*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.*

## MOLECULAR IMAGING AND THERAPY

### EpCAM as Target in Prostate Cancer

In an article e-published on October 22 ahead of print in the *American Journal of Pathology*, Mukherjee and colleagues from several laboratories and research centers at the National Institutes of Health (Bethesda, MD) reported on extensions of their previous work identifying molecular changes in the tumor microenvironment in human prostate cancer. Their previous studies provided evidence that tumor-associated stroma showed a distinctly different expression pattern from normal stroma. The current study focused on the epithelial cell adhesion activating molecule (EpCAM), one of the transcripts upregulated in prostate cancer. EpCAM is an antigen expressed on almost all carcinomas. Analysis at the protein level in tissue from 20 prostate cancer patients showed a 76-fold EpCAM expression increase in tumor-associated stroma. These increases also correlated with Gleason tumor scores, with higher increases seen in Gleason 4 or 5 tumor stroma than in Gleason 3 tumor stroma. The authors concluded that because "the stromal compartment may be particularly accessible to vascular-delivered agents, EpCAM could become a valuable molecular target for imaging or treatment of prostate cancer."

*American Journal of Pathology*

### Imaging Amyloid-β Effects

Sheline and colleagues from the Washington University School of Medicine (St. Louis, MO) reported on October 12 ahead of print in *Biological Psychiatry* on imaging studies designed to detect the pathologic effects of amyloid-β plaques on functional resting connectivity in patients with Alzheimer disease ($n$ = 35), in cognitively normal elderly individuals with preclinical amyloid deposition ($n$ = 20), and in matched individuals without such deposition ($n$ = 48). The cognitively normal participants were categorized on the basis of Pittsburgh compound-B (PiB) PET positive or negative imaging of brain amyloid deposition. All participants underwent resting-state functional MR imaging. The PiB-positive group of cognitively normal participants differed significantly from the PiB-negative group in functional connectivity of several brain areas (precuneus to hippocampus, parahippocampus, anterior cingulate, dorsal cingulate, gyrus rectus, superior precuneus, and visual cortex). These differences correlated directly with changes identified in imaging from the Alzheimer disease group. The authors concluded that because differences in resting state connectivity in normal individuals with brain amyloid deposition can be detected well before any cognitive or behavioral changes, the early manifestations of amyloid-β toxicity can be detected clinically using resting-state functional MR imaging.

*Biological Psychiatry*

### Imaging EGFR Overexpression

Xu et al. from the Van Andel Institute (Grand Rapids, MI) reported in the October issue of *Anticancer Research* (2009;29:4005–4011) on the evaluation of a radioiodine-labeled anti-epidermal growth factor receptor (EGFR) human antigen-binding fragment (Fab) as a molecular imaging agent for diagnosis. The authors described the conjugation of $^{125}$I to a human anti-EGFR Fab. Imaging and analyses were conducted in 3 human tumor cell lines representing tumors with different levels of EGFR expression and their corresponding xenografts in mice. SPECT imaging at administration and subsequent analyses indicated that the $^{125}$I-Fab could clearly and quantitatively distinguish different expression levels of EGFR in vivo. The authors concluded that this "$^{125}$I-Fab is a potential molecular imaging agent for clinical diagnosis of EGFR-overexpressing tumors."

*Anticancer Research*

## THERAPY

### Motexafin Gadolinium with RIT in NHL

In the October 15 issue of *Clinical Cancer Research* (2009;15:6462–6471), Evens et al. from the Northwestern University Feinberg School of Medicine (Chicago, IL) reported on preclinical findings and results of a phase 1 trial on the use of motexafin gadolinium, a novel expanded porphyrin, combined with $^{90}$Y-ibritumomab tiuxetan for relapsed/refractory non-Hodgkin lymphoma (NHL). Motexafin gadolinium has been found to target redox-dependent pathways and enhance sensitivity of tumor cells to ionizing radiation. The authors first described

