Assessment of HDAC6 PET radiotracer ^{18}F-Bavarostat

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Background

Histone deacetylase 6 (HDAC6) regulates microtubule stability and function. Dysregulation is associated with certain cancers and several central nervous system disorders including Alzheimer's and Parkinson's diseases, and major depressive disorder (*1*,*2*).
Thus, HDAC6 modulation holds therapeutic potential. Previously, a novel radiotracer [^{18}F]Bavarostat (brain penetrant HDAC6 inhibitor with excellent selectivity) was developed (*3*).

Objective

This study aims to apply ^{18}F-Bavarostat in nonhuman primates to

1) perform radiation dosimetry calculations, and
2) determine the appropriate tracer kinetic model for quantification of brain imaging data.

References

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2. Anderson KW, Chen J, Wang M, Mast N, Pikuleva IA, Turko I V. Quantification of histone deacetylase isoforms in human frontal cortex, human retina, and mouse brain. *PLoS One*. 2015;10:e0126592.
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4. Celen S, Rokka J, Gilbert TM, et al. Translation of HDAC6 PET Imaging Using [^{18}F]EKZ-001-cGMP Production and Measurement of HDAC6 Target Occupancy in Nonhuman Primates. *ACS Chem Neurosci.* 2020;1;11(7):1093-1101.

Disclosures

Presenting author Xiaotian Fang, and lead investigator Richard Carson: no disclosures. ^{18}F-Bavarostat was licensed to Eikonizo Therapeutics, which was co-founded by Jacob Hooker.

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Materials & Methods

Whole body PET scan were performed on the Siemens mCT scanner in four rhesus monkeys (2 male, 2 female) to measure organ radiation dose.

Three additional monkeys underwent brain PET imaging on the Focus-220 scanner with 180 min of dynamic scans and metabolite-corrected input functions. HDAC6 selective inhibitor ACY-775 (IC_{50}: 7.5 nM) was administered at both 2 and 18 mg/kg doses prior to tracer injection to assess specific binding of ^{18}F-Bavarostat in two subjects (total of 4 blocking scans). Injected activity was 142±49 MBq (0.90±0.33 μg injected mass, n = 7). Plasma free fraction (f_p) was 0.04 ± 0.02. Regional distribution volume (V_T) was calculated using one- and two-tissue compartment models (1TCM and 2TCM) as well as the multilinear analysis-1 method.

Dosimetry

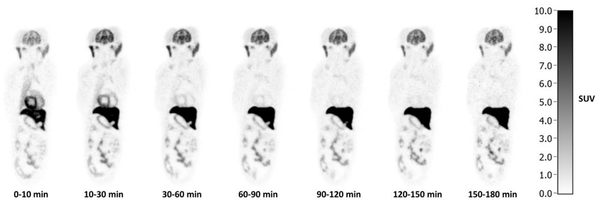

Figure 1. Maximum-intensity projection (coronal view) over 3 h of ^{18}F-Bavarostat in male rhesus monkey.

Injected activity in the dosimetry scans was 169.9 ± 12.7 MBq (0.84 ± 0.60 μg injected mass, n = 4). For males, highest uptake was observed in the liver, followed by the testes and the gallbladder wall, with the testes as the dose-limiting organ with a single study dose limit of 413 MBq (**Fig. 1**). When applied to the 55 kg adult female phantom, liver is the critical organ, with a 309 MBq single study dose limit.

