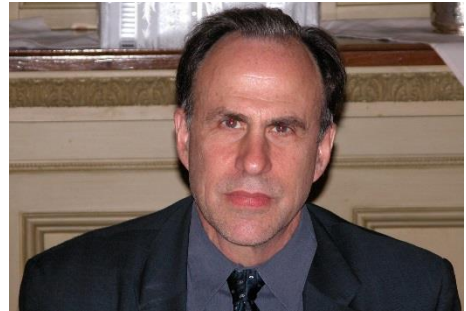


## **Speaker Bio's and abstracts**

## **Robert M. Hoffman PhD**

AntiCancer Inc. and Department of Surgery, UCSD

Robert M. Hoffman completed his Ph.D. in Biology at Harvard University in 1971. His post-doctoral training was at Massachusetts General Hospital, Boston and Institutes of Bioorganic Chemistry and Molecular Biology, Moscow, Russia. He has been a member of the University of California San Diego School of Medicine faculty since 1979 and is currently Professor of Surgery. He began his cancer research career in 1965 and in 1984 he founded AntiCancer, Inc. Dr. Hoffman has been a pioneer on tumor-targeting bacteria; fluorescent protein-expressing patient-derived orthotopic xenograft (PDOX) mouse models of cancer; recombinant protein-based cancer drugs and diagnostics; as well as pluripotent hair follicle stem cells. Dr. Hoffman has published approximately 900 scientific papers which have been cited approximately 40,000 times with an h-index of approximately 100. In 2016, Dr. Hoffman was awarded the Sun Lee Prize from the International Society for Experimental Microsurgery.



### **Abstract**

#### **Tumor-Targeting *Salmonella typhimurium* A1-R: An Overview**

The tumor-targeting *Salmonella typhimurium* A1-R (*S. typhimurium* A1-R) strain is attenuated by auxotrophic mutations for Arg and Leu, thereby precluding continuous infection of normal organs, but allowing high virulence in tumors of all types. Efficacy of *S. typhimurium* A1-R in nude-mouse models of prostate, breast, pancreatic, ovarian, lung, stomach and cervical cancer, as well as sarcoma and glioma in orthotopic mouse models has been demonstrated. *S. typhimurium* A1-R also has targeted, with high efficacy, primary bone tumors and lung metastasis of high-grade osteosarcoma, breast-cancer brain metastasis, and experimental breast-cancer bone metastasis in orthotopic mouse models. The efficacy of *S. typhimurium* A1-R on pancreatic cancer stem cells, on pancreatic cancer in combination with anti-angiogenic agents, as well as on cervical cancer, soft-tissue sarcoma, and pancreatic cancer patient-derived orthotopic xenograft (PDOX) mouse models has also been demonstrated. Perhaps most exciting is the ability of *S. typhimurium* A1-R to decoy quiescent drug-resistant cancer cells in tumors, which are often the vast majority, to begin to cycle and thereby convert to drug-sensitivity.

## **Steve H Thorne, Ph.D.**

Department of Cell Biology and Department of Immunology, University of Pittsburgh, University of Pittsburgh Cancer Institute, Chief Scientific Officer, Western Oncolytics Ltd

I have many years experience working with different oncolytic vaccinia and related viruses. This includes design, engineering, pre-clinical testing, translational development and IND-enabling and early phase clinical testing. I have pioneered the use of these vectors alone, notably as immunotherapies and in combination with immune cell-based and antibody-based therapies. My Undergraduate degree was obtained from Oxford University and my Ph.D. from Imperial College in London, with post-doctoral experience at Cancer Research UK and Stanford University. I have been faculty at The University of Pittsburgh for 8 years and have over 80 publications in refereed journals (including *Science*, *Nat Med*, *JCI*, *PLoS Medicine*, *PNAS USA*, *Can Cell*, *Can Res*, *Cell Host Microbe* and *Nat Rev Can*). In addition I have been involved with several Biotech start-ups, including Jennerex Biotherapeutics (now a part of Sillajen), and more recently Western Oncolytics Ltd. I am currently taking an entrepreneurial leave of absence from the University of Pittsburgh to act as CSO at Western Oncolytics.



### **Abstract**

#### **Oncolytic viruses as novel, multi-mechanistic immunotherapies**

The use of tumor-selective, replication competent viruses, or Oncolytic Viruses (OV) as cancer therapies has advanced recently with the first-in-class approval in a Western market (IMLYGIC) and with several other successful randomized trials. One of the driving factors behind this success has been the realization that these therapies should be considered primarily as immunotherapies. This has further allowed investigators to re-design a next generation of vectors to more effectively interact with the host immune response. This includes both activation of an anti-tumor adaptive immune response as well as modulation of the tumor micro-environment in order to overcome localized immunosuppression. Approaches to achieve these goals will be discussed with special reference to vaccinia based OV therapies, as well as description of next generation clinical candidates.

## **H. Kim Lyerly, M.D.**

Director, Center for Applied Therapeutics, Duke University

Dr. Lyerly is the Director of the Center for Applied Therapeutics, the George Barth Geller Professor of Cancer Research, Professor of Surgery, Associate Professor of Pathology and Assistant Professor of Immunology at Duke University. He was appointed in 2008 to the National Cancer Advisory Board (NCAB). He served as Chair of the Cancer Center Sub-Committee, as well the NIH Council of Councils, and NIH Office of AIDS Research Board. He has been a member of the SAB of the Susan G. Komen and Burroughs Wellcome Foundation. Dr. Lyerly has served on SAB for MD Anderson, University of Michigan, Chicago, Alabama, Arizona, Boston University, and Purdue. He has served as an advisor to the University of Washington, and Case Western Reserve Clinical and Translational Science Institutes. Dr. Lyerly served as PI of the Duke Breast SPORE, and as the Director of the Duke Comprehensive Cancer Center from 2003 to 2011. Dr. Lyerly is internationally recognized expert in cancer therapy and immunotherapy and has published over 300 scientific articles and book chapters, and has edited 10 textbooks on surgery, cancer immunotherapy, and novel cancer therapies. He serves the editorial board of 12 scientific journals.



