2017 SNMMI Highlights Lecture: General Nuclear Medicine

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2017 Highlights Lectures were delivered on June 14 at the SNMMI Annual Meeting in Denver, CO. In this issue we feature the lecture by Patrick M. Colletti, MD, a professor of Radiology, Medicine, Biokinesiology, and Pharmaceutical Sciences at the University of Southern California (Los Angeles), who spoke on highlights in general nuclear medicine. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine (2017;58[suppl 1]).

Chemistry is life—this is the underlying principle for much of the outstanding general nuclear medicine presentations at this year’s SNMMI meeting. As in previous years, multiple investigators presented novel chemical constructs for promising radiopharmaceuticals. This year, presentations elucidating methods for efficient $^{18}$F labeling and imaging were notable. One example came from Kobayashi et al. from the Research Centre Nihon Medi-Physics Co., Ltd. (Chiba, Japan) and University Hospital Würzburg (Germany), who reported on “Novel functional renal imaging with $^{18}$F-fluorodeoxysorbitol ($^{18}$F-FDS) PET” [521]. This tracer is made by simple reduction from $^{18}$F-FDG. In rat models of acute renal failure and unilateral ureteral obstruction, the researchers demonstrated favorable kinetics for functional renal imaging (Fig. 1). Urine concentrations of $^{18}$F-FDS were comparable to those with $^{99m}$Tc-diethylenetriamine pentaacetic acid. Last year the same group showed that sorbitol urinary clearance was also closely correlated with inulin clearance. This year they presented results that suggest that the advantage of high spatial/temporal resolution and the simple production method for $^{18}$F-FDS could improve both the diagnostic performance and availability of renal imaging. In the future this tracer might be helpful in identifying bacterial infections, among other applications.

Choi et al. from the Brigham and Women’s Hospital/ Dana-Farber Cancer Center, Harvard Medical School (Boston, MA), and Hanyang University College of Medicine (Seoul, Korea) [1200] asked “Is cholecystokinin (CCK) administration or delayed imaging necessary when bowel excretion does not occur but the gallbladder fills promptly?” [1200]. Preferential gallbladder filling without $^{99m}$Tc-HIDA excretion into the small bowel up to 1 hour is occasionally seen after CCK pretreatment or in the fasting state. Although this is recognized as a normal variant, many nuclear medicine physicians choose to administer CCK or obtain delayed images to exclude the possibility of common bile duct obstruction.

This study included the records of 155 patients in whom the gallbladder was quickly visualized but the small bowel remained without tracer at 1 hour. The authors looked at time of gallbladder visualization and time to liver parenchymal clearing. They found prompt clearance of liver parenchymal activity in 142 patients (91.8%), with the remaining 13 having mild-to-moderately delayed clearance with or without initial decreased hepatic uptake. None of the 142 patients had any event attributable to common bile duct obstruction on follow-up, and all patients in the group of 13 had additional imaging, with no common bile duct-related issues in 11. The authors concluded that when hepatobiliary scintigraphy partially visualizes the gallbladder but not the small bowel “the probability of identifying clinically relevant common bile duct obstruction by additional imaging with CCK or delayed imaging is virtually zero in the acute clinical setting, if liver parenchymal clearance is prompt.” They suggested that CCK or delayed imaging can be reserved for those with delayed liver clearance of $>50\%$ at 60 minutes, either visually or by parenchymal retention.

FIGURE 1. Dynamic 3D functional imaging with $^{18}$F-fluorodeoxysorbitol ($^{18}$F-FDS) PET in a rat model of unilateral ureteral obstruction, acquired (left to right) 2.5, 7.5, 17.5, and 27.5 minutes after injection. The high spatial/temporal resolution and simple production method for $^{18}$F-FDS could improve both the diagnostic performance and availability of renal imaging.
Jones et al. from Johns Hopkins University and School of Medicine (Baltimore, MD) and the Universitätsklinikum Würzburg (Germany) reported on “Application of quantitative SPECT/CT reconstructions with $^{99m}$Tc-sestamibi renal imaging of patients with cT1 renal masses” [745]. They have previously shown that relatively benign renal masses, such as oncocytomas, will take up sestamibi, whereas renal cell carcinoma does not. They have demonstrated this with both SPECT and planar imaging. In the study presented at this meeting, they showed that quantitative SPECT/CT (QSPECT), an emerging method that implements corrections for image-degrading factors that yield physically repeatable quantitative uptake in target and reference organs, is better able to differentiate lesions as “cold” or “hot” tumors. Figure 2 shows a comparison of conventional Flash-3D and the QSPECT technique in hot (oncocytoma) and cold (renal cell carcinoma) masses. The authors concluded that “this methodology will serve as a framework on which to build more robust quantitative biomarkers such as SPECT SUV” that “may provide more diagnostic certainty and improved classification of tumor subtypes to help guide patient management and avoid unnecessary surgeries.” The possibility that someday surgeons will not be performing total or partial nephrectomies for benign lesions is encouraging.

