
11. Muik A, Kneiske I, Werbizki M, Wilflingseder D, Voelker I, Galli CR, Johnston JC, Lauer UM, Herold-Mende C, et al. Specific elimination of CD3+3 tumor cells with targeted oncolytic measles virus. Cancer Res 2013; 73:865-74; PMID:23292378; http://dx.doi.org/10.1158/0008-5472.CAN-12-2221
12. Donnelly O, Harrington K, Melcher A, Pandha H. Live viruses to treat cancer. J R Soc Med 2013; 106:310-4; PMID:23824333; http://dx.doi.org/10.1177/1477780013491496
13. Muik A, Kneiske I, Werbizki M, Wilflingseder D, Galli CR, Johnston JC, Lauer UM, Herold-Mende C, et al. Specific elimination of CD3+3 tumor cells with targeted oncolytic measles virus. Cancer Res 2013; 73:865-74; PMID:23292378; http://dx.doi.org/10.1158/0008-5472.CAN-12-2221
14. Donnelly O, Harrington K, Melcher A, Pandha H. Live viruses to treat cancer. J R Soc Med 2013; 106:310-4; PMID:23824333; http://dx.doi.org/10.1177/1477780013491496
15. Uchida H, Maruzzi M, Nakano K, Goins WF, Chan J, Hong CS, Mazzacurati L, Yoo JY, Hasley A, Nakashima H, et al. Effective treatment of an orthotopic xenograft model of human glioblastoma using an EGRF-retargeted oncolytic herpes simplex virus. Mol Ther 2013; 21:561-9; PMID:23070115; http://dx.doi.org/10.1038/mtn.2012.211
16. Bach P, Abel T, Hoffmann C, Gal Z, Braun G, Voelker I, Ball CR, Johnston JC, Lauer UM, Herold-Mende C, et al. Specific elimination of CD133+ tumor cells with targeted oncolytic measles virus. Cancer Res 2013; 73:865-74; PMID:23292378; http://dx.doi.org/10.1158/0008-5472.CAN-12-2221
17. Nanni P, Gatta V, Menotti L, De Giovanni C, Ianzano M, Palladini A, Grosso V, Dall’ora M, Croci S, Nicoletti G, et al. Preclinical therapy of disseminated HER-2+ ovarian and breast carcinomas with a HER-2-retargeted oncolytic herpesvirus. PLoS Pathog 2013; 9:e1003355; PMID:23832683; http://dx.doi.org/10.1371/journal.ppat.1003355
18. Passer BJ, Cheema T, Zhou B, Wakiimoto H, Zaupa C, Razmiooj M, Sarte J, Wu S, Wu CL, Noah JW, et al. Identification of the ENT1 antagonists dipyridamole and dilazep as amplifiers of oncolytic herpes simplex virus-1 replication. Cancer Res 2010; 70:3809-5; PMID:20424118; http://dx.doi.org/10.1158/0008-5472.CAN-10-0555
19. Lee CY, Bu LX, DeBenedetti A, Williams BJ, Rennie PS, Jia WW. Transcriptional and translational dual-regulated oncolytic herpes simplex virus type 1 for targeting prostate tumors. Mol Ther 2010; 18:929-35; PMID:20179076; http://dx.doi.org/10.1038/mt.2010.26

Oncoimmunology Volume 3

e28694-6
20. Curvas Y, Hernández-Alcoleba R, Aragonés J, Narango-Suárez S, Castellanos MC, Esteban MA, Martín-Puig S, Landazuri MO, del Peso L. Specific oncolytic effect of a new hypoxia-inducible-factor-dependent replicative adenovirus on von Hippel-Lindau-defective renal cell carcinomas. Cancer Res 2003; 63:6877-84; PMID:14583486.

21. Post DE, Van Meir EG. A novel hypoxia-inducible factor (HIF) activated oncolytic adenovirus for cancer therapy. Oncogene 2003; 22:2065-72; PMID:12687009; http://dx.doi.org/10.1038/sj.onc.1206464.

22. Lin WH, Yeh YH, Yang WJ, Yeh KH, Fujikawa T, Nii A, Chang SS, Chen PJ. Telomerase-specific oncolytic adenovirus therapy for orthotopic hepatocellular carcinoma in HBx transgenic mice. Int J Cancer 2013; 132:1451-62; PMID:22886913; http://dx.doi.org/10.1002/ijc.27770.

23. Takahashi H, Hyakusoku H, Horii C, Takahashi T, Fujiwara T, et al. Enhanced safety profiles of the telomerase-specific replication-competent adenovirus expressing the chemokine RANTES/CCL5 and NK-92 cells exerts enhanced antitumor activity in hepatocellular carcinoma. Oncol Rep 2013; 29:895-902; PMID:23296577.

