FINAL REPORT

FOR CRADA NO. C-05-13

BETWEEN

BROOKHAVEN SCIENCE ASSOCIATES

AND

GLAXOSMITHKLINE

Project Entitled: An open-label, randomized positron emission tomography (PET)study in healthy male volunteers consisiting of Part A and Part B.Part A: Clinical validation of norepinephrine transporter (NET) PET ligand, (S,S)-[11C]O-methylreboxetine ([11C]MRB) using different doses of oral atomoxetine as NET reuptake inhibitor.Part B: Evaluation of NET occupancy, as measured by [11C]MRB, with multiple dosing regimens of orally administered GSK372475.

Brookhaven PI: Joanna Fowler

Submitted by: Michael J. Furey
Manager, Research Partnerships
Brookhaven National Laboratory

DISCLAIMER

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Manager, Research Partnerships
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Memorandum

Date: December 2, 2009

To: Mike Furey

From: Joanna S. Fowler

Subject: Final Report CRADA No. BNL-C-05-13

Imaging the norepinephrine transporter in humans with (S,S)-[11C]O-methyl reboxetine and PET: problems and progress. Logan J, Wang GJ, Telang F, Fowler JS, Alexoff D, Zabroski J, Jayne M, Hubbard B, King P, Carter P, Shea C, Xu Y, Muench L, Schlyer D, Learned-Coughlin S, Cosson V, Volkow ND, Ding YS. Nucl Med Biol. 2007 Aug;34(6):667-79

Abstract: Results from human studies with the PET radiotracer (S,S)-[(11)C]O-methyl reboxetine ([(11)C](S,S)-MRB), a ligand targeting the norepinephrine transporter (NET), are reported. Quantification methods were determined from test/retest studies, and sensitivity to pharmacological blockade was tested with different doses of atomoxetine (ATX), a drug that binds to the NET with high affinity (K(i)=2-5 nM). METHODS: Twenty-four male subjects were divided into different groups for serial 90-min PET studies with [(11)C](S,S)-MRB to assess reproducibility and the effect of blocking with different doses of ATX (25, 50 and 100 mg, po). Region-of-interest uptake data and arterial plasma input were analyzed for the distribution volume (DV). Images were normalized to a template, and average parametric images for each group were formed. RESULTS: [(11)C](S,S)-MRB uptake was highest in the thalamus (THL) and the midbrain (MBR) [containing the locus coeruleus (LC)] and lowest for the caudate nucleus (CDT). The CDT, a region with low NET, showed the smallest change on ATX treatment and was used as a reference region for the DV ratio (DVR). The baseline average DVR was 1.48 for both the THL and MBR with lower values for other regions [cerebellum (CB), 1.09; cingulate gyrus (CNG) 1.07]. However, more accurate information about relative densities came from the blocking studies. MBR exhibited greater blocking than THL, indicating a transporter density approximately 40% greater than THL. No relationship was found between DVR change and plasma ATX level. Although the higher dose tended to induce a greater decrease than the lower dose for MBR (average decrease for 25 mg=24+/-7%; 100 mg=31+/-11%), these differences were not significant. The different blocking between MBR (average decrease=28+/-10%) and THL (average decrease=17+/-10%) given the same baseline DVR indicates that the CDT is not a good measure for non-NET binding in both regions. Threshold analysis of the difference between the average baseline DV image and the average blocked image showed the expected NET distribution with the MBR (LC) and hypothalamus>THL>CNG and CB, as well as a significant change in the supplementary motor area. DVR reproducibility for the different

brain regions was approximately 10%, but intersubject variability was large. CONCLUSIONS: The highest density of NETs was found in the MBR where the LC is located, followed by THL, whereas the lowest density was found in basal ganglia (lowest in CDT), consistent with the regional localization of NETs in the nonhuman primate brain. While all three doses of ATX were found to block most regions, no significant differences between doses were found for any region, although the average percent change across subjects of the MBR did correlate with ATX dose. The lack of a dose effect could reflect a low signal-to-noise ratio coupled with the possibility that a sufficient number of transporters were blocked at the lowest dose and further differences could not be detected. However, since the lowest (25 mg) dose is less than the therapeutic doses used in children for the treatment of attention-deficit/hyperactivity disorder (approximately 1.0 mg/kg/day), this would suggest that there may be additional targets for ATX's therapeutic actions.