### **Abstract**

#### **Viral Vectors as Vaccines Targeting Cancer Antigens**

Recent clinical activity observed with antigen specific T cells targeting cancer antigens as therapeutics, has resulted in a variety of strategies to enhance the presences, magnitude and quality of T cells in cancer patients. A long standing attribute of vaccines has been the induction of antigen specific T cells. A number of recombinant viral vectors have been employed as vaccines to induce adaptive immune responses to cancer associated and cancer specific antigens. Recombinant vectors, in combination with other vaccines and/or immune modulators have demonstrated anticancer activity in animal models, and are being tested in clinical studies.

## Steven Fiering PhD

Geisel School of Medicine at Dartmouth.

Dr. Fiering is Professor of Microbiology and Immunology at Geisel School of Medicine at Dartmouth. His lab focuses on *in situ* vaccination as immunotherapy for tumors. This approach is essentially a therapeutic cancer vaccine using an identified tumor as the site of vaccination and the tumor itself as the antigen source, with the treatment injecting immunostimulatory reagents. When optimal the approach disrupts local immunosuppression and stimulates a local antitumor immune response that becomes systemic and fights metastatic disease. The lab has used attenuated microorganisms with various combinations of reagents with adjuvant properties and nanoparticles that are directly injected into the treated tumors. The studies are done in mice and community dogs with spontaneous cancer and the mechanisms are investigated to understand the underlying immunology and how it can be applied clinically.



### Abstract

#### **In situ vaccination for cancer immunotherapy: treat locally, respond systemically**

Steven Fiering<sup>1</sup>, Pat Lizotte<sup>1</sup>, Amy Wen<sup>2</sup>, Nicole Steinmetz<sup>2</sup>

<sup>1</sup> Geisel School of Medicine at Dartmouth, <sup>2</sup>Case Western Reserve University

Immunotherapy for cancer is making impressive impacts in the clinic. One strategy dating back to William Coley in 1900 is *in situ* vaccination. This approach puts immunostimulatory reagents into an identified tumor to break the local immunosuppression, stimulate a local anti-tumor response and most importantly stimulate systemic antitumor immune responses to eliminate metastatic disease. This is essentially an antitumor therapeutic vaccination, because the tumor provides the antigens and the adjuvants are the immunostimulatory reagents, thus “*in situ* vaccination”. The approach has been part of standard of care for superficial bladder cancer using BCG bacteria. There are many immunostimulatory reagents that can be used and each has different capabilities. We have done studies with attenuated microorganisms including *Toxoplasma gondii*, and *Listeria monocytogenes* as well as known agonists for TLRs and STING. Our recent focus has been on a noninfectious plant virus, cowpea mosaic virus (CPMV). Nanoparticles from CPMV were used in mouse cancer models and community dogs with oral melanoma and other tumors. These particles are composed of assembled viral capsid proteins, have no nucleic acids and have no recognized immunostimulatory reagents. However, they are strongly immunostimulatory through unknown pathways and cause dramatic changes in the tumor microenvironment that lead to primary tumor reduction or elimination and potent resistance to metastatic tumors. The treatment is immune-mediated but response in the lungs requires different immune components than response in flank tumors of the same B16F10 melanoma cell line. Tumor reduction or elimination occurs in many anatomic locations with multiple tumor types and in multiple strains of inbred mice. Treatment of a primary tumor by direct intratumoral injection mediates robust rejection of a rechallenge with the same tumor. The mechanisms and pathways of immunostimulation are under investigation. In addition to the inherent immunostimulatory adjuvant properties of these nanoparticles, they are a versatile platform to which other reagents for immune modulation can be attached. This demonstration of the value of select viral-like nanoparticles for treatment of cancer opens a new avenue of cancer immunotherapy.

**Neil S. Forbes Ph.D.**  
University of Massachusetts Amherst

Dr. Forbes is a Professor of Chemical Engineering at the University of Massachusetts, Amherst. He is an adjunct member of the Molecular and Cell Biology Program and a member of the Institute for Applied Life Sciences. His laboratory focuses on developing cancer therapeutics and understanding molecular transport in tumors. Dr. Forbes received a BS in Chemical Engineering from Case Western Reserve University and a PhD in Chemical Engineering from the University of California at Berkeley. There he studied cancer metabolism with Harvey Blanch and Douglas Clark. He did postdoctoral training with Rakesh Jain in Radiation Oncology at Harvard Medical School / Massachusetts General Hospital.



**Abstract**

Engineered Salmonella for Drug Delivery to Solid Tumors

Engineered bacteria have the potential to overcome the limitations that cause cancer therapies to fail. We are engineering bacteria to deliver therapeutic payloads and quantifying the mechanisms that control bacterial therapy. We have shown that bacteria preferentially target tumors and actively penetrate tissue. Bacterial motility has a linear relationship with colonization density. Manipulating chemoreceptors in the membrane can direct bacteria to drug-resistant tumor regions and inducing inflammation can promote colonization by modifying tumor vasculature. When engineered to express  $\alpha$ -hemolysin from *Staphylococcus aureus*, bacteria kill 99% of culture cells in 5 minutes and reduces tumor volume in mice. Engineering salmonella with a quorum-sensing, provides a density-dependent switch that induces protein expression only after bacteria have colonized tumor tissue. This technique prevents system toxicity after delivery of therapeutic molecules. We have also developed bacteria that selectively invade cancer cells and release molecules that modulate epigenetic targets, e.g. EZH2 and PP1. Salmonella were engineered with a genetic cassette that induces lysis specifically after invasion into mammalian cells. Lysis releases the bacterial content into the cytoplasm of cells. In culture, Salmonella lyse inside cancer cells and release GFP, which diffuses throughout the cellular cytoplasm. Releasing a peptide that interferes with the binding of the phosphatase, PP1, with its regulator, NIPP1, induces cell death after bacterial lysis. In three dimensional tissue culture, administration of these bacteria induces cell death. These techniques establish Salmonella as a tunable platform for cancer therapy. By understanding the mechanisms of bacterial delivery, new strategies will be developed to treat hard-to-treat cancers.

