ABSTRACT

Positron emission tomography (PET) imaging along with the synthesis and characterization of [^{11}C]UCB-J has allowed for the *in vivo* analysis of synaptic density. PET imaging with [^{11}C]UCB-J has identified lower synaptic density attributed to neurodegenerative diseases, developmental disorders, psychiatric disorders, and epilepsy across species. The utility of a radiotracer is not only dependent on its applications, but also the feasibility of radiotracer production. In this thesis project, the synthesis of [^{11}C]UCB-J was optimized to ensure consistent radiochemical yields for its novel application in Down syndrome and for use in a large Alzheimer's disease study investigating the association between synaptic density and AD proteinopathies.

For [^{11}C]UCB-J to be used within large-scale human studies, the radiotracer must be made with consistent radiochemical yields that will pass all quality control parameters ensuring suitability for human injection. With the repeated synthesis of [^{11}C]UCB-J, there were inconsistencies in radiochemical yield and chemical purity that were improved with synthesis optimizations. The radiosynthesis and these optimization methods are included as a chapter in this thesis work.

Following this is a chapter investigating the association between [^{11}C]UCB-J and AD biomarkers in a cohort of older adults on and off the Alzheimer's disease continuum using PET imaging. The primary section here examines the association between synaptic density and neurofibrillary tau in this cohort, with secondary analyses including correlation analyses between global amyloid plaque burden and regional metabolic activity. Supplemental analyses were performed evaluating the effect of age and sex on synaptic density.

The following chapter presents the results from a pilot study that, for the first time, utilized [^{11}C]UCB-J to image synaptic density in individuals with Down syndrome (DS). This portion of the thesis project was primarily intended to determine whether a larger study using [^{11}C]UCB-J in DS would be feasible, while also reporting on differences in [^{11}C]UCB-J specific binding between DS and neurotypical individuals. This section also reports on studies analyzing [^{11}C]UCB-J in rodent models of the developmental disorders Rett Syndrome and Alexander's disease.

In summary, this thesis advances the field of PET imaging by optimizing the synthesis and analysis of [^{11}C]UCB-J, enabling its reliable use in large-scale human studies. The work demonstrates the potential of [^{11}C]UCB-J to provide critical insights into synaptic density across a range of neurological conditions, including Down syndrome and Alzheimer's disease. By ensuring consistent radiochemical yields and addressing the challenges associated with radiotracer production, this research not only enhances the feasibility of in vivo synaptic imaging but also paves the way for future studies to explore the underlying mechanisms of neurodegenerative and neurodevelopmental disorders. The findings underscore the broad applicability of [^{11}C]UCB-J in both human and animal models, contributing to a deeper understanding of synaptic alterations and their role in disease progression.