Ceccarini et al. from University Hospitals Leuven–KU Leuven (Belgium) reported on “Accurate discrimination of alcoholic patients using a multivariate support vector machine (SVM) approach of metabotropic glutamate receptor subtype 5 (mGluR5) PET” [288]. The authors used $^{18}$F-FPEB PET imaging to construct a voxel-based discriminative cerebral mGluR5 pattern for patients with alcohol dependence using an SVM approach to define the spatial discriminative features and identify individuals likely to respond to treatment from those likely to relapse. The study included 16 patients with a DSM-IV diagnosis of alcohol dependence and 32 age-matched healthy controls, all of whom underwent $^{18}$F-FPEB PET imaging. The biodistribution visualized was similar to that seen with MR spectroscopy. However, with the addition of the SVM analysis the investigators were able to identify regional decreased mGluR5 availability in the cortico-subcortical network in alcoholic patients (Fig. 3) and separate out fairly effectively those whose alcohol dependency might be successfully treated from those who might not respond to such treatment or might relapse. The authors pointed to the potential for personalized decision making in alcohol and other dependencies and called for additional studies to assess multivariate machine learning techniques to test the prognostic capacity of this approach for relapse propensity.

Watanabe et al. from Hokkaido University, Hokkaido University Graduate School of Medicine, and Hokkaido University Hospital (all in Sapporo, Japan) reported on “First-in-human study of $^{18}$F-DiFA, an improved PET probe for tumor hypoxia, in 6 healthy volunteers” [839]. $^{18}$F-DiFA is a new imaging tracer that targets tumor hypoxia, with the
potential to overcome some of the timing disadvantages of 

18F-fluoromisonidazole, with lower lipophilicity and easier 
radiosynthesis. In this study, they looked at radiation dosage, 
biodistribution, human safety, tolerability, and early elimina-
tion of 18F activity in urine after injection of a single dose of 

18F-DiFA in healthy volunteers. No adverse effects were 
found to be associated with tracer injection, and the tracer 
was rapidly excreted from all organs, with an effective dose 
that was within the range of other common 18F PET tracers. 

Figure 4 (top) shows biodistribution over a 1-h period after a 

717.8 MBq injection, and Figure 4 (bottom) is a representa-
tive image of uptake at (left to right) 1, 2, 4, and 6 hours after injection. 18F-DiFA targets 
tumor hypoxia, with the potential to overcome some of the timing 
disadvantages of 18F-fluoromisonidazole, with lower lipophilicity and easier radiosynthesis.

Another “first application” study came from Lao et al. 
from the University of California Irvine, the University of 
Pittsburgh (PA), and the University of Wisconsin–Madison, 
who reported on “First-in-humans PET study: biodistribu-
tion, test–retest variability, and dosimetry of the α4β2* nic-
otinic acetylcholine receptor (nAChRs).” 18F-nifene uptake in the human brain was 
found to correspond closely with known α4β2* nAChR distributions, and test–retest variability was consistent with other neuro-
receptor radioligands. Images show that the distribution volume 
ratio in the cerebellum was similar to that in the cortex.

