2019 SNMMI Highlights Lecture: Neurosciences

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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 2019 Highlights Lectures were delivered on June 25 at the SNMMI Annual Meeting in Anaheim, CA. In this issue we feature the lecture by Henryk Barthel, MD, PhD, a professor in the Klinik und Poliklinik für Nuklearmedizin at the University of Leipzig (Germany), who spoke on neuroscience highlights from the meeting. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2019;60[suppl 1]).*

Excitement continued at the 2019 SNMMI Annual Meeting about progress made over the last year in the various areas of neuroscience. We have seen important therapeutic advances in areas in which molecular brain imaging has not yet played a leading role, as well as significant progress in diagnostic strategies to track, for example, neurodegenerative disorders. These advances motivate our nuclear neuroscience community to sustain and elevate the quality and speed of our research. As one example from this year, we now (thanks to the Imaging for Dementia—Evidence for Amyloid Scanning [IDEAS] study) have high-level evidence for the significant impact of amyloid imaging on clinical management. This evidence represents an important step toward broader utilization of amyloid imaging for the benefit of our patients. The motivation and enthusiasm of our neuroscience community is reflected again this year by the large number of high-quality contributions on amyloid imaging and related topics in neurodegeneration.

All areas of nuclear neuroscience presented at this year's SNMMI meeting offered fascinating data that could be considered highlights. High-quality presentations—either as talks or posters—were given by leading brain imaging scientists. Once again, these neuroscience presentations have been truly international. Even more than in previous years, these studies have been significantly shaped by a high number of younger scientists, a fact that is wonderful and provides assurances that the future of our field is bright. Before we start, I must present my apologies to all those authors whose outstanding research I am unable to review in this lecture because of time constraints.

Brain Imaging Council Kuhl–Lassen Award

This year's prestigious Brain Imaging Council Kuhl–Lassen Award was presented to Alexander Drzezga, MD, from the University of Cologne (Germany). His intriguing lecture, titled "Neurodegeneration illuminated," summarized the great progress made in improving our understanding of the pathophysiology and pathobiochemistry of neurodegenerative disorders. By employing multimodality brain imaging, for example with ^{18}F-FDG and amyloid and tau tracers and also with functional MR imaging, he and his research teams have made significant contributions to progress in the field. Dr. Drzezga is a deserving and accomplished recipient of this award, rightly joining the ranks of distinguished heroes who have received this honor in the past. He and his team remain extremely productive, as will be shown later in these highlights.

Henryk Barthel, MD, PhD

Novel Brain PET Imaging Probes

The development of novel probes for molecular imaging of brain processes and the translation of these probes from bench to bedside constitute a central effort in advancing our field. One example came from Naganawa et al. from Yale University (New Haven, CT), who reported on "Evaluation of ^{18}F-LY2459989 for imaging the kappa opioid receptor in humans" [577]. These receptors are a relevant target for PET imaging and potential therapeutic approaches in a number of different neuropsychiatric conditions. The study, conducted in healthy humans, showed that ^{18}F labeling of the compound the researchers had previously explored using an ^{11}C label resulted in favorable (and in some areas superior) kinetics and binding characteristics for PET imaging and quantification of kappa opioid receptors (Fig. 1). These data support not only wider availability of this tracer but suggest that improved imaging of kappa opioid receptors can be expected in the future.

Multiple sclerosis (MS) is a devastating brain disorder in which B cells or B lymphocytes tend to accumulate, with a negative impact caused, in part, by the production of proinflammatory cytokines. B cells have been recognized as an interesting experimental treatment target in MS, but investigators have found selective imaging of such cells in vivo to be challenging. Stevens et al. from Stanford University (CA) reported on "Radiolabeling and preclinical evaluation of a first-in-class CD19 PET tracer for imaging B cells in multiple sclerosis" [129]. This group used ^{64}Cu to label an antibody against the B cell surface antigen CD19. The tracer was then used for PET/CT imaging in a mouse model of experimental autoimmune encephalitis (EAE) and in control mice. Subsequent analysis of brain tissue from the 2 groups determined whether the load and location of pathogenic B cells

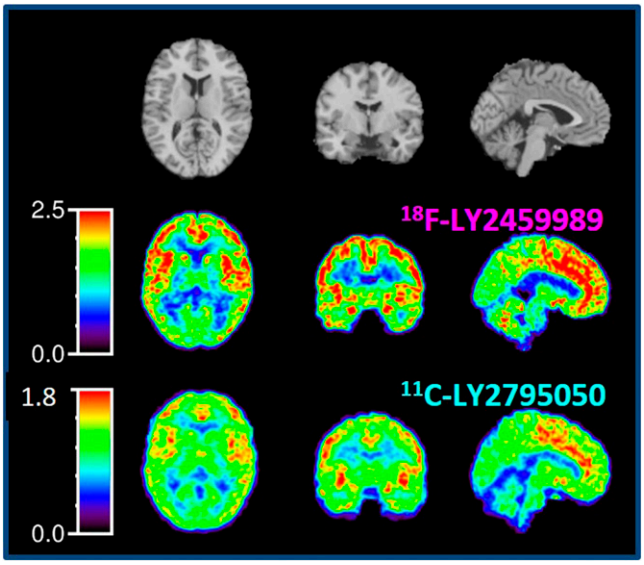

FIGURE 1. ^{18}F-LY2459989 imaging of the kappa opioid receptor in humans (middle row) compared with ^{11}C-LY2459989 PET imaging (bottom row). Comparison MR images in the same healthy subject are shown in the top row. The ^{18}F-labeled tracer showed favorable kinetic and binding characteristics, making it suitable for PET imaging and quantification of kappa opioid receptors in the human brain.

corresponded with uptake on imaging findings. PET image analysis (Fig. 2) showed significantly increased tracer uptake in the brains of EAE mice, which was confirmed by histopathology. Ex vivo spinal cord gamma counting indicated significantly higher tracer uptake in both cervical/thoracic and lumbar spinal cords of EAE mice compared to controls. Ex vivo autoradiography of brain sections showed regionally specific tracer accumulation in the cerebellum of EAE mice but not controls. The authors concluded that this novel tracer has excellent potential to guide and monitor anti–B cell therapies in MS. MS is a good example of an area in which we should work to identify novel applications of molecular imaging that will improve early diagnosis and longitudinal assessment. The current standard techniques (MR imaging approaches) have significant limitations in this regard.

Nuclear imaging of general neuroinflammation has thus far focused mainly on so-called translocator protein (TSPO) tracers binding to activated microglia. Increasing interest and research are looking at alternative imaging probes that target other components of the neuroinflammatory process. One alternative solution is the enzyme cyclooxygenase-1 (COX-1), which has (among other activities) proinflammatory properties. Kim et al. from the National Institute of Mental Health (Bethesda, MD) reported at this meeting on a "First-in-human evaluation of ^{11}C-PS13 for imaging COX-1 in brain and peripheral organs" [321]. The study, in 28 healthy humans, looked at whole-body in vivo selectivity of COX-1 compared to COX-2 and at test–retest reproducibility of the COX-1 tracer (Fig. 3). In addition to documenting important extracerebral observations, the authors were able to model brain tracer kinetics and offer interesting information on local tracer retention. The tracer was found to have maximal retention in occipital and hippocampal areas, and general brain distribution reflected the distribution of *PTGS1*, the gene coding COX-1. These data provide initial evidence for ^{11}C-PS13 as a promising tracer of COX-1 and a probe for assessing neuroinflammation in brain disorders, in addition to opening potential avenues for target engagement by therapeutic drugs.

