COLLEGE OF PHARMACY
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

The Department of Medicinal Chemistry is pleased to announce the

Ph.D. Dissertation Defense Seminar of

Sean Tanzey

Medicinal Chemistry, Ph.D. Candidate
(Mentor: Dr. Peter J.H. Scott)

"Novel Approaches to PET Imaging Neurodegeneration"

Monday December 14, 12:00 p.m.

Zoom Meeting:
https://umich-health.zoom.us/j/94241118228

Meeting ID: 942 4111 8228

COLLEGE OF PHARMACY
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

Public Oral Examination
For the Degree of Doctor of Philosophy

Sean Tanzey

"Novel Approaches to PET Imaging Neurodegeneration"

Monday, December 14, 2020
12:00 p.m.
Remote, Zoom
https://umich-health.zoom.us/j/94241118228

Committee Members

Dr. Peter J.H. Scott (Chair)
Dr. Timothy Cernak
Dr. Robert Koeppe
Dr. Andrew White

Abstract

Early detection of neurodegenerative diseases (NDs) has remained challenging for clinicians. To improve diagnostic confidence across the ND spectrum, there is considerable research devoted to the discovery of potential biomarkers of disease onset and progression. Neurodegenerative Diseases (NDs) have the common feature of progressive loss of structure and function of neurons resulting from different protein aggregates responsible for the various diseases. Alzheimer's Disease (AD), the most prevalent ND, is characterized by amyloid plaques (composed of amyloid ß (Aß) protein) and neurofibrillary tangles (composed of tau protein) within the hippocampal and cortex regions of the brain. Parkinson's Disease (PD), the second most common ND, is caused by dopaminergic neuronal loss within the basal ganglia, which controls voluntary movement, as a result from α-synuclein (α-syn) aggregation within the same region. Biologically relevant transition metals such as iron, copper, and zinc are reportedly accumulating and causing the aggregation of known neurotoxic protein aggregates at sites afflicted by neurodegenerative diseases. Detecting such metal ions may provide a means of early detection of these otherwise hard to diagnose diseases through the use of positron emission tomography (PET) imaging agents. Radiopharmaceuticals available today for imaging of the central nervous system (CNS) are limited to those imaging the mid- to late-stages of CNS disease progression. This imaging modality provides information at the molecular level of living organisms that clinicians can use to confirm a diagnosis or assess the effectiveness of a treatment. Small molecules, peptides, and large proteins can be radiolabeled with a wide range of positron emitting isotopes with various half-lives such as carbon-11 (C-11, ^{11}C, $t_{1/2}$ = 20 min) and fluorine-18 (F-18, ^{18}F, $t_{1/2}$ = 109.7 min). Although several PET tracers are approved by the Food and Drug Administration (FDA), some of them are challenging to synthesize for routine production. Efforts to improve the synthesis of such a tracer ([^{18}F]FDOPA) in accordance with current good manufacturing processes (cGMP) will be discussed in this presentation. The objective of this work is to design and analyze novel PET tracers ([^{18}F]FL2-b and [^{11}C]Deferiprone) that bind physiological transition metals (Cu, Zn, and Fe) which are hypothesized to accumulate abnormally in the brain early in NDs. Known metal chelators will be radiolabeled and used in preclinical animal studies to determine brain uptake, binding kinetics, metabolism, biodistribution, and be evaluated in both diseased brains and healthy controls. Another objective of this work includes developing a novel radiotracer, [^{11}C]AZ683, for neuroinflammation imaging, where it is thought that inflammation is a result of toxic metal accumulation.

Publications

Tanzey, S. S., Mossine, A. V., Sowa, A.R., Torres, J., Brooks, A. F, Sanford, M.S., Scott, P. J. A Spot Test for Determination of Residual TBA levels in ^{18}F-radiotracers for Human Use Using Dragendorff Reagent. *Anal. Methods*, 2020, **Accepted Manuscript.** https://doi.org/10.1039/D0AY01565B

Wright, J.S., Kaur, T., Preshlock, S., **Tanzey S.S.**, Winton, W.P., Wiesner, N., Brooks, A.F., Scott, P.J.H. Copper-mediated late-stage radiofluorination: five years of impact on preclinical and clinical PET imaging. *Clin Transl Imaging* **8,** 167–206 (**2020**). https://doi.org/10.1007/s40336-020-00368-y

Mossine, A. V., **Tanzey, S. S**., Brooks, A. F., Makaravage, K. J., Ichiishi, N.M, Miller, J.M., Henderson, B.D., Earhard, T., Bruetting, C., Skaddan, M.B., Sanford, M.S., Scott, P.J.H. Synthesis of High Molar Activity [^{18}F]6-Fluoro-L-DOPA Suitable for Human Use by Cu-Mediated Fluorination of a BPin Precursor. *Nat. Prot*. **15,** 1742–1759 (**2020**). https://doi.org/10.1038/s41596-020-0305-9

