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 recently 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 both 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. These shifting lines are reflected in the briefs presented here, for example, in the last brief under DIAGNOSIS and the first brief under THERAPY.

DIAGNOSIS

^{99m}Tc-Aprotinin Imaging in Amyloidosis

In an article e-published on November 5 ahead of print in the *European Journal of Haematology*, Han et al. from the Royal Infirmary (Glasgow, UK), reported on a study designed to assess the effectiveness of ^{99m}Tc-aprotinin scintigraphy in systemic amyloidosis. The retrospective study included the records of 35 patients who had undergone such imaging, 18 with biopsy-proven amyloidosis (5 of whom had final diagnoses of cardiac amyloidosis) and 17 in whom amyloidosis was excluded by negative biopsy and/or noninvasive testing. Physiologic uptake of the tracer was seen in the urinary tract and liver of all individuals in the study, and nonspecific uptake was visualized in the spleen and orofacial structures in most individuals. However, myocardial ^{99m}Tc-aprotinin uptake was seen in all 5 patients with diagnoses of cardiac amyloidosis and in none of the remaining 30 individuals. Thoracic SPECT studies confirmed tracer localization in the myocardium. In individuals with amyloidosis, site-specific ^{99m}Tc-aprotinin uptake was also seen in the subcutaneous tissue of the legs and in a breast nodule positive for amyloidosis on biopsy. The authors concluded that "^{99m}Tc-aprotinin imaging may be a useful noninvasive method for the assessment of the presence and extent of extraabdominal amyloid, particularly cardiac amyloidosis," but cautioned that it appears ineffective in the diagnosis of amyloidosis involving the orofacial and abdominal structures.

European Journal of Haematology

Second Primary Risk in Thyroid Ca Survivors

Subramanian et al. from Stanford University (Palo Alto, CA) reported on November 16 ahead of print in *Thyroid* on a systematic review and meta-analysis of the risk of second primary malignancies (SPMs) in thyroid cancer survivors. The authors screened relevant citations and reviewed 13 full-text papers to examine standardized incidence ratios (SIRs) of SPMs in 70,844 thyroid cancer survivors and to compare these ratios with those in individuals without thyroid cancer. They found that the incidence of SPMs in survivors was increased, with a SIR of 1.20. SIRs of the following SPMs were significantly increased: salivary gland, stomach, colon/colorectal, breast, prostate, kidney, brain/central nervous system, soft tissue sarcoma, non-Hodgkin's lymphoma, multiple myeloma, leukemia, bone/joints, and adrenal. At the same time, a significantly reduced risk of lung and cervical cancers was observed among thyroid cancer survivors. The authors concluded that these survivors "are at increased risk of SPMs, which may be related to disease-specific treatments or genetic predisposition."

Thyroid

Hashimoto's Thyroiditis and Thyroid Cancer

In an article e-published on October 29 ahead of print in the *Journal of Surgical Research*, Repplinger et al. from the University of Wisconsin (Madison) reported on a retrospective study designed to determine whether a correlation exists between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC), with a special focus on whether additional diligence may be needed in monitoring women with HT. The authors reviewed 13 years of institutional data on 1,198 patients who underwent thyroid surgery. Of these, 217 were diagnosed with HT (196 women, 21 men). After analysis of these records, PTC was found to have occurred in 63 of 217 (29%) HT patients and 230 of 981 (23%) patients without HT. Of these groups, 56 of 196 women (29%) with HT had coexistent PTC, compared with 160 of 730 women (22%) without HT. Among women with any type of thyroid malignancy, 56 of 59 cases (95%) with HT had PTC, compared with 159 of 196 cases (81%) in women without HT. Women with HT and goiters had a significantly lower rate of PTC than women without goiters (9% and 36%, respectively). Such differences were not observed in men with HT. Women with HT undergoing thyroidectomy were 30% more likely to have PTC than those without HT. The authors concluded that HT is associated with an increased risk of developing PTC and that "aggressive surveillance for PTC may be indicated in patients with HT," especially women.

