THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Hailey Houson

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Department of Graduate Pharmaceutical Sciences

Friday, October 12, 2018, 1:00 pm
College of Pharmacy Building, Room 339

Glucaric Acid as a Positron Emission Tomography Agent to Detect Necrosis

COMMITTEE IN CHARGE: Vibhudutta Awasthi, PhD, Chair; Kelly M. Standifer, PhD; Alexander L. Mdzinarishvili PhD; Michael A. Ihnat, Ph.D.; Garo P. Basmadjian PhD; Rheal A. Towner, PhD

ABSTRACT: Necrosis is a type of cell death that is characterized by cytoplasmic swelling, rupturing of the cell membrane, and the externalization of cellular contents. It is characteristic of many pathologies including conditions which produce tissue ischemia (stroke, myocardial infarction), cancer treatment, traumatic injury, and contact with toxic agents. Noninvasive detection of tissue necrosis is primarily dependent on the presence of plasma markers for tissue death. Unfortunately, this type of measurement is unable to provide information about the location and extent of the necrotic area. Noninvasive nuclear imaging is able to determine both the presence and extent of injury in the body with high sensitivity. The field of nuclear imaging includes the modalities of single photon emission computed tomography (SPECT) and positron emission tomography (PET). Of the two, PET generally has higher resolution and sensitivity than SPECT. Nuclear imaging of necrosis, referred to as infarct-avid imaging, produces high quality images with low radiotracer accumulation in normal tissues. Infarct-avid imaging has been used for the detection of myocardial infarction, stroke, and tumor necrosis. Currently available infarct-avid agents include ^{99m}Tc-pyrophosphate and ^{111}In-antimyosin, which are for SPECT. We are developing ^{18}F-2-deoxy-2-fluoro-glucaric acid (^{18}F-FGA) as an agent to detect necrosis by PET.

Reaction conditions to produce glucaric acid were standardized using non-radioactive glucose. Radiopharmaceutical ^{18}F-FGA was synthesized in one-step by 5 min controlled oxidation of commercially available ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Quality control of ^{18}F-FGA was performed by ion-exchange HPLC and thin-layer chromatography. ^{18}F-FGA synthesis routinely produced 100% yield within 5 minutes of initiation. In addition, a shelf stable synthesis kit was made, and was usable for at least 6 months post production. We first demonstrated positive targeting of ^{18}F-FGA to regions of tissue damage in a rat model of drug induced cardiomyopathy. Additionally, we have shown that ^{18}F-FGA is able to target necrosis in other models of tissue infarction. This includes ischemic brain stroke necrosis produced in a mouse model of transient middle cerebral artery occlusion. Noninvasive detection of necrosis with a modality with high resolution and sensitivity such as PET will allow more accurate diagnosis and better treatment of many pathologies.