**Richard Vile, Ph.D.**  
Mayo Clinic

Richard Vile, Ph.D., and his research team develop experimental cancer therapies, all based on stimulating antitumor immune responses. Dr. Vile's research combines in vivo and in vitro assays, but predominantly focuses in murine immune-competent models and syngeneic tumors. Although his team has a major interest in melanoma, they also have models of prostate cancer, glioma and brain metastases, and can be applied across tumor sites.



Oncolytic viruses (OV) have been one of Dr. Vile's key areas of research for several years, and his team previously demonstrated the critical role of the immune system in successful therapy with OV. In addition to making OV expressing cytokines and tumor-associated antigens, they have developed a novel approach in which the vesicular stomatitis virus (VSV) can be engineered to express a library of tumor antigens, resulting in exceptional treatment. Dr. Vile's team deliberately focuses on developing therapies that can be rapidly taken to clinical trials. Accordingly, the team works closely with the Mayo Clinic team, as well as those at other U.S. hospitals and worldwide, and have been directly involved in clinical trials of several oncolytic viruses. An ongoing clinical trial for patients with hepatocellular carcinoma is being performed at Mayo Clinic in Arizona with a VSV the team designed to express interferon. Internationally, Dr. Vile's research lab has strong links with researchers in the UK and other countries, to test OV in patients with a range of cancers.

**Abstract**  
**Reovirus Based Therapies for Cancer.**

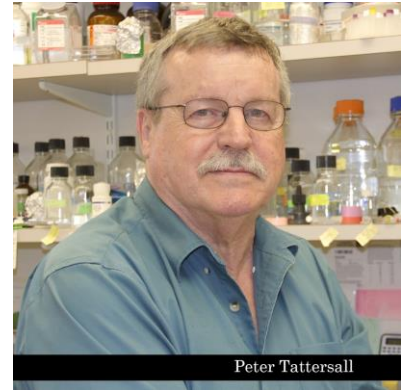
We have previously shown that intravenously delivered reovirus is trafficked to subcutaneous tumors by “hitch-hiking” on the Cd11b+ cell compartment, which can be further mobilized by pretreatment with GM-CSF. Consistent with this, multiple rounds of a systemic treatment of GM-CSF, followed by intravenous reovirus, was effective against both subcutaneous melanomas, as well as against intra-cranial melanoma (B16) and glioma (GL261). Therefore, we initiated a Phase 1 study of replication competent Reovirus REOLYSIN® in combination with GM-CSF in pediatric patients with relapsed or refractory brain tumors.

Three patients have been treated to date. While receiving her second course of treatment Patient #3 developed altered mental status and clinical worsening which was resolved upon treatment with dexamethasone. A MRI scan two months later showed reduced generalized FLAIR changes in addition to unexpectedly slow tumor progression. The slow progression of the glioblastoma lesions is quite uncharacteristic for a patient with this degree of highly refractory and malignant tumor. Both of the other two patients experienced worsening symptoms. As this trial continues to accrue patients, we have shown that combination of GM-CSF/Reovirus with anti-PD-1 generated long term cures in 80% of mice under conditions in which either treatment alone cured no animals. Anti-PD-1 therapy in combination with GM-CSF/Reovirus significantly enhanced the Th1 IFN-g anti tumor response. Taken together, our clinical results suggest that intravenous Reolysin may be trafficking to intra-cranial tumors and initiating a local inflammatory response. Possible development of this approach could use checkpoint inhibition in addition to the GM-CSF/reovirus regimen. However, careful monitoring will be essential to balance the anti-tumor benefits of inflammation with its potential toxicity.

## **Peter Tattersall, PhD**

Department of Laboratory Medicine and the Department of Genetics, Yale University School of Medicine.

Peter Tattersall, PhD, is a Professor in the Department of Laboratory Medicine, with a joint appointment in the Department of Genetics, at Yale University School of Medicine. He has been studying most aspects of the replication of mammalian parvoviruses for many years, the latter 35 of them running a research laboratory at Yale. His research group has used a combination of genetics and immunochemistry, supported by collaborations with structural biology and immunobiology groups, to delineate the mechanisms by which these very small, single-stranded DNA-containing viruses invade target cells, enslave the host cell to express the viral genes, replicate their unique, linear viral DNA genome, assemble viral capsids, then package and export progeny virions. This work has provided much of the current text book copy on the biology of the autonomously replicating parvoviruses. Dr. Tattersall received his Bachelor's Degree in Molecular Biology from the University of Glasgow in Scotland, in 1968 and his doctorate in Molecular Virology from University College, London, in 1971, for work performed at the Imperial Cancer Research Fund (now Cancer UK).



