

## Report on the NCI Microbial-Based Cancer Therapy Conference

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### Abstract

The National Cancer Institute Inaugural Microbial-Based Cancer Therapy Conference was held in Bethesda, Maryland, on July 11–12, 2017. This interdisciplinary forum included industry leaders, academic investigators, and regulatory officers involved in the development of microbial-based therapies for the treatment of cancer. The aim of the meeting was to discuss the potential of

virus- and bacteria-based therapies to halt tumorigenesis and induce immune responses in cancers where conventional therapy is inadequate. This summary highlights topics and viewpoints raised by the presenters and discussants and should not be viewed as the conclusions or recommendations of the workshop as a whole. *Cancer Immunol Res*; 6(2); 122–6. ©2017 AACR.

### Introduction

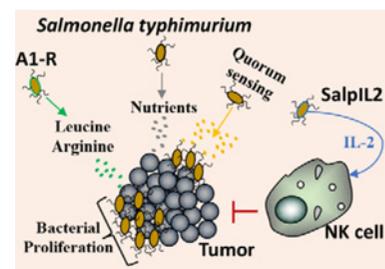
An inverse association between infection and tumor progression was observed more than two centuries ago (1). In 1891, William Coley formulated a heat-inactivated *Streptococcus pyogenes* and *Serratia marcescens* mixture called "Coley's toxin" to treat cancer, with some reported success (2, 3). In 1912, an attenuated rabies virus exhibited antitumor responses in some patients with cervical cancer (4). Various attempts to treat cancers with attenuated or genetically engineered bacteria or viruses have been successful, including treatment of bladder tumors with an attenuated *Mycobacterium bovis* (Bacillus Calmette–Guerin) in 1976 (3–5). To continue to expand upon these century-old approaches with modern era insight from an improved understanding of cancer biology, the National Cancer Institute sponsored an inaugural Microbial-Based Cancer Therapy Conference in Bethesda, Maryland, on July 11–12, 2017.

Robert Hoffman (U California-San Diego and AntiCancer, Inc.) introduced the meeting with a discussion of the potential advantages of microbial-based therapy over traditional oncologic therapy. Chemotherapy and radiation lack target specificity and may damage healthy tissue. These treatments are also often inhibited by a hypoxic tumor microenvironment with high interstitial fluid pressure and reduced blood flow. Bacteria and viruses have a natural tropism toward different tumor

types and physiologic conditions, which can overcome such barriers. Researchers can use live genetically engineered bacteria and viruses to treat human tumors, either as direct oncolytic agents, or as vectors for delivery of gene therapy, prodrugs, cytotoxic agents, therapeutic peptides/proteins, miRNA, and antibodies. This experimental therapeutic strategy can enhance host immunity, induce tumor vascular collapse, and promote tumor cell death.

### *Salmonella Typhimurium* Therapy

Neil S. Forbes (U Massachusetts-Amherst) presented his work with *Salmonella typhimurium*, which accumulate 10,000-fold higher in tumors compared to healthy organ tissue. *Salmonella* bacterial chemoreceptors are activated by metabolic nutrients (aspartate, serine, ribose/galactose) released from dead and dying cells (6). Robert M. Hoffman added that these mechanisms can be enhanced by engineering *Salmonella typhimurium* to express auxotrophic mutations for leucine and arginine (*S. typhimurium* strain A1-R). The immune-privileged tumor environment, coupled with the bacteria's ability to utilize a cell-density signaling system called quorum sensing, encourages bacterial proliferation. In murine models, intravenous or intratumorally administered A1-R invaded and replicated intracellularly within tumor cells, resulting in the targeted killing of primary tumors and metastases in the lymph and lung (7). A1-R may also be tagged for imaging tumors, which may make the microbe useful diagnostically and therapeutically. Engineering *Salmonella* to release drugs into the tumor via quorum sensing or lytic release of molecules increases target specificity, penetration, and release of therapeutic agents.



