Abstract ID: 024 **A New Series of 3-Pyridyl Ether Analogs of A-85380 for Positron Emission Tomography (PET) Imaging of Nicotinic Acetylcholine Receptors. Yongjun Gao**, Hayden T. Ravert, Daniel Holt, John Hilton, Chris Endres, Mohab Alexander, Anil Kumar, Arman Rahmim, Hiroto Kuwabara, Dean F. Wong, Robert F. Dannals, Andrew G. Horti. Johns Hopkins University, Baltimore, MD, USA. Contact e-mail: yongjgao@yahoo.com.

The most abundant subtype of cerebral nicotinic acetylcholine receptors, α4β2-nAChR plays a critical role in various brain functions and pathological states, including Parkinson's disease (PD), Alzheimer's disease (AD), pain, tobacco dependency, schizophrenia, anxiety, and depression. Radiolabeled nAChR agonists, such as 5-[^{123}I]iodo-A-85380, 2-[^{18}F]fluoro-A-85380, and 6-[^{18}F]fluoro-A-85380, are used for in vivo imaging in humans. However, these probes are limited by their slow brain kinetics. In this study, we report the synthesis of a new series of 3-pyridyl ether analogs of A-85380 with high binding affinities (K_i=19 to 86 pM) and lipophilicities in the range of logD = 0.5-1.2. Some of these analogs were radiolabeled with the positron emitting isotope ^{11}C and evaluated by microPET studies in rats and PET studies in baboons to determine if these tracers have improved brain kinetics compared with 2-[^{18}F]-fluoro-A-85380. Three radioligands (JHU85157, JHU85208, JHU85270) of this series have improved brain kinetics and hold great promise as potential PET tracers for imaging of nAChR in human subjects.

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Abstract ID: 025 **Comparison of Two ^{11}C-Labeled Benzofuran Derivatives for PET Imaging of Senile Plaques in Alzheimer's Disease. Hidekazu Kawashima**[1], Masahiro Ono[2], Tomoki Kawai[3], Hiroharu Kitano[4], Mei-Ping Kung[5], Hank F. Kung[5], Yuji Kuge[3], Morio Nakayama[2], Hideo Saji[3]. [1]Graduate School of Medicine, Kyoto Univ., Kyoto, Japan; [2]Graduate School of Biomedical Sciences, Nagasaki Univ., Nagasaki, Japan; [3]Graduate School of Pharmaceutical Sciences, Kyoto Univ., Kyoto, Japan; [4]Kyoto University Hospital, Kyoto, Japan; [5]Univ. of Pennsylvania, Philadelphia, PA, USA. Contact e-mail: kawap@kuhp.kyoto-u.ac.jp.

Objectives: Since it is commonly accepted that senile plaques (SPs) are concerned in Alzheimer's disease (AD) development, quantitative evaluation of SPs in the brain with non-invasive nuclear medicine techniques would allow early detection of AD. In this study, we synthesized two ^{11}C-labeled benzofuran derivatives, 2-hydroxy-(4-[^{11}C]methylaminophenyl) benzofuran: [^{11}C]HMBZF and 2-methoxy-(4-[^{11}C]methylaminophenyl) benzofuran: [^{11}C]MMBZF as PET tracers targeting β-amyloid (Aβ) plaques which constitute SPs, and compared the kinetics of those compounds in normal mice brain.

Methods: Affinity of each compound to SPs was evaluated by *in vitro* competitive inhibition study using [^{125}I]IMPY (6-[^{125}I]iodo-2-(4′-dimethylamino)phenyl-imidazo[1,2]pyridine) with gray matter homogenate prepared from postmortem brain of AD patients. ^{11}C-labeled compounds were synthesized from corresponding *N*-desmethyl precursors with [^{11}C]methyl triflate (radiochemical purity: > 99%, specific activity: 37 GBq/μmol), and then, were injected intravenously to ddY mice (male, 6-week-old) to measure the time-dependent changes of radioactivity in the brain.

Results: Both probes showed remarkable affinities to SPs with inhibition constant (Ki) value of 0.7 nM (HMBZF) and 1.3 nM (MMBZF), respectively. [^{11}C]HMBZF exhibited fast and high uptake to the brain (4.8% ID/g at 2 min after injection) and rapid clearance (0.2% ID/g at 60 min). However, [^{11}C]MMBZF was 4.9% ID/g at 15 min (peak) and 2.5% ID/g at 60 min, indicating longer retention in the brain.

