2021 SNMMI Highlights Lecture: Neuroscience

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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 2021 Highlights Lectures were delivered on June 15 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the lecture by Julie Price, PhD, a professor of radiology at the Harvard Medical School and director of PET Pharmacokinetic Modeling in the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital (Boston, MA), 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 *(2021;62[suppl 1]).*

It is my pleasure to present the 2021 SNMMI Neurosciences Highlights lecture. We will start things off with the Kuhl–Lassen award, given annually by the Brain Imaging Council for the past 25 years. The first recipient was Louis Sokoloff, MD, the functional imaging pioneer, who received the award in 1996. The list of awardees over the years constitutes a truly impressive group of scientists and physician scientists. I am immensely humbled to have been this year's recipient and thank the Brain Imaging Council for selecting me for this tremendous honor. The topic of my Kuhl–Lassen lecture was "PET methodology in amyloid imaging."

I want to congratulate the individuals who were selected to take part in the 2021 Neurosciences Young Investigator Award session at this meeting. This is a challenging competition each year, with excellent presentations from our future research leaders. This year the first-place awardee was Emma M. Coomans, the second-place awardee was Matthew Zammit, PhD, and the third-place awardee was Ganna Blazhenets, PhD. Each of their presentations will be featured in this Highlights lecture. I strongly encourage you to view all the Young Investigator Award presentations on the SNMMI Annual Meeting virtual site.

Three oral sessions (Novel Radiotracers and Multimodal Imaging of the Brain, Neurosciences Young Investigator Award Session, and Advances in Clinical Neuroimaging) focused on the neurosciences at this meeting, as did 3 poster sessions covering the basic neurosciences, general neuroscience, and neurology/psychiatry. A rough assessment of these presentations indicated that the topic distribution was largely focused again this year on neurodegeneration and related targets (36%), then on synaptic function and metabolism (23%) and receptor/transporter imaging (14%), with fewer abstracts on inflammation (9%) and brain tumor assessment (4%). The talks highlighted in this lecture will reflect this general distribution.

Julie Price, PhD

Neurotransmitters, Synaptic Function, and Designer Receptors

We will begin with glutamate, the most abundant excitatory neurotransmitter in the vertebrate nervous system. The GluN2B subunit of the *N*-methyl-D-aspartate (NMDA) receptor complex is a therapeutic target for a range of neuropsychiatric disorders, including dementia and schizophrenia. Ongoing efforts to develop GluN2B-specific radiotracers for clinical use have produced several promising compounds. Smart (a Young Investigator) et al. from Yale University PET Center (New Haven, CT), Institute of Pharmaceutical Sciences ETH Zürich (Switzerland), Union Hospital/Tongji Medical College/Huazhong University (Wuhan, China), Jiangsu Institute of Nuclear Medicine (China), and the National Institute of Mental Health (Bethesda, MD) reported on "In vivo comparison of 3 novel radiotracers for the NMDA receptor GluN2B subunit in nonhuman primates" [46]. They compared in rhesus macaques the imaging properties of 3 candidate radiotracers for the GluN2B site: *(R)*-^{18}F-OF-Me-NB1, *(R)*-^{11}C-NR2B-Me, and *(S)*-^{18}F-OF-NB1. In baseline imaging and in blocking scans with selective antagonists for GluN2B and σ1, the researchers compared tracer metabolism in plasma, plasma binding, tissue kinetics, modeling, and selectivity among the 3 compounds. Figure 1 shows the brain distribution for each radiotracer at baseline, as well as the reduction in signal achieved with the blocking scans. *(R)*-^{11}C-NR2B-Me and *(S)*-^{18}F-OF-NB1 showed similar distribution in brain as well as cortical nondisplaceable binding potential values of 2–3, making them particularly promising candidates for evaluation in humans. Pretreatment with the FTC-146 σ1 antagonist reduced uptake and volume of distribution values in all tracers, most notably for the NR2B ligand, suggesting possible interaction of radiotracers and/or GluN2B targets with σ1 receptors. Additional pharmacologic studies will explore these in vivo properties and interactions.

Afshar et al. from Massachusetts General Hospital/Harvard Medical School (Boston, MA) reported on "Longitudinal assessment of the glutamatergic neurosystem in a fragile X

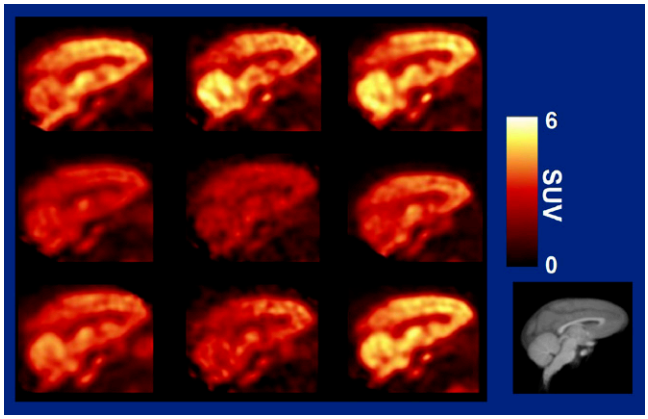

FIGURE 1. Three novel radiotracers for the NMDA receptor GluN2B subunit in nonhuman primates. Brain distribution of (left to right) *(R)*-^{18}F-OF-Me-NB1, *(R)*-^{11}C-NR2B-Me, and *(S)*-^{18}F-OF-NB1 PET at (top to bottom) baseline, after GluN2B blocking, and after σ1 blocking. *(R)*-^{11}C-NR2B-Me and *(S)*-^{18}F-OF-NB1 showed similar distribution in brain as well as cortical binding potential values of 2–3 and are particularly promising candidates for evaluation in humans. Pretreatment with the σ1 antagonist reduced uptake and volume of distribution values of all tracers, most notably for the NR2B ligand, suggesting possible interaction of radiotracers and/or GluN2B targets with σ1 receptors.

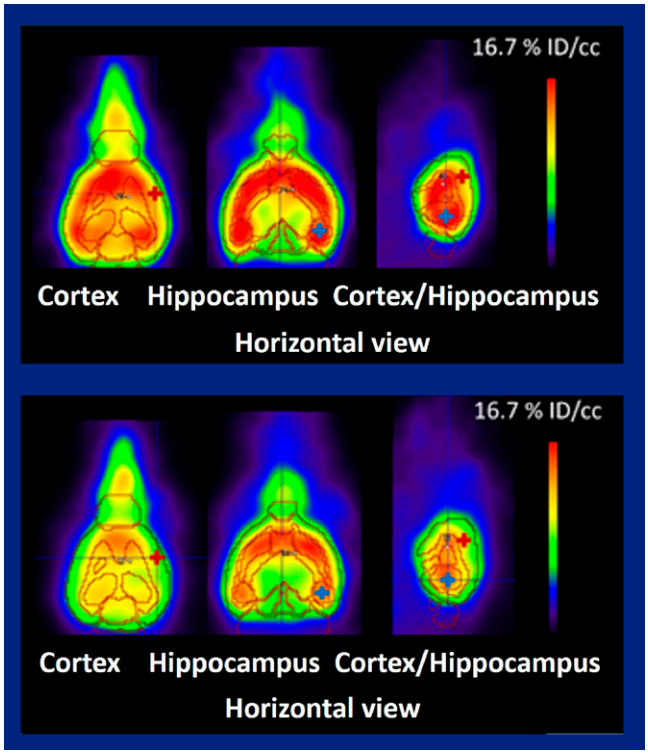

FIGURE 2. Longitudinal assessment of the glutamatergic neurosystem in a fragile X knockout mouse model. Cumulative distribution of ^{18}F-FPEB binding 20–45 min after administration is shown in control male mice (top block) and fragile X syndrome mice (bottom row) in (left to right) cortex, hippocampus, and cortex/hippocampus horizontal views. Differences in distribution reflect the critical brain areas (striatum, cortex, and hippocampus) known to be impacted by progression of fragile X syndrome. Additional biobehavioral studies correlated disease progression as assessed by imaging with symptomatic behaviors and offered potential for identification of targets for pharmacologic intervention.

