"Radiology can play a central role, helping evolve and shape this emerging vision for the benefit of cancer patients," he said. Among many accomplishments, Gambhir and his laboratory teams have developed methods to image gene expression in living subjects and overseen the translation of these techniques into clinical trials for cancer gene/cell therapies. He has also led the development of strategies for studying basic cell/molecular biological events, such as imaging protein–protein interactions.

"By using magnetic nanoparticles to 'tag' proteins indicative of cancer and reading them out using magnetic sensors, we have demonstrated much higher sensitivity than with conventional detection," Gambhir said, highlighting one aspect of his group's work. He also described clinical uses for photoacoustic molecular imaging, a method in which light enters the body and interacts with photoacoustic particles that absorb the light and produce sound. The sound produced, unlike the light, penetrates through tissue. He displayed the first photoacoustic images of tumor molecules in a human breast taken earlier in November at Stanford. The technology captures the image in only 30 s, produces excellent resolution, does not require contrast agents, and can be used with light-absorbing targets. "You're going to hear a lot more about photoacoustic molecular imaging in years to come," Gambhir said. "I think it has a lot of potential to become the ultimate imaging technology."

Radiological Society of North America

FROM THE LITERATURE

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. We have added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

MOLECULAR IMAGING/THERAPY

PET Imaging of Myelin Changes

In an article e-published on November 9 ahead of print in *Bioorganic and Medicinal Chemistry*, Wu et al. from Case Western Reserve University (Cleveland, OH) described the synthesis and evaluation of a novel ^{11}C-labeled PET marker for in vivo quantification of myelination. In vitro and ex vivo staining studies showed that ^{11}C-*N*-methyl-4,4'-diaminostilbene (^{11}C-MeDAS) accumulated in myelinated regions of the brain, including the corpus callosum and striatum. Ex vivo autoradiography studies showed that the tracer entered the mouse brain and selectively labeled myelinated regions with high specificity. Biodistribution studies indicated both abundant initial brain uptake of the tracer and prolonged retention in the brain at 60 min after injection. Additional in vivo microPET studies in a hypermyelinated mouse model revealed a pharmacokinetic profile that directly correlated radioactivity concentrations in the brain with levels of myelination. The authors concluded that these studies "suggest that MeDAS is a sensitive myelin probe that provides a direct means to detect myelin changes in the brain" and that the tracer "can be used as a myelin imaging marker to monitor myelin pathology in vivo."

Bioorganic and Medicinal Chemistry

Ultrasound Targeting of VEGFR2

Liu et al. from the Third Military Medical University (Chongqing, China) reported on November 12 ahead of print in the *Journal of Clinical Ultrasound* on a study using contrast-enhanced microbubble ultrasound for molecular imaging of vulnerable plaques in rabbits by targeting vascular endothelial growth factor receptor-2 (VEGFR2). The authors created a vulnerable plaque rabbit model by delivering recombinant p53 adenovirus to atherosclerotic plaques induced in the rabbit abdominal aorta by a high cholesterol diet and ballon endothelial injury. Biotinylated microbubbles were conjugated with biotinylated VEGFR2 antibody to prepare microbubbles targeting VEGFR. Average ultrasound intensity was assessed at the injury site with both targeted and nontargeted microbubbles before injury and 12 wk later. VEGFR2 expression and vascular density were assessed by immunochemical staining. Plaques retained the targeted ultrasound contrast agent at significantly higher levels than the nontargeted agent, and VEGFR2 expression was directly correlated with the video intensity of the targeted agent but not the untargeted agent. The authors concluded that these "results validate the use of targeted ultrasound contrast agents for sonographic imaging of vulnerable abdominal artery plaques in rabbits."