### **Abstract:**

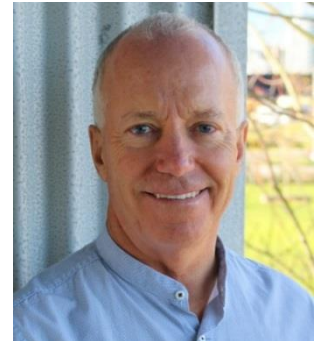
#### **Developing immunomodulatory anti-cancer vectors from tiny viruses.**

Rodent parvoviruses can infect human cells only if the cells are neoplastically transformed. We have shown that one of these viruses, LuIII, can efficiently infect and kill the majority of low passage tumor cell cultures derived directly from patients with malignant melanoma. In parallel, we have developed a replicating, but non-propagating, vector system from these viruses, capable of expressing up to two immunomodulatory genes in place of the viral coat protein coding sequences. This dual-transgene comprises both a co-stimulatory molecule, designed to enhance arming of CD8 T cells specific for non-self antigens expressed by the tumor cell, and a competitor molecule, designed to locally inhibit the PD-1/PD-L1 immunosuppressive pathway. A strategy for establishing a murine model to examine the efficacy of this approach will be discussed. LuIII shows little propensity for infecting murine melanoma cells, but MPV1A, a separate serotype of rodent parvovirus, showed some activity and has been evolved to higher infection efficiency by serial passage in a transplantable murine melanoma cell line. The components contributing to this enhanced melanoma tropism have been mapped and are being incorporated into the vector system.



**Hal Gunn MD**  
CEO, Qu Biologics Inc.

founder and CEO of Qu Biologics, is a physician/inventor who has dedicated his professional life to understanding how to optimally support the body's immune response to chronic disease. He is co-founder, in 1997, of InspireHealth, Canada's leading supportive cancer care centres (Vancouver, Victoria and Kelowna). Under Dr. Gunn's leadership, InspireHealth grew to become a world leader in supportive cancer care, with three centres (Vancouver, Victoria and Kelowna), treating 2,500 new patients per year.



Dr. Gunn obtained his Bachelor's Degree in Zoology and Doctorate of Medicine from the University of British Columbia (UBC) and is a Clinical Assistant Professor at UBC's School of Medicine. Dr. Gunn discovered the concept of site specific immunomodulation in clinical practice and founded Qu Biologics, a clinical stage biotechnology company based in Vancouver, Canada, in 2007. He is holder of more than 30 granted patents.

**Abstract:**

**Site-Specific Immunomodulators: Harnessing the Intrinsic Immune Capacity to Prevent and Fight Malignancy**

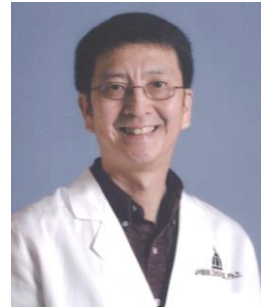
Optimal use of microbial cancer immunotherapeutic strategies has been hampered by a limited understanding of underlying complex mechanisms and the consequent inability to consistently provoke a safe therapeutic response. Qu Biologics has discovered the intrinsic innate immune mechanism, mediated by acute infection, that directs an activated innate immune response to targeted organ sites based on pattern recognition, stimulating cancer regression. Based on our pre-clinical and clinical research (3 completed Phase 2 trials in lung cancer, Crohn's disease and ulcerative colitis), we believe that we have discovered the important immunological mechanism that underlies the 'hygiene hypothesis'.

Qu Biologics' Site-Specific Immunomodulators (SSIs), comprised of inactivated microbial components administered subcutaneously, stimulate an activated innate immune response in the targeted organ, initiating an anti-cancer response through multiple immunological mechanisms simultaneously. These important mechanisms include recruitment of activated innate immune cells (including M1 macrophage and NK cells) to the targeted organ, shift in macrophage polarization from M2 to M1 dominance in the tumor microenvironment, up-regulation of NKG2D ligands on tumor cells, down-regulation of PD-1 and PD-L1, and enhanced cytotoxic lymphocyte activity.

**Shibin Zhou, MD, PhD.**

Associate Professor of Oncology, Johns Hopkins University School of Medicine

Shibin Zhou is an Associate Professor of Oncology at The Sidney Kimmel Comprehensive Cancer Center and Director of Experimental Therapeutics at The Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University School of Medicine. He specializes in developing novel therapeutic approaches based on live biological agents and enhancing anticancer immune responses. Dr. Zhou's research program involves both laboratory and translational efforts. His group has developed an attenuated anaerobic bacterial strain named *C. novyi-NT* that selectively colonizes solid tumors, resulting in massive tumor necrosis and regression. *C. novyi-NT* has been tested in several canine clinical trials and is being tested in a human Phase I clinical trial. Current preclinical efforts are focused on engineering *C. novyi-NT* as well as combining it with a variety of pharmacologic or immunologic agents to enhance its efficacy and/or further reduce its toxicity. Dr. Zhou received his Medical Degree in China and PhD in Molecular Biology from University of Pittsburgh.



**Abstract**

**Therapy with Oncolytic Bacterium *C. novyi-NT*: From Mice to Men**

The hypoxic tumor compartment poses challenges for both chemo and radiation therapies as hypoxia diminishes the therapeutic effects of chemotherapeutic agents and radiation. Conversely, this tumor compartment, hypoxic and immune-privileged, provides a unique niche for anaerobic bacteria to grow. *C. novyi-NT* is an attenuated strain of the anaerobic bacterium *Clostridium novyi*. When injected intravenously, *C. novyi-NT* spores are not toxic to healthy animals but can selectively germinate within and colonize tumors, resulting in massive necrosis and tumor regression. In addition to direct tumor destruction resulting from bacterial growth, intratumoral infection by *C. novyi-NT* elicits both innate and adaptive antitumor immune responses, leading to long-term cures in animal models. Combining *C. novyi-NT* with other therapeutic approaches such as chemo, radiation, and immunotherapy further enhance its efficacy. Based on the promising preclinical data, several canine clinical trials and a human Phase I clinical trial have been initiated.