knockout mouse model" [118]. Fragile X syndrome is a developmental disorder characterized by learning disabilities and cognitive impairments, caused by mutations of the FMR1 gene. In this study, a cohort of fragile X syndrome mice and age- and sex-matched healthy control mice underwent PET using the allosteric modulator radiotracer ^{18}F-FPEB to examine mGluR5 expression as well as Morris water maze testing of spatial learning and memory at 4 time points, beginning 34–41 days after birth and extending to about 1 year. The images in Figure 2 show the cumulative distribution of ^{18}F-FPEB binding to be greater in control mice than in male fragile X knockout mice in cortical and subcortical areas. This was consistent with data that showed a higher binding potential in controls than in knockout mice. Age- and sex-dependent binding potential variations were also observed in different brain areas in the fragile X knockout mice. In male mice, mGluR5 binding potential increased significantly from early adolescence to late adolescence but then decreased in adulthood, suggesting that optimal treatment age may be in adolescence. Increased spatial learning rates during aging was evidenced in the fragile X syndrome mice in mean swim latencies across trials in the Morris water maze studies. The results of these studies provide potential mechanistic insights for design of therapeutic interventions for fragile X and are consistent with the clinical observation that females often have milder symptoms than males. The authors concluded that these findings "reflect the critical brain areas known to be impacted by the progression of the fragile X syndrome, namely striatum, cortex, and hippocampus." In addition, they noted that "biobehavioral vulnerability was predicted on the basis of disease progression and holds exciting potential" as a target for pharmacologic interventions.

Gravel et al. from Yale University (New Haven, CT) and F. Hoffmann-La Roche Ltd. (Basel, Switzerland) reported on "Kinetic modeling of novel radiotracers for the GABA transporter-1 (GAT-1) in nonhuman primates" [117]. γ-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in humans, and GAT-1 is of particular interest because of its potential role in neuropsychiatric disorders. Two novel radiotracers, ^{18}F-GATT-34 and ^{18}F-GATT-44, were evaluated at baseline and after blocking with tiagabine, an antiepileptic compound. The uptake images (Fig. 3) for these 2 compounds show that tiagabine blocking decreased the signal for both radiotracers, with moderate success for GATT-34 (48% blocking of specific binding) and better success for GATT-44 (57%–66% blocking of specific binding). The nondisplaceable volume of distribution and average nondisplaceable binding potential values were respectively 0.98 and 0.71 mL/cm^3 for GATT-34 and 0.85 and 2.20 mL/cm^3 for GATT-44. Injection properties were similar for the 2 tracers. The authors plan to evaluate additional ligands and progress the best to humans.

Yan et al. from the National Institute of Mental Health (Bethesda, MD) and the National Institutes for Quantum and

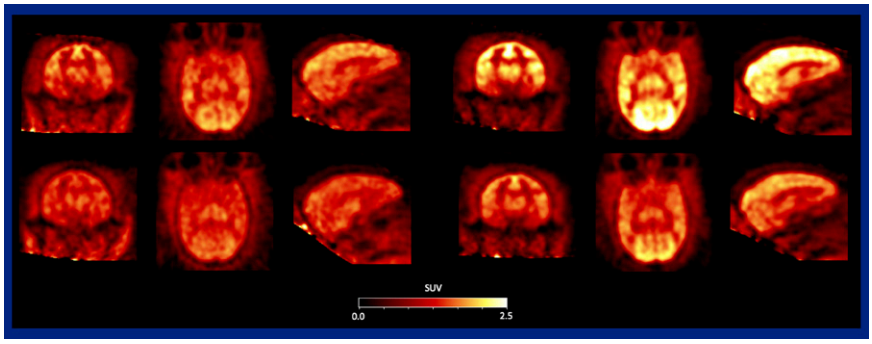

FIGURE 3. Kinetic modeling of novel radiotracers for GABA transporter-1 in nonhuman primates. SUV images with ^{18}F-GATT-34 (left block) and ^{18}F-GATT-44 (right block) at baseline (top row) and after administration of tiagabine as a blocking agent (bottom row).

Radiological Science and Technology (Chiba, Japan) reported that "^{11}C-deschloroclozapine (^{11}C-DCZ) is an improved PET radioligand for quantifying a human muscarinic DREADD (Designer Receptors Exclusively Activated by Designer Drugs) expressed in monkey brain" [120]. DREADDs are a powerful technique for selectively manipulating neuronal activity. Recent studies indicate, however, that ligands used for DREADDs, such as clozapine-*N*-oxide or its parent compound clozapine, are not as selective as expected, even at reasonable concentrations. This study was motivated by a previous investigation that found that ^{11}C-DCZ was superior to ^{11}C-clozapine (^{11}C-CLZ) for imaging DREADDS. The researchers used PET to quantitatively and individually measure signal from transfected receptors, endogenous receptors/targets, and nondisplaceable binding in other brain regions to assess qualities that contribute to the higher signal-to-background ratio of ^{11}C-DCZ compared to ^{11}C-CLZ. A genetically modified muscarinic type-4 human receptor was injected into the right amygdala of an 11-year-old male rhesus macaque. ^{11}C-DCZ and ^{11}C-CLZ PET scans were conducted at baseline and after receptor blockade, and uptake was quantified relative to the concentration of parent radioligand in arterial plasma at both timepoints. Both tracers had high-affinity displaceable binding to DREADDs relative to endogenous receptor(s) (Fig. 4). The overall signal was 5 times lower for ^{11}C-DCZ than for ^{11}C-CLZ, but the background was 10 times lower for ^{11}C-DCZ, yielding an overall 2-fold gain in signal-to-background ratio for ^{11}C-DCZ. This higher signal-to-background ratio suggested superior imaging characteristics for ^{11}C-DCZ, although the percentage of off-target binding (~16%) was similar for the 2 tracers. This is an important study evaluating DREADD in vivo, with implications for behavioral and translational investigations.

Clinical Neuroimaging: Oncology and COVID-19

This category includes 2 studies aimed at improving therapy response in patients with glioblastoma and a third on COVID-19–related alterations in ^{18}F-FDG metabolism.

Gan et al. from the Olivia Newton-John Cancer Research Institute/Austin Hospital (Melbourne, Australia) and Royal Brisbane and Women's Hospital (Brisbane, Australia), QIMR Berghofer Medical Research Institute (Brisbane, Australia), and Humanigen, Inc. (Burlingame, CA) reported on "Phase I safety and bioimaging trial of ifabotuzumab in patients with glioblastoma" [104]. Ifabotuzumab is an immunoglobulin G1κ humaneered antibody that targets the EphA3 receptor, which is a tumor-restricted antigen expressed in stroma and in the tumor vasculature of 100% of glioblastoma multiforme. This study is interesting, because it includes evaluation of the biodistribution and pharmacokinetics of ^{89}Zr-labeled ifabotuzumab, the frequency of EphA3-positive glioblastoma multiforme (tumor targeting), and response rates. Twelve patients (7 men, 5 women; mean age, 51.6 ± 14.24 years) were enrolled, with 6 individuals in each dose cohort (3.5 and 5.25 mg/kg). Treatment was well tolerated with no dose-limiting toxicities observed. Posttreatment MR imaging showed T2/FLAIR changes consistent with treatment effect on tumor vasculature. Figure 5 shows consistent targeting of the tumor microenvironment. The absence of normal tissue uptake of the tracer indicated ideal characteristics for a range of therapeutic