High-quality research on another exciting novel PET tracer, this time to image potassium channels, was presented by Neelamegam et al. from the Massachusetts General

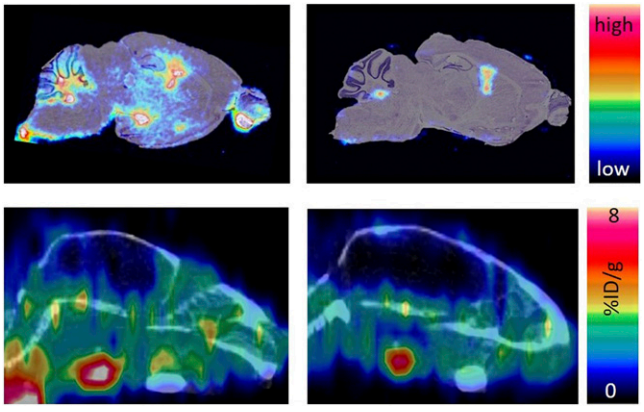

FIGURE 2. First-in-class CD19 PET tracer for imaging B cells in multiple sclerosis. A ^{64}Cu-labeled antibody against the B cell surface antigen CD19 was used for PET/CT imaging (acquired 19 h after injection) in a mouse model of experimental autoimmune encephalitis (EAE, left column) and in control (naïve, right column) mice. PET image analysis (bottom row) showed significantly increased tracer uptake in the brains of EAE mice, which was confirmed by autoradiography (top row) and histopathology. The tracer has potential to guide and monitor anti–B cell therapies in multiple sclerosis.

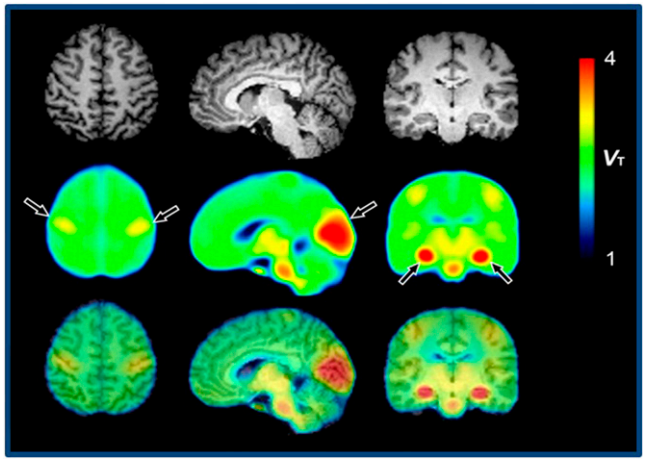

FIGURE 3. ^{11}C-PS13 for imaging COX-1 in brain and peripheral organs. Representative ^{11}C-PS13 brain PET images (middle row) in a healthy subject. High uptake was seen in the bilateral hippocampus and occipital cortices as well as bilateral pericentral cortices. Top row: MR images. Bottom row: fusion images. These data provide initial evidence for ^{11}C-PS13 as a tracer of COX-1, as a probe for assessing neuroinflammation, and as an agent to determine target engagement by therapeutic drugs.

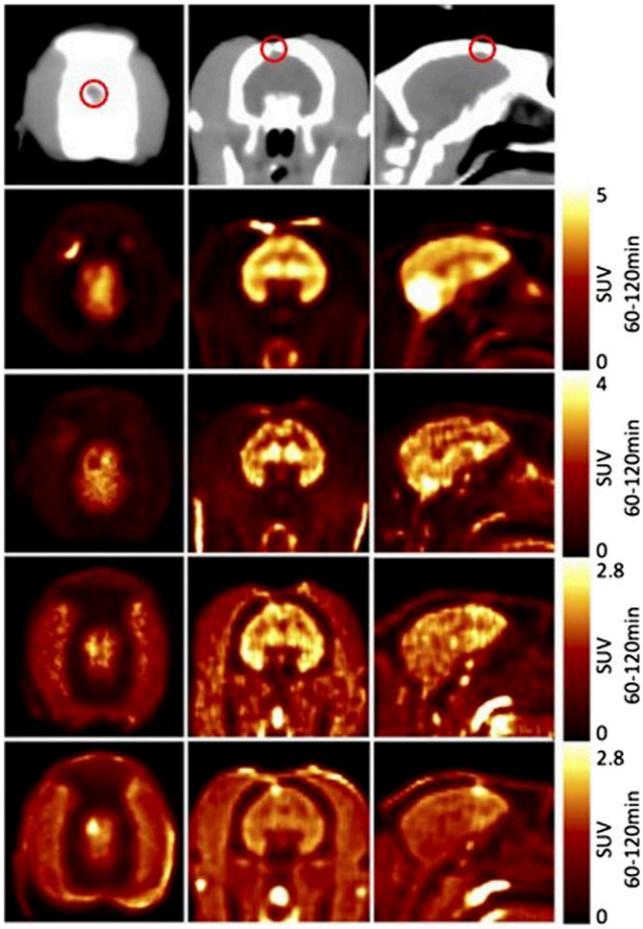

FIGURE 4. ^{11}C-labeled tracer for K^+ channels in the brain in nonhuman primates after experimental traumatic brain injury (TBI). Rows top to bottom: CT (red circles indicate TBI sites), ^{18}F-FDG, ^{11}C-PBR28, ^{11}C-3MeO4AP, and ^{13}F-3F4AP. The investigational agent, ^{11}C-3MeO4AP, showed increased accumulation, similar to that of ^{13}F-3F4AP, in the region of trauma, with potential future clinical advantages of reduced radiation exposure and the ability to perform longitudinal PET imaging of demyelinating lesions in the brain.

Hospital/Harvard Medical School (Boston, MA) and the Universidad de Guadalajara (Tlaquepaque, Mexico) in "Novel ^{11}C-labeled tracer for K^+ channels in the brain: Synthesis and imaging in nonhuman primates" [486]. In MS, demyelination causes axonal K^+ channels to become exposed and increase in expression, which hampers conduction of electrical impulses. Blocking these structures is an established therapeutic approach in multiple sclerosis. Based on previous work on an ^{18}F-labeled aminopyrine compound, these researchers successfully synthesized and tested an ^{11}C-labeled version in rhesus monkeys after experimental brain injury. Similarly increased tracer accumulation was observed for both the ^{11}C- and ^{18}F-labeled agents in the region of trauma (Fig. 4). After this evidence of equivalence between the 2 tracers, the authors will explore the advantages of the ^{11}C-labeled agent, including reduced radiation exposure and the ability to perform multiple studies on the same patient on the same day. Translation into humans may allow longitudinal PET imaging of demyelinating lesions in the brain.

The ^{11}C-labeled synaptic vesicle glycoprotein 2A tracer UCB-J was highlighted last year as a promising PET agent to visualize and quantify synaptic density in the brain. This year, Li et al. from Yale University (New Haven, CT) reported on an ^{18}F-labeled alternative in "First-in-human evaluation of ^{18}F-SDM-8, a novel radiotracer for PET imaging of synaptic vesicle glycoprotein 2A" [49]. This tracer provided high-quality images (Fig. 5) that correlated well with our knowledge about synapse distribution throughout the brain and showed fast and very high brain uptake, appropriate tissue kinetics, and nondisplaceable binding potentials that were higher than those for the ^{11}C-labeled compound. This is a major achievement, because the availability of a synaptic density tracer with longer half-life allows not only simplified PET procedures but may also lead to multicenter clinical trials to monitor the efficacy of new drugs targeted at synaptic rescue and recovery. This, in turn, could lead to broader availability of the tracer. I am curious to see more research identifying the most promising applications of synaptic density imaging, with epilepsy and neurodegeneration certainly among the top candidates. For this excellent research, Dr. Li was recognized with the second-place Young Investigator Award from the Brain Imaging Council.