24. Glass M, Busche A, Wagner K, Messere M, Borst P, et al. Differential regulated interferon response by the SCG3 promoter and ASH1 enhancer for oncolytic adenovirus driven by the SGC3 promoter and ASH1 enhancer for neuroblastoma therapy. Hum Gene Ther 2013; 24:766-75; PMID:23889332; http://dx.doi.org/10.1089/hum.2012.132.

25. Wang W, Hu H, Ma J, Li X, Mei W, et al. Survivin promoter-regulated oncolytic adenovirus with Hsp70 gene exerts effective antitumor efficacy in gastric cancer immunotherapy. Oncotarget 2013.

26. Sugio K, Sakurai F, Katayama K, Tashiro K, Matsui H, Kawahara K, Kawase A, Iwaki M, Hayakawa TK, Saga Y, et al. Enhanced safety profiles of the telomerase-specific replication-competent adenovirus by incorporation of normal cell-specific microRNA-targeted sequences. Clin Cancer Res 2011; 17:2087-18; PMID:21346455; http://dx.doi.org/10.1158/1078-0432.CCR-10-0808.

27. Kelly EJ, Nace R, Barber GN, Russell SJ. Attenuation of vesicular stomatitis virus encephalitis through microRNA targeting. J Virol 2010; 84:3560-2; PMID:1999061; http://dx.doi.org/10.1128/JVI.00629-09.

28. Edge RE, Falls TJ, Brown CW, Lichy BD, Atkins H, Bell JC. A let-7 MicroRNA-sensitivity vesicular stomatitis virus demonstrates tumor-specific replication. Mol Ther 2008; 16:1437-43; PMID:18328963; http://dx.doi.org/10.1038/mً.2008.130.

29. Kelly EJ, Hadic EM, Greiner S, Russell SJ. Engineering microRNA responsiveness to decrease virus pathogenicity. Nat Med 2008; 14:1278-83; PMID:18939352; http://dx.doi.org/10.1038/nm.1776.

30. Callegari E, Elamin BK, D’Abundo L, Falzoni S, Čančer M, Nilsson B, Leja J, Essand G, Christensen JT, et al. Poliovirus recombinant for clinical application by the mt.2008.130.

31. Li JM, Kao KC, Li LF, Yang TM, Wu CP, Horig YM, Jia WW, Yang CT. MicroRNA-145 regulates oncolytic herpes simplex virus-1 for selective killing of thyroid cancer cells in vitro and in vivo. Cancer Lett 2013; 2014:24; PMID:23876001; http://dx.doi.org/10.1016/j.canlet.2013.08.010.

32. Ylisaukki E, Lavila-Alonso S, Jäämaa S, Vähäkosela M, al Halltont T, Hemminci A, Arola J, Makisalo H. Inhibition of vesicular stomatitis virus replication in human liver. PLoS One 2013; 8:e54506; PMID:23349911; http://dx.doi.org/10.1371/journal.pone.0054556.

33. Yang X, Chen E, Jiang H, Muszynski K, Harris M, Gromier M, Mirta G, Soman G. Evaluation of IRES-mediated, cell-type-specific cryoexpression of poliovirus using a colorimetric cell proliferation assay. J Virol Methods 2009; 155:44-54; PMID:19223022; http://dx.doi.org/10.1016/j.jviromet.2008.09.020.

34. Ammayappan A, Nace R, Peng KW, Russell SJ. Neurotanslation of vesicular stomatitis virus through picornaviral internal ribosome entry sites. J Virol 2013; 87:5317-28; PMID:23283963; http://dx.doi.org/10.1128/JVI.02984-12.

35. Goetz C, Gromier M. Preparing an oncolytic poliovirus recombinant for clinical application against glioblastoma multiforme. Cytochrome.95; PMID:16819848.

36. Wolter O, Blaes AM, Morris JC. Therapy of colon cancer with oncolytic adenovirus is enhanced by the addition of herpes simplex virus-thymidine kinase. Cancer Res 1999; 59:410-3; PMID:9927055.

37. Tseng J, Zancanoni PR, Levin B, Finn R, Larson SM, Meric-Davidow D. Tumor-specific in vivo transduction with HSV1 thymidine kinase gene using a Sindbis viral vector as a basis for prodru ganciclovir activation and PET. J Nucl Med 2006; 47:1136-43; PMID:16819848.

38. Leveille S, Samuel S, Goulet ML, Hiscott J. Enhancing HSV oncolytic activity with an improved cytosine deaminase suicide gene strategy. Cancer Gene Ther 2011; 18:455-55; PMID:21941049; http://dx.doi.org/10.1038/cgt.2011.14.

39. Dong X, Qiu W, Ma S, Zhu Z, Zheng C, He A, Karlsson A, Xu K, Zheng X. Potent antitumoral effects of targeted promoter-driven oncolytic adenovirus armed with Dm-dNK for breast cancer in vitro and in vivo. Cancer Lett 2013; 328:95-103; PMID:23000515; http://dx.doi.org/10.1016/j.canclet.2012.09.003.