## Daniel Saltzman MD PhD

Chief, Division of Pediatric Surgery, University of Minnesota Masonic Children's Hospital  
and Chief Medical Officer, Salspera Microbial Immunotherapy Oakdale, MN

Dr. Daniel Saltzman is the AS Leonard Professor of Surgery and Pediatrics and the Chief of the Division of Pediatric Surgery at the University of Minnesota Medical School. A native of the Panama Canal Zone, Dr. Saltzman obtained his B.S., M.D., and Ph.D. degrees from the University of Minnesota. He completed his surgical residency at the University of Minnesota and a Pediatric Surgery Fellowship at the University of Arkansas. Dr. Saltzman has authored over 130 articles (manuscripts and abstracts), has written 10 book chapters, and holds 5 patents. Dr. Saltzman is an examiner for the Pediatric Surgery Portion of the American Board of Surgery. He sits on the editorial board of the Journal of Surgical Education and is an ad hoc reviewer for the Journal of Pediatric Surgery and five other journals. In addition to an active clinical practice where Dr. Saltzman has expertise in Pediatric Cancers, Gastrointestinal Disorders, and Chest Wall Deformities, the Saltzman Research Lab studies the use of bacteria to deliver immunomodulatory proteins directly to cancers. He wrote the very first journal article ever published on the use of Salmonella for cancer therapy.



### Abstract

#### ***Salmonella* Derived Immunotherapy for Solid Malignancies**

Daniel Saltzman MD PhD<sup>1</sup>, Lance Augustin PhD<sup>2</sup>, and Janet Schottel PhD<sup>2</sup>  
Departments of Surgery<sup>1</sup> and Biochemistry<sup>2</sup>, University of Minnesota Minneapolis,  
Minnesota

The idea of using bacterial derived therapy for cancer dates back well over 100 years. Our laboratory has concentrated efforts on the use of attenuated *Salmonella* to deliver immunomodulatory proteins to the tumor microenvironment. Our first generation of *Salmonella*-based cancer therapy, *Salmonella*-IL2, has completed a phase 1 trial in both humans with metastatic GI cancers and dogs with metastatic osteosarcoma. *Salmonella*-IL2 is now on a path toward commercialization. We have constructed numerous attenuated strains of *Salmonella* using various genetic methods. These strains secrete cytokines and immune checkpoint inhibiting scFv antibodies that bind PD-L1 and CTLA-4. We are examining these strains in an autochthonous mouse tumor model. We hypothesize that secretion of a “cocktail” of immunomodulatory proteins into the microenvironment of solid tumors will result in elimination of the primary tumor and establish immune memory to eradicate micro metastases and guard against relapse. This can be accomplished without the extreme systemic toxicities inherent in current cancer therapies. Realizing that monotherapy for cancer is unrealistic, we are also investigating a treatment strategy that combines standard of care (chemotherapy) with our *Salmonella* constructs. The results indicate that anti-tumor efficacy, similar to that accomplished with maximum tolerated dose chemotherapy, can be achieved without significant toxicities when *Salmonella* is combined with low dose chemotherapy. A *Salmonella* based cancer treatment strategy demonstrates promise of success with effective delivery of immunomodulatory proteins to the tumor microenvironment and in combination with conventional chemotherapy.

**James L. Gulley M.D., Ph.D., F.A.C.P.**  
The NIH Center for Cancer Research (CCR)

Dr. Gulley is an internationally recognized expert in immunotherapy for cancer. He serves within the Center for Cancer Research (CCR) of the National Cancer Institute, USA, as Chief of the Genitourinary Malignancies Branch, Director of the Medical Oncology Service and Head of the Immunotherapy Section. He has been instrumental in the clinical development of Prostavac, an experimental prostate cancer vaccine developed within the CCR and is the principal investigator of the Prospect Trial, an international randomized phase 3 study of Prostavac which completed enrollment in 2015 with results expected this year. He also has been instrumental in the clinical development of avelumab (EMD Serono / Pfizer), an anti-PDL1 antibody that the first-in-human study was done at the CCR and was recently approved by the FDA with multiple additional studies ongoing or planned. He has been an investigator on >100 trials, authored >240 scientific papers or chapters, and has made numerous presentations at national and international meetings.



**Abstract**

**Vectors to Guide Anti-tumor Immune Responses**

Immunotherapy for cancer has received substantial attention and resources due in part to the rapid, profound, and durable responses seen with immune checkpoint inhibitors. While these results are impressive, they are only seen in a minority of patients who have a robust underlying anti-tumor immune response held in check by an immune checkpoint within the tumor microenvironment (T-cell inflamed tumor). Most patients do not have such an immune response (T-cell poor tumor) and strategies to induce a robust immune response are needed. Vector based therapeutic vaccine can provide an off-the-shelf approach that includes danger signals (in the vector), tumor associated antigens (full length constructs) and other immune enhancing components such as T-cell costimulatory molecules and toll-like receptor ligands. Within the Center for Cancer Research, NCI we have ongoing clinical trials evaluating 3 different therapeutic vaccines based on vector platforms including several pox viral vaccines, several *saccharomyces cerevisiae* vaccines and several adenoviral vaccines. Ongoing studies are evaluating these vaccines alone or in combination with other therapies to induce a robust immune response with the goal of translating into patient benefit.