Dr. Li's contribution is only 1 example of the already mentioned observation that younger researchers at this year's SNMMI meeting provided an extraordinarily high number of high-quality contributions in neuroscience. One

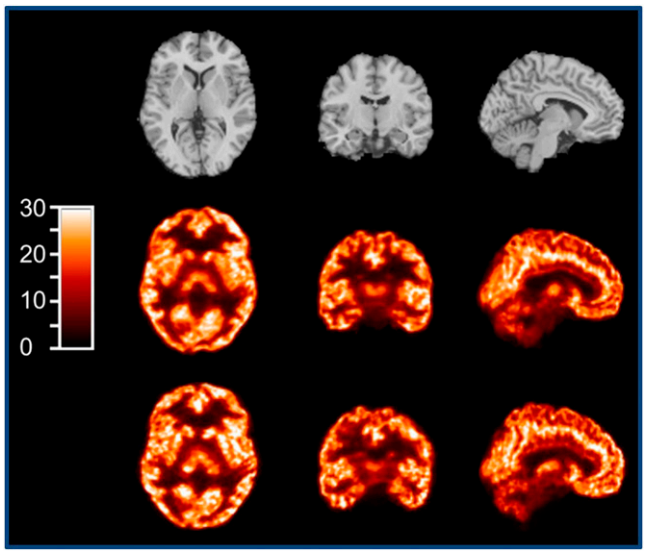

FIGURE 5. ^{18}F-SDM-8 PET imaging of synaptic vesicle glycoprotein 2A in humans. Top: comparative MR images. Middle: ^{18}F-SDM-8 PET. Bottom: ^{11}C-UCB-J PET. The ^{18}F-labeled tracer provided high-quality images, fast and high brain uptake, appropriate tissue synapse distribution throughout the brain, and nondisplaceable binding potentials that were higher than those for the ^{11}C-labeled compound. The availability of a synaptic density tracer with longer half-life allows not only simplified PET procedures but may also lead to multicenter clinical trials to monitor the efficacy of new drugs targeted at synaptic rescue and recovery.

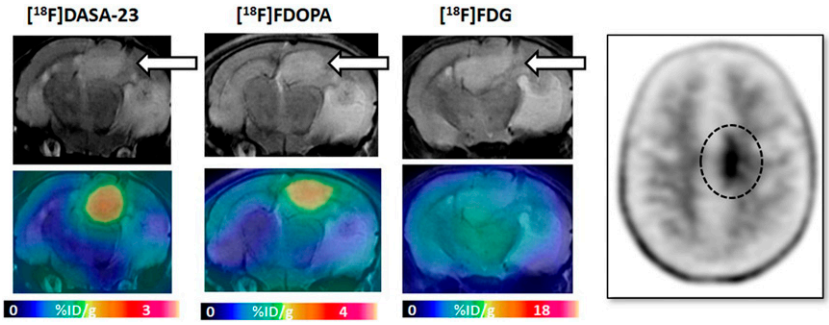

FIGURE 6. ^{18}F-DASA-23 for noninvasive measurement of aberrantly expressed pyruvate kinase M2 in glioblastoma. Left block of images: Representative 10–30-minute summed images showing ^{18}F-DASA-23 uptake (left column) were compared with ^{18}F-FDOPA (middle column) and ^{18}F-FDG (right column) in mice bearing orthotopic U87 human glioblastoma xenografts (tumors, white arrows). Right: PET imaging with^{18}F-DASA-23 in a human glioblastoma (circled).

key piece of advice for scientific creativity and productivity for junior investigators was given by Henry Wagner, Jr, MD, in his memoirs: "Do not think as you are told, and do not do as others do according to the rules." Dr. Wagner, with his wisdom and humor, had an outstanding ability to inspire younger colleagues. Like so many others in the field, I miss him. The quality of his highlight lectures, summarizing all aspects of the annual meeting in a single talk, may never again be achieved. He would be pleased to see so many young scientists advancing the nuclear neuroscience field at the moment—this helps to keep us and the entire SNMMI young and enthusiastic.

Beinat et al. from Stanford University/Stanford University School of Medicine (CA) addressed the need for more specific brain tumor imaging tracers in their presentation "Evaluation of ^{18}F-DASA-23 for noninvasive measurement of aberrantly expressed pyruvate kinase M2 in glioblastoma: Preclinical and first-in-human studies" [52]. They developed this novel tracer to bind to pyruvate kinase M2, an important enzyme of glycolysis and a target that is highly expressed in glial tumors. Imaging and quantification of ^{18}F-DASA-23 uptake were compared with ^{18}F-FDOPA and ^{18}F-FDG in a human glioblastoma xenograft mouse model, The results showed that the new tracer had the highest image contrast (Fig. 6). Promising first-in-human data were also provided. Ongoing federally funded studies are now evaluating the utility of this agent in patients with intracranial malignancies. I look forward to the results of this clinical evaluation and to the presentation of results at a future SNMMI meeting. For this promising research, Dr. Beinat achieved third place in the Brain Imaging Council Young Investigator Award competition.

Brain Imaging Instrumentation and Data Analysis

Much like the development of new brain imaging probes, novel imaging technologies and innovative data analysis approaches are key drivers in moving our field forward. Many exciting innovations in this area were presented at this annual meeting; because of time constraints I can highlight only 2. The first is the successful design and preclinical testing of a novel helmet-type brain PET system. Akamatsu et al. from ATOX Co., Ltd. (Tokyo, Japan) and the National Institute of Radiological Sciences (Chiba, Japan) reported on a "NEMA NU2-like performance evaluation of a helmet-type brain time-of-flight PET prototype" [192]. Their original goals were to develop a dedicated brain PET camera that would be compact and less expensive without compromising high sensitivity and spatial resolution. The group had previously reported on the design, a combination of a hemispherical and cylindrical array of detectors with an optimized surface area. In this performance evaluation, the prototype was able to deliver phantom data with spatial resolution, sensitivity, and count rate characteristics that were improved with time-of-flight information and were quite similar to those of a standard PET system. It will be exciting to see further progress with this PET system in imaging in humans. These phantom data suggest promising diagnostic capabilities and unprecedented economies in cost and space for standard clinical brain PET procedures.

Artificial intelligence or deep learning was much in evidence at this year's meeting. Zhao et al. from Fudan

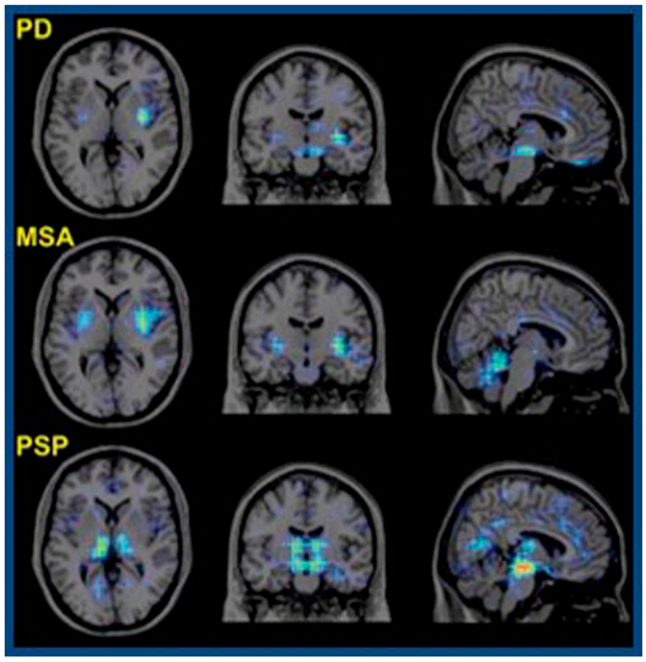

FIGURE 7. 3D deep residual convolutional neural network for differential diagnosis of parkinsonian syndromes with ^{18}F-FDG PET. Images are ^{18}F-FDG PET–derived implicit attention saliency maps during artificial intelligence decision making. Top: idiopathic Parkinson disease; middle: multiple system atrophy; bottom: progressive supranuclear palsy. This work represents an example of the ways in which artificial intelligence may support brain image pattern recognition in the future.

