2020 SNMMI Highlights Lecture: Cardiovascular Nuclear and Molecular Imaging

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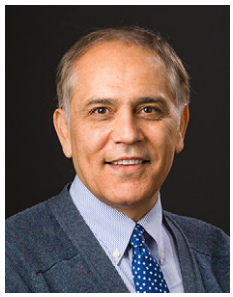
From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2020 Highlights Lectures were delivered on July 14 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the lecture by Mehran M. Sadeghi, MD, a professor in the Department of Internal Medicine (Cardiology) at Yale University School of Medicine (New Haven, CT), and Veterans Affairs Connecticut Healthcare System, who spoke on highlights in cardiovascular nuclear and molecular imaging. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2020;61[suppl 1]).*

It is an honor to review some of the best cardiovascular abstracts presented at the 2020 SNMMI Annual Meeting. As in previous years, we saw a large number of cardiovascular abstracts from around the globe. The top 3 contributing countries were the United States, China, and Japan, with 14 other countries represented. Forty-eight abstracts were planned as oral presentations and 53 as posters. Of the 101 total abstracts, 75% were on clinical and 25% on basic and translational science topics. These presentations can be categorized into 3 groups: those focused on refining the practice of nuclear cardiology, those addressing diagnostic gaps and new applications, and those advancing scientific discovery.

The program committee selected 6 abstracts as finalists for the Cardiovascular Council Young Investigator Award (YIA) competition. These finalists included investigators from 3 continents and covered a broad range of topics. I would like to congratulate these authors, who are on their way to being the future leaders of our field. I will be highlighting each of their contributions in different parts of today's lecture. Special recognition goes to Nele Hermanns and Jacek Kwiecinski, MD, who were the Cardiovascular Council YIA winners.

Hermanns et al. from the Hannover Medical School (Germany) reported on "Molecular imaging of inflammation in the brain–heart axis after ischemic stroke: Comparison of 2 murine stroke models" [88]. Stroke is associated with increased risk of myocardial infarction (MI) and cardiac dysfunction, and systemic inflammation is present after stroke. These authors used 2 mouse models of induced stroke: middle cerebral artery occlusion (MCAO) and topical application of a vasoconstrictor, endothelin-1. They used a translocator protein (TSPO)–targeted tracer, ^{18}F-GE180, to image neuroinflammation with whole-body PET, along with MR imaging of the brain and the heart, followed by autoradiography (Fig. 1). Their study showed a larger area of infarct in the MCAO model, which was associated with increased TSPO signal on both PET and autoradiography. The increase in the brain TSPO signal was associated with an increase in the cardiac TSPO signal and a reduction in left ventricular ejection fraction (LVEF) at both 1 and 2 weeks after stroke induction. They noted an inverse relationship between the extent of stroke and LVEF. The authors concluded that their MCAO model enables imaging studies of brain–heart networking after stroke, which evokes elevated TSPO PET signal in both brain and heart, and that "the severity of cerebral ischemic damage may contribute to cardiac dysfunction via systemic inflammation."



Mehran M. Sadeghi, MD

Kwiecinski et al. from the Institute of Cardiology (Warszawa, Poland), Cedars-Sinai Medical Center (Los Angeles, CA), and the University of Edinburgh (UK) reported on "Clinical predictors of ^{18}F-sodium fluoride PET coronary uptake in patients with advanced coronary artery disease (CAD)" [87]. ^{18}F-NaF PET has been used to image calcification in coronary arteries, with higher signal detected in foci of microcalcification than in macrocalcification. Uptake of ^{18}F-NaF was previously shown in culprit lesions after MI, and, more recently, a high global ^{18}F-NaF signal has been shown to be associated with a higher risk of MI. These authors compared ^{18}F-NaF PET results with those from calcium scoring in ~300 patients and showed that ^{18}F-NaF PET outperformed calcium scoring for prediction of MI. In addition, they developed a machine learning model that incorporated ^{18}F-NaF PET, clinical, and CT data and showed that these 3 together outperformed either clinical data or clinical data plus CT. This method can be used to upscale or downscale the estimated risk of MI in specific patients. On the left in Figure 2, ^{18}F-NaF signal was seen in the coronary artery in a 49-year-old man, leading to an increase in estimation of risk of MI. On the right, estimation of risk was reduced in a patient with no coronary ^{18}F-NaF signal.

The Cardiovascular Council presents 2 prestigious awards. The Hermann Blumgart Award is the top award and recognizes outstanding scientific contributions to the field and service to the council. At this meeting, the award went to

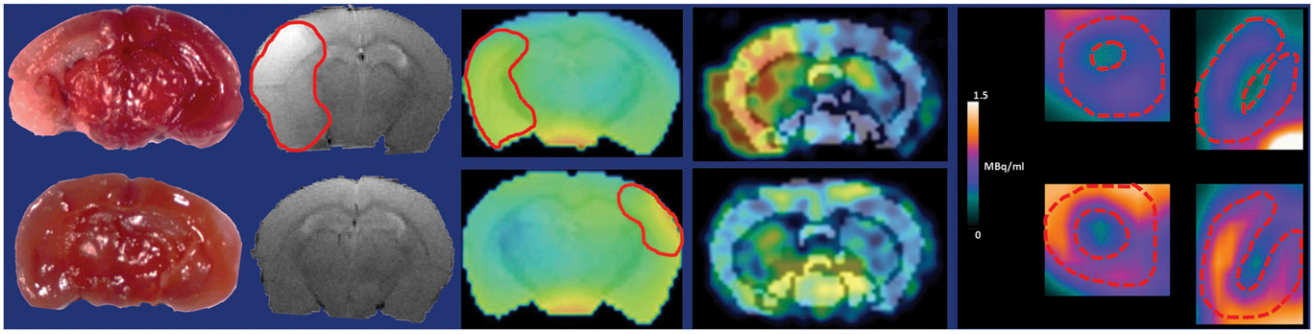


FIGURE 1. Molecular imaging of inflammation in the brain–heart axis after ischemic stroke in 2 murine models. Top row, first 4: Middle cerebral artery occlusion (MCAO) model imaged with triphenyltetrazolium chloride staining, MRI, ^{18}F-GE180 PET, and autoradiography at 7 days after occlusion showed large-size stroke and neuroinflammation. Bottom row, first 4: Model with topical application of a vasoconstrictor, endothelin-1, to cortex evoked limited stroke and neuroinflammation. Larger stroke size led to greater cardiac dysfunction. Far right block: Short- and vertical long-axis cardiac images; top: sham-operated mice at 7 d after surgery; bottom: MCAO model mice at 7 d after surgery. The study expands understanding of brain–heart networking after stroke.

Piotr Slomka, PhD, Professor of Medicine at the Cedars-Sinai Medical Center (Los Angeles, CA) and the David Geffen School of Medicine at the University of California, Los Angeles. The new Outstanding Educator Award recognizes the contribution of cardiovascular educators. The awardee was Diwakar Jain, MD, from Westchester Medical Center (Valhalla, NY).

We had a large number of outstanding abstracts this year on various aspects of nuclear cardiology and molecular imaging. Because of time limitations I have selected a few representative examples and apologize to the authors of important work not reviewed here.

Refining the Practice of Nuclear Medicine

Myocardial Perfusion Imaging. Myocardial perfusion imaging (MPI) is the cardiovascular procedure we perform most often in our laboratories and that in many ways defines the field of nuclear cardiology. This year several innovations in MPI were presented during the meeting. These included refinements to imaging and image analysis protocols and ways to enhance the value of perfusion imaging in patient management. As an example, Arida-Moody et al. from the University of Michigan Health System (Ann Arbor) and INVIA (Ann Arbor, MI, and Ottawa, Canada) reported on "Comparison of weight- and body mass index [BMI]–adjusted dosing for dynamic ^{82}Rb PET myocardial perfusion imaging" [1592]. The BMI-dosing protocol significantly reduced both the frequency and severity of detector saturation, as well as the overall mean ^{82}Rb dose and effective radiation exposure.