40. Hartkopf AD, Bousow S, Lampe J, Zimmermann M, Taran FA, Walliener D, Fehm T, Bitzer M, Lauer UM. Enhanced killing of ovarian carcinoma using oncolytic measles vaccine virus armed with a yeast cytosine deaminase and uracil phosphoribosyltransferase. Gynecol Oncol 2013; 130:362-6; PMID:23676551; http://dx.doi.org/10.1016/j.ygyno.2013.03.008.

41. Lampe J, Bousow S, Westermann C, Smirnov I, Lehmann R, Neubert W, Bitzer M, Lauer UM. An armed oncolytic measles vaccine virus eliminates human hepatoma cells independently of apoptosis. Gene Ther 2013; 20:1033-41; PMID:23719065; http://dx.doi.org/10.1038/gtn.2013.28.

42. Shinoura N, Yoshida Y, Asai A, Kirino T, Hamada H. Adenovirus-mediated transfer of p53 and Fas ligand drastically enhances apoptosis in gliomas. Cancer Gene Ther 2000; 7:732-8; PMID:10830720; http://dx.doi.org/10.1038/nm.1776.

43. Zhou L, Dong A, Gu J, Liu Z, Zhang Y, Zhang W, Wang Y, He L, Qian C, Qian Q, et al. The antitumor activity of TRAIL and IL-24 with replicating oncolytic adenovirus in colorectal cancer. Cancer Gene Ther 2006; 13:1011-22; PMID:16799468; http://dx.doi.org/10.1038/sj.cgt.7001569.

44. Zhu W, Zhang H, Shi Y, Song M, Zhu B, Wei L. Oncolytic adenovirus encoding tumor necrosis factor-related apoptosis inducing ligand (TRAIL) inhibits the growth and metastasis of triple-negative breast cancer. Cancer Biol Ther 2013; 14:1016-23; PMID:24025362; http://dx.doi.org/10.4161/cbti.26043.