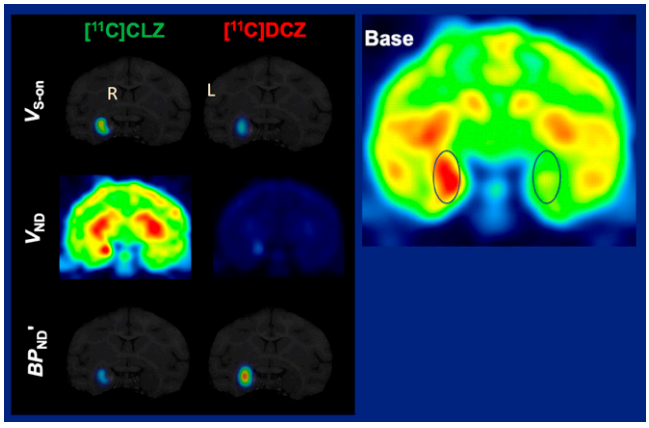

FIGURE 4. ^{11}C-deschloroclozapine (^{11}C-DCZ) is an improved PET radioligand for quantifying a human muscarinic Designer Receptors Exclusively Activated by Designer Drug (DREADD) expressed in monkey brain. Left: The signal-to-background ratio of ^{11}C-DCZ (right column) on PET imaging was found to be ~2-fold higher than that of ^{11}C-clozapine (^{11}C-CLZ) (left column). RIGHT: Baseline ^{11}C-CLZ image for which right amygdala uptake (circle, left) reflects nonspecific, off-target, and on-target signals, whereas left amygdala (circle, right) reflects only nonspecific and off-target signals. The difference between the uptake in right and left amygdala yields the on-target signal, and the difference between baseline and blocking uptake in other regions yields the off-target signal. In vivo exploration of DREADDs holds broad potential for behavioral and translational investigations.

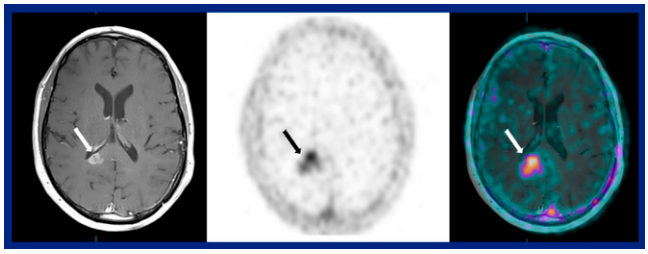

FIGURE 5. ^{89}Zr-ifabotuzumab targeting of tumor microenvironment in glioblastoma multiforme. Left: Post-ifabotuzumab-treatment MR imaging showed T2/FLAIR changes consistent with treatment effect on tumor vasculature (arrow). Middle: ^{89}Zr-ifabotuzumab showed high specific targeting of the tumor microenvironment in all patients, with no normal tissue uptake, indicating ideal characteristics for a range of therapeutic approaches. Right: PET/MR image. The study evaluated not only the biodistribution and pharmacokinetics of the ^{89}Zr-labeled immunoglobulin G1κ humaneered antibody, but also the frequency of EphA3-positive glioblastoma multiforme (tumor targeting) and response rates to treatment.

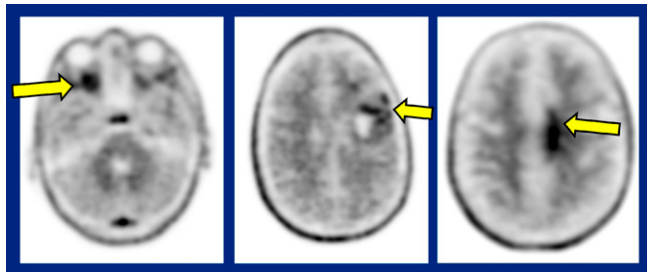

FIGURE 6. Initial clinical studies of ^{18}F-DASA-23 PET for evaluation of aberrantly expressed pyruvate kinase M2 in glioblastoma. ^{18}F-DASA-23 delineated primary brain tumors with a trend toward increasing uptake with increasing tumor grade. Left: low-grade optical nerve glioma (tissue-to-background ratio maximum [TBR_{max}], 2.1). Middle: grade 3 oligodendroglioma (TBR_{max}, 2.5). Right: grade 4 glioblastoma (TBR_{max}, 2.8).

approaches. Median overall survival was 7.17 months (range, 2–28 months), with 3 patients in survival follow-up at the time of the report. Although no objective therapeutic responses were observed (the best being stable disease for 23 weeks), additional studies are planned to evaluate the monoclonal antibody as part of an antibody–drug conjugate in various solid tumor types.

Beinat and Molecular Imaging Program colleagues from Stanford University/Stanford University School of Medicine (CA) reported on "Initial clinical evaluation of ^{18}F-DASA-23, a PET imaging tracer for evaluation of aberrantly expressed pyruvate kinase M2 (PKM2) in glioblastoma" [99]. PKM2 catalyzes the final step in glycolysis and is highly expressed in glioblastoma cells, with minimal expression in healthy brain. In healthy volunteers, dynamic ^{18}F-DASA-23 scans exhibited high initial uptake (SUV ~5) in most brain structures, followed by washout over the 60-minute acquisition period. In patients, ^{18}F-DASA-23 delineated primary brain tumors with a trend toward increasing uptake with increasing tumor grade. This is the first report of the evaluation of a PKM2-specific radiopharmaceutical in humans (Fig. 6). Figure 7 is an example of imaging acquired in an individual in whom ^{18}F-DASA-23 identified metabolic nonresponse to temozolomide chemotherapy and Avastin antiangiogenic therapy within 1 week of treatment initiation, almost 3 months earlier than contrast-enhanced MR imaging. A promising potential application of ^{18}F-DASA-23 is in detection of early glycolytic response to therapy in patients with glioblastoma multiforme, with the need for further evaluation of utility. I would like to take a moment to remember a truly exceptional colleague and leader at Stanford University, Sanjiv Sam Gambhir, MD, PhD, who will forever be missed.

Blazhenets et al. from the University of Freiburg (Germany) reported on "Altered regional cerebral function and its association with cognitive impairment in COVID-19: A prospective FDG PET study" [41]. The study included 29 adult patients from the Freiburg Neuro-COVID Registry, with an inclusion criterion of 1 new neurologic symptom related to COVID-19 (disturbed gustation, 100%; disturbed olfaction, 86%; and cranial nerve palsies, 10%). Those with premorbid neurologic conditions, such as dementia, were excluded. Participants underwent neurologic examination, a cognitive test battery, cerebrospinal fluid investigation, and multimodal imaging. Fifteen of the 29 patients with a least 2 new neurologic symptoms underwent cerebral ^{18}F-FDG PET imaging. Visual reads of the resulting images indicated that 10 of the 15 showed pathologic results. The investigators compared these subjects with a group of controls using principal component analysis, which yielded a distinctive COVID-19–related FDG spatial covariance pattern involving multiple brain

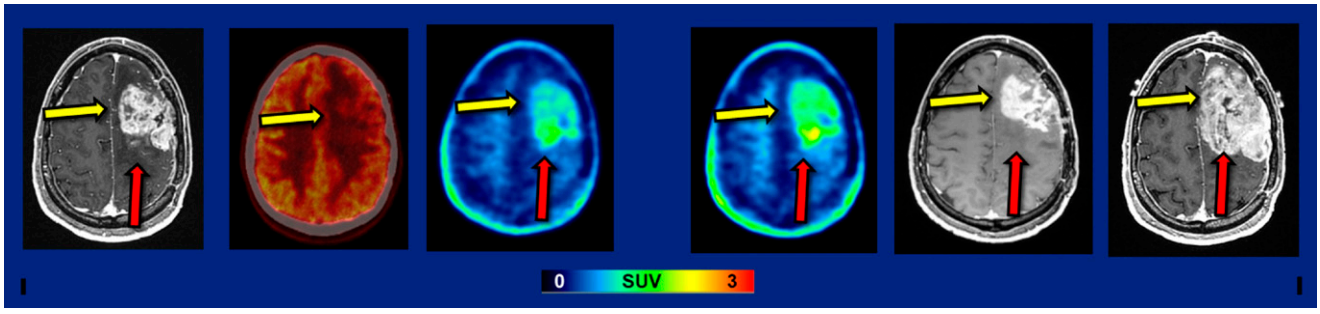

FIGURE 7. ^{18}F-DASA-23 PET in early evaluation of glioblastoma. ^{18}F-DASA-23 identified a metabolic nonresponder to temozolomide chemotherapy and Avastin antiangiogenic therapy within 1 week of treatment initiation, almost 3 months earlier than contrast-enhanced MR imaging. Left to right: T_1 + C MR imaging at 15 days pretreatment, ^{18}F-FDG PET at 12 days pretreatment, ^{18}F-DASA-23 PET at 3 days pretreatment, ^{18}F-DASA-23 PET at 6 days posttreatment, T_1 + C MR at 6 days posttreatment, and T_1 + C MR at 90 days posttreatment.