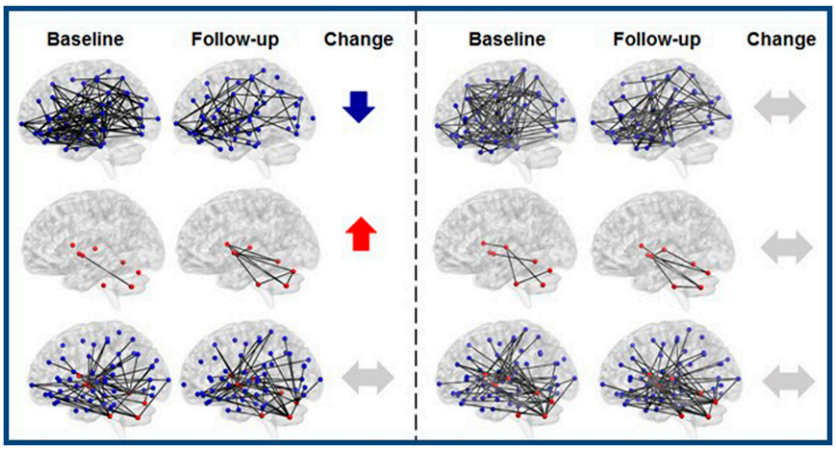

FIGURE 8. ^{18}F-FEOBV PET and longitudinal changes in brain cholinergic connectome in Parkinson disease. The authors asked how cholinergic connections change within the basal forebrain and brainstem subsystems over time and whether these changes are interrelated. ^{18}F-FEOBV vesicular acetylcholine transporter PET images were acquired at a 2-y interval in individuals with Parkinson disease. A decrease in cholinergic connectivity was observed only within the basal forebrain subsystem of the clinically most affected hemisphere, with an increase only in the brainstem subsystem, again in the clinically most affected hemisphere. Left block, most affected hemisphere at baseline and follow-up and, right block, least affected hemisphere at baseline and follow-up, within the basal forebrain subsystem (top row) and the brainstem system (middle row) and for the overall interactions between hemispheres (bottom row). Spheres represent nodes (brain regions) of cholinergic pathways.

University (Shanghai, China), the Technische Universität München (Germany) the University of California Los Angeles, and the University of Bern (Switzerland) reported on "A 3D deep residual convolutional neural network for differential diagnosis of parkinsonian syndromes on ^{18}F-FDG PET images" [418]. The researchers trained their network to automatically analyze and differentiate brain ^{18}F-FDG PET data in 920 patients with parkinsonian syndrome (idiopathic Parkinson disease, 502; multiple system atrophy, 239; and progressive supranuclear palsy, 179). The technique showed convincing accuracies in discrimination among the 3 groups in expected regions of the basal ganglia and also in the visual cortex and prefrontal cortex. The method is currently being investigated in a separate group of several hundred parkinsonian patients, with emphasis on interpretation of resulting saliency maps in diagnosis (Fig. 7). This work represents only 1 example of the ways in which artificial intelligence may support brain image pattern recognition in the future. The results of such approaches in controlled prospective clinical trials will be interesting and informative.

Basic Science Brain Imaging

Molecular brain imaging and advanced computer algorithms can combine to help improve our understanding of basic brain processes, and I will present 2 excellent examples from the meeting. The first was a presentation by Sanchez-Catasus et al. from the University of Michigan (Ann Arbor) on "Longitudinal changes in brain ^{18}F-FEOBV cholinergic PET connectome in Parkinson disease" [322]. The ability to quantify such changes could assist in better understanding disease progression in neurodegenerative disease. To assess changes, the researchers used a model based on the inverse covariance

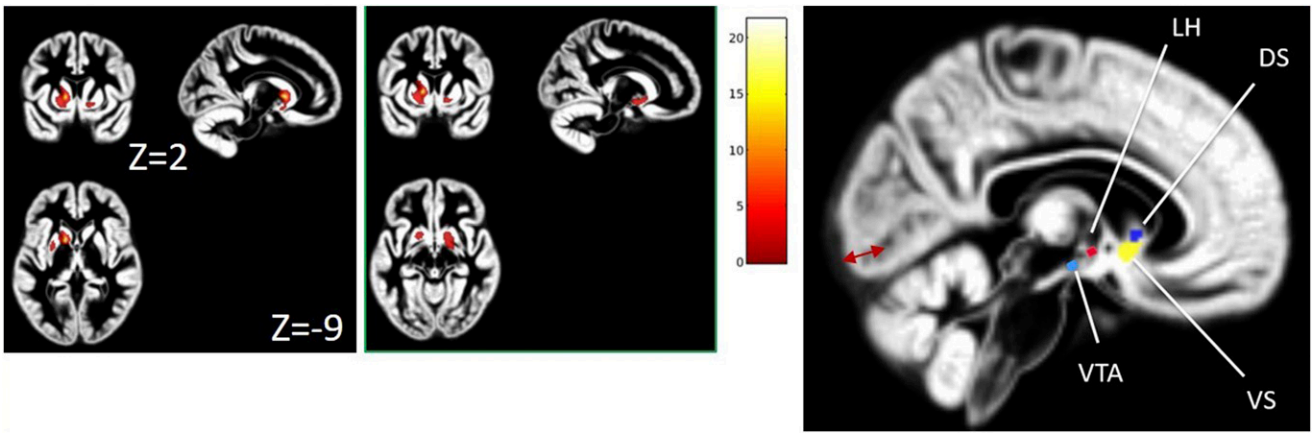

FIGURE 9. ^{11}C-raclopride displacement and altered functional connectivity after intranasal application of insulin in humans. A correlation was found between change in ^{11}C-raclopride binding as a surrogate of synaptic dopamine levels via insulin in the ventral striatum and the change of functional connectivity by insulin between this brain region and the ventral tegmental area, another brain region known to mediate food intake signaling. This is the first study in humans showing that central insulin action modulates dopaminergic activity and functional connectivity in the striatum. Left: T maps derived from hybrid PET/MR imaging showed that insulin induced an increase in ^{11}C-raclopride binding potential. Right: Resting-state functional MR imaging showed that insulin induced increased correlation between ventral striatum (VA) and the ventral tegmentum area (VTA).

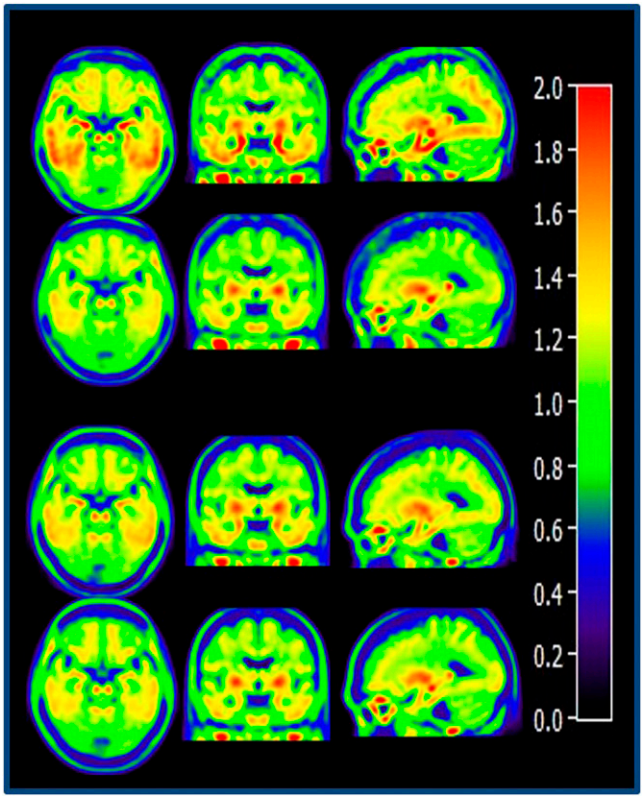

FIGURE 10. Tau ^{18}F-AV-1451 PET and sex-based modulation of the apolipoprotein E (APOE) ε4 effect in mild cognitive impairment (MCI). The study included both cognitively normal elderly controls and individuals with MCI. Analysis included preprocessed ^{18}F-AV-1451 PET images, T1-weighted structural MR scans, and demographic information. Mean images here show women (top block of 6) and men (bottom block of 6) who were ApoE ε4 carriers (top row in each block) and noncarriers (bottom row in each block). The results suggest that female ApoE ε4 carriers are more susceptible than males to tau accumulation in preclinical Alzheimer disease.