Another example of innovations in imaging protocols and image analysis came from Yang et al. from the University of California San Francisco and Yale University (New Haven, CT), who reported on "CT-less attenuation correction in image space using deep learning for dedicated cardiac SPECT: A feasibility study" [223]. Many dedicated cardiac SPECT scanners with cadmium-zinc-telluride (CZT) do not have an integrated CT for attenuation correction. These authors developed a deep learning approach to generate attenuation-corrected SPECT images directly from non-corrected SPECT without undergoing an additional image reconstruction step. The results yielded more uniform images on a segmental basis than non–attenuation corrected images. This can be seen in Figure 3, where the diaphragmatic attenuation artifact is improved with both the CT attenuation correction and the deep learning approach.

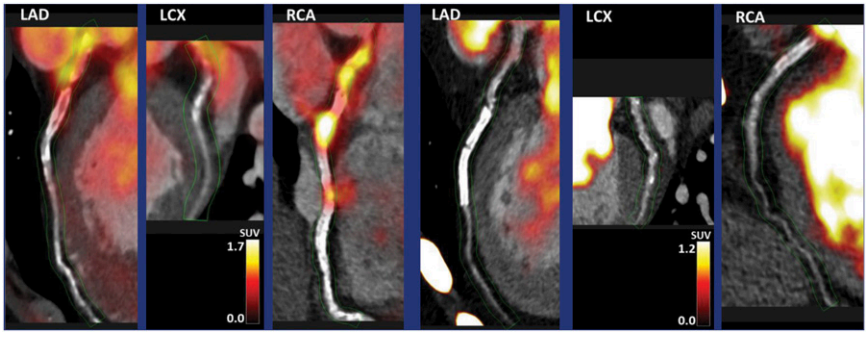


FIGURE 2. Upscaling and downscaling of patient risk with ^{18}F-NaF–based machine learning. Left 3 images, left to right: left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) ^{18}F-NaF PET/CT in a 49-year-old male with coronary microcalcification activity of 10.5. Clinical and CT data alone provided a 1.5% risk estimate of MI (47th percentile). Combining ^{18}F-NaF PET, CT, and clinical data produced a risk estimate of 8% (81st percentile). Right 3 images: corresponding images in a 75-year-old man with no microcalcification activity and a 2.3% clinical plus CT-estimated risk (57th percentile). The addition of ^{18}F-NaF PET downscaled this predictive risk to 1.1% (the 32nd percentile).

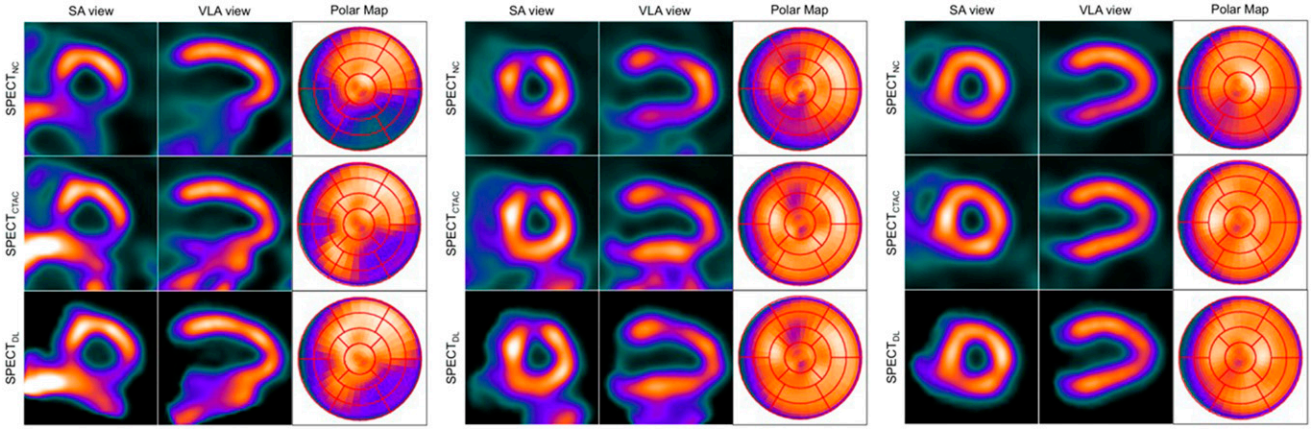


FIGURE 3. CT-less attenuation correction in image space using deep learning for dedicated cardiac SPECT. Examples from 3 subjects in (left to right in blocks) short- and vertical long-axis views and polar maps. Top row: non–attenuation corrected SPECT; middle row: CT–attenuation corrected SPECT; and bottom row deep learning–attenuation corrected SPECT. The deep learning approach yielded more uniform images on a segmental basis than non–attenuation corrected images.

Another deep learning application in MPI analysis came from Otaki (a YIA finalist) et al. from Cedars-Sinai Medical Center (Los Angeles, CA), Israel and Ben Gurion University of the Negev (Beer Sheba Israel), Veterans General Hospital (Taipei, Taiwan), Columbia University Medical Center (New York, NY), Oregon Heart and Vascular Institute (Springfield), University of Ottawa Heart Institute (Canada), University Hospital Zurich (Switzerland), Yale University (New Haven, CT), and Brigham and Women's Hospital (Boston, MA), who reported on "Diagnostic accuracy of deep learning for MPI in men and women with a high-efficiency parallel-hole-collimated CZT camera: Multicenter study" [92]. They used data from the REgistry of Fast Myocardial Perfusion Imaging with NExtgeneration SPECT (REFINE), including 1,160 MPIs from patients with no history of prior CAD and with results from invasive angiography within 6 months of MPI. These authors developed a novel deep learning model that incorporates analysis of raw upright and supine stress polar maps, with specification of sex and BMI. Gradient-weighted class activation mapping was employed to visualize regions contributing to disease prediction on polar maps (Fig. 4). This deep learning model outperformed both total perfusion defect and visual scoring by summed stress score in both men and women. They did find, however, that there are differences in sensitivity between women and men and are continuing to study the reasons for this. These authors concluded that their deep learning approach can be applied clinically on a PC to help readers.

Other examples of presentations on novel analytic advances in perfusion imaging included that of Miller et al. from Cedars-Sinai Medical Center Program (Calgary, Canada, Los Angeles, CA, West Hollywood, CA), Assuta Medical Center (Tel Aviv, Israel), Columbia University Medical Center (New York, NY), Oregon Heart and Vascular Institute (Springfield), University of Ottawa Heart Institute (Canada), University Hospital Zurich (Switzerland), Yale University (New Haven, CT), Cardiovascular Imaging Technologies (Kansas City, MO), and Brigham and Women's Hospital (Boston, MA), who reported that "Quantitation of ventricular morphology provides incremental

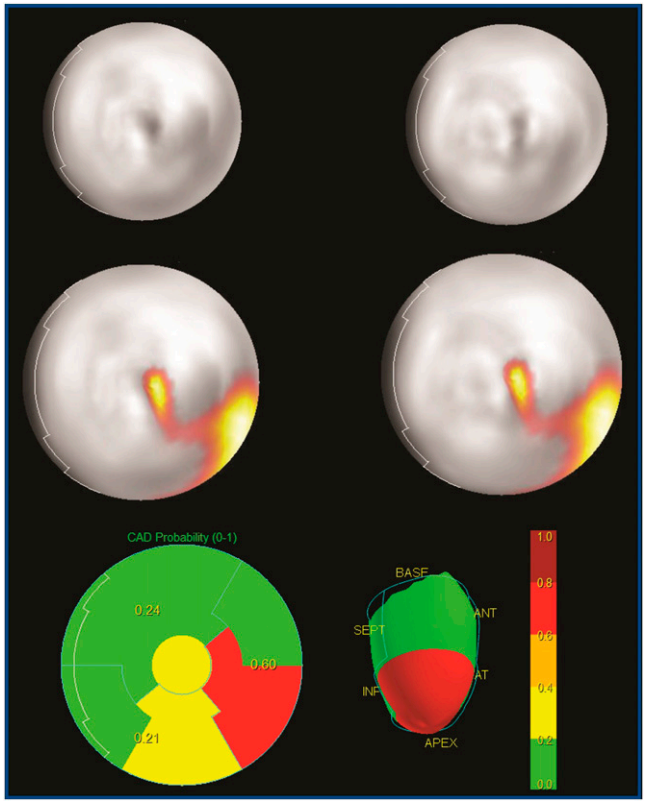


FIGURE 4. Deep learning for myocardial perfusion with a high-efficiency parallel-hole-collimated cadmium-zinc-telluride camera. Top row: Upright and supine raw polar perfusion maps used as input for the deep learning model. Middle row: Upright and supine coronary artery disease (CAD) stress-perfusion attention maps. Bottom row: CAD probability maps as generated by the deep learning model, which outperformed both total perfusion defect and visual scoring by summed stress score in men and women, although sex-based differences in sensitivity were noted.

prognostic utility in patients undergoing SPECT MPI" [660]. They concluded that "changes in ventricular morphology have important prognostic utility and should be included in patient risk estimation following SPECT MPI." Wells and Ruddy from the University of Ottawa Heart Institute (Canada), reported that "Respiratory motion alters measurement of SPECT myocardial blood flow" [654], with respiratory motion causing displacement of the heart by >10 mm in 17% of dynamic scans.