**Halle (Huihong) Zhang, RN, MMedSci, PhD**  
Director, Translational Sciences BioMed Valley Discoveries

Dr. Halle Zhang is a Director and Project Leader at BioMed Valley Discoveries, where she leads the clinical development of *Clostridium novyi*-NT, a bacterial oncolytic therapy. Prior to joining BioMed Valley Discoveries, Halle served as a Clinical Trial Lead within the Harvard Catalyst network. Her previous positions also include LAM Foundation Research Fellow at the Harvard T.H. Chan School of Public Health and Research Scientist at Tufts University, where she examined cell signaling in cancer and metabolic diseases. Halle is an RN with over ten years of clinical experience in medical, surgical, pediatric, and operating room settings. Halle received a Master in Medical Sciences in immunology and a PhD in medicine from the University of Birmingham, UK.



**Abstract**  
**Vectors to Guide Anti-tumor Immune Responses**

*Clostridium novyi*-NT (*C. novyi*-NT) is an attenuated strain of *Clostridium novyi*, an obligate anaerobe that germinates in hypoxic tumor environments. When administered intravenously or intra-tumorally, *C. novyi*-NT spores replicate within the hypoxic regions of tumors, eliciting robust tumor lysis in a variety of preclinical animal models as well as in companion dogs bearing spontaneous solid tumors. *C. novyi*-NT lyses malignant cells by secreting lipases, proteases, other hydrolytic enzymes, and recruiting inflammatory cells to elicit an anti-tumor immune response. In the ongoing 3+3 dose escalation, human Phase 1 study, evidence of *C. novyi*-NT germination including fever, elevated WBC, elevated C-reactive protein, tumor inflammation and abscessation has been noted at all six dose levels following a single intra-tumoral injection. Efficacy and safety data will be reported for the 23 patients enrolled to date. The current dose escalation study is near completion. Potential additional clinical trials are being considered.

**Robert Petit Ph. D**  
Chief Scientific Officer at Advaxis, Inc

Dr. Robert Petit is the Chief Scientific Officer at Advaxis, Inc., a Princeton, New Jersey company that employs a proprietary live attenuated microbial-based vector system to develop as cancer immunotherapies. Advaxis has advanced 4 immunotherapies into clinical development to date, and has Phase 3 clinical programs underway for its lead candidate used to treat and prevent HP associated malignancies. Dr. Petit and his team invented 2 additional bacterial-based platforms focused on delivery of neo-epitopes resulting from somatic mutations that are either personal or “private” to each individual patient in ADXS-NEO, or shared public “hotspot” mutations in ADXS-HOT



Constructs. Scientifically, he is responsible for shaping future products and combinations and general oversight of the scientific team. Professionally, he has over 25 years of experience in all medical and scientific aspects of pharmaceutical development, primarily in oncology and immunology. Within academia and industry, Robert has led programs in drug discovery, translational medicine, and clinical development at all stages. Robert has designed and conducted U.S. and international clinical evaluation programs for numerous for products big pharma as well as small biotech or specialty pharmaceutical companies. Robert has contributed significantly to 5 different BLA and NDA /EMA approvals. Dr. Petit joined Advaxis from Bristol-Myers Squibb where he was U.S. Medical Strategy Lead for the ipilimumab (Yervoy) program, Director of Medical Strategy for New Oncology Products, and Director of Global Clinical Research. Prior to joining Bristol-Myers Squibb, Robert served as Vice President of Clinical Development at MGI Pharma and also at Aesgen Inc. And was formerly director of clinical development at Pharmacia/Pharmacia-Upjohn. Prior to joining industry, Robert co-founded an immune-oncology program affiliated with St. Luke’s and the Medical College of Wisconsin and had an academic appointment in pathology and laboratory medicine. He holds a doctorate from the Ohio State University College of Medicine in Immunology and Medical Microbiology and a Bachelor of Science from Indiana University.

**Abstract**

**Cancer bacterial vaccines - live, attenuated strains of Listeria and Salmonella as vaccine vectors in cancer treatment**

Bacteria based vaccines provide a number of potential advantages over other antigen delivery strategies. In addition, bacterial vaccines delivering tumor-associated antigens (TAAs) stimulate innate immunity and can also activate both arms of the adaptive immune system to induce anti-tumor immunologic effects. *Listeria monocytogenes* and strains of *Salmonella* have been most extensively studied and are advancing in clinical testing. As cancer vaccine vectors, these bacteria have some key similarities as well as fundamental differences. Both share intracellular elements of their life cycle capable of generating T cell responses within mammalian hosts, and can be used to deliver peptide or payloads. However differentially, they represent Gram positive and Gram negative origins, require different attenuation methods, and differentially invoke immune responses with vector-specific characteristics. These differences can affect dosing, antigen presentation, co-stimulatory signaling, the nature of the resulting immune response and potential for retreatment. The promise and shortcomings of checkpoint inhibition for cancer has led to a reconsideration of cancer vaccines in general and combination regimens with checkpoint inhibition in particular.

**Ke Liu, MD, PhD**  
**U.S. FDA's Center for Biologics Evaluation and Research (CBER)**

Dr. Liu is Chief of Oncology in the Office of Tissues and Advanced Therapies (OTAT, previously known as Office of Cellular, Tissue and Gene Therapies (OCTGT)) in the U.S. FDA's Center for Biologics Evaluation and Research (CBER). This Office reviews, evaluates and approves most innovative cancer therapeutics with curative potential. Examples include chimeric antigen receptor (CAR) T-cells, dendritic cells, adoptive T cell therapies, tumor neoantigen-based personalized medicine (vaccine or cell therapy), natural killer cells, oncolytic viruses, therapeutic cancer vaccines, and combinations of these immune-oncologic therapeutics with checkpoint inhibitors and other agents.



Liu is a medical oncologist and internist, certified by the American Board of Internal Medicine (ABIM). He is also an attending medical oncologist in Washington Veterans Administration Medical Center. He received his M.D. from Henan Medical University in China and his PhD in Molecular Biology from Cornell University Graduate School of Medical Sciences in New York City, NY. He completed his Internal Medicine internship and residency training in Albert Einstein College of Medicine (Long Island campus) in New York City and his Medical Oncology fellowship training at the U.S. National Cancer Institute (NCI). He also received his cancer immunotherapy training in the Surgery Branch, NCI. His primary academic interests include clinical trial design, immunotherapy, cellular and gene therapies for cancer.

