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To interview Liang Deng, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896, or Rick Buck at rick.buck@aacr.org or 856-562-5668. For a photo of Deng, click [here](#). Visit our [newsroom](#).

Inactivated Vaccinia Virus Safe and Effective Against Advanced Cancers Alone or in Combination with Immune Checkpoint Inhibitors

MAINZ/FRANKFURT, GERMANY — Modified vaccinia virus Ankara (MVA), a poxvirus, was found to be safe when administered in an inactivated form in mice, and delivering it into the tumor in addition to systemic delivery of an immune checkpoint inhibitor yielded synergistic antitumor effects in mice with large tumors and those with multiple tumors, according to data presented at the [Third CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival](#), held Sept. 6-9.

“Immune checkpoint blockade therapy, such as anti-CTLA-4 and anti-PD1/PD-L1 antibodies, has been approved for the treatment of many advanced or metastatic cancers; however, the response rate to this form of therapy alone is still quite low,” said [Liang Deng, MD, PhD](#), dermatologist/investigator and Assistant Member in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York (MSKCC).

One of the reasons for failure to respond or for developing resistance to immune checkpoint inhibitors is that there is paucity of infiltrating immune cells in these tumors, making them “cold tumors,” Deng explained. “Microbial-based cancer immunotherapy has the potential to turn ‘cold tumors’ to ‘hot tumors,’” she added.

Microbes, such as the MVA tested in this study, can be detected by the host immune system as “foreign” and can induce the production of certain immune substances including interferons (IFN), proinflammatory cytokines and chemokines. “The production of these factors in the tumors by the immune cells and tumor cells leads to the activation of immune cells and the generation and recruitment of tumor-specific T cells, which can destroy tumor cells,” noted Deng. “Therefore, it is important to develop potent microbial-based agents to ‘light the fire’ in the tumor microenvironment.”

Deng and colleagues found that the combination of intratumoral injection of heat-inactivated MVA (iMVA) and immune checkpoint inhibitors led to efficient eradication of large, established tumors and distant non-injected tumors in mice. They showed that the antitumor activity was possible because iMVA is a potent inducer of type I IFN and proinflammatory immune mediators. Intratumoral injection of iMVA also altered the immunosuppressive tumor microenvironment and generated antitumor CD4⁺ and CD8⁺ T cells, which could be amplified by the addition of immune checkpoint blockade. The researchers published these findings in [Science Immunology](#) in May 2017.

Current oncolytic viruses including talimogene laherparepvec (T-VEC), an engineered herpes simplex virus that has been approved by the U.S. Food and Drug Administration for the treatment of advanced melanoma, are replication competent, said Deng. These infectious agents are generally handled in infection-controlled rooms, and adverse events have been reported in patients when the viruses are administered at high doses or if the patients are immune-compromised. It is not known whether viral replication is necessary for the antitumor effects of the DNA virus when delivered intratumorally. To test this, the researchers compared the antitumor efficacy of live oncolytic vaccinia virus (which can replicate) with its heat-inactivated counterpart (which cannot replicate) in mice. They found that the heat-inactivated oncolytic vaccinia virus induced higher numbers of activated CD4⁺ and CD8⁺ T cells than the live virus. This meant that the inactivated form of the virus is both safe and effective.

“We were pleasantly surprised that inactivated oncolytic vaccinia virus works better than live virus,” noted Deng. “These results tell us that in order for viral-based therapy to work, it has to engage the host immune system through induction of innate immunity and activation of tumor antigen-presenting dendritic cells,” she added.

“Our results support the intratumoral delivery of inactivated vaccinia virus as a safe and effective cancer immunotherapy either alone or in combination with immune checkpoint blockade antibodies,” said Deng.

“We anticipate that iMVA could be used in several clinical settings, including patients with metastatic cancers that are resistant to immune checkpoint blockade, or those with metastatic cancers that are initially responsive to immune checkpoint blockade and later develop resistance, or it could be used as a combinatory therapy with immune checkpoint blockade,” she noted. “We plan to bring these viral-based products into clinical trials in the coming years.” This work is the result of a collaboration of several investigators at MSKCC, including Deng, Stewart Shuman, MD, PhD, Jedd D. Wolchok, MD, PhD, and Taha Merghoub, PhD.