We also heard notable information highlighting the value of MPI. Mannarino et al. from the University Federico II (Naples, Italy) and the Manchester University NHS Foundation Trust (UK) reported on "Prognostic value of coronary vascular dysfunction assessed by hybrid ^{82}Rb PET/CT imaging in patients with resistant hypertension" [640]. They concluded that ^{82}Rb PET/CT in patients with resistant hypertension can help to identify a higher risk of cardiovascular events and could be useful in "guiding alternative potential therapeutic strategies aimed to directly improve myocardial perfusion reserve." Khan et al. from the Marshfield Clinic Health System (WI) and the Hospital of the University of Pennsylvania (Philadelphia) reported that "Risk prediction of coronary flow reserve is strongly influenced by the burden of coronary calcification" [653]. These authors concluded that coronary flow reserve helps to risk stratify patients with coronary artery calcium ≥10.

Imaging Infiltrative Cardiomyopathy and Device and Valve Infection. Imaging of infiltrative cardiomyopathy and of device and valve infection are routinely performed in many nuclear imaging laboratories. The focus has now shifted from proof of principle to refining the ways in which these tests are performed, acquiring quantitative information, and improving accuracy. Several associated innovations were reported this year. As an example, Bukhari et al. from the University of Pittsburgh Medical Center (PA) reported on "Clinical predictors of positive ^{99m}Tc-pyrophosphate scan in patients hospitalized for decompensated heart failure" [659]. At their institution, they found that almost one-third of hospitalized patients with clinically suspected cardiac amyloidosis had final diagnoses of wild-type transthyretin amyloid cardiomyopathy. A history of carpal tunnel syndrome, ECG findings of low QRS voltage, atrioventricular block and left anterior fascicular block, and echocardiographic features of LV hypertrophy and high-grade diastolic dysfunction were prevalent in these patients. Poitrasson-Riviere et al. from INVIA Medical Imaging Solutions (Ann Arbor, MI) and the University of Michigan (Ann Arbor, MI) reported on "Quantitative assessment of inflammatory ^{18}F-FDG PET scans for diagnosis of cardiac sarcoidosis" [650]. They found that "quantification of LV myocardial ^{18}F-FDG activity above blood pool SUV is a reliable method for diagnosis of myocardial inflammation and is associated with worse prognosis."

Other investigators looked at imaging device and valve infection. Abikhzer et al. from the Jewish General Hospital (Montreal, Canada), Health Sciences Centre (Winnipeg, Canada), and the Institut de Cardiologie de Montreal (Canada) reported on "FDG-PET CT for the evaluation of native valve endocarditis" [645]. They found that "the addition of positive ^{18}F-FDG PET/CT as a major criterion in the modified Duke Criteria improved performance of the criteria for diagnosis of patients with native valve endocarditis, particularly in those subjects with possible infectious endocarditis." [645].

Sommerlath Sohns et al. from the Hannover Medical School (Germany) reported that "Inflammatory volume from ^{18}F-FDG PET/CT assists in prognostic assessment of patients with LV assist device (LVAD) infection" [644]. Looking at data from 50 patients with LVAD infections, they quantified the ^{18}F-FDG signal in different components of the device (Fig. 5). They found that patients with high c-reactive protein and high ^{18}F-FDG signal volume on PET had worse outcomes than other groups and suggested

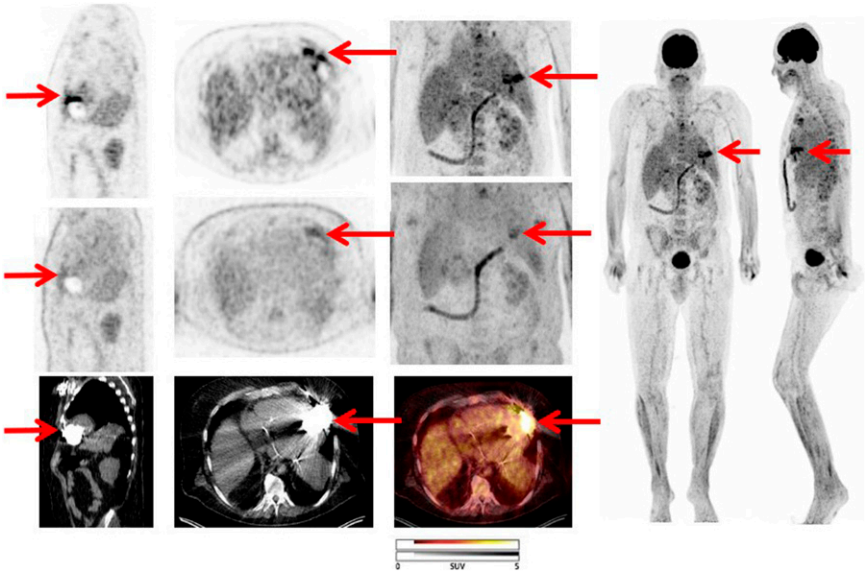


FIGURE 5. Inflammatory volume from ^{18}F-FDG PET/CT in prognostic assessment of patients with left ventricular assist device (LVAD) infection. Example of a patient with LVAD infection. Left to right: Sagittal, axial/transverse, MIP and fusion PET/CT, and MIP coronal/sagittal images. Top to bottom, first 3 columns, attenuation-corrected ^{18}F-FDG PET, non–attenuation corrected ^{18}F-FDG PET, and CT. Patients with high c-reactive protein and high ^{18}F-FDG signal volume on PET had worse outcomes than other groups. This combination of parameters was suggested as a useful way to identify a patient subset at highest risk of adverse outcomes.

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Expanding the Horizon

Beyond the tests routinely performed in many nuclear laboratories, investigators are introducing new applications and tracers to expand the horizons for molecular imaging in cardiovascular medicine. Some notable examples of these innovations are listed here, spanning from heart failure to aneurysm and calcific aortic valve disease. Examples of research presented on new applications included, among others, Thayumanayan et al. from the All India Institute of Medical Sciences (New Delhi, India), who reported on "Fluorine-18 fluoro-L-dihydroxyphenylalanine (^{18}F-FDOPA) PET-CT in evaluation of cardiac sympathetic innervation in heart failure patients" [648]; Nakahara et al. from the Keio University School of Medicine (Tokyo, Japan), Fukushima Medical University (Japan), Memorial Sloan Kettering Cancer Center (New York, NY), and Mount Sinai (New York, NY), who reported that "The combination of ^{18}F-FDG and ^{18}F-NaF uptake predicts the development of abdominal aortic aneurysm in rat model" [31]; Zadeh et al. from Children's Hospital of Philadelphia (PA), the Perelman School of Medicine at the University of Pennsylvania (Philadelphia), Odense University (Denmark), and Oslo University Hospital (Norway), who reported on "Assessing risk of atherosclerosis in smoldering multiple myeloma patients by means of ^{18}F-sodium fluoride with global assessment" [635]; Diekmann et al. from the Hannover Medical School, Charité Universitätsmedizin Berlin, and the Technische Universität München (all in Germany), who reported that "Clinical imaging of chemokine receptor CXCR4 early after acute MI predicts subsequent ventricular dysfunction and remodeling" [663]; and Farber et al. from the University of Ottawa/University of Ottawa Heart Institute (Canada), who reported on "Multimodality imaging to predict calcific aortic valve disease progression in animal models" [27]. An example of research presented on new tracers was Gali et al. from the University of Oklahoma Health Science Center (Oklahoma City) and Hexakit, Inc. (Oklahoma City, OK), who reported on "Evaluation of ^{18}F-FGA PET/CT for specific imaging of necrotic tissue in a mouse model of coronary artery ligation" [228].