Journal of Clinical Ultrasound

ImmunoPET and Lymph Node Metastasis

In the November 1 issue of *Cancer Research* (2010;70:8842–8851),

Mumprecht et al. from the Swiss Federal Institute of Technology (Zurich, Switzerland) reported on immunoPET imaging of inflammation- and tumor-induced lymph node lymphangiogenesis. The authors serially injected antibodies to lymphatic epitopes into mouse models of lymph node lymphangiogenesis and found that these antibodies accumulated selectively in the lymphatic vasculature in tissues and lymph nodes. They used a ^{124}I-labeled antibody against the lymphatic vessel endothelial hyaluronan receptor-1 and PET to image inflammation- and tumor-draining lymph nodes with expanded lymphatic networks in vivo. This immunoPET technique allowed visualization of lymphatic vessel expansion in lymph nodes with metastases that were not detected by ^{18}F-FDG PET. The authors concluded that "immuno-PET with lymphatic-specific antibodies may open up new avenues for the early detection of metastasis, and the images obtained might be used as biomarkers for the progression of diseases associated with lymphangiogenesis."

Cancer Research

Pretargeting for Apoptosis Imaging

Ungethum et al. from Maastricht University (The Netherlands) reported on November 15 ahead of print in the *Journal of Biological Chemistry* on a study of engineered annexin A5 variants with impaired cell entry for molecular imaging of apoptosis using pretargeting strategies. The researchers described a structure/function analysis of annexin A5 binding to phosphatidylserine on apoptotic cells and subsequent internalization. Through a strategy involving site-directed mutagenesis to disrupt amino acid–generated salt bridges, annexin A5 trimer formation and cell surface entry were impaired without affecting phosphatidylserine binding. The resulting annexin A5 variants with impaired cell internalization abilities were found to be superior molecular imaging agents and to have promise for targeting phosphatidylserine on apoptotic cells for diagnosis and therapy.

Journal of Biological Chemistry

Optimizing EGFR Tumor Targeting

In an article e-published on November 1 ahead of print in the *Journal of Controlled Release*, Medina et al. from Memorial Sloan–Kettering Cancer Center (New York, NY) reported on techniques for optimizing tumor targeting of the lipophilic epidermal growth factor receptor (EGFR)–binding PET tracer SKI 243 using a liposomal nanoparticle delivery system. The tracer is one of a series the group has developed that irreversibly bind with EGFR for PET imaging. The addition of a liposomal nanoparticle delivery system was designed to counter the relatively low tumor uptake of these tracers and improve tumor targeting. The pharmacokinetics of SKI 243, an EGFR kinase–targeting radiotracer, were compared with and without embedding in liposomes. Both the bare and liposomal SKI 243 were readily taken up by tumor xenografts, but liposomal SKI 243 remained in the blood longer and showed a 3–6-fold increase in uptake in tumors.

Journal of Controlled Release

THERAPY

Targeting Viral Antigens in Cervical Tumors

Phaeton et al. from the Albert Einstein College of Medicine and Cancer Center (Bronx, NY) reported on November 12 ahead of print in *Cancer Biology and Therapy* on radioimmunotherapy (RIT) in experimental cervical tumors expressing low levels of E6 genes of oncogenic human papillomavirus (HPV) types. The authors previously reported on mouse studies in which RIT targeted viral antigens with monoclonal antibodies (mAbs) to HPV16 E6 and resulted in suppression of growth in cervical tumors expressing high levels of E6. The question addressed in the current study is whether the same result could be expected in suppression of growth in tumors expressing low levels of E6 and E7, as most often seen in patients. Initial studies verified the similarity of low levels of expression of E6 in patients' tumors and in the SiHa cell line. SiHa tumors were initiated in mice, with an mAb to E6 (C1P5) labeled with ^{188}Re. Mice were then divided into 5 treatment groups and a control group, and tumor growth was monitored. The 5 groups were treated with: ^{188}Re-C1P5 alone, proteasome inhibitor MG132 alone, MG132 followed by ^{188}Re-C1P5, unlabeled C1P5, or a ^{188}Re-labeled isotope-matching control mAb. ^{188}Re-C1P5 alone and in combination with MG-132 proved to slow tumor growth significantly compared with other treatments/controls. The authors concluded that the possibility of suppressing tumor growth by targeting viral antigens even in cervical tumors with low E6 expression provides "additional evidence for the potential usefulness of RIT targeting HPV-related antigens in the clinic."