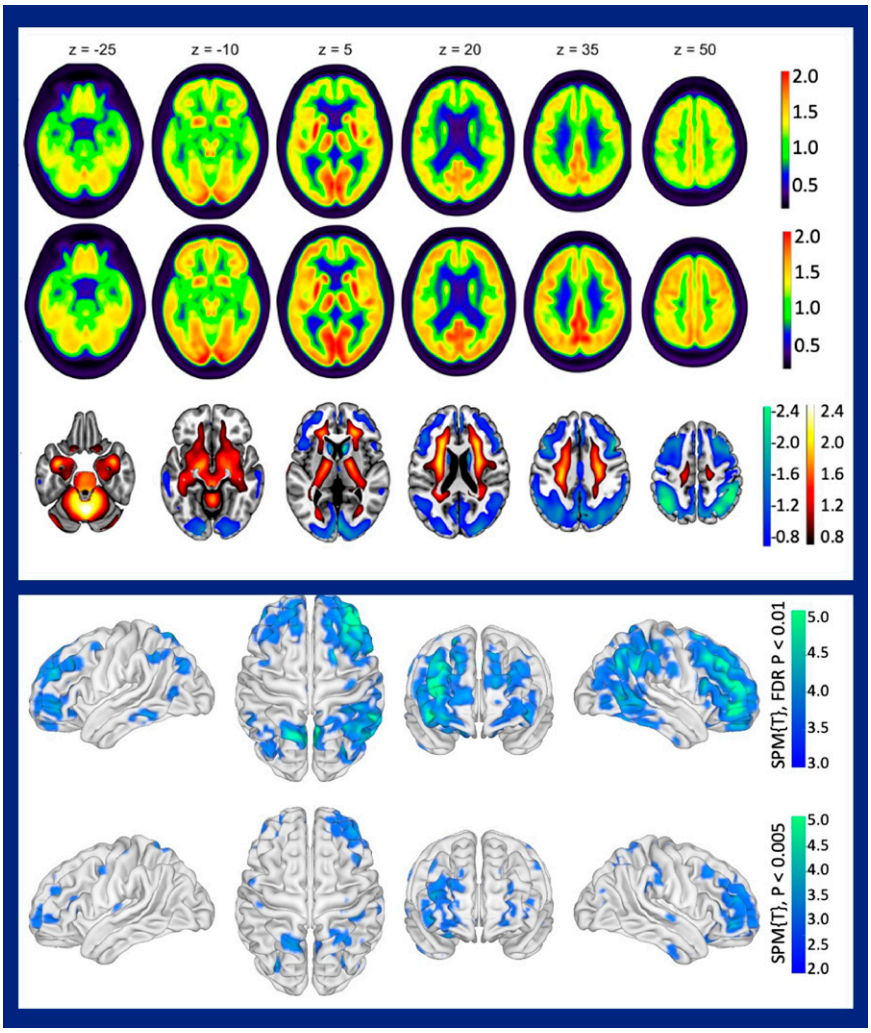

FIGURE 8. ^{18}F-FDG PET and altered regional cerebral function and cognitive impairment in patients after COVID-19. Top block: ^{18}F-FDG PET in COVID patients (top row) and a control group (middle row). COVID-19–related spatial covariance patterns engaged multiple brain regions and were characterized by negative weights (hypometabolism) in widespread neocortical areas (bottom row). Bottom block: Statistical parametric mapping in subacute COVID patients (top row) and at 6-month follow-up (bottom row), with higher pattern expression associated with worse cognitive performance. Although significant recovery of regional neuronal function and cognition was evident, COVID-19–related residuals were still measurable even 6 months after recovery.

regions and characterized by negative weights (hypometabolism) in widespread neocortical areas (positive weights = preserved regions), brain stem, cerebellum, white matter, and mesiotemporal structures and negative weights in widespread neocortical areas (with frontoparietal predominance) (Fig. 8). Conventional statistical parametric mapping analysis also showed widespread frontoparietal-dominant neocortical hypometabolism, whereas there were no hypermetabolic clusters. In the 8 COVID-19 patients presented for follow-up, the mean pattern expression score at the chronic stage was significantly lower than in the subacute stage. Although significant recovery of regional neuronal function and cognition was clearly evident in these individuals, COVID-19–related residuals were still measurable even 6 months after recovery. Higher ^{18}F-FDG pattern expression was also associated with worse cognitive performance (i.e., COVID-19–related pattern expression score versus Montreal Cognitive Assessment global cognitive score, adjusted for education). This is a very important study, as it quantifies the neurologic impact of the COVID-19 infection over time. The authors concluded that "post–COVID-19 patients with persistent cognitive complaints should be presented to a neurologist and possibly allocated to cognitive rehabilitation programs." Images from this presentation were named as the winner of the prestigious SNMMI Image of the Year award for 2021.

Neurodegeneration

Coomans et al. from Vrije Universiteit Amsterdam/Amsterdam UMC (The Netherlands), Lund University (Sweden), Rodin Therapeutics, Inc. (Boston, MA), and University College London Institutes of Neurology and Healthcare Engineering (UK) reported that "In vivo tau pathology is associated with synaptic loss and altered synaptic function" [43]. The authors applied a novel multimodality approach in amyloid-positive Alzheimer disease subjects from the Amsterdam Dementia Cohort who underwent dynamic 130-minute ^{18}F-flortaucipir PET, dynamic 60-minute ^{11}C-UCB-J PET with arterial sampling, and 2 × 5-minute resting-state MEG measurements. Figure 9 demonstrates spatial overlap and differences between tau pathology and synaptic loss observed respectively by T1 MR imaging, ^{18}F-flortaucipir PET, and ^{11}C-UCB-J PET. The locations of increases in distribution of the PET ligands were markedly different. Across subjects, higher regional ^{18}F-flortaucipir uptake was associated with lower ^{11}C-UCB-J uptake, consistent with lower synaptic density. Within subjects, the association between ^{18}F-flortaucipir and ^{11}C-UCB-J ligand binding was dependent on the within-subject neocortical tau load or degree of neurodegeneration. Both higher ^{18}F-flortaucipir and lower ^{11}C-UCB-J uptake were associated with altered synaptic function, indicative of slowing of oscillatory activity, most pronounced in the occipital lobe. These results indicated that in Alzheimer disease tau pathology is closely associated with reduced synaptic density and synaptic dysfunction. This study illuminates ways in which ^{11}C-UCB-J synaptic parameters relate to other imaging parameters in neurodegeneration and