preclinical studies of motexafin gadolinium combined with rituximab and/or radiation in lymphoma cells. In HF1 lymphoma cells, motexafin gadolinium and rituximab resulted in "synergistic cytotoxicity." Motexafin gadolinium/rituximab combined with radiation (1–3 Gy) resulted in additional apoptosis. The phase 1 trial included 28 patients (median age, 65 y; range, 47–87 y) with relapsed or refractory NHL (marginal zone, 1; mantle cell, 3; diffuse large cell, 6; follicular lymphoma, 18) who received escalating doses of motexafin gadolinium concurrently with the standard $^{90}$Y-ibritumomab tiuxetan protocol. No dose-limiting toxicities were observed, with an overall response rate of 57% and complete remission rate of 43%, a median time-to-treatment failure of 10 mos (range, 1–48+ mo), and median response duration of 17 mo. In the 14 patients with rituximab-refractory follicular lymphoma, the overall response rate was 86% and complete remission was 64%, with a median time-to-treatment failure of 14 mo (range, 2–48+ mo). The authors described these results as "the first report of a novel agent to be combined safely concurrently with radioimmunotherapy" and emphasized that the combined therapy resulted in early documented tumor response (at 4 wk in all patients) and a high rate of complete remissions, especially in rituximab-refractory follicular lymphoma.

*Clinical Cancer Research*

## Triple-Gene Transfection with Combined Therapy

In an article e-published on October 8 ahead of print in *Cancer Letters*, Lee et al. from the Kyungpook National University (Daegu, Republic of Korea) reported on combined radionuclide and chemotherapy with in vivo imaging of hepatocellular carcinoma cells after transfection of a triple-gene construct. The study investigated the hypothesis that transfection of both sodium iodine symporter (NIS) and mutant herpes-simplex virus type1 sr39 thymidine kinase (HSV1-sr39tk) genes to hepatocellular carcinoma cells (Huh-7/NTG) could enhance intracellular accumulation of therapeutic radionuclides and guanosine nucleoside analog chemotherapeutic drugs to produce better outcomes than single-gene therapy. In in vitro studies, hepatocellular carcinoma cells were transfected with NIS, HSV1-sr39tk, and green fluorescent protein. All 3 were found to be stably expressed in Huh-7/NTG cells, and uptake of both radionuclides and chemotherapeutic agents was markedly increased in the Huh-7/NTG cells. In in vivo studies, combination therapy with $^{131}$I and ganciclovir was imaged using $^{124}$I SPECT, $^{18}$F-FHBG PET, and optical imaging. Cellular survival and tumor growth of Huh-7/NTG was inhibited by either $^{131}$I or ganciclovir but was significantly enhanced with the combination therapy, with markedly increased uptake in the Huh-7/NTG tumors. The authors concluded that these results demonstrated "the potential of combination gene therapy using NIS and HSV1-sr39tk followed by radioiodine treatment and chemotherapy in human hepatocellular carcinoma cells."

*Cancer Letters*

## $^{90}$Y-DOTATATE Treatment of GEP-NETs

Cwikla et al. from the Medical Center for Postgraduate Education and Central Clinical Hospital of the Ministry of Internal Affairs and Administration (Warsaw, Poland) reported on October 15 ahead of print in *Annals of Oncology* on a phase 2 study of the clinical and radiologic responses to $^{90}$Y-DOTATATE treatment in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs). The study included 60 patients with histologically proven GEP-NETs who underwent treatment with $^{90}$Y-DOTATATE. Clinical responses were assessed at 6 wk after completion of therapy and at 3–6-mo intervals thereafter. Radiologic response was classified using the Response Evaluation Criteria in Solid Tumors, with partial response defined as ≥30% decrease in the sum of the longest diameter of target lesions and stable disease defined as a <30% decrease in the sum of the longest diameter of target lesions or <20% increase in the sum of the longest diameter of target lesions. At 6 mo after final treatment, imaging studies indicated partial responses in 13 (23%) patients and stable disease in 47 (77%) patients. Clinical assessment at the same timepoint indicated partial responses in 43 (72%) patients. Median progression-free survival was 17 mo, with median overall survival at 22 mo. In the 8 patients with early progressive disease, progression-free survival was 4.5 mo and median overall survival was 9.5 mo, whereas the corresponding figures for those with stable disease or partial response were 19.5 and 23.5 mo. Hematologic toxicities of World Health Organization (WHO) grades 3 and 4 were experienced by 10% of patients and persisted during follow-up in 5%. At 1-y follow-up, 5 patients were identified with WHO grades 2 or 3 renal toxicity. The authors concluded that $^{90}$Y-DOTATATE treatment is "effective and relatively safe in patients with GEP-NET" but cautioned that because of the ongoing risk of renal toxicity, careful posttreatment monitoring is recommended.

