Development of PET Tracers of Glutamine Metabolism

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The labeling of amino acids with positron-emitting radionuclides (such as fluorine-18) has been a widely used approach for the imaging of tumors as it often provides higher diagnostic accuracy than what is observed with [18F]FDG. In particular, PET tracers of glutamine metabolism have garnered significant attention in recent years. *O*-(2-[^{18}F]fluoroethyl-*L*-tyrosine (^{18}F-FET) is a promising PET tracer in this regard and is currently under investigation at Indiana University (IU) through an expanded access IND for patients with brain malignancies. Clinical production of ^{18}F-FET at IU previously required the use of HPLC for purification, following the reaction of fluorine-18 with the precursor molecule for FET. While this method has been successful in removing undesirable impurities and byproducts, HPLC significantly increases synthesis time and is a common failure point in the synthesis of FET on our current radiochemistry module. To address this issue, we aimed to deploy a solid-phase-extraction (SPE) method for the purification of FET, thereby eliminating the need for HPLC purification. Several methods for the SPE purification of FET have been previously reported; however, none of these strategies afforded pure [18F]FET on our synthesis module, thus development of new methods was required.

While several tracers capable of measuring different aspects of glutamine metabolism have been evaluated in both preclinical and clinical studies, there are metabolic liabilities that limit their utility and complicate data analysis. [18F]-4F-glutamine is one such tracer that has shown promise but has limitations due to undesirable metabolism *in vivo*. Herein we report our progress towards an improved synthesis of [18F]FET for ongoing clinical studies as well as our progress towards the development of a novel tracer that would address metabolic liabilities associated with currently available PET tracers of glutamine metabolism.