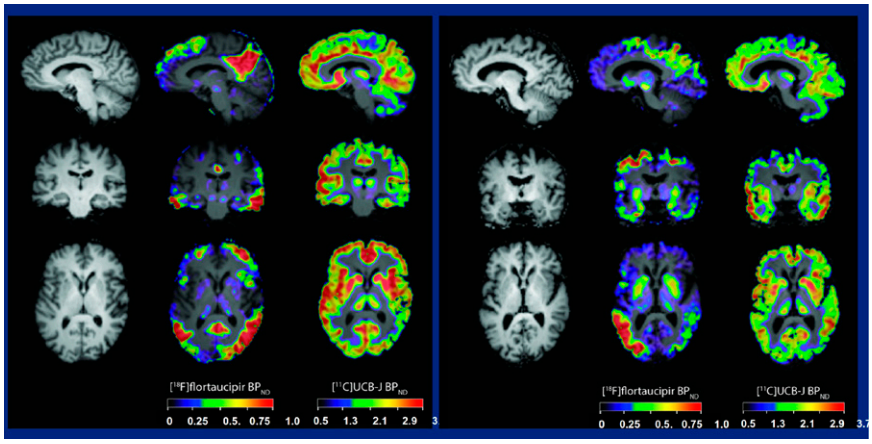

FIGURE 9. In vivo imaging of tau pathology associated with synaptic loss and altered synaptic function. Images demonstrate spatial overlap between tau pathology and synaptic loss observed in T1 MR imaging (left column in each block) and binding potential maps of ^{18}F-flortaucipir (middle column) and ^{11}C-UCB-J PET/CT (right column). Left block acquired in a 50–55-year-old woman with a Mini Mental State Examination (MMSE) score of 22. Right block acquired in a 55–60-year-old man with an MMSE = 24. Both higher ^{18}F-flortaucipir and lower ^{11}C-UCB-J uptake were associated with altered synaptic function, indicative of slowing of oscillatory activity, most pronounced in the occipital lobe. These results indicated that tau pathology in Alzheimer disease is closely associated with reduced synaptic density and synaptic dysfunction.

continues to build on information that can inform future therapeutic strategies.

Zammit et al. from the University of Wisconsin Madison, University of Pittsburgh (PA), University of Cambridge (UK), and Washington University in St. Louis (MO) reported that "Neurofibrillary tau emerges in adults with Down syndrome during the earliest stages of Aβ accumulation" [42]. Adults with Down syndrome are predisposed to early Alzheimer disease, accumulating amyloid-β early in life. The aim of the study was to evaluate neurofibrillary tau deposition (using ^{18}F-AV-1451 or ^{18}F-flortaucipir PET) in adults with Down syndrome classified as amyloid-negative (A–) or amyloid-positive (A+) at subthreshold levels. Figure 10 is an SUV ratio (SUV_r) difference image between the subthreshold A+ and A– participants, with greater uptake difference indicating elevated AV-1451 retention in the subthreshold A+ group. Even at very low amyloid load levels, the subthreshold A+ group exhibited significantly higher tracer uptake in Braak regions I–III. Higher off-target binding in choroid plexus and basal ganglia was observed in the subthreshold A+ group compared to the whole sample of A–, whereas the SUV_r difference in off-target binding was lower in the age-matched group, indicating age-related AV-1451 off-target binding in Down syndrome. These findings indicate that neurofibrillary tau burden is evident even in the early Braak stage regions during the subthreshold amyloid-β accumulation phase in Down syndrome, suggesting a short latency between the onset of amyloid-β and the spread of neurofibrillary tau.

High neocortical tau is rarely observed in the absence of high amyloid-β in Alzheimer disease. We also know that there is believed to be a threshold of amyloid beyond which tau accumulation progresses with cognitive decline. Krishnadas et al. from Austin Hospital Heidelberg, the University of Melbourne Parkville, Florey Institute of Neurosciences and Mental Health Parkville, CSIRO Biomedical Imaging Health and Biosecurity Flagship Parkville, and the Australian Dementia Network (Victoria; all in Australia) reported on "Discordant low amyloid-β PET and high neocortical tau PET retention" [100]. In a large cohort (466 participants) from the Australian Imaging Biomarkers and Lifestyle study of aging and Alzheimer disease, 287 individuals were found to have low/negative amyloid-β on ^{18}F-NAV4694 PET (centiloid < 25), 12 of these had both low/negative amyloid-β PET and quantitatively high neocortical ^{18}F-MK6240 tau,

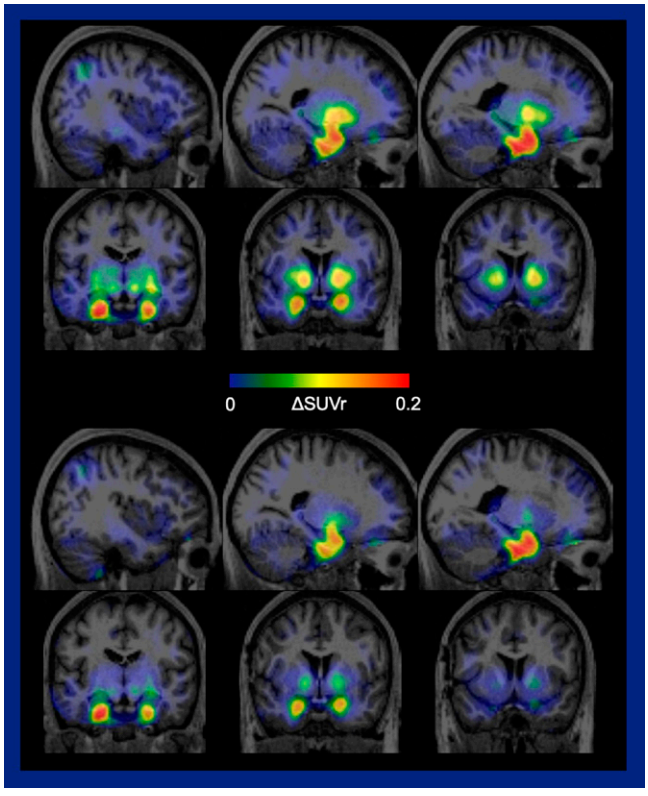

FIGURE 10. Neurofibrillary tau in adults with Down syndrome. ^{18}F-AV-1451 PET SUV_r difference imaging between amyloid-negative and subthreshold amyloid-positive participants (top block, whole sample; bottom block; age-matched sample). Even at very low amyloid load levels, the subthreshold amyloid-positive group exhibited significantly higher tracer uptake in Braak regions I–III, indicating that neurofibrillary tau burden is evident even in the early Braak stage regions during the subthreshold amyloid-β accumulation phase in Down syndrome.

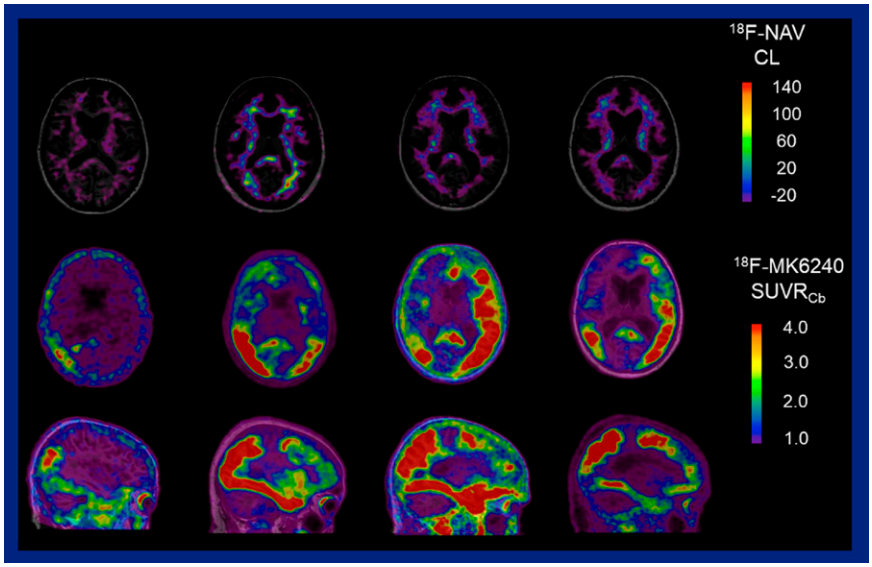

FIGURE 11. Discordant low amyloid-β PET and high neocortical tau PET retention. Only 4 out of 466 individuals in a large Alzheimer disease study were found to have low/negative amyloid-β PET and quantitatively high neocortical tau with visually positive tau PET consistent with Alzheimer disease. These individuals (left to right, assessed as clinically unimpaired, with mild cognitive impairment, with mild cognitive impairment, and with Alzheimer disease) were imaged with ^{18}F-NAV4694 (top row) and ^{18}F-MK6240 (middle and bottom rows). Despite this atypical presentation, alternative biomarkers were suggestive of Alzheimer disease in all 4 participants.