*Annals of Oncology*

## Novel Probes for Amyloid-β Deposits

Ran et al. from the Massachusetts General Hospital/Harvard Medical School and the Brigham and Women's Hospital (Boston) reported on October 6 ahead of print in the *Journal of the American Chemical Society* on the design, synthesis, and testing of a difluoroboron-derivatized curcumin, CRANAD-2, as a near-infrared probe for in vivo detection of amyloid-β deposits. In vitro studies indicated that CRANAD-2 undergoes a range of changes when interacting with amyloid-β, including greatly enhanced fluorescence intensity (70-fold), a 90-nm blue shift (from 805 to 715 nm), and a large increase in quantum yield,

with a high affinity for amyloid-β aggregates. In vitro studies using intravenous injections of the probe in a mouse model showed significantly higher signal than in control mice. The authors concluded that these data suggest the feasibility of monitoring Alzheimer disease progression with near-infrared imaging with CRANAD-2, adding that the probe has significant potential as a tool for drug screening.

*Journal of the American Chemical Society*

**DIAGNOSIS**

## Axillary Reverse Mapping During Lymphadenectomy

In the October issue of the *American Journal of Surgery* (2009;198:482–487), Boneti et al. from the University of Arkansas for Medical Sciences (Little Rock) reported on a study designed to assess the ability of axillary reverse mapping (ARM) to identify and preserve lymphatics draining the arm and the subsequent effect on lymphedema in patients with breast cancer. The results were recognized earlier this year with the Scientific Impact Award at the annual meeting of the American Society of Breast Surgeons. The study included 220 patients undergoing sentinel lymph node biopsy with or without axillary lymph node dissection. After sentinel lymph node localization with γ imaging, blue dye was used to perform ARM of lymphatics. Variables assessed included number and variations in lymphatic drainage, crossover rate (between a hot breast node and a blue arm node), metastases, and nodal status. Crossover occurred in only 6 (2.8%) patients, and ARM lymphatics were identified in or near the sentinel lymph node field in 40.6% of patients, suggesting risk for disruption of ARM lymphatics during lymphadenectomy. ARM lymphatics near hot sentinel lymph node biopsy were preserved in 12 (5.6%) patients. Fifteen ARM nodes were excised but were negative even in positive axillae. No cases of lymphedema at 6-mo follow-up were seen in patients where ARM nodes were preserved. The authors summarized their findings that the confluence of arm and breast drainage is rarely the sentinel lymph node and that none of these nodes contained metastases. They concluded that "preserving the ARM nodes may translate into a lower incidence of postoperative lymphedema."

*American Journal of Surgery*

## Breast-Specific γ Imaging

In the same issue of the *American Journal of Surgery* (2009;198:470–474), Killelea et al. from the Beth Israel Medical Center (New York, NY) reported on a study using breast-specific γ imaging to determine the incidence of additional, mammographically occult lesions in patients with newly diagnosed breast cancer. The results were recognized earlier this year with the George Peters Award at the annual meeting of the American Society of Breast Surgeons. The study included 82 patients who underwent breast-specific γ imaging for newly diagnosed breast cancer. Of these, 18 patients were found to have additional abnormalities. Seventeen biopsies were performed with results indicating 4 invasive ductal carcinomas, 1 invasive lobular carcinoma, 1 ductal carcinoma in situ, 1 lobular carcinoma in situ, and 2 papillomas; 8 biopsy results were benign. Over all, breast-specific γ imaging findings resulted in a change in surgical management for 22% of patients in the study. The imaging technique detected additional cancer in 9% of patients. The authors concluded that "breast-specific γ imaging plays an important role in the clinical management of patients with known breast cancer."