Cancer Biology and Therapy

Imaging Anti-Inflammatory Treatment in Atherosclerosis

In an article e-published on November 8 ahead of print in *Molecular Pharmaceutics*, Lobatto et al. from a consortium of researchers in The Netherlands, the UK, Spain, and the United States reported on a study advancing the ability of multimodal clinical imaging to longitudinally assess a nanomedical anti-inflammatory treatment in experimental atherosclerosis. The authors used ^{18}F-FDG PET and dynamic contrast-enhanced MR imaging to assess the therapeutic efficacy of a liposomal formulation designed to increase the anti-inflammatory action and decrease adverse effects of glucocorticoids in a rabbit model of atherosclerosis. Significant anti-inflammatory effects were observed as early as 2 d after a single dose of the liposomal glucocorticoid, and these lasted up to at least d 7. Immunohistochemical analysis of macrophage density in the vessel wall corresponded with these observations.

The authors concluded that their 2-pronged strategy for efficient treatment of atherosclerosis, including nanomedical therapy of atherosclerotic plaques and application of noninvasive and clinically approved imaging techniques to monitor delivery and therapeutic responses, also demonstrated "unprecedented rapid anti-inflammatory effects in atherosclerotic lesions after the nanomedical therapy."

Molecular Pharmaceutics

Nanoparticles Targeting Macrophages

Kamat et al. from Michigan State University (East Lansing) and the University of Tennessee Health Science Center (Memphis) reported in the November 17 issue of *Bioconjugate Chemistry* (2010;21:2128–2135) on a study of hyaluronic acid (HA)–functionalized nanoparticles for active targeting and imaging of macrophages. The authors described the design, synthesis, and characterization of iron oxide–based magnetic nanoparticles bearing HA on the surface to target activated macrophages. In vitro cell uptake studies showed significant uptake of the nanoparticles by activated macrophage cell line THP-1, which enabled MR imaging of THP-1 cells. Prussian blue staining showed that the magnetite cores of the HA-coated nanoparticles were only present for a short time inside the cells, reducing potential concerns about nanotoxicity. At the same time, fluorescein on the nanoparticle was found to be delivered to the cell nucleus. The authors concluded that "with further development, these HA functionalized magnetic nanoparticles can potentially become a useful carrier system for molecular imaging and targeted drug delivery to activated macrophages," with special potential in atherosclerosis.

Bioconjugate Chemistry

Radiation Dose and Parotid Metabolism

In an article e-published on October 27 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics*, Roach et al. from Duke University (Durham, NC) reported on the utility of ^{18}F-FDG PET assessment of the effect of head and neck radiotherapy on parotid gland glucose metabolism. The retrospective study looked at the radiation dose–response relationship of parotid gland glucose metabolism in patients with head and neck squamous cell carcinoma before and after curative-intent intensity-modulated radiation therapy (IMRT). The study included the records of 49 such patients who also underwent ^{18}F-FDG PET and CT imaging before and after treatment. Changes in standardized uptake values (SUVs) and volumes for CT-defined parotid gland areas after radiation therapy were correlated with parotid gland dose–volume histograms from IMRT plans. The average parotid gland volume was 30.7 mL. This volume decreased by 3.9% ± 1.9% with every increase of 10 Gy in mean dose. Within the first 3 mo after treatment, however, a uniform reduction of 16.5% ± 7.3% was noted, regardless of dose. The average mean SUV for the parotid glands was 1.63 ± 0.48 before treatment and decreased by 5.2% ± 2.5% for every increase of 10 Gy in mean dose. The average maximum SUV was 4.07 ± 2.85 before treatment and decreased with mean dose. At a threshold of 32 Gy for mean dose, however, maximum SUV decreased rapidly. In addition to demonstrating that radiation dose responses in the parotid glands can be measured by integrated PET-CT scans, the authors noted that "future studies should correlate this decline in FDG uptake with saliva production to improve treatment planning."