45. Jiang G, Li J, Zeng Z, Xiao L. Lentivirus-mediated gene therapy by suppressing survivin in BALB/c nude mice bearing oral squamous cell carcinoma. Cancer Biol Ther 2006; 5:435-40; PMID:16575205; http://dx.doi.org/10.4161/cbti.5.4.2542.
106. Fang L, Cheng Q, Bai J, Qi YD, Liu JJ, Li LT, Gaston DC, Odom CI, Li L, Markert JM, Roth JC, Pesonen S, Diaconu I, Cerullo V, Escutenaire S, Raki 107. Choi IK, Li Y, Oh E, Kim J, Yun CO. Oncolytic superagonist ALT-803 promotes the antigen- 108. PMID:24404427; http://dx.doi.org/10.1038/ oncolytic immuno therapy of cancer. Immunotherapy 2013; 5:817-9; PMID:2390895; http://dx.doi.org/10.1080/ juro.2012.07.097 109. Heo J, Reid T, Luo L, Breitbach CJ, Rose S, Bloomston M, Cho M, Lim HY, Chung HC, Kim CW, et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia VX-944 in liver cancer. Nat Med 2013; 19;329-36; PMID:23396206; http://dx.doi.org/10.1038/nm.3809 110. Thorne SH. The role of GM-CSF in enhancing immunotherapy of cancer. Immunotherapy 2013; 5:227-44; PMID:23642239; http://dx.doi.org/10.1089/hum.2012.205 111. Grossardt C, Engeland CE, Bossov S, Halama N, Zauoi K, Leifer MF, Springfeld C, Jaeger D, von Kalle C, Ungerechts G. Granulocyte-macrophage colony-stimulating factor armed oncolytic measles virus is an effective therapeutic cancer vaccine. Hum Gene Ther 2013; 24:644-54; PMID:23276056; http://dx.doi.org/10.1038/ng.1538 112. Engleza NK, Harden JL, Roswell-Turner RB. Chemoimmunotherapy as long-term maintenance therapy for cancer. Oncoimmunology 2012; 1:563-5; PMID:22754788; http://dx.doi.org/10.4161/onci.19369 113. Dempse S, Lavie M, Strauf S, Bhat R, Verbecke H, Paschek S, Berghmans N, Geibig R, Rommelaere J, Van Damme J, et al. Antitumor activity of parvovirus-mediated IL-2 and MCP-3/CCL7 delivery into human pancreatic cancer: implication of leukocyte recruitment. Cancer Immunol Immunother 2012; 61:2113-23; PMID:22576056; http://dx.doi.org/10.1007/s00262-012-1279-4 114. Li J, O’Malley M, Sampath P, Kalinski P, Bartlett ML. Myxoma virus virotherapy for glioma xenografts in immunodeficient mice. Blood 2003; 97:3746-54; PMID:12390612; http://dx.doi.org/10.1182/blood.V97.12.3746 115. Peng KW, TenEyck CJ, Galanis E, Kalli KR, Alain T, Kim M, Johnston RN, Urbanski S, Hartmann CJ, Galanis E, Kalli KR, Alain T, Kim M, Johnston RN, Urbanski S, Hartmann CJ, Russell SJ, Cornu TI, Cattaneo R, Vile R, Poland GA, Fielding AK. Live attenuated measles virus induces regression of human lymphoma xenografts in immunocompromised mice. EMBO Rep 2001; 2:977-83; PMID:11541778; PMC-06-0002 116. Brode T, Russell SJ. Intraperitoneal therapy for cancer. Oncoimmunology 2012; 2:23658; PMID:23734319; http://dx.doi.org/10.4161/onci.23658 117. Colombo F, Barzon L, Franchin E, Pacenti M, Pinna V, Daniali D, Zanussi M, Pali G. Combined HSV-TK/IL-2 gene therapy in patients with recurrent glioblastoma multiforme: biological and clinical results. Cancer Gene Ther 2005; 12:853-48; PMID:15917712; http://dx.doi.org/10.1038/sj.bjt.2805125 118. Lan X, Alain T, Zemp FF, Zhou H, Rahman MM, Hamilton MG, McFadden G, Bell J, Senger DL, Forsyth PA. Myxoma virus virotherapy for gloma in immunocompetent animal models: optimizing administration routes and synergy with rapamycin. Cancer Gene Ther 2008; 15:598-608; PMID:18061858; http://dx.doi.org/10.1038/sj.bjt.2805125 119. Ram Z, Culver KW, Oshiro EM, Viola JJ, DeVroom JL, Otto E, Long Z, Chiang Y, McGarry CJ, Mudl LM, et al. Therapy of malignant brain tumors by intracarotid injection of retror vector-producing cells. Nat Med 1997; 3:1354- 120. Smyth JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147- 121. Yahi-Koskela MJ, Kallio JP, Jansson LC, Heikkilä JE, Zakharchenko VA, Kallajojki MA, Kahvori VM, Hinkkanen AE. Oncolytic capacity of attenuated replicative semliki forest virus in human melanoma xenografts in severely compromised immunodeficient mice. Cancer Res 2006; 66:7185-94; PMID:16849565; http://dx.doi.org/10.1158/0008-5472.CAN-05-2214 122. Cordaro TA, de Visser KE, Timir FH, Grau YM, Haenen JB, Kioussis D, Kruisbeek AM. Tumor size at the time of adoptive transfer determines whether tumor rejection occurs. Eur J Immunol 2000; 30:129- 123. Shen Y, Bhardwaj S, Delfante D, Mooney DJ, Bergsma K. Vaccinia enhanced immunotherapeutic vaccinia JX-594 in liver cancer. Nat Med 2013; 19;329-36; PMID:23396206; http://dx.doi.org/10.1038/nm.3809 124. Vähä-Koskela MJ, Kallio JP, Jansson LC, Heikkilä JE, Zakharchenko VA, Kallajojki MA, Kahvori VM, Hinkkanen AE. Oncolytic capacity of attenuated replicative semliki forest virus in human melanoma xenografts in severely compromised immunodeficient mice. Cancer Res 2006; 66:7185-94; PMID:16849565; http://dx.doi.org/10.1158/0008-5472.CAN-05-2214 125. Li ZY, Ni S, Yang X, Kiviat N, Lieber A. Xenograft models for liver metastasis: Relationship between tumor morphology and adenovirus vector transduction. Mol Ther 2004; 9:650-7; PMID:15102525; http://dx.doi.org/10.1006/imtm.2003.6140 126. Shayakhmetov DM, Li ZY, Ni S, Lieber A. Targeting of adenovirus vectors to tumor cells does not enable effective transduction of breast cancer metastases. Cancer Res 2002; 62:1063-8; PMID:11861383 127. Stoker M, Boucher Y, Stangassinger M, Jain RK. Oncotic pressure in solid tumours is elevated. Cancer Res 2002; 62:91-9; PMID:11638477; http://dx.doi.org/10.1158/0008-5472.CAN-01-0333 128. Grote D, Russell SJ. Cornu TI, Cattaneo R, Vile R, Poland GA, Fielding AK. Live attenuated measles viruses induce regression of human lymphoma xenografts in immunocompromised mice. Cancer Res 2003; 63:60-6; PMID:12183442 129. Kanerva A, Zinn KR, Peng KW, Ranki T, Kanganisni L, Chaudhuri TR, Desmond RA, Wang M, Takayama K, Hakkarainen T, et al. Noninvasive dual modality in vivo monitoring of the persistence and potency of a tumor targeted conditionally replicating adenovirus. Gene Ther 2005; 12:87- 130. Smither JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147- 131. Ramsay JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147- 132. Ramsay JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147- 133. Ramsay JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147- 134. Ramsay JW, Fleeton MN, Sheahan BJ, Atkins GJ. Treatment of rapidly growing K-BALB and CT26 mouse tumours using Semliki Forest virus and its derived vector. Gene Ther 2005; 12:147-
134. Vitale I, Galluzzi L, Senovilla L, Cirillo A, Jemaá M, Castedo M, Kroemer G. Illuminant survival of cancer cells during polyploidization and depolyploidization. Cell Death Differ 2011; 18:1403-13; PMID:21072053; http://dx.doi.org/10.1038/cdd.2010.145.

