

## MEETING REPORT

# Oncolytic viruses on the cusp of success?: proceedings of the 9th International Conference on Oncolytic Virus Therapeutics

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Boston, Massachusetts, was the site of the 9th International Conference on Oncolytic Virus Therapeutics held 13–16 June 2015. An overarching theme of the meeting was the continued development of combinatorial treatment regimens to bolster the therapeutic potential of oncolytic viruses (OVs). Several talks focused on combining OVs with immune checkpoint inhibitors in a wide array of tumors, signaling an experimental and thematic shift toward driving immune activation to clear a tumor versus relying on direct viral oncolysis. An important aspect of the meeting was the variety of ongoing OV clinical trials. Topics ranged from basic virology to clinical trials and from academic research to intellectual property and biotechnology. There was much excitement due to the US Food and Drug Administration's recent consideration of talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma (T-VEC was approved in October, following the conference). Here, we summarize the meeting's primary themes, which reflect the current state of the field.

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## INTRODUCTION

The meeting opened with a lecture by OV pioneer and Golden Virus Award recipient Robert Martuza (Massachusetts General Hospital, Boston, MA), who discussed the interplay between bench and bedside and the importance of good communication between the two to drive the field. He emphasized the aspects that all tumors have in common and the key role of basic research in designing vectors to target the intrinsic differences between normal and tumor tissue. Gordon Freeman (Dana-Farber Cancer Institute, Boston, MA) followed with a plenary presentation on immune checkpoint inhibitors and cancer, a focus of upcoming clinical trials. He described how PD-1 and PD-L1 tumor expression plays a role in therapeutic responses to blockade of these immune checkpoints and its correlation with expression of neoantigens that arise from somatic mutations in the cancer genome. He also discussed how a cytotoxic T cell (CTL) response to tumor neoantigens leads to activation of PD-L1 and PD-1 signaling in tumors and CTLs and highlighted potential combination strategies with OVs.

## MECHANISMS OF OV KILLING

The question of how an OV kills a tumor cell and spares normal cells drives OV research. However, the field has recently become more focused on pushing validated OVs into new tumor models rather than characterizing how and why certain tumors respond to OVs and others do not. Len Seymour (University of Oxford, UK) detailed the ability of oncolytic adenovirus (oAd) ColoAd1 to cause tumor cell necroptosis, a programmed form of inflammatory cell death that is thought to stimulate antitumor immunity.

ColoAd1 in combination with a caspase 8 inhibitor was shown to cause necroptosis, which is efficient at clearing tumor cells, more so than apoptosis. Different OVs initiate different innate responses and types of cell death in glioblastoma cell lines, as found by Anne Kleijn (Rotterdam, The Netherlands) using RNA microarray analysis, and this likely impacts antitumor efficacy. Direct comparison of different OVs in the same models provides insights into their advantages and disadvantages.

Viral-induced translational inhibition is a potential roadblock for OVs, especially since many OVs have mutations in viral genes or internal ribosome entry sites (IRESs) that prevent translational shutoff. Mike Brown (Duke University, Durham, NC) described Ser-Arg-rich protein kinase 1 and 2 (SPRK1/2) activity as a major block to poliovirus IRES-dependent translation. However, SPRK signaling is inhibited by MNK1, which is upregulated in glioblastoma, thus promoting oncolytic poliovirus cytotoxicity. Juan Corredo (University of Calgary, Canada) explained how high-risk neuroblastoma-associated N-myc overexpression downregulates interferon (IFN)-stimulated gene expression, which sensitizes neuroblastoma cells to vesicular stomatitis virus (VSV) replication.