A limitation of the study is that although heat-inactivated MVA induces IFN and proinflammatory immune mediators in human melanoma cells and human immune cells, the antitumor efficacy data were obtained in murine tumor models, Deng said. “Human clinical trials will be necessary to address whether this approach works in the treatment of human cancers,” she added.

This study was funded by the National Institutes of Health, MSKCC, the Dermatology Foundation, the American Skin Association, Swim Across America, and Ludwig Institute for Cancer Research. MSKCC filed a patent application for the use of MVA and iMVA (or vaccinia) as monotherapy or in combination with immune checkpoint blockade for solid tumors. Deng is a co-author on the patent applications.

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About the CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference

The International Cancer Immunotherapy Conference covers all areas of inquiry in cancer immunology and immunotherapy. Launched in 2015, the meeting is jointly sponsored by the [Cancer Research Institute \(CRI\)](#), the [Association for Cancer Immunotherapy \(CIMT\)](#), the [European Academy of Tumor Immunology \(EATI\)](#), and the [American Association for Cancer Research \(AACR\)](#). The meeting is held every year and alternates between the United States and Europe. Through this collaboration, the organizations aim to more effectively and efficiently disseminate the latest cutting-edge information and research in cancer immunology and immunotherapy, and to provide an opportunity for teaching, learning, and networking among all stakeholders in the field. Additional support for this year's meeting comes from Roche (Diamond level), Glaxo Smith-Kline, Lilly Oncology (Platinum level), Sanofi, Merck, Biontech (Gold level), Bristol-Myers Squibb, and Lytix Biopharma (Silver level), Merck Sharp & Dohme (Educational Grant), and Boehringer Ingelheim. For more information about the meeting, please visit www.cancerimmunotherapyconference.org.

Abstract: B068

The combination of intratumoral injection of inactivated MVA and systemic delivery of immune checkpoint blockade leads to eradication of large established tumors and distant tumors

Dai P.¹, Wang W.¹, Yang N.¹, Serna-Tamayo C.¹, Ricca J.M.¹, Zamarin D.¹, Shuman S.¹, Merghoub T.¹, Wolchok J.D.¹, Deng L.²

¹Memorial Sloan Kettering Cancer Center, New York, United States, ²Memorial Sloan Kettering Cancer Center, Medicine, New York, United States

Advanced cancers remain a therapeutic challenge despite recent progress in targeted therapy and immunotherapy. Novel approaches are needed to alter the tumor immune-suppressive microenvironment and to facilitate the recognition of tumor antigens that leads to antitumor immunity. Poxviruses, such as modified vaccinia virus Ankara (MVA), have potential as immunotherapeutic agents. Here we show that infection of conventional dendritic cells (DCs) with heat-inactivated or UV-inactivated MVA leads to higher levels of IFN induction than MVA via the cGAS-STING cytosolic DNA-sensing pathway. Intratumoral injection of inactivated MVA (iMVA) was effective and generated adaptive antitumor immunity in murine melanoma and colon cancer models. iMVA-induced antitumor therapy was less effective in STING- or Batf3-deficient mice than in wild-type mice, indicating that both cytosolic DNA-sensing and Batf3-dependent CD103⁺/CD8a⁺ DCs are essential for iMVA immunotherapy. The combination of intratumoral delivery of iMVA and systemic delivery of immune checkpoint blockade generated synergistic antitumor effects in bilateral tumor implantation models as well as in a unilateral large established tumor model. Furthermore, the combination therapy generates stronger systemic antitumor memory CD8⁺ T cell responses than either agent alone. We attribute iMVA's antitumor activity to three key properties as follows: (i) iMVA is a potent inducer of type I IFN as well as proinflammatory cytokines and chemokines in cDCs and melanoma cells; (ii) iMVA infection of cDCs induces DC maturation and the expression of MHC class I on melanoma cells; and (iii) intratumoral injection of iMVA leads to alteration of the tumor suppressive microenvironment with the recruitment, activation, and proliferation of CD8⁺ and CD4⁺ T cells, as well as the reduction of the percentage of Tregs among CD4⁺ T cells within the tumors, and thereby providing "in situ therapeutic vaccine" effects, which are amplified in the presence of immune checkpoint blockade. Our results suggest that inactivated vaccinia virus could be used as a safe and effective cancer immunotherapeutic agent for human cancers. The combination of iMVA virotherapy and immune checkpoint blockade provides synergistic effects on the development of systemic antitumor immunity.