Journal of Surgical Research

PET and Alcohol Detox

In another of their groundbreaking collaborations elucidating the neurologic mechanisms of addiction, Volkow et al. from the National Institute on

Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism (Bethesda, MD) and Wang et al. from the Brookhaven National Laboratory (Upton, NY) and the State University of New York at Stony Brook reported in the November 14 issue of the *Journal of Neuroscience* (2007;27:12700–12706) on a study using ^{18}F-FDG and ^{11}C-raclopride PET to determine whether the prefrontal cortex regulates the value of "rewards" by modulating dopamine increases in the nucleus accumbens and whether this regulation is disrupted in addicted subjects. The study included 20 healthy individuals and 20 detoxified alcoholics who were imaged before and after dopamine increases induced by methylphenidate administration. In all participants, methylphenidate significantly increased dopamine in the striatum. In the ventral striatum and in the putamen, dopamine increases were associated with the rewarding effects of methylphenidate (drug liking and high) and were profoundly attenuated in both areas in alcoholics. In control participants, metabolism in the orbitofrontal cortex (region involved with salience attribution) was negatively associated with methylphenidate-induced dopamine increases in ventral striatum; this association was not seen in alcoholics. The authors noted that "these results are consistent with the hypothesis that the orbitofrontal cortex modulates the value of rewards by regulating the magnitude of dopamine increases in the ventral striatum and that disruption of this regulation may underlie the decreased sensitivity to rewards in addicted subjects."

Journal of Neuroscience

Novel Radioligand for PET in Neuroinflammation

Boutin et al. from the Laboratoire d'Imagerie Moléculaire Expérimentale (Orsay, France), a part of the Commissariat à l'Énergie Atomique, reported in the November 1 issue of *Glia* (2007; 55:1459–1468) on a new peripheral benzodiazepine receptor (PBR) ligand proposed as an alternative to PK11195 in PET imaging of brain lesions. The authors described in vitro studies and in vivo imaging properties of ^{11}C-CLINME in a rat model of local acute neuroinflammation and compared the results with those from ^{11}C-PK11195 studies. The novel tracer showed a higher contrast between the PBR-expressing lesion site and the intact side of the same rat brain than ^{11}C-PK11195, a result of lower uptake of ^{11}C-CLINME in noninflamed brain. Uptake levels in the lesion were similar for both tracers. Additional analyses indicated that localization of the novel tracer correlated well with that of activated microglial cells and that ^{11}C-CLINME showed a higher binding potential than ^{11}C-PK11195. The authors concluded that these results suggest that ^{11}C-CLINME may have distinct advantages in PET imaging of neuroinflammation.

Glia

PET and Effects of Cardiac Resynchronization

In an article e-published on October 25 ahead of print in the *Journal of Cardiovascular Electrophysiology*, Christenson et al. from the Mayo Clinic and Mayo Clinic College of Medicine (Rochester, MI) reported on a study using ^{11}C-acetate PET and echocardiography to explore the effects of sequential cardiac resynchronization therapy (CRT) on myocardial oxidative metabolism (MVO_2). The study included 8 patients diagnosed with New York Heart Association class III heart failure who were studied 196 ± 180 days after CRT implant. Each patient underwent dynamic ^{11}C-acetate PET and echocardiography for 3 different pacing modes: fixed-rate atrial pacing, simultaneous CRT, and sequential CRT. ^{11}C-acetate clearance rate on PET was used to calculate MVO_2, and myocardial efficiency was expressed in terms of the work metabolic index. Global left and right ventricular MVO_2 did not differ significantly among the 3 pacing modes, but significant differences were noted in the septal/lateral MVO_2 ratios. Stroke volume index and work metabolic index also differed among pacing modes, but additional analysis indicated that these changes were not significant between simultaneous and sequential CRT. The authors concluded that in this small-population study, CRT increased left ventricular stroke volume index without increasing MVO_2, resulting in improved myocardial efficiency, but that "additional improvements in left ventricular work, oxidative metabolism, and efficiency from simultaneous to sequential CRT were not significant."

Journal of Cardiovascular Electrophysiology

Direct Implantation of Bone Marrow Cells in CAD

Tse et al. from the Queen Mary Hospital (Hong Kong) reported on November 5 ahead of print in the *European Heart Journal* on early results from a prospective randomized trial of direct endomyocardial implantation of bone marrow cells for therapeutic angiogenesis of severe coronary artery disease (the PROTECT-CAD trial). The study included 28 patients with CAD who had been unresponsive to conventional treatments and were assigned to receive low (n = 9) or high (n = 10) doses of autologous bone marrow cells or autologous plasma injections (controls; n = 9). Catheter-based direct endomyocardial injections (total of 422, or an average of 14 per patient) were guided by electromechanical mapping of ischemic regions. Participants were assessed at several time periods up to 6 months for increase in exercise treadmill time performance and for Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA) class status. They also underwent baseline and 6-month SPECT to assess myocardial perfusion and MR imaging to assess left ventricular ejection fraction (LVEF). Direct endomyocardial implantation of bone marrow cells (in both the high- and low-dose groups) led to significant improvements in exercise time (20% improvement), LVEF (7.5% improvement), and stress-induced myocardial ischemia (30% decrease) at 6 months compared with results from controls. The treated groups also had lower NYHA class statuses after 6 months, but CCS status was reduced similarly in

all groups. No acute or long-term complications were noted in association with bone marrow cell implantation. The authors concluded that "direct endomyocardial implantation of autologous bone marrow cells significantly improved exercise time, LVEF, and NYHA functional class in patients with severe CAD who failed conventional therapy."

