



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170066

Project Title:
Oncolytic Immunotherapy for Gliomas and Cancer Metastases in the Era of
Checkpoint Regulation

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

At the end of last year, an oncolytic herpesvirus that induces an immune response against cancer cells became the first therapy of its kind to be approved for use in the United States, paving the way for a long-awaited class of treatments for cancer. On 27 October 2015, the US Food and Drug Administration (FDA) approved a genetically-engineered virus called talimogene laherparepvec (T-VEC) to treat advanced melanoma. Four days earlier, advisors to the European Medicines Agency had endorsed the drug. After many years of step-by-step improvements of the virotherapy/immunotherapy strategy, many scientists believe that the era of the oncolytic virus is probably here. In 2005, regulators in China approved an oncolytic adenovirus called H101, extremely similar to an adenovirus tested in USA termed dl1520, to treat head-and-neck cancer in combination with chemotherapy, after evidence –gathered in USA and China in independent clinical trials- showed that the treatment could induce the regression of a percentage of tumors. Due to incomplete follow-up with patients, the Chinese trials did not provide sufficient information about long-term patient survival.

For the last 18 years, our group has been working on the development of an oncolytic virus platform called Delta-24. The second generation of this tumor-selective oncolytic adenovirus arrived to the clinical scene in 2012. Since then, several clinical trials have begun in the USA and Europe to treat patients with recurrent glioblastoma. "Recurrent glioblastoma" refers to a malignant glioma that, after treatment with surgery, radiotherapy and chemotherapy, has come back and is threatening the life of the patient. In fact, patients with recurrent glioblastoma are resistant to radio- and chemotherapy, and often survive weeks after diagnosis. In this subset of patients, a single injection of Delta-24-RGD was capable of inducing survival longer than 3 years in 20% of the patients - these results are extraordinary for any drug. Importantly, examination of the tumors after treatment showed that Delta-24-RGD triggered an immune response that likely helped in the complete elimination of the tumor.

In this project, we aim to modify Delta-24-RGD such that the initial immune response is amplified and enhanced, and thereby significantly improve the percentage of patients sensitive to the oncolytic virus treatment. With advances in cancer immunotherapy such as immune checkpoint regulators, increased interest has been given to the prospect of oncolytic viruses as immunotherapies. In fact, the coupling of agents that block or

activate immune checkpoints with oncolytic viruses has been viewed as a natural marriage. Our strategy is to adapt other forms of immunotherapy, including activators of tumor-destroying T cells. These T-cells are the execution arm of the immune system and, once they recognize a cancer cell as such, immediately induce a fulminant type of cell death. In our approach, these T-cell activators will be incorporated in the genome of the virus, and thus only the infected cancer cells -but no normal cells- will be capable of activating the immune response. Armed with these T-cell activators, these viruses will be much more powerful than Delta-24-RGD. We propose to extend our studies from malignant gliomas (solid tumors localized exclusively in the brain) to the treatment of metastases, specifically to late-stage, metastatic breast and lung cancers. Taking live, replication-competent viruses to human testing involves all of the complex issues surrounding production, quality control, and release criteria for biological agents. As such, many laboratory-anchored groups cannot move their projects to human testing. We have developed a business partner that has assisted and will assist us in the future clinical development of this new generation of virotherapy/immunotherapy. We believe that, by the end of the award, patients with malignant gliomas and metastatic cancer may count among their options treatment with genetically-engineered, immune-activating, tumor-selective Delta-24 adenoviruses.