Luo et al. from Peking Union Medical College Hospital 
(Beijing, China) reported that “68Ga-exendin-4 PET/CT is 
both sensitive and specific in diagnosing insulinomas” 
[237]. In previous investigations, this group showed that 
glucagon-like peptide-1 receptor imaging with this agent 
can be used effectively for identification of insulinomas. 
In this study, 164 patients with hyperinsulinism were im-
aged with 68Ga-exendin-4 PET/CT, contrast-enhanced CT 
with perfusion, MR, endoscopic ultrasound, and somato-
statin scintigraphy. 68Ga-exendin-4 PET/CT was positive for
insulinoma in 110 of those patients, with 101 confirmed at surgery (the remaining 9 underwent either nonsurgical ablation or biopsy of distant metastasis). PET/CT also identified multiple lesions in a significant subset of patients. The sensitivity, specificity, accuracy, and positive and negative predictive values for $^{68}$Ga-exendin-4 PET/CT in diagnosing insulinoma were 99.0%, 100%, 99.3%, 100%, and 98.3%, respectively. This is a welcome innovation—trying to locate these lesions with dynamic CT or MR is somewhat difficult. Figure 6 shows comparison imaging in 4 patients in whom CT, MR, endoscopic ultrasound, and somatostatin scintigraphy were negative but who were positive on $^{68}$Ga-exendin-4 PET/CT. The delineation is clear on PET/CT—this is nuclear medicine at its best. The authors concluded that this may be developed into an accurate screening test for insulinomas in patients with hypoglycemia.

Jiang et al. from the Mayo Clinic (Rochester, MN) reported on “Current Good Manufacturing Practice (cGMP) synthesis of sodium iodide symporter (NIS) probe $^{18}$F-tetrafluoroborate ($^{18}$F-TFB) and biodistribution in healthy male and female human subjects” [682]. $^{18}$F-TFB is an iodide analogue with potential for imaging of differentiated thyroid cancer and as an NIS gene reporter probe. The authors’ objectives were to develop an automated and cGMP-compatible method for synthesis of $^{18}$F-TFB and to evaluate safety and biodistribution in healthy volunteers. Automated cGMP synthesis of $^{18}$F-TFB via $^{18}$F-fluorination of BF$_3$ was successful, with radiochemical yields of 32% ± 2% and specific radioactivity of 2.2 ± 0.9 GBq/mmol. The injected tracer was well tolerated, with no adverse events. Biodistribution was consistent with that of radioiodide, supporting the potential for clinical application of $^{18}$F-TFB PET imaging of differentiated thyroid cancer and in NIS gene reporter studies. Figure 7 (top) shows coronal $^{18}$F-TFB PET/CT images (left, CT; middle, fused; right, PET) at 2.5 h after injection in a healthy woman. Activity in the salivary glands, thyroid, stomach, and bladder excretion are clearly visible—much as in a radioiodine scan. Figure 7 (bottom) shows the same series in a healthy man. If further development shows this tracer to be effective, one clear advantage will be the ability to perform the procedure efficiently in a single day with, of course, no possibility of stunning.

O’Donoghue et al. from Memorial Sloan Kettering Cancer Center (New York, NY) and MabVax Therapeutics (San Diego, CA) reported on “Biodistribution and radiation dose estimates for $^{89}$Zr-DFO-HuMab-5B1 (MVT-2163) in CA19-9–positive cancer: first-in-man results” [837]. More than 90% of pancreatic cancers are positive for the CA19-9 antibody. The investigators examined 12 patients with metastatic pancreatic cancer, each of whom received ~185 MBq of the tracer but different amounts of cold antibody (0, 17, or 47 mg). Patients underwent multiple full-body $^{89}$Zr-DFO-HuMab-5B1 PET acquisitions as well
as serum analysis and whole-body counts acquired using a NaI(Tl) scintillation detector during 7 days after injection. Image- and count-derived residence times were used with OLINDA/EXM to estimate normal tissue radiation doses. Clearance rates averaged around 218 hours for the whole body. Cohort comparisons showed that increasing antibody mass dose and increasing time between cold and hot administrations tended to reduce liver and spleen uptake. Figure 8 shows biodistribution in a patient over 141 hours. It is important to note the theranostic potential of agents such as this. It is very likely that this agent could be labeled with $^{177}$Lu (in fact, groups are already working on this) or other therapeutic agents. Theranostic applications offer extraordinary promise for new horizons in nuclear medicine, taking us beyond diagnosis and monitoring.