

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 radio-nuclide-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.

## DIAGNOSIS

### Molecular Imaging and Monkeypox Disease

In an article e-published on October 19 ahead of print in the *Journal of Infectious Diseases*, Dyall et al. from the National Institute of Allergy and Infectious Diseases (Bethesda, MD) reported on PET and PET/CT imaging used to identify inflammatory patterns as predictors for outcomes of monkeypox virus disease in nonhuman primates. The work is part of a larger effort to develop an animal model of variola infections in humans. The authors inoculated primates (intravenously or intrabronchially) and performed sequential  $^{18}\text{F}$ -FDG imaging, using tracer uptake as a nonspecific marker of inflammation/immune activation. Inflammation was observed in the lungs of the intrabronchially infected animals, and bilobular involvement was

associated with morbidity. Lymphadenopathy and immune activation in the axillary lymph nodes were evident in animals infected by both administration routes. The researchers noted that surviving primates had significant tracer uptake in axillary lymph nodes at the time of monkeypox virus challenge with no clinical signs of illness, suggesting an association between preexisting immune activation and survival. The authors concluded that, in general, “molecular imaging identified patterns of inflammation/immune activation that may allow risk assessment of monkeypox disease.”

*Journal of Infectious Diseases*

### PET and Infection in Hip Arthroplasty

Huang et al. from Chang Gung Memorial Hospital (Taoyuan, Taiwan) reported in the October 5 issue of *Orthopedics* (2011;34:e605–e609) on the use of PET to detect infection around antibiotic-loaded cement spacers in patients with high C-reactive protein (CRP) levels and to provide valuable information relevant to reimplantation arthroplasty. The study included 13 patients (mean age, 60 y) whose clinical conditions were determined to be suitable for reimplantation but whose serum CRP levels were persistently elevated (over an average of 4 mo) after the first-stage procedure.  $^{18}\text{F}$ -FDG PET imaging was positive for infection around antibiotic-loaded cement spacers in 6 and negative in 7 patients. Reimplantation total hip arthroplasty was performed in the 7 patients negative on PET for infection. In 3 of the PET-positive patients, infection was confirmed by another debridement surgery. Staged reimplantation arthroplasty was delayed in 1 patient who underwent repeat debridement and in 3 who were treated with extended periods of oral antibiotics. In all, 11 patients proceeded to reimplantation total hip arthroplasty, with only 1 reinfection noted over an average follow-up of 48 mo. The authors concluded that this “success rate of 91% suggests

FDG PET could help in the differential diagnosis of infection around cement spacers, especially in patients with normal clinical findings but elevated CRP levels.”

*Orthopedics*

### PET and Cerebellar Function

In an article e-published on October 8 ahead of print in *Hearing Research*, Petacchi et al. from the University of Texas Health Science Center at San Antonio reported on a study using PET imaging and a pitch discrimination task to test for cerebellar involvement in active control of sensory data acquisition. The study included 10 healthy volunteers who were trained to discriminate deviant tones presented with a slightly higher pitch than a standard tone, using a go/no go paradigm. Additional steps were taken to ensure that discrimination performance was matched across participants. Individuals underwent serial imaging while: (1) resting in the absence of any sounds; (2) passively listening to standard tones; and (3) detecting deviant tones slightly higher in pitch among these standard tones at 4 different performance levels. The authors found that passive listening alone elicited cerebellar activity (lobule IX), that cerebellar activity increased during pitch discrimination (crus I and II, lobules VI, VIIIB, and VIIIB), and that this increase correlated directly with the difficulty of the discrimination task (lobules V, VI, and IX). They concluded that these results support a role for the cerebellum in sensory data acquisition and described anatomic and physiologic evidence functionally connecting the auditory system and cerebellum.

*Hearing Research*

### PET and Heroin Dependence

Martinez et al. from Columbia University College of Physicians and

Surgeons (New York, NY) reported on October 18 ahead of print in *Biological Psychiatry* on a study using PET to investigate the parameters of striatal dopamine transmission in heroine dependence and their association with drug seeking behaviors. The study included 16 heroine-dependent and 16 healthy control participants who underwent  $^{11}\text{C}$ -raclopride PET imaging before and after methylphenidate administration to measure striatal  $\text{D}_2$  and  $\text{D}_3$  receptor binding and presynaptic dopamine release. After scanning, substance-dependent participants were allowed to self-administer heroine. The authors found that although both striatal  $\text{D}_2$  and  $\text{D}_3$  receptor binding and dopamine release were reduced in the heroine-dependent individuals (as in addiction studies with other drugs of abuse), neither PET measure of dopamine transmission predicted the choice to self-administer heroine.