I will highlight here a few of the new applications and tracers that are currently in different stages of development. Woodard et al. from Washington University St. Louis (MO) and the University of California at Santa Barbara reported on "Targeted natriuretic peptide receptor-C (NPR-C) PET/MR imaging of carotid atherosclerosis in humans: Correlation with ex vivo plaque immunohistochemistry (IHC)" [636]. This was a first-in-human study. There is considerable debate on how patients with asymptomatic carotid stenosis should be managed, and molecular imaging may help risk-stratify these individuals. These researchers have developed a nanoparticle radiotracer, ^{64}Cu-CANF-Comb, that targets NPR-C, a molecule expressed on macrophages and smooth muscle cells and is upregulated in atherosclerosis. In 15 patients scheduled for carotid endarterectomy they showed uptake of the tracer in cardiac atherosclerosis on PET/MR imaging (Fig. 6) and were able to characterize the plaque. After carotid endarterectomy and IHC, they identified a significant correlation between the tracer signal and NPR-C expression in the tissue, indicating that they are indeed imaging this target in vivo. Follow up studies should establish whether this approach can be used routinely for risk stratification in carotid stenosis.

Improving risk stratification in abdominal aortic aneurysm (AAA) is another potential novel application of molecular imaging. This is a rapidly advancing field with several innovations introduced this year. Heo et al. from the Washington University School of Medicine (St. Louis, MO) reported on "Assessment of AAA inflammation and rupture prediction with chemokine receptor 2 [CCR2] PET" [23]. They evaluated ^{64}Cu-DOTA-ECL1i, a novel tracer that binds to CCR2, in a rat model of AAA. Their in vivo PET imaging studies showed higher uptake of the tracer in the rat model of AAA than in sham-operated animals at 7 days after surgery (Fig. 7). They showed that the signal was specific, and, of particular note, that the signal was higher in animals that experienced aneurysm rupture than in animals that did not. They concluded that CCR2 PET might be used for growth and/or rupture prediction in AAA.

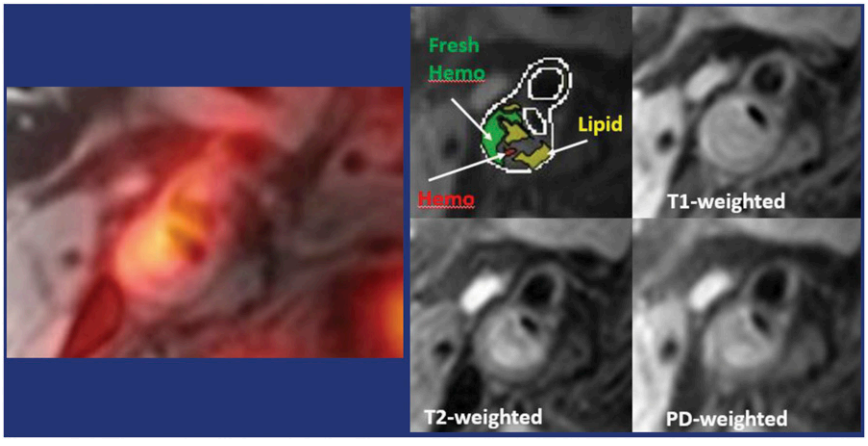


FIGURE 6. Targeted natriuretic peptide receptor-C (NPR-C) PET/MR imaging of carotid atherosclerosis. Fused PET/MR image (left) in a patient with high ^{64}Cu-CANF-Comb PET uptake in the right common carotid artery in a plaque with intraplaque hemorrhage on multiweighted MRI (right images). This first-in-human study correlated the carotid tracer signal with immunohistochemistry-assessed NPR-C expression in carotid endarterectomy tissue, an approach with promise for clinical risk stratification in carotid stenosis.

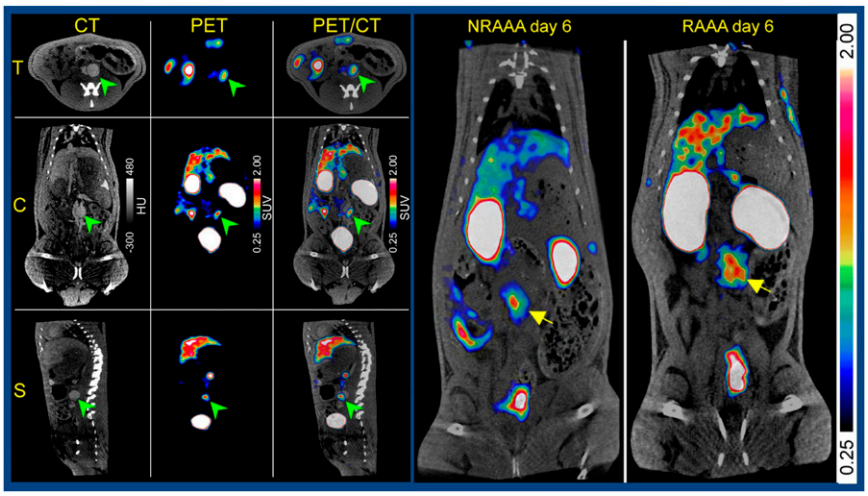


FIGURE 7. Improving risk stratification in abdominal aortic aneurysm (AAA) with chemokine receptor 2 (CCR2) PET. ^{64}Cu-DOTA-ECL1i PET in a rat model of AAA showed tracer binding in AAA [left 3 columns: CT, PET, and PET/CT in (top to bottom) transverse, coronal, and sagittal views]. Imaging at 7 days postsurgery showed higher uptake of the tracer in the AAA rat model than in sham-operated animals. Right 2 images: Tracer uptake in AAAs that subsequently ruptured (right) demonstrated uptake nearly twice that of nonruptured AAAs (left), despite comparable diameters of aneurysms in the 2 models.

Following the same theme, Toczek (a YIA finalist) et al. from the Yale University School of Medicine (New Haven, CT) and the Veterans Affairs Connecticut Healthcare System (West Haven) reported on "Multimodal molecular imaging of phagocytic and proteolytic activity in AAA" [89]. Using a nanoparticulated CT contrast agent in a mouse model of AAA, they were able to detect aortic dilation 5 minutes after contrast administration (Fig. 8). Within 24 hours, uptake of the tracer was evident in the AAA wall. Transmission emission microscopy showed that this nanoparticle localizes in adventitial macrophages, and immunostaining of aneurysm showed a significant correlation between macrophage marker expression and CT signal but not between smooth muscle or endothelial cell markers and CT signal. In addition, a group of animals in this study underwent dual-modality SPECT/CT imaging to