135. Peng Y, Yang J, Green NK, Ulbrich K, Maunter V, Seymour I. Polymer-coated adenovirus permits efficient retargeting and evades neutralizing antibodies. Gene Ther 2001; 8:341-8; PMID:11338098; http://dx.doi.org/10.1038/sj.gt.3301389.

136. Massari I, Donnini A, Argentati K, Striano S, Mangoni A, Gaetano C, Viticelli C, Capogrossi M, Provinciali M. Age-dependent effects of repeated immunization with a first generation adenovirus vector on the immune response and transgene expression in young and old rats. Exp Gerontol 2002; 37:823-31; PMID:12175482; http://dx.doi.org/10.1016/S1551-2501(02)00011-6.

137. Ikeda K, Waki moto H, Ichikawa T, Jiang S, Hochberg FH, Louis DN, Chiocca EA. Complement depletion facilitates the infection of multiple brain tumors by an intravascular, replication-conditioned herpes simplex virus mutant. J Virol 2000; 74:4765-75; PMID:10775615; http://dx.doi.org/10.1128/JVI.74.11.4765-4770.2000.

138. Pensiero MN, Wysocki CA, Nader K, Kikuchi GE, Pensiero M, Wang Y. Systemic administration of an adenovirus vector in a rodent model of multifocal pancreatic adenocarcinoma: complexity in action. Annu Rev Immunol 2003; 21:746-55; PMID:14564000; http://dx.doi.org/10.1146/annurev.immunol.21.110301.114744.

139. Bernet KM, Ni S, Gaggar A, Li ZY, Shayakhmetov M, Pensiero MN, Wysocki CA, Nader K, Kikuchi GE. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 2003; 348:255-6; PMID:12529469; http://dx.doi.org/10.1056/NEJMoa0216380.

140. Underhill DM, Ozinsky A. Phagocytosis of Bernt KM, Ni S, Gaggar A, Li ZY, Shayakhmetov M, Pensiero MN, Wysocki CA, Nader K, Kikuchi GE. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 2003; 348:255-6; PMID:12529469; http://dx.doi.org/10.1056/NEJMoa0216380.

141. Hacan-Bey-Abina S, van Kalle C, Schmidt M, Le Deist F, Wulffraat N, McIntyre E, Radford I, Villeneuve JL, Fraser CR, Cowap C, Calvo M, et al. An armed oncolytic adenovirus with enhanced oncolytic activity for the treatment of pancreatic cancer express the thymidine kinase gene. Oncoimmunology 2013; 2:e268867; http://dx.doi.org/10.4161/onci.20908.

142. Ferguson MS, Lemoine NR, Wang Y. The secret al.y: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012; 11:327-38; PMID:23149866; http://dx.doi.org/10.1038/nrd3791.

143. Eisenstein S, Coakley BA, Birley-Saboo K, Ma G, Chen HM, Meesek M, Ward S, Divino C, Woo S, Chen SH, et al. Myeloid-derived suppressor cells as a vehicle for tumor-specific oncolytic viral therapy. Cancer Res 2013; 73:490-5; PMID:23172310; http://dx.doi.org/10.1158/0008-5472.CAN-12-1056.

144. Akira RA, Scott KJ, Ferrer A, Kiyokawa-Harrington KJ, et al. Cytotoxic and immune-mediated killing of human colorectal cancer by oncolytic herpes simplex virus with gemcitabine. Clin Cancer Res 2013; 19:999-1006; PMID:23867315; http://dx.doi.org/10.1158/1078-0432.CCR-12-2791.

145. Devaud C, John LB, Westwood JA, Darcy PK, Kershaw MH. Immune modulation of the tumor microenvironment for enhancing cancer immunotherapy. Oncoimmunology 2013; 2:e25561; PMID:24083084; http://dx.doi.org/10.4161/onci.26907.

146. Chandra D, Gravekamp C, Myeloid-derived suppressor cells: Cellular missiles to target tumors. Oncoimmunology 2013; 2:e220967; PMID:24427545; http://dx.doi.org/10.4161/onci.25083.

