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Immune Checkpoint Targeted Immuno-PET to Identify Therapy-Induced Adaptive Resistance

Principal Investigator: HANNAN, RAQUIBUL
Institution Receiving Award: TEXAS, UNIVERSITY OF, SOUTHWESTERN MEDICAL CENTER AT DALLAS
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TECHNICAL ABSTRACT

Background: Immunotherapy has emerged as an effective treatment for many cancers. One promising strategy blocks the interaction between Programmed Death 1 (PD-1) receptor, present on T and B cells, specifically, and one of its ligands (PD-L1), expressed on cancer cells and other immunocytes. This immune checkpoint inhibitory (ICI) therapy can enhance the T cell-mediated immune response against cancer cells by reversing T-cell inactivation by PD-L1. While ICI immunotherapy appears promising in multiple cancer sites, including kidney, its response rate is 30% at best, indicating that 70% of patients are non-responders. Strategies are being studied to increase the efficacy of ICI, including the concurrent use of stereotactic ablative radiation therapy (SAbR) with ICI, often referred to as i-SAbR. However, we believe that SAbR may increase response rates by only 10%-15%, leaving 50%-60% of patients without benefit. Cancer cells evade immune-mediated attack from ICI by upregulating PD-L1 itself, through a mechanism known as adaptive immune resistance, which may be responsible for the failure of cancer immunotherapy in patients. Confirming this hypothesis will require multiple invasive biopsies of metastatic sites before and during ICI immunotherapy followed by immunohistochemistry (IHC). Furthermore, different metastatic sites, which are known to exhibit a high level of inter- and intra-lesional heterogeneity, are expected to show variable degrees of adaptive resistance. The temporal and spatial variance in adaptive resistance cannot be detected by biopsy, indicating the critical need for a highly sensitive, non-invasive method that can quantify the expression of PD-L1 accurately.

Objective/Hypothesis: The objective of this proposal is to validate Immuno-PET imaging with atezolizumab, an anti-PD-L1 antibody, when radiolabeled with a positron emitter (89Zr) for non-invasive assessment of PD-L1 in preclinical and clinical settings. Atezolizumab is currently approved by the FDA for clinical use in multiple cancer sites and is being investigated to treat kidney cancer (RCC). Furthermore, the goal of this proposal is to identify the response of PD-L1 expression, non-invasively and in real time, to anti-tumor therapy such as immune checkpoint inhibitors and stereotactic radiation. The hypothesis is that the imaging signal from Immuno-PET with 89Zr-atezolizumab will correlate with the RCC tumor's IHC expression levels of PD-L1 in vivo.

Specific Aims and Study Design:

Aim I: Develop and validate standard operating procedures (SOPs) to prepare and formulate 89Zr-atezolizumab while preserving its corresponding immunoreactivity in a cGMP (Current Good Manufacturing Practice) facility for US-FDA regulatory filing.

Aim II: Perform Immuno-PET in RCC patient-derived xenograft (PDX) mouse models and in syngeneic RCC models to validate imaging methods (imaging data acquisition, quantitative data analysis, and statistical correlation with IHC).

Aim III: Evaluate the correlation of Immuno-PET with adaptive resistance in RCC PDX models and syngeneic mouse models to assess therapy-induced adaptive resistance and imaging interference with either therapeutic doses of the anti-PD L1 antibodies or SAbR.

Aim IV: Obtain regulatory approvals from the US-FDA to use Immuno-PET with 89Zr-atezolizumab in RCC patients, and correlate imaging signals with IHC staining of tumor tissues in patients being treated with ICI or SAbR and participating in a pilot trial.

Impact: Immuno-PET will serve as an imaging biomarker of ICI treatment efficacy, toxicity, and resistance. Immuno-PET may find application in (1) selecting patients, (2) predicting toxicity when the antibody cross-reacts with normal tissue, and (3) evaluating treatment efficacy and monitoring the development of adaptive resistance to identify the optimal time to change therapy long before detecting progression radiographically. Furthermore, Immuno-PET will provide insights into the mechanisms of resistance to ICI and other anti-tumor immunotherapies toward developing strategies to overcome resistance. Once the methodology is established, other molecules linked to therapy resistance can also be evaluated in a similar manner.

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1077 Patchel Street
Fort Detrick, MD 21702-5024

(301) 619-7071

cdmrpwebmaster@webcdmrp.org (mailto:cdmrpwebmaster@webcdmrp.org)

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