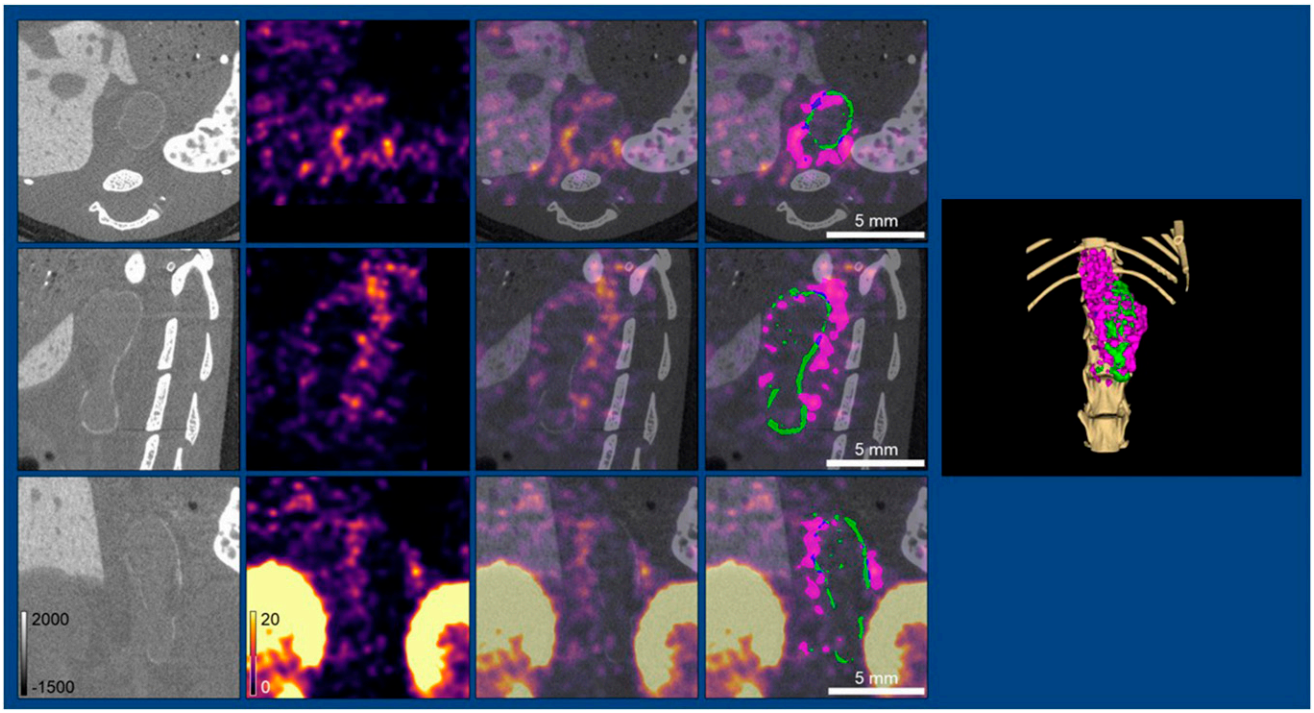


FIGURE 8. Dual-modality SPECT/CT imaging of phagocytic and matrix metalloproteinase (MMP) activity in abdominal aortic aneurysm (AAA). Columns, left to right: CT imaging of phagocytic activity, SPECT imaging of MMP activity, fusion SPECT/CT, and segmentation. Using a nanoparticulated CT contrast agent in this mouse model of AAA, the authors were able to detect aortic dilation 5 minutes after contrast administration and, within 24 hours, uptake of the tracer was evident in the AAA wall. In animals that underwent both CT imaging to detect phagocytic activity and MMP SPECT imaging, both signals were present in the AAA but not necessarily at the same location, indicating distinct patterns of phagocytic activity and MMP-associated proteolytic activity in AAA.

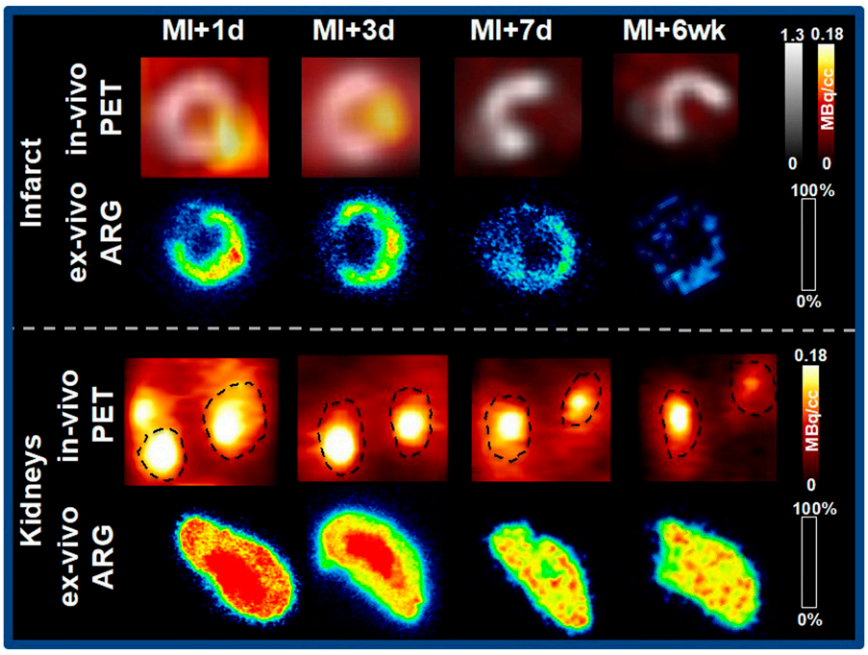


FIGURE 9. Imaging inflammation crosstalk along the cardio–renal axis after myocardial infarction (MI) in a mouse model. Serial ^{68}Ga-pentixafor PET images of chemokine receptor 4 expression at (left to right) 1, 3, and 7 days and 6 weeks after MI showed transient upregulation in the infarct region (top 2 rows, in vivo PET and ex vivo autoradiography) early after MI with, a corresponding increase in renal uptake (bottom 2 rows, in vivo PET and ex vivo autoradiography). Serial ^{68}Ga-pentixafor uptake in the infarct strongly correlated with kidney uptake, suggesting crosstalk between the injured heart and kidneys after MI, which may contribute to adverse outcomes for both organs.

detect phagocytic activity with CT and matrix metalloproteinase activity with SPECT. Both signals localized in aneurysm but did not exactly co-localize. Distinct uptake patterns suggested that the 2 processes are not overlapping but, instead, are complementary.

Accelerating Scientific Discovery

Other investigators took advantage of molecular imaging to accelerate scientific discovery. Werner et al. from the Hannover Medical School and the Technische Universität München (Garching; both in Germany) reported on "Imaging inflammation crosstalk along the cardio–renal axis after acute MI" [28]. Using ^{68}Ga-pentixafor, a tracer that targets the chemokine receptor CXCR4 found in inflammation, they imaged a large group of mice at different time points after coronary artery ligation to induce MI. Serial ^{68}Ga-pentixafor PET images of CXCR4 expression revealed transient upregulation in the infarct region early after MI with a corresponding increase in renal uptake (Fig. 9). This signal declined proportionally in both organs over 6 weeks. In addition, the ^{68}Ga-pentixafor uptake in the infarct strongly correlated with

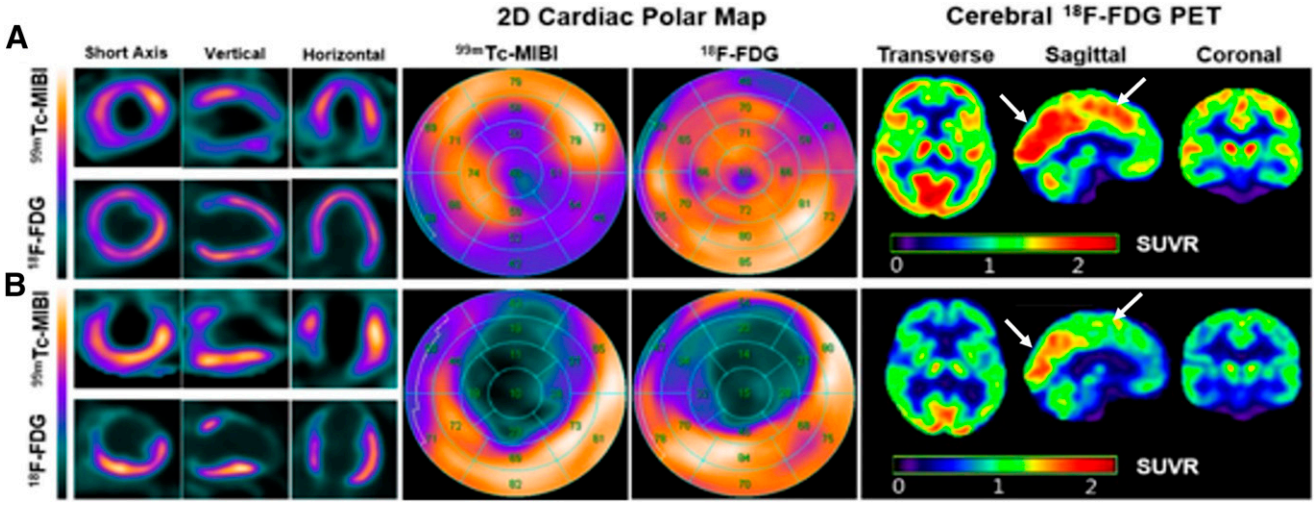


FIGURE 10. Gated SPECT myocardial perfusion and cardiac/cerebral ^{18}F-FDG PET imaging in 2 patients with heart failure, highlighting differences found in various groups in the study. (A) ^{99m}Tc-sestamibi SPECT (top row) and ^{18}F-FDG PET of the heart, 2D cardiac polar maps, and cerebral ^{18}F-FDG PET/CT images acquired in a 41-year-old man with New York Heart Association (NYHA) stage IV disease, 42% left ventricular (LV) hibernating myocardium (HM), 3% LV scar, LV ejection fraction (LVEF) of 20%, end-diastolic volume (EDV) of 258 mL. B. Bottom rows of corresponding imaging in a 42-year-old man with NYHA stage III disease, 3% LV HM, 57% LV scar, LVEF of 15%, EDV of 363 mL. Overall, cerebral metabolism in the whole brain was reduced but maintained in cognition-related frontal areas in heart failure patients with HM and moderately impaired LV function.