European Heart Journal

PET Monitoring of Hypoxia

In an article published in the November 15 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2007;69:1024–1031), Evans et al. from the University of Pennsylvania (Philadelphia) reported on the use of EF5, a 2-nitroimidazole hypoxia marker, to study the levels and prognostic significance of hypoxia in primary head and neck squamous cell tumors. The study included 22 patients newly diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, or larynx. The researchers performed quantitative analyses of EF5 immunofluorescence and compared these with outcomes from at least 2 years of follow-up. Three patterns of EF5 binding in cells were identified using criteria based on whether immunofluorescence staining was in peripheral or central cellular regions and the relationship of binding to necrosis. Results indicated that patients with tumors containing EF5-binding regions corresponding to severe hypoxia had shorter event-free survival times than patients with higher pO_2 values. Nodal status was also predictive for outcome. The authors concluded that "these data illustrate the potential utility of EF5 binding based on quantitative immunohistochemistry of tissue pO_2" and provide support for the development of ^{18}F-EF5 PET monitoring of hypoxia.

International Journal of Radiation Oncology, Biology, Physics

^{18}F-Galacto-RGD PET for $\alpha_v\beta_3$ Imaging

Beer et al. from the Technische Universität München (Germany) and the Medizinische Universität Innsbruck (Austria) reported in the November 15 issue of *Clinical Cancer Research* (2007;13:6610–6616) on the use of ^{18}F-galacto-RGD PET for imaging $\alpha_v\beta_3$ expression in patients with squamous cell carcinoma of the head and neck (SCCHN). The group has previously described the pharmacokinetics and biodistribution of this tracer in *The Journal of Nuclear Medicine* (2006;47:763–769; 2005;46:1333–1341). The current study included 11 patients with primary diagnoses of SCCHN who underwent static emission scans from the head to the abdomen at 60 minutes after tracer injection. Six of these patients also underwent dynamic scans covering the tumor region more than 1 hour after tracer injection. Standardized uptake values (SUVs) were measured in tumors, muscle, and oral mucosa. Additional steps included immunohistochemistry using an $\alpha_v\beta_3$-specific antibody in 7 patients, MR or CT scans in 8 patients for image fusion, and calculation of tumor subvolumes based on SUVs. ^{18}F-galacto-RGD PET identified 10 of 12 tumors (SUVs 2.2–5.8). The 2 tumors missed were <5 mm in diameter. Tumor kinetics were consistent with reversible specific binding. Immunohistochemistry confirmed $\alpha_v\beta_3$ expression on microvessels in all tumors. Fusion of PET and MR or CT images was feasible in all attempted cases and facilitated definition of tumor subvolumes. The authors concluded that ^{18}F-galacto-RGD PET "allows for specific imaging of $\alpha_v\beta_3$ expression in SCCHN with good contrast" and that this technique shows promise in the assessment of angiogenesis and for planning and response evaluation of $\alpha_v\beta_3$-targeted therapies.

Clinical Cancer Research

THERAPY

Model for Bimodal Imaging of SSTR Expression

In an article e-published on November 16 ahead of print in *Neuroendocrinology*, Stelter et al. from the Universitätsmedizin Berlin (Germany) reported on an orthotopic mouse model of pancreatic somatostatin receptor (SSTR)–positive tumors that facilitates MR and PET imaging of SSTR expression in experimental studies of neuroendocrine tumor treatments. The authors implanted amphicrine SSTR-positive pancreatic AR42J cells in mice, which resulted in rapidly growing tumors and metastatic spread into abdominal lymph nodes and the peritoneal cavity. ^{68}Ga-DOTATOC or ^{68}Ga-DOTANOC was injected, and mice underwent small animal PET and MR imaging. Digital image fusion of the PET and MR data showed radionuclide accumulation in the primary tumor in all animals and confirmed anatomic correlation. Greater accumulation of ^{68}Ga-DOTANOC was seen in tumor tissue, and ^{68}Ga-DOTATOC showed a higher renal clearance. The kidney-to-tumor ratio was higher for ^{68}Ga-DOTATOC, so that this tracer achieved better signal enhancement in the primary tumor and allowed detection of metastatic lesions. The authors concluded that this animal model "will be of innovative value for further investigation in the imaging of neuroendocrine tumors."