Mossine, A. V., **Tanzey, S. S**., Brooks, A. F., Makaravage, K. J., Ichiishi, N.M, Miller, J.M., Henderson, B.D., Skaddan, M.B., Sanford, M.S., Scott, P.J.H. One-pot synthesis of high molar activity 6-[^{18}F]fluoro- l -DOPA by Cu-mediated fluorination of a BPin precursor. *Org. Biomol. Chem.* **17**, 8701–8705 (**2019**). https://doi.org/10.1039/C9OB01758E
Chen, W.*, **Hu, S.***, et al. Identification and characterization of novel

Tanzey, S. S., Shao, X., Stauff, J., Arteaga, J., Sherman, P., Scott, P., Mossine, A. Synthesis and Initial In Vivo Evaluation of [^{11}C]AZ683 – a Novel PET Radiotracer for Colony Stimulating Factor 1 Receptor (CSF1R). *Pharmaceuticals*. **11**(4), 136 (**2018**). https://doi.org/10.3390/ph11040136

Tanzey, S. S., Thompson, S., Scott, P. J., Brooks, A. F. Gallium-68: methodology and novel radiotracers for positron emission tomography (2012-2017). *Pharm. Pat. Anal.* **7**, 193–227 (**2018**). https://doi.org/10.4155/ppa-2018-0016

Manuscripts in Preparation

Tanzey, S., Brooks, A.F., Desmond, T., Scott, P. Evaluation of [18F]FL2-b for detecting TDP-43 aggregates in amyotrophic lateral sclerosis.

Tanzey, S., Shao, X., Brooks, A., Scott, P. Synthesis of [^{11}C]Deferiprone for Evaluation of Brain Iron Homeostasis.

Select Presentations

2020 **Tanzey, S**., Brooks, A.F., Desmond, T., Scott, P. Extraction of Enriched Phophorylated TDP43 from ALS Tissue for Evaluation of New TDP-43 Radiotracers. *J. Nucl. Med. 2020 vol. 61. supplement 1 1038*
(**POSTER SNMMI 2020**)

2020 **Tanzey, S.S**, Brooks, A.F., Shao, X., Scott, P.J.H. Synthesis of [^{11}C]deferiprone and inhibition of radiolysis *J Nucl Med May 1, 2020 vol. 61 no. supplement 1 1119*
(**POSTER SNMMI 2020**)

2020 **Tanzey, S**. Development of Positron Emission Tomography Radiotracers for Clinical and Preclinical Targets of Neurodegeneration: The Journey from Bench to Bedside
(**ORAL COP Research Forum 2020**)

2019 **Tanzey, S.S**, Brooks, A.F., Shao, X., Desmond, T., Scott, P.J.H. Evaluation of [^{18}F]FL2-b for detecting TDP-43 aggregates in amyotrophic lateral sclerosis. Brain PET 2019, Yokohama, Japan, Journal of Cerebral Blood Flow & Metabolism, 39 (1S), 525-526, 2019. DOI: 10.1177/0271678X19851018
(**POSTER BrainPET 2019**)

2019 Mossine A, **Tanzey S,** Brooks A, Henderson B, Skaddan M, Sanford M, Scott P.: Automated production of high specific activity [18F]6F-l-DOPA using a TRACERLab FXFN synthesis module, 23rd International Symposium on Radiopharmaceutical Sciences, Beijing, China, J. Label. Compd. Radiopharm., 62, Suppl. 1, S225, 2019.
(**NON PRESENTING AUTHOR, ISRS 2019)**

2019 **Tanzey, S**., Shao, X., Brooks, A., Scott, P. Synthesis of [^{11}C]Deferiprone for Evaluation of Brain Iron Homeostasis. *J Nucl Med May 1, 2019 vol. 60 no. supplement 1 1621*
(**POSTER SNMMI 2019**)

2018 Brooks AF, **Tanzey S**, Shao X, Scott PJH.: Binding Potential of Radioligand [18F]FL2-b by Autoradiography in Amyotrophic Lateral Sclerosis and Lewy Body Dementia., Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Philadelphia, PA, J. Nucl. Med., 59, Suppl. 1, 613, 2018.
(**NON PRESENTING AUTHOR, SNMMI 2018)**

2018 **Tanzey, S. S.**, Shao, X., Stauff, J., Arteaga, J., Sherman, P., Scott, P., Mossine, A. Synthesis and Initial In Vivo Evaluation of [^{11}C]AZ683 – a Novel PET Radiotracer for Colony Stimulating Factor 1 Receptor (CSF1R)
(**POSTER Annual Med Chem Symposium 2018)**

2018 **Tanzey, S.**, Thompson, S., Shao, X., Brooks, A., Scott, P. Preparation of Metal-Protein Aggregate Radioligand
[^{11}C]HQ415 and Evaluation by Small Animal PET Imaging. *J Nucl Med May 1, 2018 vol. 59 no. supplement 1 1019*
(**POSTER SNMMI 2018**)

2018 **Tanzey, S**. Synthesis and Evaluation of Metal-Specific Chelating Radioligands for Neurodegeneration Imaging.
(**ORAL Medicinal Chemistry Seminar 2018**)

Future Plans

Sean is currently considering postdoctoral positions at University of California San Francisco and University of Washington.