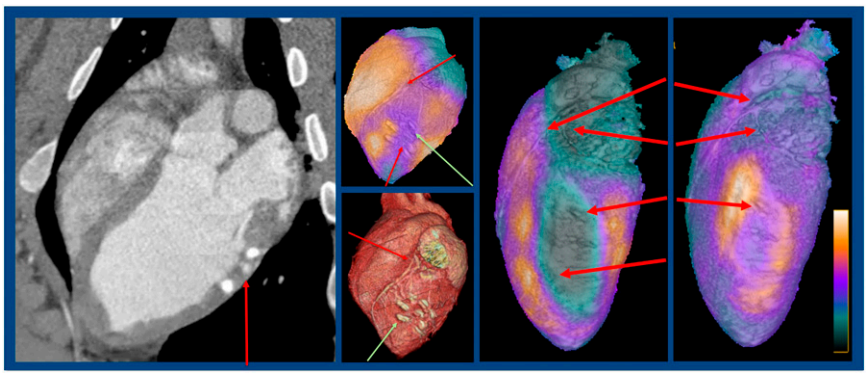


FIGURE 11. Intramyocardial hydrogel delivery after myocardial infarction (MI) in a pig model of induced MI. Left to right: CT imaging tracked the delivery of the hydrogel (which contained a contrast agent); SPECT/CT ^{201}Tl imaging identified the infarct area, and, along with 3D CT, indicated that the hydrogel was delivered to the right place; and ex vivo imaging with SPECT/CT with ^{201}Tl or ^{99m}Tc-maraciclatide, an $\alpha_v\beta_3$ integrin–targeted tracer, showed that the latter tracer localized within the infarct area. Intramyocardial delivery of hydrogel post-MI resulted in increased integrin activation in the MI region and decreased left ventricular remodeling.

kidney uptake. Of note, the kidney PET signal at 7 days post-MI predicted cardiac functional decline at 6 weeks post-MI in mice with severely impaired EF (<30%) but not with modestly impaired ejection fraction (≥30%). This suggests crosstalk between the injured heart and the kidneys after MI, which may contribute to adverse outcomes for both organs.

Following the same theme, this time in humans, Yun et al. from the Beijing Anzhen Hospital (China), the Chinese Academy of Sciences (Beijing, China), the Medical University of Vienna (Austria), and the David Geffen School of Medicine University of California Los Angeles reported on "Assessment of the metabolic heart–brain axis with cardiac and brain ^{18}F-FDG PET/CT imaging in patients with heart failure" [91]. Heart failure may be associated with cognitive impairment. The authors sought to evaluate a potential association between the brain and heart metabolic activity in patients with heart failure. Their patients with ischemic cardiomyopathy underwent ^{99m}Tc-sestamibi SPECT/CT MPI as well as cardiac and cerebral ^{18}F-FDG PET/CT. Participants were categorized based on the extent of hibernating myocardium and EF values, and these were compared with data from healthy/normal volunteers. A significant difference in whole-brain SUV was observed among the patient subgroups and volunteers, most notably between the normal group and the group with hibernating myocardium <10% LV. Differences were also noted in different regions of the brain between the study groups. Figure 10 shows examples of 2 subjects with different extents, high and low, of hibernating myocardium based on ^{18}F-FDG PET and MIBI SPECT, with differing levels of ^{18}F-FDG signal in the brain. Overall, cerebral metabolism in the whole brain was reduced but maintained in cognition-related frontal areas in heart failure patients with hibernating myocardium and moderately impaired LV function.

Changing direction, Melvinsdottir et al. from Yale University (New Haven, CT) and the University of Pennsylvania (Philadelphia) reported that "Intramyocardial hydrogel delivery post MI results in increased integrin activation and reduction in LV modeling" [90]. The work was conducted in a pig model of induced MI. As seen in Fig. 11, the delivery of the hydrogel (which contained a contrast agent) was tracked by CT, and SPECT/CT ^{201}Tl imaging identified the infarct area, and, along with 3D CT, indicated that the hydrogel was indeed delivered to the right place. Ex vivo imaging with ^{99m}Tc-maraciclatide, an $\alpha_v\beta_3$ integrin–targeted tracer, showed this agent localized within the infarct area, and gamma well counting showed higher $\alpha_v\beta_3$ tracer uptake in animals with MI and hydrogel compared to MI alone. Intramyocardial delivery of hydrogel post-MI resulted in increased integrin activation in the MI region and decreased LV remodeling. The authors concluded that multimodality imaging is a feasible approach for guiding delivery and monitoring the effects of a therapeutic hydrogel.

Summary

The presentations reviewed here covered a broad range of topics representing the state of the art in nuclear and molecular imaging in cardiology, including refining the practice of nuclear cardiology, addressing diagnostic gaps and novel applications of molecular imaging, and advancing scientific discovery. Ongoing improvements in MPI increase its value for patient care, and novel molecular imaging approaches continue to be incorporated into patient management. Emerging molecular imaging approaches may address a number of existing diagnostic gaps in cardiovascular medicine. Molecular imaging is advancing basic cardiovascular research beyond what is possible with traditional laboratory techniques. This year's SNMMI Annual Meeting was held virtually, in a time of global uncertainty. The quality of abstracts presented at the meeting and the dedication of the scientists and clinicians who shared their work here constitute a testimony to the vitality and prospects of our field in improving patient care and advancing science.

Research—The Key to Nuclear Medicine's Past and Future

Alan B. Packard, PhD, 2020–2021 SNMMI President

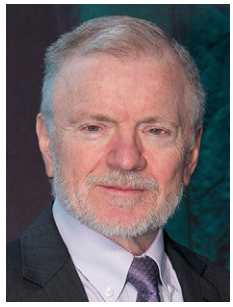
I often speak about the energy at SNM annual meetings in the 1980s and 1990s, when at every meeting there was a great deal of anticipation about what new radiopharmaceuticals or camera developments would be introduced that year. I am very excited to see that energy reappearing at recent SNMMI meetings. The energy has reappeared because we are on the leading edge of a new wave of exciting developments in nuclear medicine, with several new diagnostic and therapeutic radiopharmaceuticals expected to be approved within the next year or so and continued advances in camera technology—a truly amazing surge of innovation.

These innovations grow out of a strong tradition of research that has been the backbone of nuclear medicine since the first use of ^{128}I to study the thyroid in 1938. In the 1950s and 1960s, several breakthroughs fundamentally changed the field, starting with the development of the ^{99}Mo/^{99m}Tc generator by Tucker, Green, and Richards at Brookhaven National Laboratory (BNL) and the development of the gamma camera by Hal Anger in the late 1950s. The introduction of the ^{99}Mo/^{99m}Tc generator was soon followed by the first use of ^{99m}Tc in a patient by Harper and Lathrop. In the early 1970s, the invention of the ^{99m}Tc "instant kit" by Eckelman and Richards at BNL led to the development of large number of new ^{99m}Tc agents, many of which are still in use today. It was not until the 1980s, however, that the first chemically well-defined ^{99m}Tc compounds were developed.

In the PET arena, critical developments include the invention of the PET camera by Phelps, Hoffman, and Ter-Pogossian at Washington University in 1973; the synthesis of ^{18}F-FDG at BNL and its first use in humans at the University of Pennsylvania in 1976; the development of synthesis modules (aka "black boxes") that facilitate the automated synthesis of ^{18}F-, ^{15}O-, ^{13}N-, and ^{11}C-labeled compounds under cGMP conditions so that they can be more widely used; and the more recent introduction of "non-standard" PET radionuclides, such as ^{64}Cu, ^{68}Ga, and ^{89}Sr.

In the area of physics and instrumentation, the introduction of PET/CT, SPECT/CT, and PET/MR has changed how images are interpreted, and the whole-body PET camera, digital PET, and digital SPECT have dramatically improved image quality and the way in which PET images are acquired.