and only 4 of the 12 had low/negative amyloid-β PET and quantitatively high neocortical tau with visually positive tau PET consistent with Alzheimer disease. Figure 11 shows example PET images in 4 participants with discordant low amyloid-β PET (^{18}F-NAV4694) and high neocortical tau (^{18}F-MK6240). Despite this atypical presentation, alternative biomarkers were suggestive of Alzheimer disease in all 4 participants. The authors proposed that in these very rare instances of discordance, "the amyloid-β PET ligand may not be detecting Aβ, maybe due to a different conformation of the aggregates." They called for larger studies to validate the findings, as well as genetic testing and postmortem correlation to enhance understanding and determine whether this constitutes a different form of Alzheimer disease.

Previous studies have shown that amyloid-β likely promotes the spread of tau beyond the medial temporal lobe. However, the amyloid-β levels necessary for tau to spread in the neocortex remain unclear. Dore et al. from CSIRO Heidelberg, Austin Hospital Heidelberg, CSIRO Herston, and the Florey Institute of Neuroscience and Mental Health (Melbourne; all in Australia) reported on the "Relationship between amyloid and tau levels and its impact on tau spreading" [116]. In the same large cohort from the Australian Imaging Biomarkers and Lifestyle study, participants underwent tau imaging with ^{18}F-MK6240 and amyloid-β imaging with ^{18}F-NAV4694. Amyloid-β scans were quantified on the centiloid scale with a cutoff of 25 for abnormal levels of amyloid-β (A+). The prevalence of abnormal tau levels along the centiloid continuum was also determined. Below 50 on the centiloid scale, the prevalence of individuals with an abnormal tau scan was low in mesial temporal and rare in temporoparietal areas. Above 50 centiloids, the prevalence of abnormal tau levels accelerated in all areas. In cognitively unimpaired individuals, the prevalence of abnormal tau increased along the centiloid continuum. The highest prevalence of tau abnormality was found in the entorhinal cortex, reaching 40% at 40 and 80% at 60 on the centiloid scale. Outside the entorhinal cortex, abnormal levels of cortical tau on PET were rarely found with amyloid-β levels below 40. Moderate amyloid-β levels, then, appear to be required before neocortical tau becomes detectable.

Conclusion

I would like to end this lecture by thanking my colleagues for this honor and paying tribute to Henry N. Wagner, Jr., MD, for his stewardship, mentorship, and extraordinary efforts to advance the field of nuclear medicine.

ABNM: Interim Report on Provisional Requirements for Radionuclide Therapy

George M. Segall, MD, Executive Director, American Board of Nuclear Medicine

In 2020, the American Board of Nuclear Medicine (ABNM) proposed new requirements for radionuclide therapy (*J Nucl Med.* 2020;61[12]:41N). The proposed changes were based on the evolution of practice since the requirements were changed in 2014, with fewer radioiodine therapies for hyperthyroidism and thyroid cancer and more parenteral therapies due to U.S. Food and Drug Administration (FDA) approval of additional radiopharmaceuticals for cancer treatment. Before making changes, the ABNM polled the directors of all 38 Accreditation Council for Graduate Medical Education (ACGME)–accredited nuclear medicine programs. Fifty-three percent approved the proposal in its entirety. Thirty-four percent supported the proposal with reservations about decreasing the minimum number of radioiodine therapies and increasing the minimum number of parenteral radiopharmaceuticals, including requiring experience with at least 2 different FDA-approved radiopharmaceuticals. Four directors (10%) did not support the proposal because of challenges in providing experience with parenteral therapies. Based on this feedback, the ABNM decided that candidates for the 2021 and 2022 certification examinations could fulfill the requirements using the current ACGME-based criteria or by using the new provisional criteria proposed by the ABNM. The ACGME Nuclear Medicine Review Committee decided that programs would not be cited if trainees met the ABNM provisional requirements instead of the ACGME requirements.

The ABNM provisional requirements did not change the minimum number of all therapies, which was maintained at 35. The minimum number of radioiodine therapies using ≤33 mCi of ^{131}I was decreased from 10–15 to 5, and the minimum number using >33 mCi of ^{131}I was also decreased from 10–15 to 5. The minimum number of parenteral therapies was increased from 5 to 10, with the additional requirement that experience must include at least 2 different FDA-approved radiopharmaceuticals, excluding ^{90}Y microspheres. The requirement for 35 total therapies could be met by any therapy beyond the specified minimum.

Sixty-five candidates took the 2021 ABNM certification examination. Seven candidates (11%) met the new provisional requirements, with the remaining candidates meeting the current ACGME-based requirements. Six of the 7 candidates also met the eligibility requirements for certification by the American Board of Radiology (ABR) in diagnostic radiology and had 16 months of nuclear medicine training. Four of the candidates completed the ABNM and ABR requirements during 4 years of diagnostic radiology residency, and 2 candidates completed the requirements in 5 years, with 1 year of nuclear medicine plus 4 years of diagnostic radiology training. One candidate was certified by another specialty board and met the requirements with 2 years of nuclear medicine training.

George M. Segall, MD

The radionuclide therapy case logs of the 7 candidates who met the new provisional requirements were reviewed. The parenteral radionuclides listed included ^{223}Ra-dichloride (41 therapies) and ^{177}Lu-DOTATATE (37 therapies). Candidates were required to list only the minimum requisite number of 10 parenteral therapies (although some listed more than 10), so it is not known whether these candidates had additional experience with these or other FDA-approved radiopharmaceuticals. No candidates listed ^{89}Sr-chloride, ^{153}Sm-lexidronam, ^{90}Y-ibritumomab tiuxetan, or ^{131}I-iobenguane. It is also unknown how many trainees had experience with prostate-specific membrane antigen (PSMA)–targeted radiopharmaceuticals, which are still in clinical trials.

The number of trainees meeting the provisional radionuclide therapy criteria this year was small. The ABNM does not expect any significant change in the number of trainees having greater experience with parenteral therapies until the FDA approves PSMA-targeted radiopharmaceuticals for treatment of prostate cancer. FDA approval will likely be too late to impact training during the current academic year at sites that are not participating in clinical trials, but adoption of the new treatment is expected to be rapid at teaching institutions once these therapies are approved.

SNMMI Mid-Winter and ACNM Annual Meeting Convene In-Person

Virginia Pappas, CAE, SNMMI CEO

After almost 2 years of virtual meetings, we are pleased to announce that the SNMMI Mid-Winter and American College of Nuclear Medicine (ACNM) Annual Meeting will be held in person January 27–29, 2022, in Orlando, FL. We are eager to welcome nuclear medicine and molecular imaging professionals for 3 days of outstanding programming and much-missed in-person networking.

The meeting will feature 3 educational tracks highlighting the latest innovations and techniques in the field. The Nuclear Cardiology track will focus on basic concepts in nuclear cardiac imaging and stress testing, as well as exciting new areas in nuclear cardiology. The track kicks off with a cardiac CT workshop on Thursday morning, January 27. Sessions throughout the weekend will provide attendees with tangible outcomes for optimizing cardiovascular imaging in clinical practice.

The General Nuclear Medicine education track will feature the latest clinical applications and best practices across the field. The track features a wide-ranging scope of sessions on topics including ^{18}F-DOPA, fibroblast-activation protein PET, artificial intelligence in imaging, amyloid imaging, newly approved PET/CT imaging agents, and more.