estimation method applied to ^{18}F-FEOBV vesicular acetylcholine transporter PET images acquired at a 2-y interval in 46 individuals with Parkinson disease (Fig. 8). They found that a decrease in cholinergic connectivity was observed only within the basal forebrain subsystem of the clinically most affected hemisphere, with an increase only in the brainstem subsystem, again in the clinically most affected hemisphere. In addition to new insights about changes in the brain cholinergic pathways in Parkinson disease, the results also showed the central hub function of the cholinergic striatum, especially the globus pallidus, and brainstem in whole-brain cholinergic covariation patterns. The authors called for additional research on the symptomatic sequelae and potential clinical applications of their findings. These are important data, because they show that it is possible to use MR and metabolic PET data not only for analysis of brain connectivity phenomena as we know them but to extend this connectome analysis approach to neurotransmitter processes.

Another good example on the ways in which brain imaging can support basic brain science came from Blum et al. from the Eberhard Karls Universität Tübingen (Germany), who reported on "^{11}C-raclopride-displacement and altered functional connectivity after intranasal application of insulin in humans. A PET/MRI study" [390]. These researchers were interested in investigating the effect of insulin on the dopaminergic system and its interplay with functional brain connectivity. A clear elucidation of these effects would provide a significant and so far missing piece of the puzzle to understand obesity and other eating disorders. They identified a correlation between the change in ^{11}C-raclopride binding as a surrogate of synaptic dopamine levels via insulin in the ventral striatum and the change of functional connectivity by insulin between this brain region and the ventral tegmental area, another brain region known to mediate food intake signaling (Fig. 9). This is the first study in humans showing that central insulin action modulates dopaminergic activity and functional connectivity in the striatum. This approach may illuminate understanding of the role of central insulin action in obesity. In general, hybrid PET/MR imaging, with its unique capability to acquire multiple data points at the same time, is considered by many to be the optimal tool for our neuroscience work. This study by Blum et al., for example,

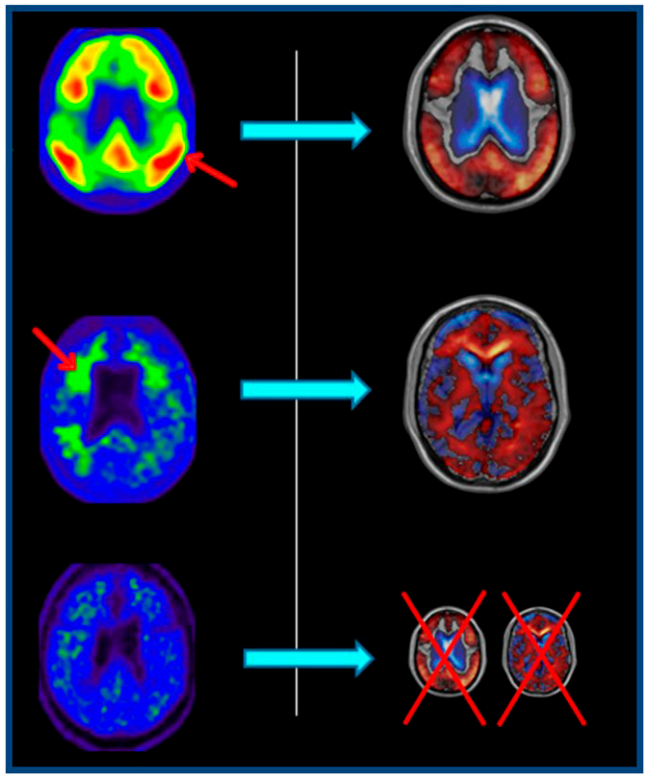

FIGURE 11. ^{18}F-AV-1451 tau PET pattern and prediction of amyloid positivity in neurodegenerative diseases. The researchers found that it was possible to predict amyloid states with high accuracy based solely on tau accumulation patterns. Images are shown in individuals with amyloid-positive tauopathy (Alzheimer disease) (top row, with gray matter–dominant tau pattern); with amyloid-negative tauopathy (frontotemporal dementia) (middle row, with white matter–dominant tau pattern); and in healthy controls (no tau pattern) (bottom row).

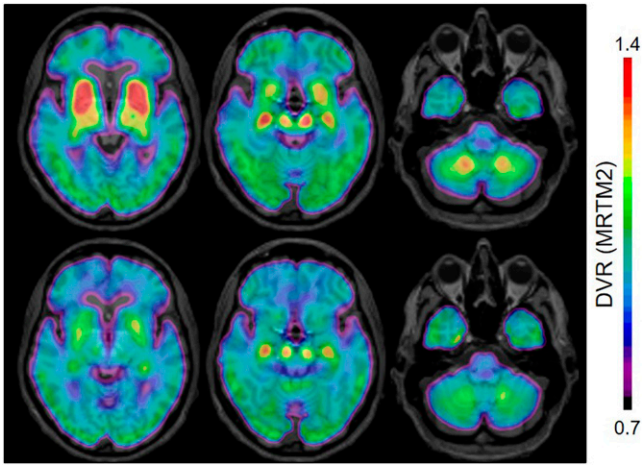

FIGURE 12. ^{18}F-PI2620 tau PET in progressive supranuclear palsy (PSP). ^{18}F-PI2620 was shown to bind, in a blockable manner, to PSP tau brain tissue postmortem as well as to identical brain regions in vivo (top row) and to a significantly higher degree than in healthy controls (bottom row).

would not have been easily possible with sequential PET and MR imaging. It is impressive to observe the constantly increasing numbers of brain research contributions at SNMMI meetings that make use of hybrid PET/MR technology.

Clinical Brain Imaging

The area of clinical brain imaging was again dominated at this meeting by the use of PET tracers to image amyloid and tau pathologies in dementia and other brain disorders. Our increasing ability to visualize and quantify histopathologic changes in the living brain and, consequently, to shift the time point of accurate diagnosis from post- to antemortem (and even to early prodromal or asymptomatic disease stages) in an increasing number of neurodegenerative disorders is a central accomplishment of the last decade of nuclear brain imaging. One impressive example of the clinical use of amyloid imaging for prediction of Alzheimer dementia (AD) was provided by Blazhenets et al. from the University of Freiburg (Germany), who reported on "Predictive value of quantitative ^{18}F-florbetapir and ^{18}F-FDG PET for conversion from mild cognitive impairment [MCI] to AD" [249]. Voxel-based principal component analysis was applied to data from 319 individuals with MCI from 2 large Alzheimer's Disease Neuroimaging Initiative (ADNI) datasets. Researchers convincingly showed that progression toward AD was best predicted by a combination of nonimaging factors and ^{18}F-FDG and amyloid PET data. Hypometabolism, Aβ burden, and clinical variables were found to represent complementary predictors of conversion from MCI to AD. This and similar prediction models hold promise for guiding individual prevention or treatment strategies and decision making.