Therapy has been central to nuclear medicine since its beginning, from the first use of radioiodine to treat hyperthyroidism in 1941. It is now seeing a rebirth with the current excitement about ^{68}Ga and ^{177}Lu as theranostic pairs to diagnose and treat neuroendocrine tumors and prostate cancer, as well as possible future uses of ^{68}Ga or ^{18}F diagnostics paired with α-emitting therapeutics.



Alan B. Packard, PhD

All of which is a backdrop to remind us that one of SNMMI's most important roles is to help encourage, accelerate, and promote research. The society is uniquely able to accomplish this goal because it brings together a broad spectrum of professionals—physicians, radiochemists, physicists, pharmacists, and technologists—who, together, make our society the world leader in innovation and excellence in nuclear medicine. This does not, however, happen in a vacuum. For innovation to continue, it must be supported and valued. This must happen on multiple levels, beginning with graduate students and postdoctoral fellows but also including medical students and clinical fellows who, optimally, will have an opportunity during their training to participate in a research project, perhaps spurring interest in nuclear medicine to such an extent that they become clinician-scientists.

SNMMI's Value Initiative includes multiple programs to provide this support. New initiatives are underway aimed at building a strong pipeline of new researchers and clinicians to grow the field in the future, at helping to ensure continued support for research and demonstrating the exciting future of nuclear medicine to medical students and undergraduates, and at helping ensure continued research support from federal agencies, such as the National Institutes of Health, the Department of Energy, and the Department of Defense.

We must also ensure that this exciting research has impact by sharing the results with our colleagues and with the broader medical community. It is essential that SNMMI continue to promote high-visibility venues for that purpose, such as *The Journal of Nuclear Medicine*, which continues to excel as the leading journal in nuclear medicine, and the SNMMI Annual Meeting, where younger scientists often have first opportunities to present their work to an audience of their peers.

All of these pieces must work together to ensure that nuclear medicine continues to be as exciting and innovative today and tomorrow as it has been in the past. SNMMI's role, as in the past, is to focus and amplify this energy, ensuring that the future of nuclear medicine is brighter than ever.

NRC and Regulatory Relief for Training for Imaging/ Localization Studies

SNMMI announced on September 19 the receipt of a response from the U.S. Nuclear Regulatory Commission (NRC) addressing a previous request for regulatory relief for training for imaging and localization studies during the COVID-19 Public Health Emergency (PHE). In the response, addressed to SNMMI, the American Society of Nuclear Cardiology (ASNC), the American Society for Radiation Oncology (ASTRO), and the American College of Radiology (ACR), NRC staff stated that the agency was "prepared to consider, on an expedited basis, requests for an exemption from the requirement to obtain the hands-on work experience described in [10 CFR] 35.290(c)(1)(ii)(G)."

The current regulation reads: "Work experience must involve: Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs." On June 11, the SNMMI, ASNC, ASTRO, and ACR sent a formal request that the NRC allow this requirement to be met using virtual technology (video/webinar) and to add this as an already vetted area for regulatory relief when requested by licensees. This request was similar to the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI) subcommittee recommendation for a 1-time modification because of COVID-19. The ACMUI request stated: "In situations when hands-on training (hot lab) is not feasible, then video/webinar observational training may be considered. Similarly, when work experience cannot be met in person, then virtual training may be considered."

The NRC received a similar request from the Certification Board of Nuclear Cardiology, dated June 24, 2020, and has granted that request via a temporary exemption. The exemption allows individuals seeking board certification to fulfill this work experience requirement virtually, rather than hands-on, from January 31, 2020 (when the U.S. Department of Health and Human Services declared a PHE for the United States) through December 31, 2020. Despite the regulatory relief provided by this exemption, a licensee that uses generator systems is advised to provide, as soon as safely possible, hands-on work experience involving the tasks described in 10 CFR 35.290(c)(1)(ii)(G) to its authorized users who obtained this work experience virtually.

SNMMI

Open-Source COVID-19 Medical Image Database

Representatives of the American College of Radiology (ACR), the Radiological Society of North America (RSNA), and the American Association of Physicists in Medicine (AAPM) announced in August the development of the Medical Imaging and Data Resource Center (MIDRC), an open-source database with medical images from thousands of COVID-19 patients. The National Institute of Biomedical Imaging and Bioengineering is funding the effort through a contract to Maryellen Giger, PhD, of the University of Chicago (IL), which will host the MIDRC. The effort will be led by the 3 associations, with Etta Pisano, MD, and Michael Tilkin, MS, taking the lead for the ACR; Curtis Langlotz, MD, PhD, and Adam Flanders, MD, for the RSNA; and Giger and Paul Kinahan, PhD, for the AAPM.

"The MIDRC database will provide a critical tool to help the medical imaging community, doctors, and scientists better understand COVID-19 and its biological effects on humans," said Pisano. "This knowledge, and the technological advancements the registry can enable, will ultimately help providers save lives."

Funded under the National Institutes of Health special emergency COVID-19 process, the MIDRC will create an open-access platform to collect, annotate, store, and share COVID-related medical images. The MIDRC will leverage existing data collection efforts to upload more than 10,000 COVID-19 thoracic radiographs and CT images, including many from the ACR COVID-19 Imaging Research Registry and the RSNA International COVID-19 Open Radiology Database. This will allow researchers from around the world to access images as well as clinical data to answer COVID-19 questions. The MIDRC will include 5 infrastructure development projects and oversee 12 research projects, including ~20 university labs, in support of solutions to the COVID-19 pandemic. The MIDRC will initially focus on COVID-19 but will work to expand services to provide imaging data and artificial intelligence pipelines to aid in the fight against other diseases.

"This dedicated team of research scientists, engineers, and imaging professionals will produce new tools for the detection, diagnosis, and prognosis of COVID-19 by aggregating massive amounts of imaging and other clinical data from COVID-19 patients," said Langlotz. "We look forward to linkages with other national data repositories to enable a comprehensive analysis of COVID-19 disease and its imaging manifestations."

American College of Radiology

NCI, Cancer Research UK Launch Cancer Grand Challenges

The National Cancer Institute (NCI) announced on August 27 that it will partner with Cancer Research UK to fund Cancer Grand Challenges, an international initiative to address profound and unanswered questions in cancer research. Through this effort, NCI and Cancer Research UK will seek novel ideas from multidisciplinary research teams from around the world that offer the potential to make bold advances in cancer research and improve outcomes for people affected by cancer. The new partnership builds on

Cancer Research UK's Grand Challenge initiative, which is currently funding 7 international teams of researchers across 9 countries. Cancer Research UK is the world's largest independent cancer research charity. Cancer Grand Challenges will foster a highly competitive process designed to stimulate scientific creativity of the highest order.

"This new partnership leverages the expertise of the world's leading funders of cancer research in a bold effort to identify and pursue innovative ideas that address major challenges in understanding cancer," said NCI Director Norman E. "Ned" Sharpless, MD. "We're thrilled to join Cancer Research UK in this unique collaboration to support novel cancer research on a global scale."

The goals of the partnership include identifying important cancer research opportunities, facilitating global collaboration among multidisciplinary researchers to solve these challenges, giving the global teams the freedom and scale to innovate and carry out cutting-edge research, and advancing fundamental biological knowledge and its clinical application to cancer. To gain perspectives from people affected by cancer, a patient committee will offer input and ideas throughout the Cancer Grand Challenges process.

NCI and Cancer Research UK planned to announce the list of new challenges in October 2020. Expressions of interest from research teams for the new challenges are expected to be accepted from October 2020 through April 2021. From these, a small number of teams will be selected to receive pilot funds to develop their ideas into larger, final applications. Those selected to receive pilot funding will be notified in June 2021, and the awards to final teams will be announced in 2022. NCI and Cancer Research UK expect to cofund ~4 awards for each round of Cancer Grand Challenges, with each multidisciplinary team being awarded ~$25 million over 5 years. NCI anticipates that the Cancer Grand Challenges partnership will support 3 rounds of awards, with a new round of challenges announced every other year. NCI plans to use annual funding currently set aside for the Provocative Questions (PQ) initiative and anticipates funding PQ awards and Cancer Grand Challenges awards in alternating years.