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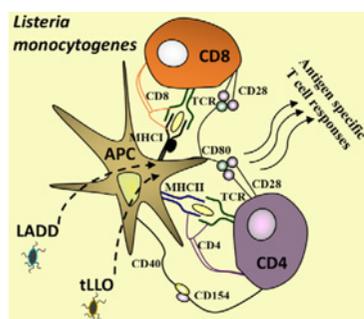
doi: 10.1158/2326-6066.CIR-17-0748

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Daniel A. Saltzman (U Minnesota, SALSPERA LLC) examined an attenuated strain of *Salmonella* engineered to express a truncated human interleukin-2 (IL2) protein called SalpIL2. In murine models, a single oral dose of SalpIL2 reduced primary tumor volume and the number of metastatic lesions as a result of increased tumor-targeted NK-cell activity (8). A phase I, dose-escalation trial demonstrated safety and an NK-mediated immunologic response in patients with metastatic GI cancers. In addition, a phase I canine study involving companion animals with appendicular osteosarcoma was conducted that demonstrated safety and feasibility.

### Listeria Monocytogenes Therapy

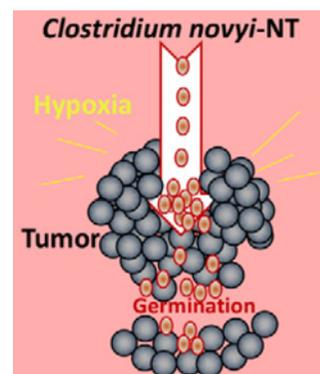
Tom W. Dubensky, Jr. (Aduro Biotech) discussed a live, attenuated, double-deleted *Listeria monocytogenes* (LADD) platform. LADD has deletions in ActA and Internalin B, which are molecules involved in the polymerization of host cell actin and host cell hepatocyte internalization, respectively. Insertion of a mesothelin transgene into LADD enables the secretion of mesothelin into the cytosol of infected antigen-presenting cells for effective peptide presentation and mesothelin-specific T-cell responses against mesothelin-expressing murine tumors. In a phase I trial involving subjects with treatment-refractory carcinoma and hepatic metastases, mesothelin-specific T-cell responses were identified after treatment with mesothelin-LADD and the protocol was deemed safe (9). Insertion of neoantigens specific to the patient is being investigated for personalized LADD (pLADD) in a phase I trial, focusing on microsatellite-stable colorectal cancers. This individualized therapy is also being considered with an intratumorally administered agonist to the stimulator of interferon genes (STING), called ADU-S100 (Aduro Biotech), that may prime and boost the production of pLADD-expressing neoantigen-specific T cells. Michael F. Princiotta (Advaxis, Inc.) described *Listeria monocytogenes* fusion protein immunotherapies. *Listeria monocytogenes* infects mononuclear cells and secretes pore-forming lysin listeriolysin O (LLO) in phagosomes. LLO escapes into the cytosol and is processed and presented via major histocompatibility (MHC)-I and MHC-II. Antigens fused to a truncated form of LLO (tLLO) prime CD8<sup>+</sup> and CD4<sup>+</sup> T cells for antigen-specific immunity. Attenuated *Listeria monocytogenes* generated with irreversible deletions in an actin polymerization gene (*ActA*) and a D-alanine synthesis gene (*dal*), as well as fragments of the epidermal growth factor receptor HER2/neu fused to tLLO (ADXS31-164, Advaxis, Inc.), was intravenously administered to dogs with osteosarcoma following amputation and adjuvant carboplatin chemotherapy. ADXS31-164 prevented



pulmonary metastatic disease and prolonged survival by inducing HER2/neu-specific T cells responses (10). Fusion of tLLO with the human papillomavirus (HPV) protein E7, Axalimogene filolisbac (ADXS11-001, Advaxis, Inc.), was also assessed in phase II clinical trials of HPV<sup>+</sup> tumors.

### Clostridium Novyi-NT Therapy

*C. novyi-NT* is an experimental, highly mobile, spore-forming anaerobe that lacks the lethal  $\alpha$ -toxin gene. Shibin Zhou (Johns Hopkins) and Halle H. Zhang (BioMed Valley Discoveries, Inc.) described the microbe's preference for hypoxic microenvironments in tumors. Intravenous injection of *C. novyi-NT* spores led to selective germination in solid tumors, but not in nonmalignant hypoxic lesions. Intratumoral or intravenous injections of *C. novyi-NT* induced significant reductions in tumor volume in various murine, rabbit, and canine models (11, 12). Mechanisms of *C. novyi-NT* antitumoral responses may involve secreted lytic factors, such as phospholipase C and lipase, as well as a robust CD8<sup>+</sup> T cell-mediated adaptive immune response (12). In phase I studies involving a single intratumoral injection of spores into 24 adult patients with advanced malignancies, *C. novyi-NT* germination led to significant destruction of injected tumors in more than a third of patients and stable disease in the injected lesion in most patients that completed a 2-month follow-up. *C. novyi-NT* toxicities correlated with the tumor size indicating that more favorable responses are identified in patients with small tumors.