The application of novel tau PET tracers to clinical questions was, as last year, a hot topic for neuroscience at the SNMMI meeting. Paranjpe et al., from the Icahn School of Medicine at Mount Sinai (New York, NY), Johns Hopkins Medicine (Baltimore, MD), the Mallinckrodt Institute of Radiology (St. Louis, MO), Peking University First Hospital (Beijing, China), and the University of California at San Francisco, reported that "Sex modulates the apolipoprotein E [APOE] ε4 effect on tau ^{18}F-AV-1451 PET imaging in individuals with normal aging and MCI" [253]. The study included data from 131 cognitively normal elderly controls (66 women, 65 men; mean age, 77.56 ± 6.91 y) and 97 individuals (39 women, 58 men; mean age 77.97 ± 7.24 y) with MCI from the ADNI database. Analysis included the preprocessed ^{18}F-AV-1451 PET images, T1-weighted structural MR scans, and demographic information. The researchers found female carriers of the AD risk factor ApoE4 exhibited higher tau loads in the entorhinal cortex and posterior cingulate than ApoE4 noncarriers, a feature not found in male participants (Fig. 10). These data offer a potential explanation for epidemiologic evidence demonstrating an increased penetrance of the ApoE4 allele in females. The authors suggested that female ApoE ε4 carriers are more susceptible to tau accumulation in preclinical AD than are males.

Hammes and colleagues from the University Hospital of Cologne (Germany), including this year's Kuhl–Lassen-Award recipient, Alexander Drzezga, MD, employed the same ^{18}F-AV-1451 tau PET tracer together with an amyloid PET tracer in patients with amyloid-associated AD and non-amyloid-associated frontotemporal lobar degeneration. They reported this as "One-stop shop: Flortaucipir PET pattern predicts amyloid positivity in neurodegenerative diseases" [255]. They found that it was possible to predict amyloid states in these patients with high accuracy based solely on tau accumulation patterns, specifically by identifying whether the tau tracer bound predominantly to cortical or white matter areas (Fig. 11). The authors concluded that "Together with a perfusion-weighted early-phase acquisition, flortaucipir PET alone as a 1-stop shop examination may convey equivalent information to additional amyloid and ^{18}F-FDG PET to characterize the form of neurodegenerative dementia." These very promising results should encourage a broader view of the potential applications of tau PET evaluation.

Brendel et al. from the Ludwig Maximilian University in Munich (Germany) and a consortium of researchers from academia and industry in Germany and the United States reported on "^{18}F-PI2620 tau PET in progressive supranuclear palsy [PSP]: A multicenter evaluation." ^{18}F-PI2620 is a second-generation tau PET tracer. The first-generation tracers have only limited or no ability to target 4-repeat tauopathies such as those associated with PSP. ^{18}F-PI2620 was shown in this study to bind, in a blockable manner, to PSP tau brain tissue postmortem as well as to identical brain regions in vivo to a significantly higher degree than in healthy controls (Fig. 12). These results should motivate us to employ the tracer for assessing longitudinal disease progression as well as for drug testing. For this work, Dr. Brendel won first place in the Brain Imaging Council Young Investigator Awards.

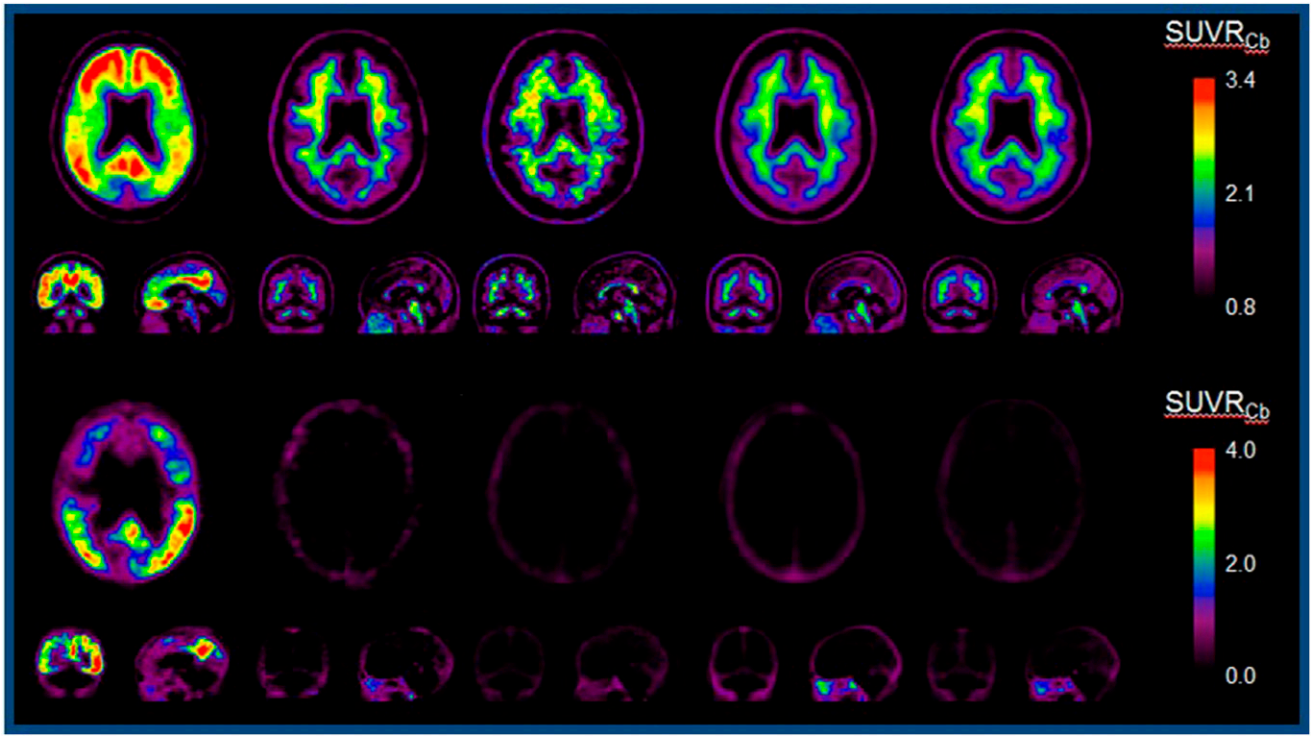

FIGURE 13. Tau imaging with ^{18}F-MK6240 in Alzheimer disease (AD) and traumatic brain injury (TBI). Top 2 rows: Amyloid-β (Aβ) imaging in (left to right): Aβ-positive (AD) patients, Aβ-negative healthy controls, individuals after repetitive sports–caused TBIs, after motor vehicle accident–caused TBIs, and after TBIs sustained in military service. TBIs had been sustained decades before the study. The results indicate that nonchronic brain trauma does not appear to lead to long-term tau accumulation in the brain (bottom 2 rows), excluding such patients from related therapeutic approaches.

Another promising second-generation tau PET tracer, the ^{18}F-MK6240 compound, was employed together with amyloid PET by Rowe et al. from the University of Melbourne, Austin Health (Heidelberg and Melbourne), the Commonwealth Scientific and Industrial Research Organisation (Brisbane and Heidelberg), the Florey Institute (Melbourne), and Monash University (Melbourne; all in Australia). The group reported on "Tau imaging with ^{18}F-MK6240 in AD and traumatic brain imaging" [256]. The study included 128 participants: 70 healthy elderly controls, 8 patients with MCI (4 of whom were amyloid-β positive), 10 with AD (all amyloid-β positive), 4 other dementias (1 of whom was amyloid-β positive), and 36 nondemented individuals (5 amyloid-β positive) who had sustained a traumatic brain injury as a result of a single event decades earlier or as a result of repetitive sports injuries. ^{18}F-MK6240 PET discriminated well between individuals with AD and healthy controls. It was convincingly shown on these tau PET images (Fig. 13) and via tracer uptake quantification in mesial temporal areas that nonchronic brain trauma does not appear to lead to long-term tau accumulation in the brain, excluding such patients from related therapeutic approaches.

Conclusion

The path we are following while doing our nuclear brain research is often not entirely straight. Instead, it is winding and sometimes even blocked for certain periods. But all the great achievements we observed over the last days here in Anaheim in the fields of novel brain imaging tracers, new brain imaging and data analysis technology, basic brain science, and clinical neuropsychiatry imaging can help to guide us toward the future on our mission to move the nuclear neuroscience field forward. The final goal, of course, remains better approaches in diagnosis and treatment of our patients.