Neuroendocrinology

Targeting Cancer as an Infectious Disease

Wang et al. from the Albert Einstein College of Medicine (Bronx, NY) reported on October 31 in *PLoS One* (2007;2:e114) on a study assessing the potential use of viral antigens as novel targets for both direct and prophylactic radioimmunotherapy (RIT) of cancers with viral etiologies (nearly 20% of human cancers worldwide). Proof-of-principle experiments were designed to demonstrate the feasibility of treating human papilloma virus 16–associated cervical cancer and hepatitis B–associated hepatocellular carcinoma by targeting viral antigens expressed on cancer cells with ^{188}Re-labeled monoclonal antibodies (mAbs) to viral antigens. In models of these diseases in mice, the treatments resulted in significant and dose-dependent slowing in tumor growth compared with results in untreated mice and mice treated with

unlabeled antibodies. The authors emphasized that this approach is "fundamentally different from the previously described uses of RIT which target tumor-associated antigens that are 'self' (ie, human) proteins." By targeting viral proteins instead, they hypothesized that mAbs could be more specifically concentrated within tumor tissue, resulting in greater efficacy and less toxicity. They concluded that the results of these initial studies offered "an exciting possibility to prevent virus-associated cancers in chronically infected patients by eliminating cells infected with oncogenic viruses before they transform into cancer."

PLoS One

Zevalin with Stem Cell Transplantation

In a study published in the November issue of the *British Journal of Haematology* (2007,139:590–599), Ferrucci et al. from the European Institute of Oncology (Milan, Italy) reported on a feasibility and toxicity pilot study of different levels of ^{90}Y-ibritumomab tiuxetan (Zevalin) radioimmunotherapy (RIT) followed by autologous stem cell transplantation in patients with refractory/resistant B-cell non-Hodgkin's lymphoma (NHL). The study included 13 patients who underwent dosimetry studies 1 week before receiving 30, 45, or 56 MBq/kg of ^{90}Y-ibritumomab tiuxetan and who underwent autologous stem cell grafting 13 days after RIT. No differences in hematologic toxicities were seen among the 3 levels, although those in the highest dosage group experienced somewhat delayed platelet recovery. Nonhematologic toxicity was related to infections and liver toxicity. One patient died 4 months after RIT from hepatitis C virus reactivation, and another patient developed a myelodysplastic syndrome 2 years after treatment. The authors concluded that this high-activity treatment regimen of ^{90}Y-ibritumomab tiuxetan and stem cell transplantation is feasible and "could be safely delivered in elderly and heavily pretreated NHL patients, including those who previously received high-dose chemotherapy and autologous stem cell transplantation."

British Journal of Haematology

MOLECULAR IMAGING

Multimodal SSTR Imaging

In an article e-published on November 20 ahead of print in *Bioconjugate Chemistry*, Edwards et al. from the Mallinckrodt Institute of Radiology at Washington University (St. Louis, MO) reported on the synthesis of a novel monomolecular agent for multimodel optical and PET or SPECT imaging of somatostatin receptors (SSTRs). The agent, called LS172, contains a subtype-2 SSTR-avid peptide, a radiometal chelating group (DOTA), and a near-infrared fluorescent dye. The agent can be radiolabeled with ^{64}Cu for PET or ^{177}Lu for SPECT. Biodistribution of the SSTR2 receptor–specific ^{64}Cu and ^{177}Lu LS172 in AR42J tumor-bearing rats showed low accumulation in tumor tissue, and both optical and radionuclide biodistribution studies indicated similar in vivo distribution profiles. Commenting on the surprising finding that the strong binding of LS172 to SSTR2 did not translate into high SSTR2-mediated endocytosis in cells or uptake in tumor in vivo, the authors pointed to the "agonist–antagonist dilemma": "Considering that LS172 is a putative antagonist, the poor accumulation of the labeled monomolecular imaging agents in SSTR2-positive tumor tissue supports the paradigm that agonists with their concomitant internalization favor appreciable target tissue accumulation of receptor-specific ligands."

Bioconjugate Chemistry

E Coli Tumor-Targeting and Imaging

In an article e-published on November 10 ahead of print in *Molecular Imaging and Biology*, Min et al. from the Chonnam National University Medical School (Gwangju, South Korea) reported on noninvasive real-time imaging using tumor-targeting, light-emitting *Escherichia coli*. The studies were conducted in mice with a diverse range of implanted tumors and metastases. Twenty-four hours after injection of luciferase-expressing *E coli*, bioluminescence signals from the bacteria were detected only in tumor tissue. A balanced-lethal host–vector system using the gene-encoding aspartate β-semialdehyde dehydrogenase enabled stable maintenance of the luciferase in the tumor-targeting bacteria. *E coli* targeted both primary tumors and metastases, with resulting optical images. The authors concluded that these results suggest "the potential clinical use of this technology for tumor targeting."