Although virus receptors are critical to infectivity, modulation of their levels on cancer cells can have varying effects, depending on the OV. Pin-Yi Wang (Nationwide Children's Hospital, Columbus, OH) unexpectedly found that the sensitivity of neuroblastoma cell lines to oncolytic herpes simplex virus (oHSV) 1716 was independent of the levels of HSV receptor nectin-1 and 3-OS heparin sulfate expression *in vitro* but was related to post-entry activities, probably innate antiviral responses. In addition, the *in vitro* sensitivity

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did not correlate with inhibition of tumor growth, suggesting multiple contributing factors such as tumor microenvironment, innate immune cells, and virus replication.<sup>1</sup> Trevor Shepard (University of Western Ontario, London, Canada) discussed Maraba virus. Its entry is mediated by the low-density lipoprotein receptor (LDLR), the expansion of which is amplified in about 14% of epithelial ovarian cancer (EOC). He showed that culturing EOC cells as three-dimensional spheroids induced resistance to Maraba virus due to reduced LDLR expression, similar to that induced by knockdown of LDLR in EOC-sensitive cell lines.

### ENGINEERING OV

Several new OVs have been engineered to target tumors or spread more efficiently. Properly selected microRNA (miR) target sequences can be engineered into OVs to restrict translation of OV genes in normal tissues, thus enhancing OV safety. Autumn Ruiz (Mayo Clinic, Rochester, MN) described a new miRNA-detargeted mengovirus (oncolytic picornavirus) containing miRNA-133 target sequences in the untranslated regions that maintained efficacy in a mouse model of multiple myeloma after intratumoral or intravenous administration, with greatly reduced pathogenicity due to miR133 expression in normal cells. Similarly, artificial miRs (amiRs) can be used to alter expression of cellular genes that affect virus replication. Caroline Ilkow (Ottawa Health Research Institute, Canada) used an amiRNA-encoding Sendai virus library to screen for replication in pancreatic cancer cells and xenografts, as well as cancer-associated versus normal fibroblasts, identifying 10 amiRNA sequences that were enriched in pancreatic cancer. From these, insertion of a miR6 into oncolytic VSV led to faster virus growth and cell killing.

Generating OV with mutated or retargeted viral glycoproteins can mitigate off-target infection and toxicity. Dillon Betancourt (University of Miami, FL) fused VSV envelope glycoprotein G to gp160 of HIV in order to retarget VSV infection to CD4<sup>+</sup> cells. VSV-gp160G lost neurotoxicity, induced syncytia formation, and was efficacious in a model of adult T-cell leukemia (ATL).<sup>2</sup> Since mice lack human CD4<sup>+</sup> cells, the question of safety in humans is still unanswered. Masato Yamamoto (University of Minnesota, Minneapolis) screened an Ad library of peptide ligands in the fiber knob and identified a mesothelin-targeted motif (VITNxxx) for pancreatic cancer and a CD133 motif (TYMLxxx) to target cancer stem cells. The retargeted oAds inhibited pancreatic and CD133<sup>+</sup> colon cancer tumors, respectively, after intravenous administration, and were not sequestered in the liver, as compared with nontargeted oAd. To increase the safety and selectivity of vaccinia virus (VV), genes encoding both vaccinia growth factor (VGF) and O1 protein, an activator of the MAPK/ERK pathway, were deleted by Takafumi Nakamura (Tottori University, Japan). The doubly deleted VGF-/O1-VV exhibited little, if any, toxicity after intraperitoneal injection and significantly prolonged survival of mice with peritoneal pancreatic cancer, as compared with control VV with only one of these genes deleted.

### COMBINATION THERAPIES

"Arming" OV with therapeutic transgenes has been a popular strategy to increase efficacy and target uninfected tumor cells and the microenvironment. Margaret Duffy (University of Oxford, UK) showed that degradation of the extracellular matrix (ECM) by expression of actin-resistant DNase I or hyaluronidase from oAd improved tumor spread and inhibition of tumor growth.<sup>3</sup> Similarly, an improved oHSV expressing matrix metalloproteinase 9 to degrade ECM was described by Paola Sette (University of Pittsburgh, PA). This virus was also engineered with miR124-based translational regulation of