*American Journal of Surgery*

## Response in Neuroblastoma

In an article e-published on October 5 ahead of print in the *Journal of Clinical Oncology*, Taggart and colleagues from the University of California–San Francisco, the University of Southern California (Los Angeles), and the University of Pennsylvania (Philadelphia) reported on a study comparing $^{123}$I-MIBG scintigraphy and $^{18}$F-FDG PET in evaluating pediatric response after $^{131}$I-MIBG therapy for relapsed neuroblastoma. $^{123}$I-MIBG scintigraphy carries the advantage of imaging the norepinephrine transporter, whereas $^{18}$F-FDG PET assesses glucose metabolic activity. The study included patients enrolled in a phase I study of sequential $^{131}$I-MIBG administration (at d 0 and 14) who had undergone both $^{123}$I-MIBG scintigraphy and $^{18}$F-FDG PET to assess response. Out of 139 unique anatomic lesions identified, scintigraphy and PET results were concordant in 39.6% of lesions. $^{123}$I-MIBG imaging was significantly more sensitive than $^{18}$F-FDG PET overall and for detection of lesions in bone, with slightly increased sensitivity of PET for detection of lesions in soft tissue. The 2 imaging approaches showed similar improvement in number of lesions identified over a 56-d period and in providing data for semiquantitative scores that correlated with overall response. PET scans were more likely than scintigraphy to become completely negative over the course of treatment and designated follow-up. The authors concluded that although $^{123}$I-MIBG imaging is significantly more sensitive for individual lesion detection in relapsed neuroblastoma than $^{18}$F-FDG-PET, PET can "sometimes play a complementary role, particularly in soft tissue lesions."

*Journal of Clinical Oncology*

## Serum Procalcitonin and Renal Parenchyma in Pediatric UTI

Mantadakis and colleagues from the Democritus University of Thrace and University General Hospital of Alexandroupolis (Greece), Henry Dunant Hospital (Athens, Greece), and the Tufts University School of Medicine (Boston, MA) reported on October 20 ahead of print in the

*Journal of Pediatrics* on a meta-analysis performed to determine whether serum procalcitonin is a useful marker of acute renal parenchymal involvement in children with culture-proven urinary tract infections (UTIs), using acute-phase $^{99m}$Tc-dimercaptosuccinic acid ($^{99m}$Tc-DMSA) renal scintigraphy as the gold standard. An extensive literature and database review included criteria of measurement of serum procalcitonin at initial presentation and performance of $^{99m}$Tc-DMSA scintigraphy within 14 d of this assessment. A total of 10 studies, including 627 children, formed the basis for the meta-analysis. Using a cutoff value of 0.5–0.6 ng/mL, the pooled diagnostic odds ratio of serum procalcitonin for UTI with renal parenchymal involvement was 14.25. The authors noted that variations in 2 of the selected studies contributed to wide ranges, but that the results from the remaining 8 uniformly favored the use of serum procalcitonin as a predictor. They concluded that "in children with culture-proven UTI, a serum procalcitonin value >0.5 ng/mL predicts reasonably well the presence of renal parenchymal involvement, as confirmed by $^{99m}$Tc-DMSA scintigraphy." They added that serum procalcitonin could be a useful biomarker in identification of children with UTIs who need more intense evaluation and management.