The process to determine the Cancer Grand Challenges is conducted through a series of international workshops to receive input from thought leaders from the cancer research community and people affected by cancer. The most compelling ideas generated from these workshops are then reviewed and the final challenges selected. Cancer Research UK launched the Grand Challenge initiative in 2015 and has since overseen 2 rounds of Grand Challenge awards. These awards are currently funding teams focusing on identifying preventable causes of cancer, creating virtual reality maps of tumors, preventing unnecessary breast cancer treatment, studying tumor metabolism from every angle, understanding why cancers grow in some tissues and not in others, finding new ways to tackle inflammation-associated cancer, and manipulating the microbiome to treat bowel cancer.

"Many of the ongoing Grand Challenge awards align with NCI research priorities, and our missions overlap in many ways," said Dinah S. Singer, PhD, NCI Deputy Director for Scientific Strategy and Development. "This initiative will expand opportunities to identify new challenges based on insights from the cancer research community and to further our understanding of cancer. We're looking forward to the new ideas proposed by creative teams from around the world."

See the NCI Cancer Grand Challenges webpage (including the newly announced Grand Challenge areas of focus) at: https://www.cancer.gov/grants-training/grants-funding/cancer-grand-challenges and the Cancer Research UK Cancer Grand Challenges webpage at https://www.cancerresearchuk.org/funding-for-researchers/cancer-grand-challenges.

National Cancer Institute

SNMMI and Partners Host Congressional Briefing

On September 17, SNMMI and its coalition partners, the Medical Imaging & Technology Alliance (MITA) and Council on Radionuclides and Radiopharmaceuticals, Inc., hosted a virtual briefing for Capitol Hill staff with leading physicians to discuss the growing impact of PET and nuclear medicine in cancer treatment, as well as the importance of expanding patient access to these drugs through passage of the Medicare Diagnostic Radiopharmaceutical Payment Equity Act of 2019 (HR 3772).

The briefing included presentations from David Mankoff, MD, PhD, Gerd Muehllehner Professor of Radiology and Vice-Chair for Research of Radiology at the University of Pennsylvania's Perelman School of Medicine (Philadelphia), and Michael Roarke, MD, MS, Chair of the Division of Nuclear Medicine for the Mayo Clinic Arizona Department of Radiology and Medical Director at the Mayo Clinic's Arizona Cyclotron Facility (Phoenix). The event also featured remarks from a prostate cancer patient who provided insights into his experience with nuclear medicine and its positive effect on his treatment pathway.

Congressman Greg Murphy, MD (NC-3), a cosponsor of HR 3772, started the briefing by noting that: "Nuclear medicine is already playing a growing role in diagnosing advanced disease, including prostate and breast cancer. Passage of HR 3772 will give patients and their physicians the tools they need to diagnose life-threatening diseases early, when they are most treatable—a key improvement that will reduce downstream costs and, more importantly, save lives."

Roarke drew on more than 24 years of experience in nuclear medicine to provide an overview of PET technology and its growing influence on the clinical mainstream. Mankoff elaborated on ways in which PET radiopharmaceuticals are used to enhance breast cancer treatment: "Diagnostic PET radiopharmaceuticals are capable of identifying metastatic breast cancer at an earlier stage and can determine if a prescribed treatment is working. Although this information can help guide treatment decisions and improve patient outcomes, patients and their providers continue to encounter severe roadblocks when seeking coverage for these innovative diagnostic approaches."

Sue Bunning, MITA Industry Director of Molecular Imaging & PET, closed the briefing with an overview of Medicare's current reimbursement policy and the ways in which it undermines patient access to innovative radiopharmaceutical diagnostics: "Unfortunately, the Centers for Medicare and Medicaid Services currently treat PET radiopharmaceuticals, including the drugs needed for diagnostic scans, as part of the packaged cost of the procedure in the hospital outpatient setting. This structure disincentivizes the utilization of many radiopharmaceuticals for Medicare patients, leading to limited patient access and stifled innovation. The Medicare Diagnostic Radiopharmaceutical Payment Equity Act of 2019 represents a legislative solution that would address structural flaws in the current payment methodology and grant greater access to life-saving PET diagnostic radiopharmaceuticals for patients."

SNMMI

SNMMI 2020–2022 Wagner–Torizuka Fellowship Recipients

SNMMI announced on September 28 the recipients of the 2020–2022 SNMMI Wagner–Torizuka Fellowship. This 2-year award, founded 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. "SNMMI is pleased to sponsor the Wagner–Torizuka Fellowship in support of the worldwide advancement of nuclear medicine and molecular imaging. The program has provided invaluable experience for many rising nuclear medicine and molecular imaging professionals over the years, equipping them to make significant contributions to the field in Japan," said Satoshi Minoshima, MD, PhD, past SNMMI president and chair of the SNMMI Awards Committee.

The 2020–2022 fellows, each receiving an annual stipend of $24,000, are: Masatoshi Hotta, MD, National Center for Global Health and Medicine (Tokyo, Japan), whose research interests include PET/CT and SPECT/CT and the roles they play in image-based treatment planning and dosimetry for theranostics. He is a visiting researcher in the Department of Molecular and Medical Pharmacology in the Ahmanson Translational Theranostics Division at the David Geffen School of Medicine at the University of California, Los Angeles, under the supervision of Johannes Czernin, MD; Yuichi Wakabayashi, MD, PhD, National Institutes of Health (NIH; Bethesda, MD), whose research focuses on utilization of PET/CT to localize and quantify specific proteins in the living brain. He is continuing his studies at the NIH Molecular Imaging Branch of the National Institute of Mental Health under the supervision of Robert Innis, MD, PhD; and Keiichiro Kuronuma, MD, PhD, Nihon University Hospital (Tokyo, Japan), whose current research interests include PET imaging using ^{18}F-flurpiridaz and artificial intelligence technology in medicine. He will study in the Department of Imaging at Cedars–Sinai Medical Center in Los Angeles, CA, under the supervision of Daniel S. Berman, MD.

The SNMMI Wagner–Torizuka Fellowship program, sponsored by Nihon Medi-Physics Co., Ltd. (Tokyo, Japan), has successfully graduated 30 fellows since its inauguration in 2008. Applications and information about requirements for the 2021–2023 SNMMI Wagner–Torizuka Fellowship are available at www.snmmi.org/grants. Applications are due by January 31, 2021. For more information about these and other scholarships, visit www.snmmi.org/grants or contact the SNMMI Development Department at Grants&Awards@snmmi.org.

SNMMI

New Nanoparticles from IAEA Coordinated Research Project

In a September 1 article on the website of the International Atomic Energy Agency (IAEA), the agency reported on the development of 2 new nanoparticles that "hold promise for a new generation of nanosized radiopharmaceuticals" for therapy. The research has been conducted under the aegis of an IAEA Coordinated Research Project (CRP). The Nanosized Delivery Systems for Radiopharmaceuticals (F22064) project involved scientists from 12 countries, who developed more than 40 new polymeric nanoparticles using chemical synthesis and/or radiation technology. The aim was to provide significant improvement in delivery of therapeutic radiopharmaceuticals through the use of nanotechnology.

The scientists experimented with different base structures, such as nanogels, proteins and inorganic nanoparticles, and different targeting agents.

The project closed in October 2019. The findings of the CRP were published throughout the duration of the project in 76 scientific journals. The IAEA CRP project page (https://www.iaea.org/projects/crp/f22064) indicates that "The participants agreed that the report to be kept confidential among the participants and not to be shared publicly. As soon as the participants announce their willingness for public access, the scientific secretary will initiate publishing the report as a 'working material'." Preliminary published joint recommendations for future work included: (1) initiation of a new CRP for completion of preclinical studies of selected nanoconstructs (with a focus on ^{68}Ga, ^{177}Lu, and ^{198}Au); initiation of a new CRP on a selected nanoconstruct from this CRP F22064 (MGF ^{198}AuNPs), with completed preclinical results; initiation of an IAEA publication on "Development of radiolabeled nanoparticles for theranostic applications" as an outcome of CRP F22064; preparation of an IAEA publication on "Guidelines on the development of human tumor models for preclinical studies of radiopharmaceuticals"; and initiation of a new activity on clinical evaluation of chemical- and radiation-produced ^{99m}Tc-nanocolloids for sentinel node scintigraphy.

IAEA