147. Pan PY, Chen HM, Chen SH. Myeloid-derived suppressor cells as a Trojan horse: A cellular vehicle for the delivery of oncolytic viruses. Oncoimmunology 2013; 2:e25083; PMID:24083075; http://dx.doi.org/10.4161/onci.25083.

148. Geevarghese SK, Geller DA, de Haan HA, Hörer T, et al. A phase I/II study of measles virus-infected mesenchymal stem cells as virus carriers for a phase I clinical trial in ovarian cancer. J Hepatol 2013; 59:999-1006; PMID:23867315; http://dx.doi.org/10.1016/j.jhep.2013.07.010.

149. Hacein-Bey-Abina S, von Kalle C, Schmidt M, Le Deist F, Wulffraat N, McIntyre E, Radford I, Villeneuve JL, Fraser CR, Cowap C, et al. An armed oncolytic adenovirus with enhanced oncolytic activity for the treatment of pancreatic cancer express the thymidine kinase gene. Oncoimmunology 2013; 2:e268867; http://dx.doi.org/10.4161/onci.20908.
178. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

179. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

180. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

181. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

182. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

183. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

184. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

185. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

186. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

187. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

188. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

189. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.

190. Vacchelli E, Vitale I, Tartour E, Eggermont A, Kroemer G. Immune parameters and mechanisms of cisplatin resistance. Oncogene 2014; 33:e1529; PMID:24735734; http://dx.doi.org/10.1038/onc.2014.152.
214. Ma Y, Adjemian S, Martarolo SR, Yamazaki T, Aymeric L, Yang H, Portela Catani JP, Hannani D, Duerst H, Steeg K, et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity 2013; 38:729-41; PMID:23538694; http://dx.doi.org/10.1016/j.immuni.2013.03.003

215. Park BH, Hwang T, Liu TC, Sze DY, Kim JS, Kwon M, Morris DG, Feng X, DiFrancesco LM, Fonseca K, et al. Reovirus-based therapy for cancer. Expert Opin Biol Ther 2009; 9:817-30; PMID:1952706; http://dx.doi.org/10.1517/17425590903002039

216. Hwang TH, Moon A, Burke J, Ribas A, Stephenson J, Markert JM, Medlock MD, Rabkin SD, Gillespie Breitbach CJ, Burke J, Jonker D, Stephenson J, Haas Mita M, Reovirus-based therapy for cancer. Expert Opin Biol Ther 2009; 9:817-30; PMID:1952706; http://dx.doi.org/10.1517/17425590903002039

217. Morris DG, Feng X, DiFrancesco LM, Fonseca K, Forsyth PA, Paterson AH, Coffey MC, Thompson B. REO-001: A Phase I trial of percutaneous intratumoral administration of reovirus type 3 dearing (Reolysin®) in patients with advanced solid tumors. Invest New Drugs 2013; 31:70-76; PMID:22886613; http://dx.doi.org/10.1007/s10637-012-9685-8

218. Hirvine M, Heiskanen R, Oksanen M, Pesonen S, Liikanen I, Joensuu T, Kanerva A, Cerullo V, Hemminki A. Fc-gamma receptor polymorphisms as predictive and prognostic factors in patients receiving oncolytic adenovirus treatment. J Transl Med 2013; 11:193; PMID:23965133; http://dx.doi.org/10.1186/1476-577X-11-193

219. Hemminki O, Immonen R, Narvainen J, Kipar A, Paasonen J, Jukkivarsi KT, Yli-Ollila H, Soininen P, Partanen K, Joensuu T, et al. In vivo magnetic resonance imaging and spectroscopy identifies oncolytic adenovirus responders. Int J Cancer 2014; 134:2878-90; PMID:24428808; http://dx.doi.org/10.1002/ijc.28635

220. Haabeth OA, Bogen B, Corthay A. A model for cancer-suppressive inflammation. Oncoimmunology 2012; 1:1146-55; PMID:23170261; http://dx.doi.org/10.4161/onci.21542

221. Koski A, Ahitnen H, Liljenback H, Roivainen A, Kovelka D, Saassen M, Partanen K, Laasonen L, Kaireno K, Joensuu T, et al. (18)F-fluorodeoxyglucose positron emission tomography and computed tomography in response evaluation of oncolytic adenovirus treatments of patients with advanced cancer. Hum Gene Ther 2013; 24:10269-41; PMID:24995555; http://dx.doi.org/10.1089/hum.2013.123

222. Beug ST, Tang VA, LaCasse EC, Cheung HH, Beauger CE, Brun J, Nuyens JP, Earl N, St-Jean M, Holbook J, et al. Smac mimetics and innate immune stimuli synergize to promote tumor death. Nat Biotechnol 2014; 32:182-90; PMID:24463573; http://dx.doi.org/10.1038/nbt.2806