*Biological Psychiatry*

## PET and Cervical Cancer Treatment

In an article e-published on October 17 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics*, Schwarz et al. from the Washington University School of Medicine (St. Louis, MO) reported on a study using  $^{18}\text{F}$ -FDG PET imaging to explore early metabolic response and patterns of failure in patients treated with definitive radiotherapy for cervical cancer. The retrospective study looked at the records of 238 women treated with a combination of external radiotherapy and intracavitary brachytherapy; 219 of these patients also received concurrent chemotherapy. All patients underwent pretreatment  $^{18}\text{F}$ -FDG PET, with a second scan performed 8–16 wk after completion of radiotherapy. Posttherapy PET findings were categorized as complete metabolic response (173 patients), partial metabolic response (40 patients), and progressive disease (25 patients). Failure patterns were categorized as none, isolated local failure (central pelvis  $\pm$  pelvic lymph nodes), distant failure, or combined

local and distant failure. Of the 91 patients (38%) who went on to experience a recurrence, 22 had isolated local failures and 69 had distant failures (49 distant failures and 20 combined local and distant failures). Of the 173 patients with a complete metabolic response on PET, 40 (23%) went on to experience treatment failure. All 25 patients with progressive disease on PET experienced treatment failure, which was distant in 24 (96%) patients. Among the 40 patients with partial metabolic response, 14 patients (35%) have experienced no failure, and 15 (58%) of the 26 failures in this group were limited to the pelvis. The authors concluded that “the majority of failures after definitive radiotherapy for cervical cancer include distant failures, even in the setting of concurrent chemotherapy” and that “partial metabolic response within the cervix or lymph nodes is more commonly associated with isolated local recurrence.”

*International Journal of Radiation Oncology, Biology, Physics*

## THERAPY

### RIT and Fungal Infections

Jiang et al. from the Albert Einstein College of Medicine (Bronx, NY) reported on October 17 ahead of print in *Antimicrobial Agents and Chemotherapy* on a study investigating the utility of radioimmunotherapy (RIT) in early and established cryptococcal infection in immunocompetent mice. The authors found that RIT with a  $^{213}\text{Bi}$ -labeled 18B7 antibody completely eliminated fungus from mice lungs and brains in early infection, whereas  $^{188}\text{Re}$ -labeled 18B7 significantly reduced colony-forming units in the lungs or both lungs and brains during early and established infection. They concluded that these “results point to the independence of RIT on the immune status of the host, which is encouraging for translation of this strategy into the clinic.”

*Antimicrobial Agents and Chemotherapy*

## $^{131}\text{I}$ -Anti-CK8 mAb in HNSCC

Andratschke et al. from the Dachau Medical Center (Germany) reported in the October issue of *Anticancer Research* (2011;31:3315–3321) on a study designed to investigate the biodistribution of a radiolabeled cytokeratin 8 (CK8)-specific monoclonal antibody (mAb) in a severe combined immunodeficiency disease (SCID) mouse model. CK-8 has been identified as a promising anchor molecule for targeted radioimmunotherapy (RIT) in head and neck squamous cell carcinoma (HNSCC). Biodistribution of the mAb was tested first in HNSCC xenografts in SCID mice. After systemic administration of the  $^{131}\text{I}$ -anti-CK8 mAb, high activity was seen in all organs, with gradual decreases in general activity and retained accumulation in tumor. Tumor activity decayed compared to the other tissues with a 2- to 3-fold prolonged radioactive half-life. The authors concluded that “specific antibody-antigen-binding is probably responsible for the prolonged radioactive half-life in the tumor and the resulting cumulative activity due to enrichment of the  $^{131}\text{I}$ -anti-CK8 mAb, so that CK8 seems to be a suitable anchor molecule for RIT in HNSCC.”

*Anticancer Research*

## MOLECULAR IMAGING

### Cardiac MR, LVEF, and Stem Cell Therapy

In an article published in the October issue of the *American Heart Journal* (2011;162:671–677), Traverse et al. from Abbott Northwestern Hospital (Minneapolis, MN), the University of Minnesota Medical School (Minneapolis), and the Cardiovascular Cell Therapy Research Network (Houston, TX) reported on a cardiac MR-based analysis of the effect of bone marrow mononuclear stem cell (BMC) administration on left ventricular ejection fraction (LVEF) after ST-segment elevation myocardial infarction (MI). The authors reviewed

the results of 10 randomized cardiovascular stem cell trials in which intracoronary BMCs or placebo were administered to 686 patients and controls after primary percutaneous coronary intervention treatment of ST-segment elevation MI. All trials used cardiac MR imaging as the main imaging measure of LVEF at baseline and again 3–6 mo later. Administration of BMCs was associated with a nonsignificant absolute increase in LVEF compared with placebo or control, with small and nonsignificant decreases in LV end-diastolic and LV end-systolic volumes. Although average infarct size uniformly decreased over time, this reduction was not improved by BMC administration. The authors concluded that “the benefit of BMC administration after ST-segment elevation MI on LVEF, LV volumes, and infarct size is small when assessed by cardiac MR imaging.”

