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Noninvasive Diagnostic Assessment of Kidney Cancer Using Hyperpolarized 13C L-Tryptophan

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Institution Receiving Award: TEXAS, UNIVERSITY OF, AT DALLAS
Program: KCRP
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Funding Mechanism: Concept Award
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TECHNICAL ABSTRACT

Background: In renal cell carcinoma (RCC), the heme-containing enzyme indole 2,3-dioxygenase (IDO) is overexpressed, leading to increased tryptophan (TRYP) uptake and overproduction of the immunosuppressive metabolite kynurenine (KYN) in kidney cancer. This hyperactive tryptophan metabolism, especially the high KYN/TRYP ratio, has been implicated in the poor prognosis of kidney cancer patients, and thus, inhibitors targeting these tryptophan dioxygenase enzymes are promising chemotherapeutic agents. This project will utilize the emerging technology known as dissolution dynamic nuclear polarization (DNP) to enhance the nuclear magnetic resonance (NMR) or imaging (MRI) signals of 13C L-tryptophan by >10,000-fold.

Hypothesis/Objective: It is hypothesized that hyperpolarized 13C MRI will be able to image the expected high uptake of tryptophan in kidney tumors relative to normal renal tissues. Due to the overexpression of dioxygenase enzyme IDO in kidney cancer, it is further hypothesized that hyperpolarized 13C MRI will be able to map out the expected high production of the metabolite kynurenine across the renal tumor. The main objective of this study is to evaluate the efficacy of hyperpolarized 13C-tryptophan as potential in vivo metabolic MRI biomarker for kidney cancer, specifically clear cell RCC (ccRCC).

Specific Aims: This proposed research aims to: (1) obtain the highest 13C MRI signal enhancements of 13C-TRYP via DNP optimization, and (2) using these optimized hyperpolarized MRI signals, map out the uptake of hyperpolarized 13C-tryptophan and the subsequent 13C-kynurenine production in real time across the normal and malignant renal tissues in vivo in murine ccRCC models.

Study Design: Orthotopic murine models of kidney cancer will be established via intrarenal injection of 2 million ccRCC cells (the classic A498 cell line and the metastatic Caki-1 cell line) into the right kidneys of Balb/c nude mice. Implanted tumors will be grown in 10 days (Group 1) and 20 days (Group 2). Hyperpolarized 13C-TRYP will be administered to tumor-bearing mice (2 cell lines, n=5 mice/cell line, 2 tumor growth groups, a total of N=20 mice) via tail-vein catheter injection. Dynamic multi-voxel hyperpolarized 13C magnetic resonance spectroscopic imaging (MRSI) will be used to map out the uptake of 13C-TRYP as well as the subsequent 13C-KYN production across the tumors and the surrounding healthy tissues in vivo in real time. The hyperpolarized 13C MRSI images across the kidney tissue will be overlaid on their corresponding standard proton anatomical MRI images. The ratio of hyperpolarized 13C signals of KYN over TRYP in each MRI voxel will be calculated and mapped out in vivo across the renal tissues.

Innovation: The primary innovation of this project is that hyperpolarized 13C MRI is the only potential non-invasive imaging modality that has the required tandem of high sensitivity and superb specificity to image not only the expected high uptake of tryptophan but also the subsequent high production of kynurenine across the renal tumors. This simple, yet novel and possibly challenging idea could potentially make a major leap in how we detect and diagnose kidney cancer due to the promising non-invasive metabolic imaging technique that can provide diagnostic information at the molecular level.

Impact: The short-term impact of this project is that, if successful, this study will provide on a basic or preclinical level an ultrasensitive MRI agent that (i) will not only non-invasively detect and locate the kidney tumor in vivo, but (ii) also reveal important metabolic information about this disease. The proposed hyperpolarized MRI using 13C-tryptophan offers a new kind of diagnostic and prognostic tool for kidney cancer, which is very sensitive, specific, non-invasive, non-radioactive, and bio-compatible. Thus, if successful, the long-term impact of this study is the diagnosis of kidney cancer in hospitals and clinics without exposure of patients to the ionizing radiation of CT scan or the pain of needle biopsy.

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