223. Ma Y, Yamazaki T, Yang H, Keg O, Galluzzi L, Zitvogel L, Smyth MJ, Kroemer G. Tumor necrosis factor is dispensable for the success of immunomodulating anticancer chemotherapy. Oncoimmunology 2013; 2:e24786; PMID:23894723; http://dx.doi.org/10.4161/onci.24786

224. Becker C, Bopp T, Steinbrink K. Interferon-α interferes with immune reprogramming. Oncoimmunology 2013; 2:e27528; PMID:24575381; http://dx.doi.org/10.4161/onci.27528

225. Smitz EL, Anguille S, Berenman ZN. Interferon-α may be back on track to treat acute myeloid leukemia. Oncoimmunology 2013; 2:e23610; PMID:23734314; http://dx.doi.org/10.4161/onci.23619

226. James BR, Griffith TS. Activation of systemic antitumor immunity via TRAIL-induced apoptosis. Oncoimmunology 2012; 1:1178-80; PMID:23170271; http://dx.doi.org/10.4161/onci.20638

227. Munich S, Soho-Vujanic A, Buchser WJ, Beer-Stols D, Vujanic NL. Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF family ligands. Oncoimmunology 2012; 1:1074-83; PMID:23170255; http://dx.doi.org/10.4161/onci.20897

228. Zamarin D, Holmgard RA, Subudhi SK, Park JS, Mansoor M, Palese P, Merghouth T, Wolcho JD, Allison JP. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. Sci Transl Med 2014; 6:226ra52; PMID:24598590; http://dx.doi.org/10.1126/scitranslmed.3008895

229. Perez OD, Logg CR, Hiraoka K, Diago O, Burnett R, Bao H, Palucka K, Chartier C, Nye J, Thorne S, Reid T, Ni S, Lieber A, Fisher K, et al. Directed evolution generates a novel oncolytic virus for the treatment of colon cancer. PLoS One 2008; 3:e2409; PMID:18560559; http://dx.doi.org/10.1371/journal.pone.0002409

230. Li H, Peng KW, Russell SJ. Oncolytic measles virus encoding thyroidal sodium iodide symporter for squamous cell carcinoma of the head and neck radiotherapy. Hum Gene Ther 2012; 23:295-301; PMID:22235810; http://dx.doi.org/10.1089/hum.2011.128

231. Oprechal M, Allen C, Iankov I, Adera I, Schroeder M, Sarkaria J, Galanis E. Effective radiotherapy for malignant gliomas by using oncolytic measles virus strains encoding the sodium iodide symporter (MV-NIS). Hum Gene Ther 2012; 23:419-27; PMID:22185260; http://dx.doi.org/10.1089/hum.2011.158

232. Penheiter AR, Wegman TR, Classic KL, Dingl D, Bender CE, Russell SJ, Carlson SK. Sodium iodide symporter (NIS)-mediated radiotherapy efficacy for pancreatic cancer. AJR Am J Roentgenol 2010; 195:341-9; PMID:20651188; http://dx.doi.org/10.2214/AJR.09.3672

233. Liu C, Russell SJ, Peng KW. Systemic therapy of disseminated melanoma by passively immunized mice using measles viruses-infected cell carriers. Mol Ther 2010; 18:1155-64; PMID:20234340; http://dx.doi.org/10.1038/mt.2010.130

234. Guedan S, Rojas JJ, Gros A, Mercade E, Cascallo M, Alemay R. Hyaluronidase expression by an oncolytic adenovirus enhances its intratumoral spread and suppresses tumors growth. Mol Ther 2010; 18:1275-83; PMID:20442708; http://dx.doi.org/10.1038/mt.2010.79

235. Huang TT, Hlavaty J, Osterrog D, Eptinova FL, Maraz B, Pernek H, Rodrigues-Aguiere MB, Ibaez CE, Kasahara N, Gunzburg W, et al. Toca 511 gene transfer and 5-fluorocytosine in combination with temozolomide demonstrates synergistic therapeutic efficacy in a temozolomide-sensitive glioblastoma model. Cancer Gene Ther 2013; 20:544-51; PMID:23969884; http://dx.doi.org/10.1038/cgt.2013.51

236. Perez OD, Llogg CR, Hiraoka K, Diago O, Burnett R, Inagaki A, Jolton D, Amundson K, Buckley T, Lobbe D, et al. Vaccine and selection of Toca 511 for clinical use: modified retroviral replicating vector with improved stability and gene expression. Mol Ther 2012; 20:1689-98; PMID:22547150; http://dx.doi.org/10.1038/mt.2012.83
Vacchelli E, Galluzzi L, Eggermont A, Fridman W, et al. Brain tumor eradication and prolonged survival from intratumoral conversion of 5-fluorocytosine to 5-fluorouracil using a lytic recombinant replication-competent adenovirus. Neurol Oncol 2012; 14:145-59; PMID:22079390; http://dx.doi.org/10.1038/neo.2011.199