I would like to close with an optimistic view of the future from German Chancellor Angela Merkel during a recent visit to the United States. She said "...if we break down the walls that hem us in, if we step out into the open and have the courage to embrace new beginnings, everything is possible." Science is a relevant component of our societies. We as scientists should not hesitate to step forward to defend personal and academic freedom whenever necessary. This is increasingly important in many parts of our world today. By doing so and by motivating our young scientists to follow this example, everything indeed may be possible, with extraordinary potential for the future of our entire field of nuclear medicine.

Bill Targets Expanded Access to Diagnostic Radiopharmaceuticals

On July 16, Representatives Scott Peters (D-CA), Bobby Rush (D-IL), and George Holding (R-NC), introduced the bipartisan Medicare Diagnostic Radiopharmaceutical Payment Equity Act of 2019 (HR 3772) in the U.S. House of Representatives. The bill would expand patient access to highly targeted precision diagnostic radiopharmaceuticals that evaluate conditions such as Alzheimer disease, Parkinson disease, and some cancers. The bill is intended to ensure that patients have faster and more reliable access to optimal treatments and calls for all diagnostic radiopharmaceuticals that reach a cost of >$500 per day to be paid separately in the Hospital Outpatient Prospective Payment System.

In 2008, the Centers for Medicare & Medicaid Services began treating diagnostic radiopharmaceuticals as supplies instead of drugs, bundling or "packaging" them with the cost of their associated procedures in hospital outpatient settings. This decision created a reimbursement structure that limited patient access to innovative diagnostic tools and, in many cases, discouraged the development and introduction of new agents. The new bill would ensure that hospitals receive adequate Medicare reimbursement to cover the high-value, low-volume diagnostic radiopharmaceuticals that are used in these nuclear medicine procedures, correcting a flawed payment philosophy and leaving hospitals free to perform the nuclear medicine procedures that patients need.

On the day after the introduction of the bill, SNMMI hosted a briefing on Capitol Hill with clinicians, patients, and industry representatives to discuss the importance of advocating for and passing the legislation. Speakers included Vasken Dilsizian, MD, SNMMI president; Josh Mailman, MBA, chair of the SNMMI Patient Advocacy Advisory Board and president of NorCal CarciNET Community; and Terri Wilson, senior director of patient access and health care policy at Blue Earth Diagnostics, Ltd. and chair of the Medical Imaging and Technology Alliance PET Group. Michael J. Guastella, MS, MBA, executive director of the Council on Radionuclides and Radiopharmaceuticals, Inc. opened the meeting and introduced the speakers. The full proceedings of the meeting are available at https://www.youtube.com/watch?v=EgvoSRRvKDo.

Dilsizian noted the challenges that rapidly evolving knowledge and innovative tracers face in the current restrictive environment. "Diagnostic radiopharmaceuticals are incredibly effective in the diagnosis of a number of different diseases, including prostate cancer, Alzheimer and Parkinson disease, and others," he said. "We've really only scratched the surface of potential with these technologies, and I expect we'll see future improvements in these diagnostic tools if policy is adjusted to better reflect patient need."

Standing: SNMMI President Vasken Dilsizian, MD; Senator Ben Cardin (D-MD); Sukhjeet Ahuja, MD, MS; Ira Goldman (Lantheus Medical Imaging); and, seated, Rosemary Cioti (Facing Our Risk of Cancer Empowered, Inc.) at the Capitol Hill meeting on HR 3772.

As a neuroendocrine tumor patient, Mailman offered a patient perspective on the benefits of radiopharmaceutical imaging. "Having advanced imaging available for neuroendocrine tumor patients is critical, as these advancements have helped clinicians determine the location and extent of disease so they can better plan appropriate therapy for improved patient outcomes," he said.

Wilson summarized the provisions of HR 3772 and described the ways in which it would eliminate specific restrictions now in place. "All patients should have access to the right tests as requested by their physicians to help provide the answers they need," she concluded.

After the congressional briefing, SNMMI members met with Representatives and staff in >40 congressional offices, asking for support for HR 3772. SNMMI also announced a letter writing campaign and asked patients and the nuclear medicine and molecular imaging community to participate. For more information, contact Dalton Clark, manager of government affairs for SNMMI (dclark@snmmi.org).

SNMMI

Fifth Anniversary of SNMMI Professional Relations Fellowship

Jack Slosky, PhD, MBA, JJS Consulting, retired from Lantheus Medical Imaging; and Katherine Zukotynski, MD, McMaster University, Hamilton, ON

A meeting marking the fifth anniversary of the SNMMI Professional Relations Fellowship (PRF) was held on June 22 at the SNMMI Annual Meeting in Anaheim, CA, with current and past fellows in attendance, along with SNMMI leadership, the original creators of the program, and others interested in advancing this unique leadership training initiative. Created in 2013, the SNMMI PRF honors the memory of Ursula Mary Kocemba-Slosky, PhD, a scientist who believed in the power of working together toward a common goal. Through the PRF, fellows experience at first hand the spectrum of interactions between the nuclear medicine community and stakeholders, in an effort to develop an understanding of professional relations and successfully navigate the increasingly complex health care environment. The PRF focuses on the ways in which the public face of nuclear medicine and molecular imaging can enhance the specialty, through interactions with professional organizations, such as medical societies, industry/trade partners, and patient advocacy groups. Synergy among all those working in the field is key to future development.

Since 2013, 5 fellows have completed the PRF: Alexandru Bageac, MD, MBA (2014), Philip Koo, MD (2015), Katherine Zukotynski, MD (2016), David Douglas, MD, MPH (2017), and Nicole Nardecchia, MBA, CNMT (2018). Each of the fellows gained different insights, depending on his or her fellowship experience and home practice settings. Dr. Bageac explored the impact of the Affordable Care Act on individual organizations and intersocietal relationships, noting that "new sources of revenue must be identified as physician association membership decreases, physician time becomes less available, and physician allegiances change" (*J Nucl Med.* 2015;56:9N). Dr. Koo wrote that "the experience facilitated a head start on several new initiatives. One involves creation of a more formal working relationship between SNMMI and the American Society of Clinical Oncology" (*J Nucl Med.* 2016;57:10N). In a letter of appreciation to the fellowship committee, Dr. Zukotynski wrote: "I believe the SNMMI, as an organization and through its members, has the potential to lead the way in patient care, teaching, and research. The path will be easier, however, if we have a vision that includes buy-in and support from other stakeholders in our community."

Dr. Douglas, having completed both the PRF and the SNMMI Government Relations Fellowship (Henkin Fellowship), noted: "Both fellowships allowed us to attend an SNMMI board meeting and visit Capitol Hill. The Government Relations Fellowship provided additional insight into governmental organizations, including the U.S. Food and Drug Administration, the National Institute of Biomedical Imaging and Bioengineering, the Centers for Medicare & Medicaid Services, and the Nuclear Regulatory Commission. The PRF provided additional insight into other professional societies like the American College of Radiology, industry organizations like the Council on Radionuclides and Radiopharmaceuticals, Inc., and patient advocacy groups. Given the different emphasis for each fellowship, I would encourage fellows who have completed one fellowship to apply for the other." Ms. Nardecchia, the first nuclear medicine technologist to be chosen as a PRF fellow, also found the experience rewarding and suggested that fellows be allowed to choose a specific project/topic that could be expanded even after the fellowship concludes.

