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Oncolytic Single-Cycle Replicating Immunotherapies for Kidney Cancer

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Institution Receiving Award: MAYO CLINIC
Program: KCRP
Proposal Number: KC180182
Award Number: W81XWH-19-1-0756
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Partnering Awards:
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TECHNICAL ABSTRACT

Area of Emphasis: Immunotherapies and Targeted Therapies

Background: There is great enthusiasm for targeting immune checkpoints to activate or re-awaken antitumor immune responses. While these approaches are promising, they may cost up to a half million dollars per year for patients. We propose here to develop a cheaper and complementary immune therapy approach for kidney cancer.

This work will use oncolytic viruses as a platform for immune therapy. Oncolytic viruses kill cancer cells. This not only debulks tumors but can also reveal cancer antigens to the immune system. Oncolytic adenoviruses (Ads) hold promise in this role because they can produce up to 10,000 copies of viral DNA per cell and massive amounts of viral antigens that can stimulate TLR receptors to act as vaccine adjuvants. The advantage of oncolytic viruses is that they are "self-amplifying" anticancer "drugs". If they are armed with a cancer antigen or cytokine gene, these replication-competent Ads (RC-Ads) also amplify those genes and their immunological effects in cancer therapy. The disadvantage of oncolytic viruses is that they can cause uncontrolled life-threatening viral infections. Injecting an unnaturally large dose of a "wild" virus can be particularly dangerous in immunocompromised patients, including cancer patients whose immune systems have been debilitated by previous therapy.

To harness the ability to amplify genes and amplify immune responses, but avoid the risk of Ad infections, single-cycle adenoviruses (SC-Ads) were developed. SC-Ads still undergo DNA replication and transgene amplification, but do not assemble infectious Ad virions. SC-Ad still kills infected cells, so it is still an oncolytic, but it will not cause Ad uncontrolled adenovirus infections that might endanger cancer patients with weakened immune systems. We engineered RC- and SC-Ad to express immunotherapeutic proteins. Low seroprevalence Ads were armed with mouse 4-1BBL, GMCSF, OX40L, and PD-L1 decoys. In immunocompetent mouse models of melanoma and lymphoma these immunotherapy viruses liberated cancer antigens and mediated significant increases after only one treatment.

Hypotheses:

We hypothesize that low seroprevalence oncolytic Ads can be used to kill kidney cancer cells to reveal cancer antigens to the immune system.

We hypothesize that oncolytic SC-Ad vectors can also deliver genes encoding proteins that stimulate immune checkpoints as an alternative or complement to expensive monoclonal antibody therapies.

We hypothesize that the development of a series of different low seroprevalence Ad serotype vectors will allow multiple rounds of oncolytic immune therapy in the same kidney cancer patient.

We hypothesize that these oncolytics can be delivered into primary kidney cancers by transcutaneous catheter or by retro-ureter delivery with a ureteroscope.

Specific Aims:

Aim 1. Test oncolytic adenoviruses armed with immune checkpoint proteins for in vivo efficacy in immune competent kidney cancer models.

Innovation: SC-Ad is a new oncolytic virus platform. Using it to carry immune checkpoint proteins has some innovation. Having Ad carry a series of PD-L1 decoys with varied valency has greater innovation.

Impact: If this project finds SC-Ads effective, this will provide proof of principle for testing systemic SC-Ad or RC-Ad therapies against disseminated kidney cancer. This project will also lay the foundation for clinical translation of these therapies in the Cancer Center at Mayo Clinic as local catheter therapies or as intravenous systemic therapies.

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