The ACNM Annual Meeting education track will offer a robust program of cutting-edge educational content and oral presentations. It will begin on Thursday, January 27, with 2 sessions of oral presentations. Friday begins the education session, with topics focusing on the coming of age of theranostics, including the use of theranostics to treat hyperthyroidism, metastatic thyroid cancer, and neuroendocrine tumors. Additional sessions will share the latest on ^{131}I-MIBG therapy, U.S. Food and Drug Administration–approved PET radiotracers for prostate cancer, and estrogen receptor–targeted PET with ^{18}F-FES for patients with breast cancer.

Along with the education program, the meeting will offer an exhibit hall, open January 28 and 29. This is a great chance for attendees to meet with top companies in person and explore the latest technologies and products available in the field. Among the exhibitors are the meeting's Title Sponsor, Advanced Accelerator Applications, and its Gold Sponsors, Ionetix and Point Biopharma. An Exhibitor Welcome Reception will be held on Friday, January 28, at which exhibitors will have information and products on display showcasing the latest technology and services available in the nuclear medicine and molecular imaging fields. Light refreshments will be served.

Several additional networking events will be offered for meeting attendees. Throughout the meeting, short networking Attendee Coffee Breaks will be scheduled into the programming. On Friday, all meeting attendees are invited to attend the ACNM Awards Ceremony and Banquet, during which the ACNM will honor its 2022 ACNM Lifetime Achievement Award and Gold Medal Award winners and present the ACNM Abstract Awards. ACNM will also induct its 2022 Class of Fellows.

This year's meeting will be held at the Hilton Orlando Lake Buena Vista Palace–Disney Springs resort area. The hotel features spacious guest rooms, multiple dining options, and 2 heated outdoor pools. The hotel is connected by a pedestrian skybridge to Disney Springs, which boasts more than 50 additional dining options, boutiques, and family-friendly activities and entertainment. Daily shuttle buses to all Disney theme parks are available, and hotel guests can enjoy 30-minute early entry to any theme park on any day.

SNMMI is committed to ensuring that appropriate and necessary health and safety measures are in place during the meeting. We will follow all Centers for Disease Control and Prevention safety protocols and recommendations and will comply with all federal, state, and local regulations. **All attendees must be fully vaccinated for COVID-19, and masks will be required.**

Travel restrictions have eased considerably over the past few months, and most medical institutions are allowing domestic travel for individuals who are fully vaccinated. Vaccinated travelers from abroad will also be able to enter the United States beginning in early November with proof of vaccination and a negative COVID test within 3 days of their flights. SNMMI recommends that international attendees check their countries' travel requirements for more specific guidance.

Please note that while SNMMI is excited to offer its first in-person meeting since 2020, we understand that the COVID-19 pandemic is continuously changing. We will monitor ongoing conditions in Florida and across the world and will communicate any changes about the meeting.

Registration for the SNMMI Mid-Winter and ACNM Annual Meeting is open. I encourage you to register today and begin making plans to join us in Orlando. It's been a long time, and we can't wait to see you in person again!

Global ^{225}Ac Partnerships Announced

The widely acknowledged promise of α-emitting radioisotopes in theranostic applications has been challenged by limitations in reliable supply and efficient production technologies. National and international companies and government agencies are addressing these shortages with formal collaborative partnerships that leverage individual strengths.

On September 8, NorthStar Medical Radioisotopes, LLC (Beloit, WI), and POINT Biopharma Global Inc. (Indianapolis, IN) announced the signing of a supply agreement for ^{225}Ac. Under the terms of the agreement, NorthStar will provide POINT with its electron accelerator–produced ^{225}Ac, which POINT will use: in investigational studies of PNT2001, a next-generation prostate-specific membrane antigen (PSMA) agent for nonmetastatic castrate-sensitive prostate cancer; in PNT2004, a fibroblast-activation protein-α candidate with multiple potential oncologic applications; and to advance its novel tumor microenvironment–targeting technology platform. "NorthStar is at the forefront of U.S. radioisotope production as the only commercialized producer of the important medical radioisotope ^{99}Mo, and we are applying that same development expertise to rapidly advance large-scale availability of ^{225}Ac," said Stephen Merrick, president and CEO of NorthStar. "Our ^{225}Ac process uses highly efficient electron accelerator production technology that provides increased capacity and scheduling flexibility. Like all NorthStar processes, it is environmentally friendly, nonuranium based, and uses highly advanced technology."

IBA (Ion Beam Applications SA; Louvain-la-Neuve, Belgium) and SCK CEN (Belgian Nuclear Research Center; Mol, Belgium) announced on September 15 a strategic research and development partnership to enable ^{225}Ac production. The first phase of the partnership will include an in-depth evaluation of technical and economic feasibility, followed by construction and commissioning of a production unit on the SCK CEN site. This initiative is in alignment with the recent European recovery plan for Belgium, in which the European Commission designated ^{177}Lu and ^{225}Ac as promising isotopes. Eric van Walle, director general of SCK CEN, said: "Theranostics have the potential to revolutionize the way we treat cancer. By partnering with IBA, we can use our nuclear knowhow to transform isotopes meant to become radioactive waste into therapeutic compounds. Our complementary expertise will enable us to work towards providing the greatest number of patients with the benefits of this latest generation of nuclear medicine."

One day later, on September 16, BWXT Medical (BWX Technologies; Lynchburg, VA) and Bayer AG (Leverkusen, Germany) announced in Ottawa, Canada, an agreement to develop ^{225}Ac supply and advance additional partnering opportunities on finished products as both companies broaden their respective commercialization strategies for targeted radionuclide therapies. BWXT Medical is a worldwide supplier of medical isotopes and radiopharmaceuticals. Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. The oncology franchise at Bayer includes 6 marketed products, including Xofigo (^{223}Ra-dichloride, the first approved targeted α therapy) and several other targeted α therapies in different stages of development, including an investigational ^{225}Ac-labeled differentiated PSMA small molecule for treatment of prostate cancer.

NorthStar Medical Radioisotopes, LLC/POINT Biopharma Global Inc.
Ion Beam Applications SA/Belgian Nuclear Research Center
BWXT Medical/Bayer AG

New SNMMI Annual Awards Guide Published

SNMMI announced on September 30 the release of its first comprehensive awards publication, *SNMMI Annual Grants & Awards Recognition 2021*, highlighting recipients of the many honors, awards, grants, and scholarships presented by SNMMI and the SNMMI Technologist Society in the past year. This will be an annual publication distributed to all members and published on the SNMMI website. The publication includes the winners of distinguished service awards, research grants, scholarships, council and centers of excellence recognitions, publication awards, professional development selections, and SNMMI Annual Meeting awards. These awards highlight groundbreaking accomplishments within the specialty of nuclear medicine as well as contributions to the society itself.

In addition to recognizing award recipients, the publication serves as a means through which SNMMI members and the public can learn more about grant and award opportunities available through the society. SNMMI provides more than $400,000 annually to advance nuclear medicine, molecular imaging, and therapy; fund professional development efforts; and support the next generation of researchers. The fall application window for the 2021–2022 Grants & Awards Program opened in October. For open opportunities and upcoming deadlines, see: http://www.snmmi.org/grants. For the 2021 grants and awards publication, see: https://s3.amazonaws.com/rdcms-snmmi/files/production/public/FileDownloads/Membership/FINAL_2021AwardsBrochure.pdf.