International Journal of Radiation Oncology, Biology, Physics

DIAGNOSIS

SPECT, Infarct Volume and Erythropoietan

Yoshimura et al. from the Niigata University Medical and Dental Hospital (Japan) reported on November 2 ahead of print in *Circulation Journal* on a software-based technique for accurately quantifying infarct volume with ^{99m}Tc-MIBI SPECT and the use of this technique in analyzing the effects of erythropoietin (EPO) administration in patients with acute myocardial infarction (AMI). The authors described the development of their software, which performs 3D reconstruction from sequential short-axis images. Data analyzed in the study came from the EPO AMI I study of the safety and efficacy of EPO administration in AMI. MI volume at baseline was found to correlate with maximum creatine kinase in all patients, but significantly decreased for the EPO-administered group over a 6-mo follow-up period. Application of the analytic software confirmed the efficacy of EPO in the treated group.

Circulation Journal

Scintigraphic Infarct Size and Prognosis

In an article in the November 1 issue of the *American Journal of Cardiology* (2010;106:1212–1217), Byrne et al. from the Technische Universität (Munich, Germany) reported on relationships among peak cardiac troponin-T and creatine kinase-MB isoenzyme levels, scintigraphic myocardial infarct size, and 1-y prognosis in patients undergoing primary percutaneous coronary interventions for acute ST-elevation myocardial infarction. Sets of relevant data, including clinical follow-up at 1 y, were available for 1,237 patients (mean age, 62.9 ± 12.9 y). Median admission and peak values for troponin-T were 0.74 and 3.70 μg/L, respectively, and for creatine kinase-MB were 44.1 and 160.0 U/L, respectively. Median infarct size on SPECT was 12% (range, 3%–25%) of the left ventricle. Peak troponin-T and creatine-kinase MB were found to be moderately correlated with final infarct size. At 1-y follow-up, 47 patients (3.8%) had died. Final infarct size on SPECT proved to better predict mortal-

ity than either peak troponin-T or creatine kinase-MB or these 2 values combined. The authors concluded that, in this largest investigation on the value of cardiac troponin for assessment of infarct size in acute ST-elevation myocardial infarction, scintigraphic infarct size remained a better correlate of 1-y mortality than either laboratory biomarker.

American Journal of Cardiology

Intrapericardial Fat and Hyperemic Coronary Perfusion

In an article e-published on October 28 ahead of print in *Arteriosclerosis, Thrombosis, and Vascular Biology*, Bucci et al. from the University of Turku (Finland) and the Institute of Clinical Physiology/National Research Center (Pisa, Italy) reported on a study using PET/CT to assess associations between intra- and extrapericardial fat and myocardial perfusion in patients with and without coronary artery disease (CAD). The study included 107 patients with an intermediate likelihood of CAD. All patients underwent PET/CT imaging to assess intra- and extrapericardial fat volumes and coronary artery calcium levels, as well as myocardial perfusion at rest and during pharmacologic challenge–induced hyperemia. All patients then underwent coronary angiography and were grouped for presence/absence of CAD and severity of myocardial hypoperfusion. Both intra- and extrapericardial fat levels were higher in men than in women and in patients who proved to have CAD ($n = 85$) than in those who did not ($n = 22$). In patients with CAD, extrapericardial fat was increased regardless of the degree of stenoses, whereas intrapericardial fat was increased selectively in patients with obstructive stenoses. When all factors were analyzed, myocardial hyperemic perfusion was predicted independently by male sex, higher coronary artery calcium scores, and intrapericardial fat but not extrapericardial fat. The authors concluded that although CAD is accompanied by augmented fat deposits surrounding the heart (which are negatively related to coronary flow hyperemia), intrapericardial fat was the only independent predictor of hyperemic perfusion, "supporting the hypothesis of a direct paracrine/vasocrine effect."