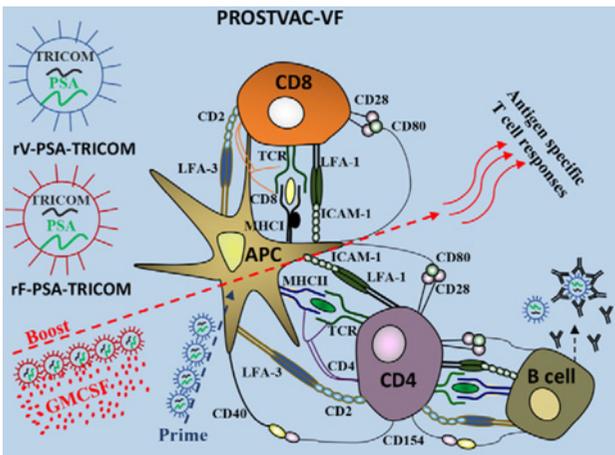


### Virotherapy That Activates TLRs

Steve Fiering (Dartmouth) discussed *in situ* vaccination with cowpea mosaic virus (CPMV; ref. 13). The CPMV viral capsid molecules are intratracheally or intradermally administered in murine tumor models as well as in community dogs with oral melanoma, revealing a significant reduction in tumor burden. These studies suggested an increased antitumor immunity through activation of neutrophils and subsequent activity of lymphocytes requiring the Toll-like receptor (TLR) signaling molecule MyD88. Steve Thorne (Western Oncolytics and U Pittsburgh) explained that deglycosylating vaccinia removed TLR2 ligands and inserting a transgene involved in the expression of the adaptor molecule, TRIF, enhanced TLR3 cell signals, which, respectively, reduced antiviral antibodies and increased antitumor activity in a murine model of renal cancer (14). Intratumoral injection of a vaccinia virus containing a vector expressing a prostaglandin E<sub>2</sub>-inactivating enzyme called hydroxyprostaglandin dehydrogenase 15-(NAD) reduced tumor volume and the numbers of tumor-associated myeloid-derived suppressor cells and T regulatory cells in murine models. The use of these viruses alone or as nanocarriers for tumor antigens, drugs, or immune adjuvants may be advantageous in creating antigen-specific and systemic tumor immunity.

## Poxviridae Therapy

H. Kim Lyerly (Duke) discussed subcutaneous and intradermal injections of *ex vivo*-generated dendritic cells modified with a recombinant viral vector. In patients with metastatic cancer expressing carcinoembryonic antigen (CEA), the fowlpox vector (rF-CEA(6D)-TRICOM), encoding both CEA and a triad of costimulatory adhesion molecules (TRICOM)—including B7.1, ICAM-1, and LFA-3—generated CEA-specific T cells and the protocol was deemed safe (15). James L. Gulley (NIH) discussed a phase II randomized-control trial of prostate-specific antigen (PSA) recombinant vaccinia vectors (rV-PSA) and recombinant fowlpox vectors (rF-PSA) that each included TRICOM, termed PROSTVAC-VF, demonstrated tolerance and improved overall survival in men with metastatic castration-resistant prostate cancer (16). This study involved a priming immunization with rV-PSA-TRICOM. Subsequent boosts involving rF-PSA-TRICOM plus the adjuvant recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) deter rV-PSA-induced neutralizing antibody responses.



