Over the first year of the grant application period, progress was achieved in advancing the research, which is aimed at obtaining potent amyloid-binding radioligands labeled with fluorine-18 for eventual positron emission tomography (PET) imaging studies of amyloid in the brains of human subjects. Towards these objectives, approximately 10 fluorinated analogues of the well known amyloid-specific dye thioflavin-T were further evaluated, using both in vitro and in vivo testing assays. Of these 10 fluorinated compounds, 4 derivatives were found to have high affinities for amyloid (binding constant values (Ki) of less than 5 nM). Radiolabeling studies with high specific activity F-18-fluoride were successfully conducted with all of these 4 analogues. In vivo studies in control mice were performed to evaluate the brain uptake and clearance of the radioligands from normal brain tissues. Three of the four lead fluorinated analogues exhibited excellent brain uptake and clearance properties in wild type mice, and additional studies were performed in non-human primates using PET imaging to further evaluate the properties of the F-18-labeled radioligands. All three of the fluorinated analogues displayed excellent in vivo properties in non-human primates and have undergone further evaluation as potential amyloid-specific radioligands for PET studies of brain amyloid deposition in human subjects. We have further reduced the list of candidate compounds down to two lead compounds, and it is anticipated that one of these two compounds will be taken into preliminary human studies by the end of the third year of DOE funding and the other compound will serve as a "back-up" to the lead compound

In the full second year of the grant period, additional progress was achieved in further advancing the research. Several high affinity F-18-labeled ligands were selected for pilot human imaging studies. One of these, the 3'-F-PIB derivative, has been taken into human studies in 4 elderly control subjects and 2 Alzheimer's disease subjects. The [F-18]3'-F-PIB derivative's properties were compared to [C-11]PIB in the same subjects using PET imaging over 4 hours post injection. An abstract reporting the results of the first [F-18]3'-F-PIB studies in human subjects has been accepted for oral presentation at the 2007 Society of Nuclear Medicine Meeting in Washington DC. Overall, the imaging results with the [F-18]3'-F-PIB compared favorably with [C-11]PIB. The 3'-F compound had a slightly higher level of nonspecific binding in white and gray brain matter compared to PIB and had a slightly higher wash-out rate from amyloid plaque rich areas in the Alzheimers disease subjects. A second ligand, termed 2'-F-PIB, has undergone toxicology screening and will be studied in human subjects later in 2007. The properties of this new 2'-F derivative are expected to be superior to the 3'-F analog, and more comparable to the outstanding in vivo amyloid imaging properties of [C-11]PIB.

The grant funding was terminated at the end of the second year full year of funding as a result of cut-backs by DOE in the Nuclear Medicine area. While the grant was limited to only 2 years and 5 months (with a third year provided as a

no-cost extension period), we accomplished most of the original specific aims of the grant application.

Five papers were published over the grant period:

Mathis CA, Klunk WE, Price JC, DeKosky ST. Imaging technology for neurodegenerative diseases: Progress toward detection of specific pathologies. Archives of Neurology 2005; 62:196-200.

This paper describes the need to develop imaging agents that bind specifically and selectively to different types of neuropathologies, with amyloid imaging agents given as an example of success towards these goals.

Price JC, Klunk WE, Lopresti BJ, Lu X, Hoge JA, Ziolko SK, Holt DP, Meltzer CC, Dekosky ST, Mathis CA. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. J Cereb Blood Flow Metab 2005; 25:1528-1547.

This paper describes compartmental pharmacokinetic modeling of an amyloid imaging agent in human subjects.

Lopresti JC, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, Meltzer CC, Schimmel K, Tsopelas N, DeKosky ST, Price JC. Simplified Quantification of Pittsburgh Compound-B Amyloid Imaging PET Studies: A Comparative Analysis. J Nucl Med 2005; 46:1959-1972.

This paper extends the pharmacokinetic analysis of an amyloid imaging agent to simplified (reference region) methods and compares them to more rigorous methods. The result is that simplified analysis methods work well.

Ziolko SK, Weissfeld LA, Klunk WE, Mathis CA, Hoge JA, Lopresti BJ, Dekosky ST, Price JC. Evaluation of voxel-based methods for the statistical analysis of PIB PET amyloid imaging studies in Alzheimer's disease. Neuroimage 2006; 33: 94-102.

This paper describes an automated method to analyze PIB amyloid imaging data without the use of a priori drawn regions of interest.

Klunk WE, Lopresti BJ, Nebes RD, Price JC, Tsopelas N, DeKosky ST, Mathis CA. Development and Application of beta-Amyloid Imaging Agents in Alzheimer's Disease. In: The Dementias: Early Diagnosis and Evaluation, Edited by Herholz K, Dekker, NY, 2006; Chapter 10, pp. 279-311.

This book chapter describes the concept and realization of imaging amyloid in the brains of living human subjects using PET and amyloid-specific radioligands labeled with C-11 and F-18.