Results

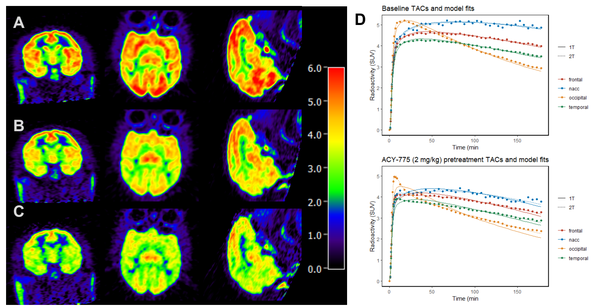

Figure 2. Representative SUV images (30-60 min summation) after ^{18}F-Bavarostat: baseline (A), after ACY-775 (2 mg/kg) pretreatment (B), after ACY-775 (18 mg/kg) pretreatment (C). (D) Time-activity curves in selected regions along with 1TCM and 2TCM fits for baseline (top), and after ACY-775 (2 mg/kg) pretreatment (bottom).

^{18}F-Bavarostat has high brain uptake and relatively slow kinetics (**Fig. 2**), with regional tracer uptake highest in the occipital cortex.
Regional time-activity curves were well fitted by all models, though 2TCM fits were better for the blocking scans, therefore we used 2TCM for all results. Baseline 2TCM V_T values (mL/cm^3) ranged from 36.0 (CS) to 95.3 (NAcc).
Baseline V_T values had less than 5% difference comparing 120 to 180 min scan duration.

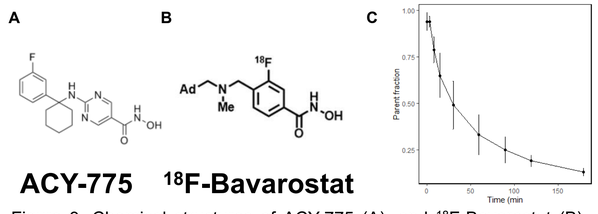

Figure 3. Chemical structures of ACY-775 (A), and ^{18}F-Bavarostat (B). ^{18}F-Bavarostat parent fraction (C), average of 7 scans (mean±sd).

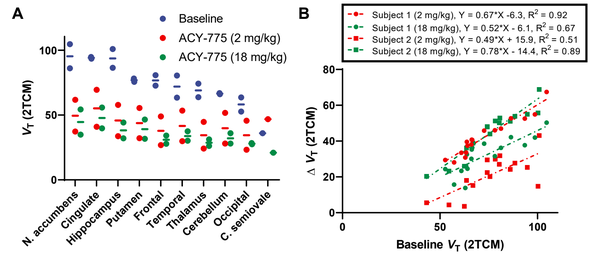

Figure 4. (A) ^{18}F-Bavarostat averaged V_T (2TCM) for baseline (blue, n = 3), after 2 mg/kg ACY-775 (red, n = 2), and 18 mg/kg ACY-775 (green, n = 2). (B) Lassen plots for ^{18}F-Bavarostat generated from 2TCM, each pretreatment scan plotted individually with lines fit by linear regression.

For scans following pretreatment, 2TCM V_T values were lower in NAcc (-48% at 2 mg/kg, -53% at 18 mg/kg), avg. GM regions (-44% at 2 mg/kg, -53% at 18 mg/kg), and in CS (-30% at 2mg /kg, -42% at 18 mg/kg) (**Fig. 4A**).
Based on occupancy plot (**Fig. 4B**), 58±13% at 2 mg/kg and 65±18% at 18 mg/kg blockade was estimated, and calculated V_{ND} was 18.1±10.4 mL/cm^3. Based on this V_{ND}, regional baseline BP_{ND} values were calculated and ranged from 5.3±0.7 (NAcc) to 2.0 (CS).

Discussion

^{18}F-Bavarostat has reasonable tracer characteristics in NHP: fast and high brain uptake, tissue kinetics appropriate for quantification, and good specific binding signals. The 2TCM appears suitable for describing the kinetics. In this small study, a consistent pattern of blockade with ACY-775 dose was not found and full blockage was not achieved. The blocking experiments suggests that ^{18}F-Bavarostat may be binding to targets that are not specifically blocked by ACY-775, unlike previously reported (*4*). Altogether, ^{18}F-Bavarostat appears to be a promising radiotracer for HDAC6 mapping and quantification.

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