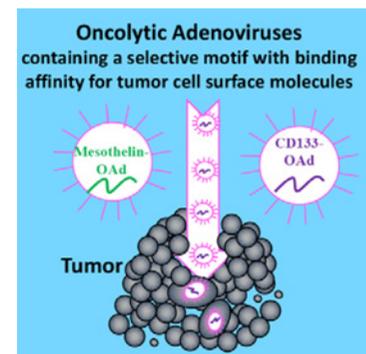
## Bacterial Components Used in Cancer Therapy

Hal Gunn (Qu Biologics) described site-specific immunomodulators (SSI), which are components of inactivated bacterial species with identified pathogenicity to the target organ (17). Preclinical assessment of SSIs identified increased survival in murine colon, lung, and skin cancer models. Mechanisms may involve organ-specific increases in the ratio of M1 compared with M2 macrophages and NK cell activity. Safety and tolerability were established in a Canadian clinical trial involving 6 non-small cell lung cancer patients treated with one SSI product. Matthew Giacalone (Vaxiion Therapeutics) described recombinant *Escherichia coli*, spherical nanoparticles called minicells. VAX014 (Vaxiion Therapeutics) is a minicell engineered to contain invasins and perfringolysin O (PFO). Invasin is a surface protein from *Yersinia pseudotuberculosis* known to bind tumor-activated/unligated cell integrins  $\alpha_5\beta_1$  and  $\alpha_3\beta_1$ . PFO is a cholesterol-dependent membrane pore-forming protein toxin from *Clostridium perfringens*. Expression of these molecules in VAX014 increases target specificity and tumor lysis. In a syngeneic, orthotopic, murine bladder cancer model,

intravesical treatment with VAX014 prevented tumor implantation and improved overall survival (18). These murine tumors also express the PD-1 ligand, programmed cell death ligand-1 (PD-L1), and combined treatment of VAX014 with antibodies to PD-L1 enhanced survival compared with VAX014 alone. Standard of care involves transurethral resection of bladder tumors and immediate postoperative intravesical instillation of a chemotherapeutic agent which can often lead to toxic side effects (18). VAX014 alone or in combination with checkpoint inhibitors may be an alternative therapeutic approach in bladder cancer.

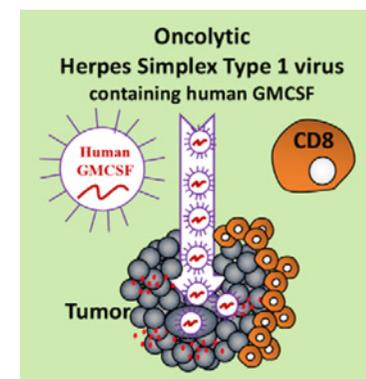
## Adenoviral Therapy

Adenoviruses exhibit high *in vivo* transduction efficiency but are not effectively targeted to many tumor types due to a lack of the Coxsackie adenovirus receptor on these cells. Masato Yamamoto (U of Minnesota) described the development of oncolytic adenoviruses (OAd) with transductional targeting capability. In a murine model of pancreatic cancer, intratumoral injections of mesothelin-OAd induced reductions in tumor volumes compared with untreated controls and a wild-type adenovirus (19). Additional assessment of another target molecule, CD133, revealed that CD133-OAd suppressed tumorigenesis and metastasis in a colon cancer model (20). Liver sequestration mediated by coagulation factor X binding to the Ad5 hexon protein was blocked by substitution of the adenovirus serotype 3 (Ad3) hexon onto the Ad5 capsid.



## Herpes Simplex Virus Type 1 (HSV-1) Oncolytic Therapy

H. Kim Lyerly (Duke) and Robert H. I. Andtbacka (U Utah) described modified HSV-1 therapies involving a gene insertion for human GM-CSF and gene deletions that increase viral replication in tumors (*ICP34.5*) and improve antigen presentation (*ICP47*). Lyerly's study included patients with refractory tumors that received dose escalation of OrienX010 (OrienGene Biotechnology Ltd.) that was well tolerated with no dose-limiting toxicities. T-cell receptor analysis of patients' peripheral blood mononuclear cells, after oncolytic therapy alone or sequential adoptive immunotherapy involving autologous dendritic cells and cytokine-induced killer cells, identified an expansion of tumor-specific populations of activated T cells



(21). Andtbacka's research involved talimogene laherparepvec (Imlygic or T-VEC). In the phase III OPTiM study, intralesional T-VEC injections resulted in an improved durable response rate compared with subcutaneously administered recombinant GM-CSF in patients with unresected stage IIIB to IV melanoma. Analysis of regressing lesions, including uninjected lesions, suggested an association between response and the presence of MART-1-specific CD8<sup>+</sup> T cells and reduction in CD4<sup>+</sup> regulatory T cells (22).