Selding KA, Barry RD, Shafren DR. Enhanced oncolysis mediated by Coxsackievirus A21 in combination with doxorubicin hydrochloride. Invest New Drugs 2012; 30:568-81; PMID:22170760; http://dx.doi.org/10.1007/s10617-010-9641-0

Selding KA, Barry RD, Shafren DR. Systemic targeting of metastatic human breast tumor xenografts with Coxsackievirus A21. Breast Cancer Res Treat 2009; 113:21-30; PMID:18256929; http://dx.doi.org/10.1007/10549-008-9899-2

Au GG, Lindberg AM, Barry RD, Shafren DR. Oncolysis of vascular malignant human melanoma tumors by Coxsackievirus A21. Int J Oncol 2009; 26:1471-7; PMID:18708989

Shafren DR, Au GG, Nguyen T, Newcombe NG, Skelding KA, Barry RD, Shafren DR. Enhanced oncolysis mediated by Coxsackievirus A21. Oncoimmunology 2012; 1:894-907; PMID:23162757; http://dx.doi.org/10.4161/onci.23510

Zitvogel L, Kroemer G. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology 2013; 2:e2538; http://dx.doi.org/10.4161/onci.2538

Ramesh N, Ge Y, Ennitt DL, Zhu M, Mina M, Ganesh S, Reddy PS, Yu DC. CG0070, a nonlytic recombinant adenovirus--armed oncolytic coxsackievirus A21--induces high antitumor activity in vivo. Cancer Res 2004; 65:53-60; PMID:14734451; http://dx.doi.org/10.1158/0008-5472.CAN-03-2617

Galluzzi L. New immunotherapeutic paradigms for castration-resistant prostate cancer. Oncoimmunology 2013; 2:e26084; http://dx.doi.org/10.4161/onci.26084

Ramek SH, Nabi HH, Khajehei P, et al. Enhanced oncolysis mediated by herpes simplex virus in vivo. Anticancer Res 2013; 33:1009-13; PMID:23746683; http://dx.doi.org/10.21875/23746683

Vasko AJ, et al. Seneca Valley virus, a systemically administered oncolytic virus, induces antitumor activity in brain tumor stem cells: role of autophagic cell death. J Natl Cancer Inst 2013; 105:1059-65; PMID:23444104; http://dx.doi.org/10.1002/ijc.28132

Duong TV, Dinh TN, Phan TH, et al. Innate immune defense defines susceptibility of sarcoma cells to measles virus vaccine-based oncolysis. J Virol 2013; 87:5484-501; PMID:23028892; http://dx.doi.org/10.1128/JVI.01206-12

Matsumura-Miyagi T, Harano K, Nomura M, Li-Wen L, Nishikawa T, Saga K, Shimbo T, Kaneda Y. TRAIL and Noxa are selectively upregulated in prostate cancer cells downstream of the RIG-I/MAVS signaling pathway by nonreplicating Sendai virus particles. Clin Cancer Res 2012; 18:6271-83; PMID:23014529; http://dx.doi.org/10.1158/1078-0432.CCR-12-1959

Galluzzi L, Kepp O, Kroemer G. Mitochondria: the Janus face of cyclophosphamide: A sterile inflammatory response that potentiates cancer therapy. Oncoimmunology 2013; 2:e2539; http://dx.doi.org/10.4161/onci.2539

Dawood S, Ali M, Yakoob YK, Fukuda K, Seo E, Kawashima R, Nakano Y, Yamae T, Nakade K, Hamada H, et al. Cyclophosphamide enhances antitumor efficacy of oncolytic adenovirus expressing uracil phosphoribosyltransferase (UPRT) in immunocompetent Syrian hamsters. Int J Cancer 2013; 133:1479-88; PMID:23444104; http://dx.doi.org/10.1002/ijc.28132

Zucchelli P, Prusti E, Moschella F. The Janus face of cyclophosphamide: A sterile inflammatory response that potentiates cancer therapy. Oncoimmunology 2013; 2:e25789; PMID:23894726; http://dx.doi.org/10.4161/onci.25789

Kontke T, Chester J, Ilett E, Thompson J, Diaz R, Colley M, Selby P, Nuovo G, Pulido J, Mukhopadhyay D, et al. Precise scheduling of chemotherapy primes VEGF-producing tumors for successful systemic oncolytic virotherapy. Mol Ther 2011; 19:1802-12; PMID:21792179; http://dx.doi.org/10.1038/mt.2011.147

Vaccelli E, Prada N, Kepp O, Galluzzi L. Current trends of anticancer immunotherapy. Oncoimmunology 2013; 2:e25396; PMID:23894726; http://dx.doi.org/10.4161/onci.25396