In 2003, Dr. Liu joined U.S. FDA's CBER as a Medical Officer / Clinical Reviewer and later was selected as a Lead Medical Officer. From 2008 to 2011, he served as a Lead Medical Officer in U.S. FDA's Center for Drugs Evaluation and Research (CDER). He has received multiple citations at the FDA and Center levels for his contributions to the regulatory science / research / policy, product review and approval, and staff mentoring. Recently, he was selected to serve as the acting associate director of oncology cell and gene therapy for the newly created FDA's Oncology Center of Excellence (OCE).

**Abstract**

**Clinical Considerations on Microbes-based Cancer Therapy -a Regulatory Perspective**

The existence of a possible relationship between infection and cancer regression was observed in the 18th century and further suggested by Dr. Coley's first publication in 1891 to treat cancer patients with bacteria (Coley's toxin). Such observation and experiment were widely regarded as the root of the modern cancer immunotherapy. Using microbial agents for cancer treatment has at least two potential advantages. One is that they could stimulate the innate immunity and second is that they could serve as vectors to express desired gene products to induce / enhance adaptive immunity.

Because of their potential to cause infection, the safety of microbes-based cancer therapy remains the top regulatory consideration. However, such a concern needs to be balanced in the context of potential benefit for trial subjects. This presentation will discuss clinical considerations from regulatory perspectives and approaches to facilitate the clinical development of microbes-based cancer therapy."

## **Matthew Giacalone, Ph.D, MBA**

Chief Operating & Scientific Officer, Vaxiion Therapeutics

Dr. Giacalone has over 15 years of experience in the area of minicell biology and the use of minicells as delivery vehicles and provides operational oversight, commercialization strategy as well as corporate, business, and product development expertise to the company. He manages Vaxiion's robust intellectual property estate and holds several patents and publications in the minicell-based delivery field. Dr. Giacalone has also served as a business development and strategy consultant for a series of start-up biotechnology companies and government organizations and is a graduate of the joint Ph.D/MBA program between San Diego State University and the University of California, San Diego.



### **Abstract**

#### **Bacterial minicell-based oncolytic therapy for non-muscle invasive bladder cancer and beyond**

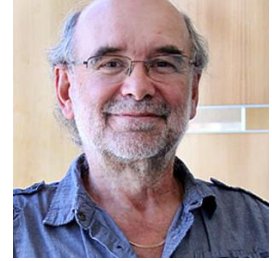
The development of new therapies that can prevent recurrence and progression of non-muscle invasive bladder cancer (NMIBC) remains an unmet clinical need. The continued cost of monitoring and treatment of recurrent disease, along with its high prevalence and incidence rate, is a strain on healthcare economics worldwide. The current work describes the characterization and pharmacological evaluation of VAX014, a novel, recombinant bacterial minicell-based oncolytic biopharmaceutical undergoing the final stages of IND-enabling pre-clinical development for the treatment of NMIBC and other oncology indications. VAX014 minicells selectively target two oncology-associated integrin heterodimer subtypes resulting in the intracellular delivery of a novel bacterial cholesterol-dependent membrane pore-forming toxin, perfringolysin O (PFO). *In vitro* characterization studies reveal that VAX014 rapidly kills integrin-expressing murine and human carcinoma cell lines via a unique oncolytic mechanism. The *in vivo* evaluation of VAX014 minicells as a single agent administered intravesically in three clinically relevant variations of a syngeneic orthotopic model of superficial bladder cancer results in a significant survival advantage with 72.0% ( $P < 0.0001$ ), 68.1% ( $P < 0.0001$ ) and 16.7% ( $P = 0.003$ ) of animals surviving after immediate, early or late treatment initiation, respectively. Follow-on studies using VAX014 in combination with an immune checkpoint inhibitor against PD-L1 increased survival in the very late treatment of established orthotopic bladder tumors from 12.5% to 87.5% ( $P < 0.0001$ ) and 100% of combination therapy survivors subsequently rejected orthotopic tumors when rechallenged and left untreated, suggesting establishment of protective immunological memory. These studies set the stage for expansion into other indications responsive to immune checkpoint inhibitor therapy as well as for combination therapy in early clinical development of VAX014 for use in NMIBC.



## Grant McFadden, PhD

Biodesign Institute, Arizona State University, Tempe, AZ

**Dr. Grant McFadden** received a Ph.D. in Biochemistry in 1975, from McGill University in Montreal, Canada. He has held previous faculty positions at the University of Alberta, the University of Western Ontario, and the University of Florida and was a visiting sabbatical Professor at Harvard Medical School. He was inducted as a Fellow of the Royal Society of Canada in 2004, the Canadian Academy of Health Sciences in 2005 and the American Academy of Microbiology in 2007. Dr. McFadden is currently a Professor at Arizona State University and is the Director of the Biodesign Center for Immunotherapy, Vaccines and Virotherapy (B-CIVV). He is the co-Editor-in-Chief of the journal PLoS Pathogens, and was the President of the American Society for Virology 2015-16. The McFadden lab investigates host-virus tropism, and the deployment of poxviruses for oncolytic virotherapy for the treatment of cancer, particularly with myxoma virus. He is also currently developing human clinical trials that exploit virotherapy with myxoma virus to improve hematopoietic stem cell transplantation therapies for cancer, in collaboration with a biotech company called DNatrix. To date, McFadden has published over 340 scientific papers and reviews.