Molecular Imaging and Biology

Molecular Imaging of EGFR Expression

Barrett et al. from the National Institutes of Health (Bethesda, MD) and the University of Tokyo (Japan) reported in the November 15 issue of *Clinical Cancer Research* (2007;13: 6639–6648) on the use of a "cocktail" of optically labeled monoclonal antibodies for in vivo assessment of epidermal growth factor (EGFR) expression. The study was performed in 14 mice after injection of A431 (overexpressing HER1), NIH3T3/HER2+ (overexpressing HER2), and Balb3T3/DsRed (nonexpression control) cell lines and establishment of tumors. Injection of a cocktail of optically labeled antibodies, including Cy5.5-labeled cetuximab (anti-HER1) and Cy7-labeled trastuzumab (anti-HER2), was followed by in vivo and ex vivo fluorescence imaging and comparison imaging using ^{111}In-labeled antibodies. A blinded diagnostic study was also performed for mice bearing a single tumor type. Spectral fluorescent molecular imaging was able to clearly pinpoint and differentiate different types of tumors, both in vivo and ex vivo. Radionuclide imaging could not clearly distinguish tumors at 24 hours. The authors summarized the results of the study: "An in vivo imaging technique using an antibody cocktail simultaneously differentiated 2 tumors expressing distinct EGFRs and enabled an accurate characterization of each subtype."

Clinical Cancer Research

Modulating Prostate Ca Metastasis

Brakenhielm et al. from the University of California at Los Angeles reported in the November 15 issue of the *International Journal of Cancer* (2007;121:2153–2161) on a study investigating the possibility of modulating prostate cancer metastasis by the use of a lymphangiogenic "switch" and the concomitant use of a noninvasive molecular imaging technique to facilitate assessment and monitoring of micrometastases. LAPC-4, LAPC-9, PC3, and CWR22Rv-1 human cancer xenograft cells were labeled with luciferase before implantation in mice. The LAPC-9 tumor cells (associated with lower numbers of and slower-growing metastases) were engineered to overexpress vascular endothelial growth factor-C (VEGF-C) to assess the role of lymphangiogenesis in mediating metastases. Immunochemistry and histopathology confirmed metastatic lesions and characterized the angiogenic and lymphangiogenic profiles of tumors. Differences in metastatic potential were found to correlate with endogenous production levels of lymphangiogenic growth factor VEGF-C and the presence of tumor lymphatics. Even in LAPC-9, induced overexpression of VEGF-C enhanced tumor lymphangiogenesis, leading to the development of metastatic lesions. The authors concluded that these studies "point to an important role of tumor lymphatics in the metastatic process of human prostate cancer. In particular, VEGF-C seems to play a key role in prostate cancer metastasis."

International Journal of Cancer

Contrast US in Breast Cancer

In an article published in the November issue of the *Journal of Ultrasound in Medicine* (2007;26:1575–1586), Lyshchik et al. from Vanderbilt University Medical Center (Nashville, TN) reported on an investigation of the use of targeted contrast-enhanced high-frequency ultrasound for molecular imaging of vascular endothelial growth factor receptor 2 (VEGFR2) expression on tumor vascular endothelium in mouse models of breast cancer. Mice were implanted with highly invasive metastatic (4T1) and nonmetastatic (67NR) breast cancer cells, and tumors were examined in vivo with targeted contrast-enhanced high-frequency ultrasound and randomized boluses of ultrasound contrast agents conjugated with an anti-VEGFR2 monoclonal antibody or an isotype control antibody (immunoglobulin G). Sonograms were analyzed, and tumors were harvested for immunochemistry and histopathology. Mean ultrasound video intensity amplitudes caused by backscatter were much higher for the retained VEGFR2-targeted contrast agent than for the control agent, and significant differences were also noted in VEGFR2-targeted contrast retention between the metastatic and nonmetastatic tumors, correlating with relative VEGFR2 expression in the 2 tumor types. The authors concluded that "Targeted contrast-enhanced high-frequency ultrasonography may enable in vivo molecular imaging of VEGFR2 expression on the tumor vascular endothelium and may be used for noninvasive longitudinal evaluation of tumor angiogenesis in preclinical studies."

Journal of Ultrasound in Medicine