Arteriosclerosis, Thrombosis, and Vascular Biology

Glucose Uptake in Intermittent Claudication

Pande et al. from the Brigham and Women's Hospital/Harvard Medical School (Boston, MA) reported on November 4 ahead of print in *Arteriosclerosis, Thrombosis, and Vascular Biology* on a study describing impaired skeletal muscle glucose uptake in ^{18}F-FDG PET imaging in patients with peripheral artery disease and intermittent claudication. The study included 37 patients with peripheral artery disease and claudication and 11 healthy volunteers. All participants underwent ^{18}F-FDG PET imaging of the legs during hyperinsulinemic–euglycemic clamping. Calf glucose uptake and whole-body insulin sensitivity were assessed. Those with peripheral artery disease were found to be insulin resistant, compared with control subjects, and had significantly lower calf muscle glucose uptake. This diminished uptake correlated with systemic insulin sensitivity in participants with peripheral artery disease (even after exclusion of those with diabetes). The authors concluded that "future studies are required to assess whether calf muscle insulin resistance contributes to exercise limitation in patients with intermittent claudication."

Arteriosclerosis, Thrombosis, and Vascular Biology

PET ± CT and Pediatric IBD

In an article e-published on October 29 ahead of print in the *European Journal of Gastroenterology and Hepatology*, Däbritz et al. from University Children's Hospital Münster and University Hospital Münster (Germany) reported on a retrospective study to evaluate the utility of ^{18}F-FDG PET with and without coregistration of low-dose CT in detecting gastrointestinal lesions in children with inflammatory bowel disease. The researchers analyzed data from 45 children (18 girls, 27 boys; ages, 3.7–16.7 y) who presented with diagnoses of inflammatory bowel disease and who had undergone ^{18}F-FDG PET imaging without ($n = 24$) and with ($n = 21$) low-dose CT. Results of imaging with and without CT were analyzed segmentally along with conventional diagnostic results in the medical records. Over all results, 253 segments of the gastrointestinal tract were explored by endoscopy/histology and PET ± CT. Twenty-five additional small bowel segments were assessed by abdominal ultrasound, and PET ± CT was able to evaluate an additional 152 segments not reached during endoscopy. PET had segment-based sensitivity, specificity, positive and negative predictive values, and accuracy for the detection of lesions of 82%, 97%, 96%, 88%, and 91%, respectively, with patient-based sensitivity and specificity of 97% and 100%, respectively. However, the addition of CT did not improve these diagnostic values. The authors concluded that ^{18}F-FDG PET seems to be a "reliable tool for detecting inflamed gut segments in inflammatory bowel disease with high sensitivity and specificity" and that although ^{18}F-FDG/CT is especially suitable for assessment in children, with justifiable radiation exposures, "coregistration of CT had no additional benefit."

European Journal of Gastroenterology and Hepatology

3-Tracer PET and RT in NSCLC

Vera et al. from the Henri Becquerel Cancer Center and Rouen University Hospital (France) reported ahead of print in the November 4 issue of *Radiotherapy and Oncology* on simultaneous