### Abstract

#### ***Ex vivo* virotherapy with oncolytic Myxoma Virus improves cancer-free outcomes after either allo- or auto- hematopoietic stem cell transplantation**

The McFadden lab studies how poxviruses interact with the host immune system, with specific focus on virus tropism, virus-encoded immune inhibitors, and the deployment of specific poxviruses for oncolytic virotherapy to treat cancer. He is currently developing human clinical trials to exploit virotherapy with one specific poxvirus, myxoma virus (MYXV), to improve hematopoietic stem cell transplantation therapies for cancer, in collaboration with the biotech company DNatrix. In his seminar, he will summarize the current status of oncolytic virotherapy with MYXV, and discuss how virus delivery to disseminated sites of cancer like multiple myeloma can be facilitated by utilizing multiple cell types found in bone marrow transplant specimens as carrier cells to ferry the oncolytic virus to sites of metastatic disease. Although the virus cannot bind or infect normal human CD34<sup>+</sup> hematopoietic stem cells, and thus is safe for immune engraftment after either autologous or allogeneic bone marrow transplantation, *ex vivo* treatments of stem cell transplant specimens with MYXV can “arm” other classes of leukocytes with this oncolytic virus. MYXV can then be ferried to sites of disseminated or metastatic cancer via other cell types found in the transplant sample, such as resident T lymphocytes and neutrophils, and significantly improve disease-free outcomes in immunocompetent models of murine myeloma.

Biotech Sponsor: DNatrix Therapeutics (<http://www.dnatrix.com/>)

**Thomas W. Dubensky, Jr., Ph.D.**  
Chief Scientific Officer, Aduro Biotech

Thomas (Tom) W. Dubensky, Jr., Ph.D. has served as the Chief Scientific Officer of Aduro Biotech since 2011. From 2009 to 2011, Dr. Dubensky served as Chief Scientific Officer of Immune Design Corp., where he was responsible for overseeing the development of immune therapies based on proprietary molecularly defined adjuvants and dendritic cell targeting vaccine platforms. He was a co-founder and Chief Scientific Officer of Anza Therapeutics, Inc., a biotechnology company which was spun out from Cerus Corporation in 2007, where he served as the Vice President of Research beginning in 2002. At Cerus and at Anza, he helped to develop vaccine platforms based on recombinant attenuated strains of *Listeria monocytogenes*, a platform that continues to be advanced by Aduro. Previously, Dr. Dubensky developed vaccine/immunotherapy and oncolytic virus platforms based on alphaviruses, adenoviruses, retroviruses/lentiviruses and plasmid DNA in positions of increasing responsibility at Viagene, Chiron Corporation and Onyx Pharmaceuticals. A major focus of his current research interests is the role of the STING (Stimulator of Interferon Genes) pathway in regulating the development of anti-tumor immunity and autoimmunity, and the development of therapeutic interventions that target this pathway to affect desired clinical outcomes. A first-in-human clinical study to evaluate a STING agonist in patients with advanced cancers is ongoing. Dr. Dubensky has numerous peer-reviewed publications and issued patents related to the discovery and development of diverse therapeutic candidates. Dr. Dubensky received his B.A. in Bacteriology and Immunology from the University of California, Berkeley; he earned his Ph.D. at the University of Colorado Health Sciences Center; and he was a post-doctoral fellow at Harvard Medical School in the Department of Pathology.



**Abstract**

**Insights from *Listeria monocytogenes* in the Development of Clinical Cancer Immunotherapeutic Approaches**

**Thomas W. Dubensky, Jr.**, on behalf of multiple scientists and clinicians from Aduro Biotech, Novartis, U.C. Berkeley, University of Chicago and Johns Hopkins University

Interventional strategies that combine tumor microenvironment (TME) remodeling with lymphocyte infiltration, induction of tumor-specific cellular immunity and blockade of immune checkpoint pathways can result in effective and durable anti-tumor efficacy. We are advancing a live, attenuated double-deleted *Listeria monocytogenes* (LADD) platform that is incapable of intracellular spread or direct infection of hepatocytes, and has been administered safely to over 350 cancer patients, resulting in promising responses in selected malignancies. In several syngeneic mouse tumor models, we demonstrate that treatment with LADD engineered to express endogenous tumor antigens induced significant changes in the TME, including enhanced CD8<sup>+</sup> T cell effector function, recruitment of critical antigen presenting cells and reduction of regulatory T cells. Interestingly, TME changes were dependent upon LADD expression of a tumor rejection antigen, and in addition correlated with significant therapeutic benefit in the mouse. LADD-induced immune remodeling and activation of the TME were required for synergistic therapeutic antitumor efficacy combined with immune checkpoint blockade. One LADD strain, known as CRS-207, has been engineered to express the tumor-associated antigen mesothelin and is being tested in pancreatic, ovarian and mesothelioma malignancies. Using multi-dimensional immunohistochemistry of paired biopsies from three patients with mesothelioma, we demonstrate the recruitment and expansion of effector tumor-infiltrating lymphocytes, including CD8<sup>+</sup> T cells, mature DCs, CD163<sup>-</sup> macrophages and NK cells, following two infusions of CRS-207. Based on these data and promising efficacy results in the front-line setting in combination with standard-of-care chemotherapy, CRS-207 is currently being evaluated as a second-line therapy in combination with pembrolizumab in patients with mesothelioma. Based on these results, established clinical safety, and an emerging efficacy profile for the LADD platform, we recently initiated a Phase I clinical study to evaluate the safety, tolerability and immunogenicity of a personalized LADD (pLADD) therapy encoding tumor-specific neoantigens in patients with advanced liver metastatic MSS colorectal cancer, a malignancy in which immune checkpoint inhibitors have poor efficacy as single agents.