*Journal of Pediatrics*

## Selective Adenosine Receptor and MPI

Mekkaoui et al. from the Yale University School of Medicine (New Haven, CT) reported in the October issue of *JACC Cardiovascular Imaging* (2009;2:1198–1208) on a study comparing the effects of a selective $A_{2A}$ adenosine receptor agonist (regadenoson) with adenosine on hemodynamics and biodistribution of $^{201}$Tl and $^{99m}$Tc-MIBI in clinically relevant canine models. The study was conducted on 7 anesthetized dogs, first in a closed-chest procedure to assess biodistribution and kinetics of the radiolabeled vasodilating agents, and then in an open-chest model of critical stenosis to evaluate the effects of regadenoson on coronary flow and myocardial uptake. Ex vivo SPECT results were compared with those from histopathology. Regadenoson was found to compare favorably with adenosine in duration and magnitude of hemodynamic effects and in biodistribution and kinetics of both tracers. Arterial blood clearance halftime was significantly faster for $^{99m}$Tc-MIBI with both regadenoson and adenosine. These and other results led the authors to conclude that regadenoson produces a hyperemic response comparable to that produced by a standard infusion of adenosine. They added that "ex vivo perfusion images under the most ideal conditions permitted detection of a critical stenosis, although $^{201}$Tl offered significant advantages over $^{99m}$Tc-MIBI for perfusion imaging during regadenoson vasodilator stress."

*JACC Cardiovascular Imaging*

## SPECT in Heart Failure

Atchley, from Duke University Medical Center (Durham, NC), and more than 300 collaborators from the multiinstitutional Heart Failure and Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, reported in a supplement to the October issue of the *American Heart Journal* (2009;158[suppl 4]:S53–S63) on baseline results from a gated SPECT arm of the study assessing myocardial perfusion, function, and dyssynchrony in patients with heart failure. HF-ACTION was a multicenter, randomized controlled trial comparing the results of aerobic exercise training with customary standards of care in 2,331 stable patients with left ventricular ejection fractions (LVEFs) ≤35% and New York Heart Association (NYHA) class II–IV heart failure symptoms treated with optimal medical therapy. In this imaging arm, 240 patients (129 ischemic etiology, 111 nonischemic etiology) enrolled in the HF-ACTION study underwent resting $^{99m}$Tc-tetrofosmin SPECT at baseline, with evaluation for extent and severity of perfusion abnormalities, LV function, and dyssynchrony. The median LVEF assessed by SPECT for the entire group was 26%. A modest correlation was identified between LVEF and summed rest scores, with a stronger correlation between phase SD (a parameter indicating dyssynchrony) and summed rest scores. Patients with NYHA class III symptoms were found to have more severe and significant degrees of dyssynchrony than those with NYHA class II symptoms. Patients with an ischemic cause for heart failure had higher summed resting scores and significantly more dyssynchrony than patients who were not ischemic. No difference in LVEFs or exercise capacity was observed between these 2 groups. Other correlations were summarized. The authors concluded that "gated SPECT imaging can provide important information in patients with HF due to severe LV dysfunction, including quantitative measures of global systolic function, perfusion, and dyssynchrony."

*American Heart Journal*

## PET/CT in Critical Infections

Simons et al. from the Radboud University Nijmegen Medical Centre (The Netherlands) reported on October 22 ahead of print in *Intensive Care Medicine* on a study of $^{18}$F-FDG PET/CT in critically ill patients with suspected infection. The study included 33 critically ill, mechanically ventilated patients (28 adults, 5 patients; ages, 1 mo−72 y) in an intensive care unit for whom PET/CT scans were requested for evaluation of a suspected infection or inflammatory process. Imaging findings were compared with follow-up results. A total of 35 PET/CT scans were performed, with 21 true-positives, 3 false-positives, and 11 true-negatives. Overall sensitivity was 100%, and overall accuracy was 91%. The authors concluded that "FDG PET/CT scanning is of additional value in the evaluation of suspected infection in critically ill

patients in whom conventional diagnostics did not lead to a diagnosis." They added the finding that a normal PET/CT effectively ruled out important infections requiring prolonged antibiotic therapy or drainage. PET/CT, however, is not appropriate for detection of infection in highly metabolically active tissues (for example, in detection of endocarditis or meningitis).