Conclusion: Difference of substituent groups contributed to the kinetics of two compounds in the brain. Since [^{11}C]HMBZF not only had a high affinity to SPs but was washed out fast from normal brain tissue, enhanced S/N ratio is expected *in vivo*. Therefore, it is suggested that [^{11}C]HMBZF could have a potential for PET imaging of SPs in the AD brain.

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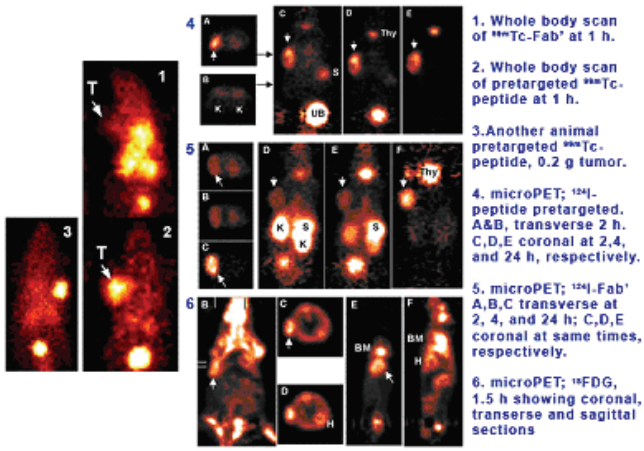
Abstract ID: 026 **Enhancing Image Specificity and Sensitivity with a Bispecific Antibody (bsMAb) Pretargeting Method for SPECT and PET. David M. Goldenberg**[1], Robert M. Sharkey[1], C.-H. Chang[2], Habibe Karacay[1], Edmund A. Rossi[2], William J. McBride[3]. [1]Center for Molecular Medicine and Immunology, Belleville, NJ, USA; [2]IBC Pharmaceuticals, Inc., Morris Plains, NJ, USA; [3]Immunomedics, Inc., Morris Plains, NJ, USA. Contact e-mail: dmg.gscancer@att.net.

Aims: Antibodies can be prepared against virtually any substance expressed by cancers or other diseases, and therefore are highly selective and specifically targeting agents. Bispecific antibody pretargeting methods take advantage of these properties, while significantly enhancing the targeting index as compared to directly radiolabeled antibodies.

Methods: Recombinant, humanized bsMAbs reactive with carcinoembryonic antigen (CEA) and a novel anti-histamine-succinyl-glycine (HSG) anti-hapten antibody have been prepared and used with divalent HSG-peptides capable of being radiolabeled with ^{99m}Tc (SPECT) or ^{124}I (PET). The bsMAb is injected intravenously in nude mice bearing human colonic tumor xenografts, and 24 h later, is cleared from the blood sufficiently to allow the radiolabeled peptide to be given. Necropsy, SPECT and microPET images measured the selective targeting of the radiolabeled peptide as compared to ^{99m}Tc- and ^{124}I-anti-CEA Fab' fragments or ^{18}F-deoxyglucose (FDG).

Results: Dynamic imaging showed the bsMAb-pretargeted ^{99m}Tc-peptide specifically localizing in tumors within 10 minutes of its injection as compared to the radiolabeled peptide alone. By 40 minutes, the pretargeted peptide in the tumor exceeded all normal tissues. Tumor uptake exceeded that of the ^{99m}Tc-Fab' by 10-fold and tumor/nontumor ratios ≈40-fold higher. Similar targeting results were seen with the pretargeted ^{124}I-peptide, which again had rapid and sustained tumor uptake that was higher with better tumor/nontumor ratios than an ^{124}I-anti-CEA Fab'. Pretargeting also had more specific targeting and better tumor uptake than FDG.

Conclusion: bsMAb pretargeting significantly improves target localization by increasing the amount of radioactivity delivered to the target and lowering the level in normal tissues providing superior contrast ratios. This method could be adapted for imaging other disease markers.



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Abstract ID: 027 **Engineered Antibody Fragments for MicroPET Imaging of B-Cell Lymphoma Xenografts. Tove Olafsen**[1], David Betting[2], Vania E. Kenanova[1], Andrew A. Raubitschek[3], John M. Timmerman[2], Anna M. Wu[1]. [1]Molecular and Medical Pharmacology, UCLA, Los Angeles, CA, USA; [2]Medical Hematology and Oncology, UCLA, Los Angeles, CA, USA; [3]Radioimmunotherapy, City of Hope, Duarte, CA, USA. Contact e-mail: tolafsen@mednet.ucla.edu.