the essential viral gene ICP4 (thus blocking virus replication in normal cells expressing miR124) and with retargeting of viral entry by glycoprotein D to epidermal growth factor receptor (EGFR). Prem Seth (NorthShore Research Institute, Evanston, IL) constructed an oAd expressing decorin (Ad.dcn), a transforming growth factor- $\beta$  (TGF- $\beta$ ) inhibitor that reprograms the tumor microenvironment and is downregulated in breast cancer. Systemic Ad.dcn was effective in inhibiting breast cancer bone metastases and preventing osteolytic bone destruction.<sup>4</sup> Noriyuki Kasahara (University of Miami, FL) presented several new modifications to the replication-competent retrovirus TOCA511; expression of the suicide gene *Escherichia coli* nitroreductase, which induced tumor regression after CB1945 pro-drug treatment and antitumor immunity, and expression of PD-L1 small interfering RNA.

Combining OV with rationally selected drugs can greatly improve activity. The induction of apoptosis can be detrimental to OV replication, so combining OV with antiapoptotic factors is a promising strategy. Oncolytic rhabdoviruses strongly induce type I IFNs, providing a rationale for combination with Smac (mitochondria-derived activator of caspase) mimetics, antagonists of inhibitor of apoptosis proteins that sensitize cancer cells to inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Shawn Beug (Children's Hospital of Eastern Ontario, Ottawa, Canada) combined a TNF- $\alpha$ -secreting oncolytic VSV with a Smac mimetic, which increased cytotoxicity *in vitro* and was more efficacious in syngeneic tumor models, possibly by shifting the type of cell death from apoptotic to necroptotic.<sup>5</sup> Conversely, ABT-737, a BCL-2 family antagonist, when combined with oncolytic parvovirus-induced apoptosis and cell death, significantly inhibited tumor growth (Antonio Marchini, German Cancer Research Center, Heidelberg, Germany). DNA damage responses are one of the "hallmarks" of cancer that can be targeted by both oHSV and DNA damaging agents or repair inhibitors. Jianfang Ning (Massachusetts General Hospital, Boston, MA) described the combination of oHSV with poly (ADP-ribose) polymerase (PARP) inhibitors, which synergized in killing glioblastoma stem cells *in vitro*, including PARP inhibitor-resistant cells, and brain tumors *in vivo*.

### IMAGING/MONITORING/DELIVERY

The use of genes that concentrate radiotracers for noninvasive nuclear imaging, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), as well as toxicity and radiotherapy, is an attractive strategy. Julia Davydova (University of Minnesota, Minneapolis) described an oAd expressing sodium iodine symporter (NIS) that allows infected cancer cells to be imaged with <sup>123</sup>I or killed with <sup>131</sup>I. An oncolytic VV expressing the somatostatin receptor (vvDD-SSTR) led to accumulation of radiolabeled somatostatin analogue <sup>177</sup>Lu-DOTATOC in tumors, which improved efficacy (Kathryn Ottolino-Perry, University of Toronto, Canada). Neuroblastoma is often treated with the noradrenaline analogue <sup>131</sup>I-mIBG; however, high-risk neuroblastoma expresses low levels of noradrenaline transporter (NAT). Keri Strey (Nationwide Children's Hospital, Columbus, OH) showed that cells infected with oHSV expressing NAT had increased <sup>131</sup>I-mIBG uptake and associated cytotoxicity. oHSV replication can be imaged by <sup>18</sup>F-FHBG-PET due to thymidine kinase (TK) expression (Darshini Kuruppu, Massachusetts General Hospital, Boston, MA)<sup>6</sup>.