FDA Clears Photon-Counting–Based CT Device

The U.S. Food and Drug Administration (FDA) announced on September 30 its 510(k) clearance of the NAEOTOM Alpha (Siemens Healthineers; Frankfurt, Germany), described

by the agency in a press release as "the first new major technological improvement for CT imaging in nearly a decade." The device includes a new photon-counting detector with an active detection layer and a cadmium telluride crystal. According to a statement on the same day from Siemens Healthineers, the device offers clear advantages over conventional CT detectors, which convert X-rays in a 2-step process first into visible light that is then detected by a light sensor, ultimately producing the final image. In this intermediate step, important information about the energy of the X-rays is lost, contrast is reduced, and images lack clarity. The photon-counting CT detector converts X-rays directly into completely digital electrical signals that are then counted without information loss, adding clinically relevant information and improving image sharpness and contrast.

"About 15 years ago, work on photon counting and its clinical vision started at Siemens Healthineers," said André Hartung, MD, Head of Diagnostic Imaging at Siemens Healthineers. "We always believed in the tremendous clinical value and relentlessly worked on it together with our partners. We are excited that we have received FDA 510(k) clearance."

U.S. Food and Drug Administration
Siemens Healthineers

Societies Urge Congress to Avert Physician Reimbursement Cuts

On October 14 SNMMI and more than 200 medical societies expressed their support for averting cuts to the Medicare Physician Fee Schedule (MPFS). Reps. Ami Bera (D-CA) and Larry Bucshon (R-IN) led this effort in a "Dear Colleague" letter to House leadership, supported by 245 members of Congress. SNMMI, along with many societies with which it shares interests, including the American College of Radiology, was instrumental in engaging members of Congress to support this effort. The MPFS has failed to keep up with inflation, and larger increases to some providers must be offset by cuts to other providers to conform to a budget neutrality provision, further contributing to the financial pressure on health care professionals. In addition, health care professionals are facing payment cuts stemming from MPFS adjustments as well as the Medicare sequester and the Statutory Pay-As-You-Go (PAYGO) Act. The Consolidated Appropriations Act, enacted on December 27, 2020, contained a 3.75% payment adjustment for all PFS services in calendar year 2021 as part of Congressional relief provided for the impending payment cuts. This payment adjustment afforded some short-term stability for health care professionals struggling with the impact of the COVID-19 pandemic. This critical piece of Congressional relief will expire at the end of 2021 and adds to impending cuts resulting from the expiring moratorium on the 2% Medicare sequester and the 4% Medicare payment cut due to PAYGO, which was triggered by the passage of the American Rescue Plan. The combined impact of these cuts means that all health care professionals are likely facing at least 9% in cuts to Medicare payment unless Congress takes action. SNMMI members, patient advocates, and concerned citizens are encouraged to send letters of support to avert physician reimbursement cuts.

SNMMI

2021–2023 SNMMI Wagner–Torizuka Fellowship

SNMMI on October 15 announced that Yoshito Kadoya, MD, PhD, assistant professor in the Department of Cardiovascular Medicine at Kyoto Prefectural University of Medicine (Japan), is the recipient of the 2021–2023 SNMMI Wagner–Torizuka Fellowship. This 2-year award, created in 2008 by the late Henry N. Wagner, Jr., MD, and the late Kanji Torizuka, MD, PhD, is designed to provide extensive training and experience in the fields of nuclear medicine and molecular imaging for Japanese physicians in the early stages of their careers. Kadoya's research focuses on the potential of nuclear medicine applications for interventional cardiology in structural heart disease. He will study in the University of Ottawa Heart Institute (Canada) Cardiac Imaging Program under the supervision of Benjamin Chow, MD. The fellowship will provide an annual stipend of US$24,000.

"We are very pleased to welcome Dr. Kadoya to North America as he begins his fellowship," said Vasken Dilsizian, MD, SNMMI past president and chair of the SNMMI Awards Committee. "As with all of the fellows, we hope that the professional development and research and clinical expertise he gains as a result of this program will equip him to make significant contributions to the field of nuclear medicine and molecular imaging in Japan."

The SNMMI Wagner–Torizuka Fellowship program, sponsored by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan), has successfully graduated 33 fellows since its inauguration in 2008. Three fellows are currently studying at host institutions across the United States. Applications and additional information about requirements for the 2022–2024 fellowship are available at www.snmmi.org/grants. Applications are due by January 30, 2022.

SNMMI

NIH Awards Grants to Address Disparities and Equity

The National Institutes of Health (NIH) announced on October 13 the award of 11 grants intended to fund "bold, new research ideas that focus on interventions to address health disparities and advance health equity." As part of the NIH Common Fund's Transformative Research to Address Health Disparities and Advance Health Equity initiative, the awards will provide more than $58 million over 5 years. Innovation in these applications was evaluated based on their focus on the significance of the research problem, the novelty of the idea or approach, and/or the magnitude of the potential impact, rather than on preliminary data or experimental details.

"It is unacceptable for persistent and pervasive health inequities to continue despite the scientific advancements and knowledge base we have achieved,"

said NIH Director Francis S. Collins, MD, PhD. "This research effort will catalyze novel interventions and hasten the opportunity to put evidence into action for populations affected by health disparities." Each of the awards includes an innovative intervention component and focuses on 1 or more NIH-designated populations that experience health disparities in the United States. Example projects include: community-based research collaborations to test financial interventions that address structural racism and health/well-being in minority neighborhoods; community-based telehealth-driven or technology-assisted interventions for physical and mental health; technology-enhanced approaches to advance cancer health equity among diverse deaf, deaf-blind, and hard-of-hearing populations; and new models of school-based, telehealth-driven preventive care for children in underserved rural and/or socioeconomically disadvantaged areas.

In addition, the initiative is targeting expansion of health disparities research at minority serving institutions (MSIs). The NIH Common Fund plans to reissue a dedicated funding opportunity specifically designed for MSIs in fiscal year 2022 to support additional projects.

National Institutes of Health

U.S. Patient Cancer Costs Topped $21 Billion in 2019

The second part of the latest *Annual Report to the Nation on the Status of Cancer* found that patients in the United States carry a large burden in cancer care costs. The report, appearing on October 26 in *JNCI: The Journal of the National Cancer Institute,* is the most comprehensive examination of patient economic burden for cancer care to date and includes information on patient out-of-pocket spending by cancer site, stage of disease at diagnosis, and phase of care. In 2019, the national patient economic burden associated with cancer care was $21.09 billion, made up of patient out-of-pocket costs of $16.22 billion and patient time costs of $4.87 billion. Patient time costs reflect the value of time spent traveling to and from health care and waiting for and receiving that care. The analysis focused only on costs directly incurred by patients; total overall costs of cancer care and lost productivity are much larger.

Among adults aged 65 years and older with Medicare coverage, average annualized net out-of-pocket costs for medical services and prescription drugs were $2,200 and $243, respectively, in the initial phase of care (first 12 mo after diagnosis) and $3,823 and $448, respectively, in the end-of-life phase (12 mo before death among those who died). Average costs were lowest in the intervening months. Across all cancer sites, average annualized net patient out-of-pocket costs for medical services in the initial and end-of-life phases of care were lowest for patients who were originally diagnosed with localized disease compared with more advanced-stage diagnoses.

Analyses of differences in patient economic burden by cancer type found substantial variation in patient out-of-pocket costs, reflecting differences in treatment intensity and duration as well as survival. In 2019, total national out-of-pocket costs were highest for breast ($3.14 billion), prostate ($2.26 billion), colorectal ($1.46 billion), and lung ($1.35 billion) cancers. "As the costs of cancer treatment continue to rise, greater attention to addressing patient medical financial hardship, including difficulty paying medical bills, high levels of financial distress, and delaying care or forgoing care altogether because of cost, is warranted," said Karen E. Knudsen, MBA, PhD, chief executive officer of the American Cancer Society (ACS). "These findings can help inform efforts to minimize the patient economic burden of cancer, and specific estimates may be useful in studies of the cost-effectiveness of interventions related to cancer prevention, diagnosis, treatment, and survivorship care."

The annual report is a collaborative effort among the ACS, the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries. Part 1 of this report, released in July, focused on national cancer statistics. For more information about the report, see https://seer.cancer.gov/report_to_nation.

National Cancer Institute