PET assessment of metabolism with ^{18}F-FDG, tumor proliferation with ^{18}F-fluorothymidine (^{18}F-FLT), and hypoxia with ^{18}F-fluoromisonidazole (^{18}F-FMISO) before and during radiotherapy in patients with non–small cell lung cancer (NSCLC). The study included 5 patients (4 men, 1 woman) with histologic proof of NSCLC who were candidates for curative-intent radiation therapy. Each patient underwent 3 PET/CT scans (1 with each of the tracers) before and during (at 46 Gy) treatment, with minimal intervals of 48 h between each different tracer scan (for a total of 6 scans for each patient). The 3 image sets at each time point were coregistered. Initial ^{18}F-FDG PET/CT images identified 4 tumors and 12 nodes. Maximum standardized uptake values (SUV_{max}) were significantly decreased between baseline and treatment scanning times in both tumors and nodes. ^{18}F-FMISO SUV_{max} assessments were significantly higher in tumors than in nodes and did not change from baseline to therapy imaging. ^{18}F-FDG uptake was significantly and separately correlated with ^{18}F-FLT and ^{18}F-FMISO uptakes at both timepoints. The authors concluded that these studies indicate that 3 different PET acquisitions can be performed quasisimultaneously (within a 4–7-d span) before and during radiotherapy in patients with NSCLC and that "a fast decrease in the proliferation of both tumors and nodes exists during radiotherapy with differences in metabolism (borderline significant decrease) and hypoxia (stable)."

Radiotherapy and Oncology

New Rat Model of Bone Cancer Pain

In an article e-published on October 29 in the online journal *PLoS One*, Doré-Savard et al. from the Université de Sherbrooke (Quebec, Canada) reported on behavioral, medical imaging, and histopathologic features of a new rat model of bone cancer pain. The authors monitored pain onset and tumor growth for 21 d in their model of rat femoral mammary carcinoma MRMT-1 cell implantation. They monitored the gradual development of mechanical allodynia and hyperalgesia, as well as behavioral signs of ambulatory pain, which were first observed at d 14 after implantation. Osteopenia with disorganization of the trabecular architecture was also first observed on this date. MR imaging visualized bone metastases as early as d 8, well before pain observation. ^{18}F-sodium fluoride PET was coregistered with MR to show intraosseous activity. Pain and bone destruction were chronicled along with histochemical and other changes. The authors concluded that "our animal model demonstrates the importance of simultaneously recording pain and tumor progression and will allow us to better characterize therapeutic strategies in the future."

PLoS One

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in late October and November. Two reviews of note were e-published on October 29 ahead of print in *Current Drug Discovery Technologies.* Lin and Iagaru from Stanford University Medical Center (CA) described "Current concepts and future directions in radioimmunotherapy," and Cornelissen and Vallis presented "Targeting the nucleus: an overview of Auger-electron radionuclide therapy." In an article in the November 15 issue *of Molecules* (2010;15:8260–8278), Hicks, from the University of Toronto (Canada), and colleagues reviewed "Radiolabeled small molecule protein kinase inhibitors for imaging with PET or SPECT." Winter and colleagues from Cincinnati Children's Hospital (OH) in the November 3 issue of the *Journal of Cardiovascular Magnetic Resonance* (2010;12:62) provided an overview of "Quantitative cardiovascular magnetic resonance for molecular imaging." In an article e-published on November 10 ahead of print in *Trends in Molecular Medicine*, Cho et al. from Washington University (St. Louis, MO) described "Inorganic nanoparticle-based contrast agents for molecular imaging." Rathore and Kadin from Roger Williams Medical Center (Providence, RI) provided perspective on "Hodgkin's lymphoma therapy: past, present, and future" in the December issue of *Expert Opinion on Pharmacotherapy* (2010;11:2891–2906).

(continued from page 17N)

appointed a task force of Cardiovascular Council members and ASNC members to generate evidence that image quality using half-dose radiopharmaceuticals with commercially available new hardware and software developments is equivalent to image quality with doses and protocols currently recommended in guidelines.

Creating new ties with other clinical specialty organizations involved with the development of AUC and practice guidelines is critical. Robert Henkin, MD, member of the SNM Committee on Collaborative Guidelines and SNM representative to the Council of Medical Specialty Societies (and to the Physician Consortium for Performance Improvement), wrote: "Over the long haul, our first goal must be to put into place an evidence-based system for SNM guidelines to support the development of quality measures. Failure to make this key commitment will undermine all other efforts we might undertake."

Dominique Delbeke, MD, PhD
SNM President