Amber Miller (Mayo Clinic, Rochester, MN) used NIS radiohistology to examine the role of hemodynamic manipulation in systemic tumor delivery of VSV. Exercise, which increases blood pressure, improved tumor delivery and reduced toxicity, whereas anesthesia, which decreases blood pressure, decreased delivery. The levels of

tumor uptake of <sup>123</sup>I were correlated with efficacy and survival.<sup>7</sup> A novel strategy for directing OV-infected macrophages to any location in the body was presented by Munitta Muthana (University of Sheffield, UK). Macrophages magnetically labeled with superparamagnetic iron oxide nanoparticles were infected with oHSV and then directed to tumor sites via pulsed magnetic-field gradients in a magnetic resonance imaging (MRI) unit. MRI steering significantly increased tumor uptake of macrophages and reduced tumor burden compared with macrophages or oHSV alone, or when steering was not applied.<sup>8</sup>

## OV AND THE MICROENVIRONMENT

In addition to targeting cancer cells in the tumor, therapeutic targeting of the local tumor microenvironment composed of vascular, stromal, and immune cells may be a favorable strategy. Cancer-associated normal cells can impact cancer cells through secreted factors. John Bell (Ottawa Hospital Research Institute, Canada) discussed the antagonistic effects of vascular endothelial growth factor (VEGF) and IFN- $\alpha/\beta$  on tumor vasculature and oncolytic VV.<sup>9</sup> VEGF induces angiogenesis and promotes tumor growth while repressing genes involved in IFN- $\alpha/\beta$  signaling, which boosts VV growth and spread. Thus, antiangiogenic agents inhibiting VEGF, such as bevacizumab, reduced VV infection after intravenous administration. VV infection induces IFN- $\alpha/\beta$ , which inhibits angiogenesis, which in turn feeds back to inhibit VV growth and spread. There may thus be a complex and antithetical interaction between antiangiogenic effects on tumor growth and OV replication. Intrahepatic cholangiocarcinoma (CCC) is a stromal-rich tumor. Jennifer Altomonte (Technische Universität, Munich, Germany) explained how VSV replication was increased when CCC cells were cocultured with hepatic stellate cells due to decreased IFN and increased TGF- $\beta$  levels.

Jaime Merchant (University of Miami, FL) targeted oncolytic measles virus (MV) infection to tumor stromal cells through the urokinase receptor (uPAR) and showed that infection of uPAR-positive cancer-associated fibroblasts (CAFs) also killed uPAR-negative breast cancer cells in coculture, suggesting heterologous fusion and transfer of MV from CAFs to breast cancer cells. This also seemed to occur *in vivo*, as intravenously administered MV-m-uPAR targeting mouse inhibited human breast cancer progression. Myxoma virus (MYXV) is effective in *ex vivo* purging of hematopoietic malignancies in autologous transplants. Grant McFadden (University of Florida, Gainesville) described studies in allogeneic grafts in which MYXV played two important roles: preventing graft-vs.-host disease through a novel interaction between MYXV and activated T cells and transferring OV from T cells to cancer cells even in the absence of virus receptors, leading to the elimination of multiple myeloma cells in recipient bone marrow.<sup>10</sup>

## IMMUNOLOGY

The combination of OV with immune checkpoint inhibitors has become a major focus of immunovirotherapy. Richard Vile (Mayo Clinic, Rochester, MN) described the use of VSV expressing brain tumor-associated antigens (VSV-TAA; HIF-2 $\alpha$ , Sox10, cMyc) in combination with checkpoint inhibitors in a glioma model.<sup>11</sup> Intravenous administration of VSV-TAA extended survival, which was further increased in combination with anti-PD-1 and anti-CTLA-4, in contrast to VSV not expressing TAA, which had no effect when used in combination. Anti-PD-1 uncovered a T helper type 1 (Th1) response against both the tumor and VSV, suggesting that an antitumor immune response against TAA is necessary for efficacy with checkpoint inhibition.