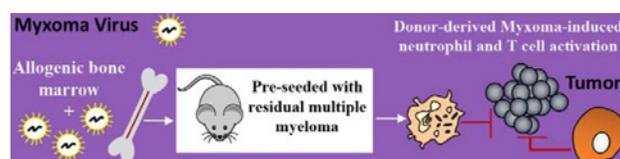
## Virotherapy with Animal Viruses

The sensitivity of vesicular stomatitis virus (VSV) to type I interferon (IFN) responses was described in a presentation from the laboratories of David Ornelles and Douglas Lyles (Wake Forest U). VSV is unable to productively infect healthy cells but can specifically infect and kill tumor cells that lack type I IFN production (23). Subcutaneous injection of prostate tumor cells (LNCaP or PC3) into mice treated intravenously or intratumorally with either a wild-type VSV or VSV containing a point mutation in the viral M protein revealed that the mutant was nonlethal compared with the wild-type. Either virus exhibited antitumor responses, but only in the LNCaP cells (24). PC3 cells were subsequently assessed for the expression of interferon-stimulated genes (ISG) after silencing two characterized genes that are absent in aggressive prostate cancers (*MAP3K7* and *CHD1*; ref. 25). Preliminary data indicate that the loss of both of these genes decreased ISG expression in PC3 cells, suggesting that the deletion of *MAP3K7* and *CHD1* in prostate tumor cells may serve as biomarkers for therapies involving VSV.

Grant McFadden (Arizona State) discussed the oncolytic potential of myxoma virus (MYXV) in resistant murine- or patient-derived brain tumor-initiating cells (BTIC). MYXV encodes M011L, which is a structural mimic of the anti-apoptotic host protein, Bcl-2. To enhance MYXV oncolytic responses, a construct that removes M011L was created (vMyx-M011L-KO) and used to infect BTICs. vMyx-M011L-KO induced the activation of apoptotic pathways in murine BTIC-implanted tumors and significantly prolonged survival that was enhanced by combined treatment with temozolomide (26). In an immunocompetent murine multiple myeloma model, *ex vivo* donor murine allogenic bone marrow was treated with MYXV. The MYXV-treated bone marrow was then transplanted into a recipient with preseeded residual multiple myeloma, leading to reduced recipient tumor burdens, through mechanisms involving donor-derived MYXV-induced neutrophil and T-cell activation (27).

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Peter Tattersall (Yale U) discussed rodent parvoviruses, which contain a linear, single-strand of DNA that encodes two genes. In a series of screening assays, the LuIII serotype was identified as the most potent oncolytic parvovirus. The melanoma-lytic activity of LuIII was mapped to the LuIII capsid gene (28). Identification of a murine parvovirus 1A (MPV1a), which infects mouse melanoma cells, provides a model for assessment of a replicating, but nonpropagating, parvovirus vector system that targets the PD-1 pathway.

## Regulation of Microorganisms in Cancer Therapy

Ke Liu (CBER/FDA) expressed regulatory concerns that need to be balanced in the context of the benefit to the trial subject. Appropriate controls, techniques, and documentation to track a systemic immune response and an effect on overall survival are essential to demonstrating a therapeutic effect. This also requires knowledge of possible adverse events that may occur with allergies, comorbidities, medications, tropism to medical implants, route of administration procedures, or natural biologics produced by the microorganism.

## Conclusions

For two centuries, scientists have assessed the functional mechanisms of pathogens as a potential therapy for the treatment of cancer. Only within the last few decades have scientists gained the knowledge and technical tools to genetically modify microorganisms to target tumors and the host immune system. Identifying bacterial or viral products that are immunogenic, or engineering a microorganism to express tumor-specific antigens, cytotoxic drugs, cytokines, or that has enhanced tropism, may provide the therapeutic benefit needed in certain cancers. Continued evaluation of the safety and efficacy of these various microorganisms in the treatment of cancer is expected to improve cancer patient outcomes and enhance current perspectives on immunotherapies and the host response to infection.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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# Cancer Immunology Research

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*Cancer Immunol Res* 2018;6:122-126.

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