*American Heart Journal*

### BBB Nanobody Permeability

Caljon and colleagues from the Vrije Universiteit Brussel (Belgium) and the Institute of Tropical Medicine Antwerp (Belgium) reported on October 20 ahead of print in the *British Journal of Pharmacology* on an analysis of blood–brain barrier (BBB) permeability to monovalent nanobodies using microdialysis. The researchers assessed the BBB permeability of Nb\_An33, a nanobody against the trypanosoma brucei brucei variant-specific surface glycoprotein. The study was conducted in healthy rats and rats that were in the encephalitic stage of African trypanosomiasis. Intracerebral microdialysis and/or SPECT were used to analyze unlabeled and <sup>99m</sup>Tc-labeled nanobodies. These methodologies showed that the distribution of Nb\_An33 was detected in the brain of healthy rats after intravenous injection and that inflammation-induced damage to the BBB significantly increased nanobody perfusion efficiency. The authors described the advantages of complementing SPECT analyses

with intracerebral microdialysis in brain disposition studies and suggested that the BBB penetrating potential of monovalent nanobodies should be investigated in other central nervous system models. They concluded that “nanobodies can perfuse into the brain parenchyma, especially in pathological conditions where the BBB integrity is compromised.”

*British Journal of Pharmacology*

### Bioluminescence and Breast Ca Mets

In an article e-published on October 20 ahead of print in *Clinical Cancer Research*, Tafreshi et al. from the H. Lee Moffitt Cancer Center and Research Institute (Tampa, FL) described noninvasive detection of breast cancer lymph node metastasis using targeted imaging probes developed by conjugation of cell surface carbonic anhydrase isozyme (CAIX and/or CAXII) specific monoclonal antibodies (mAbs) to a near-infrared fluorescent (NIRF) dye. The isozyme mAbs were validated for protein expression by immunohistochemistry on a breast cancer tissue microarray containing 47 normal breast tissue samples, 42 ductal carcinoma in situ, 43 invasive ductal carcinomas without metastasis, 46 invasive ductal carcinomas with metastasis, and 49 lymph node macrometastases of breast carcinoma. The 2 markers were found to be expressed in 100% of the lymph node metastases surveyed. Probe selectivity was confirmed by intravenous injection into nude mice bearing mammary fat pad tumors of marker expressing cells and nonexpressing cells or by preinjection of unlabeled antibody. Imaging of lymph node metastases showed that peritumorally injected probes detected nodes harboring metastatic tumor cells. Groups of as few as 1,000 cells were detected. The authors concluded that “these imaging probes have potential for noninvasive staging of breast cancer in the clinic and elimination of unneeded surgery, which is costly and associated with morbidities.”

*Clinical Cancer Research*

### 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 September and October. In an article published in the October 18 issue of *Accounts of Chemical Research* (2011;44:1050–1060), Jokerst and Gambhir from Stanford University (CA) provided an overview of “Molecular imaging with theranostic nanoparticles.” On October 15 ahead of print in the *Journal of Transplantation*, Wang et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) described “Molecular imaging: a promising tool to monitor islet transplantation.” Wong et al. from Princess Margaret Hospital (Toronto, Canada) on September 28 ahead of print in *Clinical Oncology (Royal College of Radiologists)* described “Evidence-based guideline recommendations on the use of PET imaging in oesophageal cancer.” In an article e-published on October 19 ahead of print in *Pharmacoeconomics*, Dams and colleagues from Philipps University (Marburg, Germany), UMIT/Health and Life Sciences University (Hall, Austria), and the Harvard School of Public Health (Boston, MA) summarized economic data on “Modelling the cost effectiveness of treatments for Parkinson’s disease: a methodological review.” Reiman et al. from the University of Arizona and the Arizona Alzheimer’s Consortium (Phoenix) reviewed current and promising approaches in “Fluorodeoxyglucose PET: emerging roles in the evaluation of putative Alzheimer’s disease-modifying treatments” on October 7 ahead of print in *Neurobiology of Aging*. In the October 13 issue of *Current Atherosclerosis Reports* (2011;13:381–389) Rana et al. from Cedars-Sinai Medical Center (Los Angeles, CA) highlighted “Combination of myocardial perfusion imaging and coronary calcium scanning: potential synergies for improving risk assessment in subjects with suspected coronary artery disease.”