Richard Vile also presented studies combining intratumoral reovirus with anti-PD-1 in a subcutaneous B16 melanoma model in which the combination led to long-term survivors, owing to increased natural killer cell killing and CD8<sup>+</sup> Th1 responses, and decreased regulatory T cells.<sup>12</sup> The combination of oncolytic MV with anti-CTLA-4 and anti-PD-L1 antibodies in an MV-sensitive melanoma model also exhibited an increase in cytotoxic T cells and a decrease in regulatory T cells, along with prolonged survival (Christine Engeland, National Center for Tumor Diseases, Heidelberg, Germany). Similarly, Gough Au (University of Newcastle, Australia), found that coxsackievirus A21 (CVA21) in combination with anti-PD-1 or anti-CTLA-4 was significantly more efficacious at inhibiting tumor growth than single agents alone, and it also delayed the growth of challenge tumors. Other therapeutics are being added to immune checkpoint inhibitors and OV, including sunitinib with reovirus (Ahmed Mustafa, University of Calgary, Canada) and irradiation with VV (Aladar Szalay, University of California, San Diego).

Aside from immune checkpoint inhibitors, other strategies for enhancing antitumor immune responses were presented. Immune costimulators can also improve immunotherapy. CD40L, a costimulatory ligand for OX40, was engineered to be expressed from oAd and shown to enhance antitumor immunity in a glioma model (Juan Fueyo, MD Anderson Cancer Center, Houston, TX). Carlos Fajardo (ICIBELL-ICO, Barcelona, Spain) described an oAd expressing a bispecific T-cell engager (BiTE) targeted to EGFR and CD3 that recruited T cells to tumor cells overexpressing EGFR. HSV ICP47 inhibits human TAP (transporter associated with antigen presentation) but not rodent TAP. To block rodent TAP and major histocompatibility complex class 1 antigen presentation, Matthew Mulvey (BeneVir Biopharm, Rockville MD) inserted the bovine herpesvirus UL49.5 gene, which inhibits both mouse and human TAP, into oHSV. Blocking TAP increased virus replication and OV spread in the tumor and also induced antitumor immunity.

Steve Thorne (University of Pittsburgh, PA) discussed strategies to overcome tumor resistance to VV: (i) deglycosylating viral particles to block Toll-like receptor 2 (TLR2) activation and antibody responses; (ii) VV expression of TRIF to activate the TRIF pathway, leading to induction of a CTL response; and (iii) inactivating prostaglandin E2 and myeloid-derived suppressor cell immunosuppression via VV expression of 15-hydroxyprostaglandin dehydrogenase. Adoptive T-cell therapy is another promising immunotherapy strategy. Siri Tahtinen (University of Helsinki, Finland) showed that combining oAd with adoptive T-cell transfer broke tumor tolerance and improved efficacy in a B16.OVA tumor model with OVA-specific T cells, leading to increased tumor infiltration of macrophages and endogenous antimelanoma T cells, indicative of epitope spreading.

## CLINICAL TRIALS

Several OVs are moving into the clinic. Robert Andtbacka (Huntsman Cancer Institute, Salt Lake City, UT) presented results from a phase Ib trial of recently approved oHSV T-VEC (Imlygic; Amgen) in combination with anti-CTLA-4 (ipilimumab) in patients with untreated, unresected stage IIIB–IV melanoma. T-VEC was administered intralesionally starting with 10<sup>6</sup> pfu/ml followed 3 weeks later and every 2 weeks thereafter with 10<sup>8</sup> pfu/ml, with ipilimumab initiated at week 6 and then every 3 weeks for 4 infusions. Grade 3/4 adverse events occurred in about a third of patients, not dissimilar to the rate for individual treatments. The durable response rate (DRR) was 44%, higher than expected for either treatment alone, with 67% of patients alive at 18 months. Hardev Pandha (University of Surrey, UK) described early-phase clinical trials of CVA21, which binds



to intercellular adhesion molecule-1, upregulated in some solid tumors, including melanoma. Multiple intravenous doses induced neutralizing antibody after about 7 days. Intratumoral treatment of patients with stage IIIc and IV malignant melanoma produced an impressive median overall survival of 26 months, similar to that with T-VEC. There was an increase in interleukin-6 (IL-6), IL-8, and IFN- $\gamma$  within the treated lesions from the first injection to the third, as well as an increase in T cells and PD-L1. In a clinical trial of CVA21 in combination with anti-CTLA-4 antibodies, treated patients showed increases of CD4/8 T cells in both injected and uninjected lesions (Darren Shafren, Viralytics, Sydney, Australia).

