An Exploratory Study of 3-[^{18}F]fluoro-*p*-hydroxyphenethylguanidine ([^{18}F]3F-PHPG) in Patients with Neuroendocrine Tumors

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Background and Significance. Fluorine-18 radiolabeled phenethylguanidines are a new class of radiotracers that were developed at our institution for noninvasive assessment of disease-induced damage to cardiac sympathetic nerves using PET imaging. Uptake and localization of these compounds into sympathetic nerve terminals is due to active transport by the norepinephrine transporter (NET) and the second isoform of the vesicular monoamine transporter (VMAT2). 4-[^{18}F]fluoro-*m*-hydroxyphenethylguanidine ([^{18}F]4F-MHPG) and 3-[^{18}F]fluoro-*p*-hydroxyphenethylguanidine ([^{18}F]3F-PHPG) have been tested successfully in healthy human subjects and in patients with heart failure. These compounds are structurally related to the FDA approved radiotracer [^{123}I]metaiodobenzylguanidine ([^{123}I]MIBG), which was originally developed for imaging adrenergic tumors such as pheochromocytoma and paraganglioma. These types of neuroendocrine tumors often richly express NET and VMAT2 transporters, as well as the first isoform of the vesicular monoamine transporter (VMAT1). Our preclinical and clinical tests with radiolabeled phenethylguanidines strongly suggest that they can be used for localization of neuroendocrine tumors that express NET, VMAT1 and/or VMAT2 transporters. One potential advantage of these compounds is they are much better substrates for the VMAT2 transporter than [^{123}I]MIBG, which may confer an enhanced ability to detect tumors expressing high levels of VMAT2. Whole-body PET scans of [^{18}F]3F-PHPG in healthy subjects showed that apart from high uptake in heart, liver, and salivary glands, there is very little retention of the radiotracer elsewhere in the body, which is ideal for tumor localization studies.

Based on these considerations, the primary objective of this study is to evaluate the diagnostic performance of [^{18}F]3F-PHPG in patients with pheochromocytoma and paraganglioma. A secondary objective is to compare the performance of [^{18}F]3F-PHPG with the FDA approved radiotracers [^{123}I]MIBG and [^{68}Ga]DOTA-TATE (NETSPOT™) in the same patients. While the new diagnostic agent [^{68}Ga]DOTA-TATE, which binds to the somatostatin receptor subtype 2 (sst_2), represents an important advance in the management of neuroendocrine cancers, a significant fraction of neuroendocrine tumors do not express the sst_2 receptor. A PET radiotracer that could be reliably used for localizing neuroendocrine tumors that do not express sst_2 would improve patient management options. Also, if this study demonstrates that [^{18}F]3F-PHPG consistently outperforms [^{123}I]MIBG for tumor localization, it may be possible to develop a new radiotherapeutic agent for the treatment of some neuroendocrine tumors based on the phenethylguanidine structure.

Methods and Experimental Approach. Whole body PET/CT scans will evaluate the biodistribution of [^{18}F]3F-PHPG in 24 patients with pheochromocytoma and/or paraganglioma. These will include sporadic pheochromocytoma and genetic/familial syndromes, including Von Hippel-Lindau disease

(VHL), neurofibromatosis (NF1), multiple endocrine neoplasia type 2 (MEN2), and succinate dehydrogenase (SDH) mutation. Based on our previous whole-body studies of [^{18}F]3F-PHPG in normal subjects, two PET/CT scans will be obtained at 1.5 hours and 3.0 hours after tracer administration. Metabolic breakdown of the radiotracer in plasma will be assessed using high performance liquid chromatography (HPLC) with radiation detection analysis. We will enroll at least 12 subjects with prior [^{68}Ga]DOTA-TATE (NETSPOT™) scans to enable direct comparison with [^{18}F]3F-PHPG scans in the same patients. For the other 12 subjects, we will perform an additional imaging studies with [^{123}I]MIBG, including whole-body planar scintigraphy and a single SPECT/CT scan focusing on the primary neuroendocrine tumor, to compare the diagnostic performance of [^{18}F]3F-PHPG and [^{123}I]MIBG. All images will be independently reviewed by two expert nuclear medicine physicians. Tumor uptake levels of radiotracers will be assessed using standardized uptake values (SUVs). Resected tumor samples from the subjects imaged with [^{18}F]3F-PHPG will be analyzed using immunohistochemistry to determine tumor expression levels of the NET, VMAT1 and VMAT2 transporters. These results will be correlated with observed tumor uptake levels of [^{18}F]3F-PHPG and [^{123}I]MIBG.

Conclusion. At the time this abstract is being submitted, we have obtained IRB approval to begin the study and are currently recruiting the first subjects for study in October 2020. We anticipate that we will be able to report the results of the first 3 to 4 subjects at the NETRF 2020 Research Symposium in November 2020.