*Intensive Care Medicine*

## PET/CT and Spinal Infection

In the October 15 issue of *Spine* (2009;34:2424–2430), Kim et al. from the Pusan National University School of Medicine (Busan, Republic of Korea) reported on a study designed to determine whether $^{18}$F-FDG PET/CT imaging after treatment in patients with spinal infection could identify residual infection and provide valuable prognostic data. The study included 30 patients with spinal infections who underwent $^{18}$F-FDG PET/CT at the time of treatment and during follow-up. Results of follow-up imaging were compared with preoperative symptoms, hematologic infection markers, and radiologic findings suggesting residual spinal infection. Maximum and mean standardized uptake values (SUVs) were significantly lower after treatment in all patients (in both residual and nonresidual infections). The sensitivity and specificity for PET/CT identification of residual infection varied in lesion-based analysis by the maximum SUV thresholds selected. When ≤41.78% of the mean %Δ SUV was used as a threshold value, the sensitivity and specificity were 100% and 76.9%, respectively. The authors concluded that $^{18}$F-FDG PET/CT is "useful for discrimination of residual and nonresidual spinal infection after treatment" but that the selection of quantitative indices is important.

*Spine*

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Following the ACNM Program, SNM's Mid-Winter Educational Symposium begins on January 29 and includes numerous educational sessions designed in collaboration with several of SNM's councils and centers, SNMTS, and the Clinical Trials Network. CT case review sessions—back by popular demand—will feature 100 cases, offer 16 credits, and span 2 days. The session, "The Sharp Edges of Nuclear Medicine: See What's New," will introduce technologists to the newest techniques in fusion imaging, with a focus on patients with epilepsy. In addition, technologists will gain valuable knowledge about contrast media and how it fits into nuclear medicine. New this year, for technologists, is a cosponsored session with the American Society of Radiologic Technologists—"Nuclear Medicine Unfolded: What You Need to Know"—focusing on legislative and regulatory issues that nuclear medicine technologists face, including USP 797, the recently reintroduced CARE Bill, and Medicare Improvement Providers and Patients Act of 2008.

At this year's meeting, attendees will also find expanded interactive sessions examining molecular imaging. SNM's Nanomedicine and Molecular Imaging Summit, which takes place January 31–February 1, will provide a thought-provoking setting in which to examine key issues related to the rapid growth and evolving science of nanomedicine. The summit will delve into the cutting-edge field of nanotechnology, offering 5 sessions followed by roundtable and panel discussions (see Molecular Imaging Update in this issue).

For a more hands-on approach, the Clinical Trials Network Community Workshop will give technologists and physicians nuts-and-bolts training on how to participate in industry-sponsored, multicenter clinical trials. The first 2 sessions will include an overview of the network, its components, achievements, and steps for participation. The remainder of the program is designed to help attendees learn the important details of participating in clinical trials.

With expanded offerings and more days to fit in activities, SNM's Conjoint Mid-Winter Meetings will certainly be a fulfilling event for all who attend. Attendees can expect to gain valuable knowledge—and much more as they take in the blue skies and desert landscapes of New Mexico.

For more information on the educational and scientific offerings and the rich experience that the meeting provides, as well as to register, visit the SNM Web site (www.snm.org/mwm) or call 703.708.9000.

*Virginia Pappas, CAE*
*SNM Chief Executive Officer*

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a regulatory and risk management perspective from both the United States and Canada. Two additional sessions will be dedicated to understanding the current and potential use of nanomaterials in the diagnosis and treatment of disease and the potential benefits, advantages, and risks of using nanoparticles as a therapeutic delivery system.

Registration for the summit is now open, and special pricing has been designed to encourage participation by residents and scientists in training. For registration, more information, and the full agenda, see www.snm.org/mwm.

*Julie Sutcliffe, PhD*
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