Glioblastoma, owing to its short median survival and limited improvement in patient outcomes over the past several decades, has been a common target for a variety of OV, many of which have entered clinical trial. Douglas Jolly (Tocagen, San Diego, CA) discussed clinical trials with Toca 511 and Toca FC, an extended-release formulation of 5-fluorocytosine. They pursued three routes of administration: direct intratumoral virus injection, injection into the resection cavity, and systemic intravenous injection. More than 50 patients have been treated to date, with no serious adverse events ascribed to the virus. Tomoki Todo (University of Tokyo, Japan) presented phase I results from patients with high-grade glioma treated with intratumoral oHSV G47 $\Delta$ . There was some evidence of efficacy, with 3 of 10 patients surviving more than 4 years. Interestingly, radiological imaging commonly demonstrated pseudoprogression within weeks of treatment, likely due to inflammation, which was followed months later by tumor regression. A technique to improve virus delivery and distribution throughout a tumor—convection-enhanced delivery (CED) using oAd $\Delta$ -24RGD—was described by Clemens Dirven (Erasmus University, Rotterdam, The Netherlands). Sampling of the cerebrospinal fluid revealed viral DNA at 3 months postinfusion in four of eight patients, suggesting prolonged virus replication in the tumor. Reovirus has also been delivered using CED, which was well tolerated by patients, although actual convection could not be demonstrated (James Markert, University of Alabama–Birmingham, AL)<sup>13</sup>.

A careful analysis of circulation kinetics after intravenous administration of oAd ColoAd1 in patients with a variety of solid tumors was presented by Kerry Fisher (University of Oxford and PsiOxus Therapeutics, Oxfordshire, UK). Some liver inflammation was noted, with a dose-limiting toxicity at 10<sup>13</sup> particles that could be controlled by altering the dosing schedule and infusion rate (10<sup>12</sup> particles over 5 minutes). Virus hexon expression was detected in tumor biopsies, indicative of virus replication, which correlated with areas of necrosis and CD8<sup>+</sup> cells. Eva Galanis (Mayo Clinic, Rochester, MN) described two clinical trials of oncolytic MV for patients with chemotherapy-resistant ovarian cancer and preexisting MV immunity. The overall survival after intraperitoneal administration of MV-NIS was favorable and comparable to that in an earlier MV-CEA trial. Interestingly, SPECT imaging of <sup>123</sup>I, while detected in only a minority of patients, indicated that increasing levels of NIS were associated with longer progression-free survival.<sup>14</sup> A second trial using MV-NAP, expressing *Helicobacter pylori* neutrophil-activating protein (NAP), a TLR2 agonist, to induce innate immune responses, has also been initiated. Although OV clinical trials have so far demonstrated exceptional safety, the first serious virus adverse event was reported by Mitesh Borad (Mayo Clinic, Scottsdale, AZ), in a phase I trial in which a patient with colon cancer and liver metastases treated with the highest dose of VSV expressing human IFN- $\beta$  experienced tumor lysis syndrome and severe adverse events and died of multifactorial liver injury after transitioning to palliative care, with viral genomes present in normal liver tissue.

## CONCLUSION

The wide diversity of OVs and their successful use in preclinical studies involving almost all types of cancer make them powerful new agents for cancer therapy. There have been more new and ongoing OV clinical trials this year than in previous years, with many suggestive of encouraging results. OV therapies have also garnered the attention of venture capitalists and industry scientific staff, signaling their prospective clinical application and the dawning of a new therapeutic modality that combines cytotoxicity with gene therapy and immunotherapy. Although this conference demonstrated that significant progress has been made in the field, we still have a long way to go, as we have only begun to understand both how OV therapy works and the myriad host–virus interactions that mediate safety, toxicity, and efficacy.

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