At the anniversary reunion meeting in Anaheim, current and past fellows discussed the fellowship's goals and achievements. Participants in the discussion also included: Elizabeth Dibble, MD, the new PRF fellow for 2019; Theresa Pinkham, MPA, executive director of the Education and Research Foundation for Nuclear Medicine and Molecular Imaging (ERF); Frederic Fahey, ScD, who, in 2013, presented to the SNMMI Board of Directors a proposal for the PRF program; and Jack Slosky, PhD, MBA, who also proposed the SNMMI PRF in 2013 and subsequently endowed the program. The group identified several possible ways to enhance the value of the SNMMI PRF program:

- PRF fellows could create longer term projects that might extend beyond their fellowship service;
- A task force of interested PRF fellows (including former and current fellows) could be formed to develop recommendations for SNMMI leadership about additional ventures; and
- The Government Relations fellows and participants in the SNMMI Leadership Academy could be invited to join forces with the PRF fellows through such a task force, with the goal of assisting the SNMMI in developing new programs and services.

We wish to express thanks to Ms. Pinkham for the strong ERF support of the SNMMI PRF over the years, including support for the fifth anniversary reunion lunch meeting. Going forward and based on feedback from this meeting, we will convene a working group of PRF fellows, Government Relations fellows, and members of the Future Leaders Academy.

609NL-Slosky ■ 8/22/19

Focus on International Diversity and Inclusivity

Vasken Dilsizian, MD, SNMMI President

The field of nuclear medicine and molecular imaging crosses many boundaries: among branches of science such as physics, biology, and chemistry; among disease areas such as oncology, neurology, and cardiology; and among modalities, with fusion imaging. SNMMI mirrors that amalgamation, unique among nuclear medicine societies in its inclusion of all nuclear medicine professionals, including scientists, physicians, and technologists. The society also crosses international boundaries, working synergistically with the nuclear medicine global community to stimulate innovation and research.

Working with our nuclear medicine and molecular imaging peers around the world is both necessary and beneficial to the field. This involvement facilitates the critical exchange of ideas and sharing of cutting-edge research, practice standards, and other essential information. Sixty-three percent of SNMMI's Annual Meeting abstract submissions in 2019 came from outside the United States, representing 40–50 countries each year—and 30% of our Annual Meeting attendees travel from other countries to participate in the meeting itself.

Vasken Dilsizian, MD

For *The Journal of Nuclear Medicine* (*JNM*), 72% of all article submissions come from outside the United States, with more than one-third of those coming from Europe, 28% from Asia, and 4% from Oceania, South America, and Africa. To further expand critical knowledge and information sharing internationally, *JNM* offers free access to 64 developing countries.

International leaders in nuclear medicine gather each year at the SNMMI Annual Meeting to share information and updates about current and future work in the field. At this year's meeting, from left: Wim Oyen, MD, PhD; Henrik Silber; Sonja Niederkofler; Vasken Dilsizian, MD, and Richard Wahl, MD.

Collaboration with international nuclear medicine and molecular imaging organizations is key to achieving our goals. SNMMI and the International Atomic Energy Agency (IAEA) have a long history of collaborating on educational activities, and for several years SNMMI has live-streamed educational content from its Annual Meeting to participants in IAEA member states. SNMMI also produces case review webinars in multiple languages for IAEA participants around the world.

Another collaborative effort is the Nuclear Medicine Global Initiative, comprising nuclear medicine organizations from around the globe, which has undertaken projects of mutual importance, such as harmonization of pediatric administered activity guidelines, worldwide availability of radiopharmaceuticals, and theranostics.

SNMMI aims to improve patient health by advancing precision imaging and treatment. We extend a heartfelt invitation to our international colleagues to take on leadership roles within SNMMI committees, councils, and centers of excellence.

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role.

^{18}F-FDG PET/CT and WBC SPECT/CT in Cardiac Implantable Device Infection

In an article e-published on July 11 in *Circulation Cardiovascular Imaging*, Calais, from the University of California at Los Angeles, and colleagues from the Université de Paris, the Institut National de la Santé et de la Recherche Médicale, and the Hôpital Bichat-Claude Bernard (all in Paris, France) reported on the diagnostic value of ^{18}F-FDG PET/CT and radiolabeled white blood cell SPECT/CT in patients with suspected chronic infections associated with cardiac implantable electronic devices (CIEDs). The retrospective study included data from 48 such patients who underwent both types of imaging within a ≤30-d period. Final confirmation of CIED infection was based on the modified Duke–Li classification at the end of follow-up. The 2 imaging methods were analyzed separately, with readers unaware of patient medical histories. The diagnostic sensitivity, specificity, and positive and negative predictive values for PET/CT were 80%, 91%, 80%, and 91%, respectively, with values of 60%, 100%, 100%, and 85%, respectively, for white blood cell SPECT/CT. The authors found that the addition of a positive nuclear imaging scan as a major criterion improved the Duke–Li classification at admission. They also observed that associated semiquantitative parameters did not allow discrimination between definite and rejected CIED infection and that prolonged antibiotic therapy before imaging showed a tendency to decrease the sensitivity for both imaging techniques.

Circulation Cardiovascular Imaging

Prognostic Postradiation PET in Uterine Cervical Cancer

Kim et al. from the Kangwon National University Hospital (Chuncheon), the Armed Forces Daejeon Hospital, and the University of Ulsan College of Medicine (Seoul, all in Korea) reported online in the September issue of the *Journal of Gynecologic Oncology* (2019;30[5]:e66) on a systematic review and metaanalysis of the prognostic value of ^{18}F-FDG PET in uterine cervical cancer after radiotherapy with or without chemotherapy. A search of the literature yielded 11 studies with 12 patient cohorts totaling 1,104 women. Overall and progression-free survival endpoints were included in the analysis. The pooled hazards ratio (HR) of complete metabolic response compared to partial metabolic response was 0.19. Pooled HR of complete metabolic response compared to progressive metabolic disease was stronger at 0.07, and that of complete metabolic response compared to both partial and progressive metabolic response was 0.20. In a quantitative synthesis for progression free survival, the pooled HR for complete metabolic response was 0.17 compared to progressive metabolic response, 0.02 compared to progressive metabolic disease, and 0.12 compared both to progressive metabolic response and progressive metabolic disease. The authors concluded that post–radiation treatment ^{18}F-FDG PET results were "significant prognostic factors in patients with uterine cervical cancer, and ^{18}F-FDG PET could be a reasonable follow-up imaging modality."

Journal of Gynecologic Oncology

^{18}F-FDG Uptake and Ki67 in Pancreatic NETs

In an article e-published on July 23 in *Digestive and Liver Disease*, de Mestier et al. from the Université de Paris, Beaujon-Bichat Hospital (Clichy), and the Robert-Debré Hospital (Reims, both in France) reported on a study exploring the correlation between Ki67 proliferation and ^{18}F-FDG uptake on PET at the lesion level in resected pancreatic neuroendocrine tumors (NETs). The study included 21 patents with pancreatic or associated NETs but without neoadjuvant treatment who underwent ^{18}F-FDG PET imaging before pancreatic ($n = 12$), liver ($n = 2$), or combined ($n = 7$) surgery. A total of 21 primary pancreatic NETs, 13 liver metastases, and 2 lymph node metastases were identified. Analysis included lesion-by-lesion correlation between Ki67 and tumor-to-liver SUV_{max} ratio (T/L) and between pathology grades (G1, G2, and G3) and metabolic grades (mG1, SUV_{max} T/L ≤ 1; mG2, SUV_{max} T/L 1–2.3; and mG3, SUV_{max} T/L > 2.3). Lesions showed a median Ki67 of 4%, and Ki67 correlated with SUV_{max} T/L. Median SUV_{max} T/Ls were 0.76, 1.41 and 2.67 for lesions in the G1, G2, and G3 categories, respectively. Median Ki67 measures were 1, 4 and 25 for lesions in the mG1, mG2, and mG3 categories, respectively. The authors concluded that because "uptake on FDG PET could predict the pathological grade of PanNET lesions, FDG PET could supplement pathological evaluation of tumor biological aggressiveness and could guide the choice of the most relevant lesions to biopsy."

Digestive and Liver Disease