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Targeted Pro-Inflammatory Prodrugs for the Immunotherapy of Kidney Cancer

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Institution Receiving Award: TEXAS, UNIVERSITY OF, SOUTHWESTERN MEDICAL CENTER AT DALLAS
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TECHNICAL ABSTRACT

Background: The most significant advance in the history of cancer therapy – reaching beyond combination chemotherapy and molecularly targeted therapy – is immunotherapy. Particularly impactful, because of their broad application, are immune checkpoint inhibitors, i.e., antibodies targeting the CTLA or PD1/PDL1 pathway, which take the brakes off the immune response to promote an unprecedented antitumor effect. In fact, this treatment approach has just become the standard of care for most kidney cancer patients. Unfortunately, there is still a large number of patients who do not respond to this class of drug, simply because their tumors have not yet been recognized by the immune system. These tumors are "cold" and present one of the greatest challenges in cancer immunotherapy. This project is proposing a strategy to inflame all tumors in a kidney cancer patient by systemically administering pro-inflammatory prodrugs, which specifically home to kidney cancer cells or its neovasculature.

Area of Emphasis: Treatment: Immunotherapy

Objective: To develop proinflammatory prodrugs that can successfully and selectively engage known and validated targets in kidney cancer and initiate an inflammatory response.

Hypotheses:

Immunotherapy prodrugs that target the cell surface proteins CA9 and PSMA can enter cells and release their cargo

Prodrugs carrying a TLR7 and TLR9 agonist payload can stimulate the TLR pathway in target cells.

Immunotherapy prodrugs with TLR7 and TLR 9 agonists can induce/enhance an immune response in a syngeneic renal carcinoma model

Specific Aims:

Specific Aim 1 (Year 1): Synthesis and in-vitro characterization of the TLR7 and TLR9 prodrugs, which target PSMA and CA9-expressing cell lines. We will use a straightforward chemical approach to fuse well-established small molecules that target PSMA and CA9 in kidney cancers with the potent TLR7/TLR9 agonist. The TLR7 will be released in the lysosome while the TLR9 agonist remains covalently linked. We will demonstrate selective binding, release, and target engagement of the TLR agonists.

Specific Aim 2 (Year 2): To determine the efficacy and immunological effects of TLR7 and TLR9 prodrugs in a syngeneic mouse model renal cell carcinoma. We are using an immunocompetent mouse model of kidney cancer to demonstrate the proinflammatory activity and disease response to the prodrugs either by themselves or in combination with a PD1 inhibitor.

Innovation: Current approaches with potent activators of the innate immune system are all limited to the direct injection of tumor deposits, which greatly hampers their frequent administration. Our approach will deliver these molecules safely to all kidney cancer deposits. This approach is entirely new and transformative.

Impact: Inflaming a patient's whole tumor bulk, and not just one or two irradiated or injected lesions, could have a transformative impact on the efficacy of immunotherapy in kidney cancer patients. That's because this approach could decrease the detrimental effects in tumor heterogeneity that we unfortunately also observe in patients treated with immunotherapy. Furthermore, the very design of our prodrug approach was focused on its translational potential. All the main components of the molecules, especially the PSMA probes, have been successfully applied humans. We hope that this would allow for the rapid development of these agents in patients.

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