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. This month’s selection highlights the growing transition of molecular imaging research techniques into routine clinical practice, as well as the growing trend toward targeting strategies that enhance both diagnostic and therapeutic capabilities.

DIAGNOSIS

SLN and ALND in Breast Cancer

Members of the multicenter National Surgical Adjuvant Breast and Bowel Project (NSABP) reported in the October issue of Lancet Oncology (2007;8:881–888) on a subset of studies in a randomized phase III trial to assess therapeutic outcomes and attendant side effects of sentinel lymph node (SLN) resection and axillary lymph node dissection (ALND). Here, they compared the accuracy and technical success (not long-term outcomes) of SLN plus ALND with that of SLN alone in patients with clinically node-negative breast cancer. The study included 5,611 patients who were assigned to receive either SLN resection followed by immediate conventional ALND (n = 2,807) or SLN resection without ALND (when SLNs were negative on intraoperative cytology and histologic examination) (n = 2,804). SLNs were successfully removed in 5,379 (97.2%) of the 5,536 patients who were evaluable. The overall accuracy of SLN resection in patients in the SLN + ALND group was 97.1%. Differences in tumor location, type of biopsy, and number of SLNs removed significantly affected the false-negative rate of 9.8%. Removal of more than 1 SLN and avoidance of excisional biopsy were found to be important variables in reducing this false-negative rate. The authors concluded that these findings indicate “excellent balance in clinical patient characteristics between the 2 randomized groups and that the success of SLN resection was high.” They added that these findings are especially significant because this trial is the only current research effort “of sufficient size to provide definitive information related to the primary outcome measures of survival and regional control.”

Lancet Oncology

Arm Morbidity and SLN

In an article e-published on October 8 ahead of print in Breast, Husted Madsen and the Danish Breast Cancer Cooperative Group reported on a study of arm morbidity after sentinel lymph node (SLN) biopsy or axillary lymph node dissection (ALND). The multicenter study included 395 patients with tumors <4 cm³. Patients were assessed for arm and shoulder morbidity before proceeding to SLN or ALND and at 6 and 18 months after the procedure. Results for node-negative and node-positive patients undergoing each procedure were compared. Of those patients found to be node negative, those undergoing ALND had significantly higher arm morbidity than patients undergoing SLN. Minor but significant differences were noted in shoulder mobility in the 2 groups of node-negative patients. For node-positive patients, no differences were noted between those who had 1-step ALND and those who had SLN followed by delayed ALND. The authors used both subjective and objective measures in these assessments.

Breast

Type 1 Diabetes and 99mTc-Interleukin Scintigraphy

Chianelli et al. from the Regina Apostolorum Hospital (Albano Laziale, Italy) reported on October 5 ahead of print in Diabetes/Metabolism Research and Reviews on the clinical utility of 99mTc-interleukin-2 scintigraphy to identify pancreatic inflammation in patients with newly diagnosed type 1 diabetes. The study included 42 such patients, who underwent scintigraphy before and after 1 year of treatment with nicotinamide and intensive insulin therapy, and 16 healthy volunteers. Metabolic status was monitored every 3 months during this period. At diagnostic scintigraphy, significant pancreatic accumulation of 99mTc-interleukin-2 was found in 31% of patients. At that time point, no metabolic or immunologic differences were noted in patients with positive or negative tracer uptake on scintigraphy. At 3 months, patients with positive scintigraphic results showed higher C-peptide values. This same group had lower insulin requirements than uptake-negative patients at 1 year. Patients with positive scintigraphic results at diagnosis who underwent nicotinamide therapy were the only group with significant reductions in insulin requirements after 1 year, a time-point at which all scintigraphy-positive patients showed a significant decrease in pancreatic uptake of tracer. The authors concluded that this technique shows promise in identifying pancreatic inflammation in newly diagnosed type 1 diabetes patients and that 99mTc-interleukin-2 scintigraphy “may be of potential use for assessing the autoimmune phenomena in endocrine pancreas.”

Diabetes/Metabolism Research and Reviews
P-gp Expression and Sestamibi Washout

In an article e-published on October 10 ahead of print in the British Journal of Surgery, Gupta et al. from the Addenbrooke’s Hospital (Cambridge, UK) reported on an investigation of the relationship between sestamibi accumulation and multidrug resistance (MDR)–related P-glycoprotein expression (P-gp) in a large series of excised parathyroid tumors. The study began with 78 patients who underwent dual-phase 99mTc-sestamibi scintigraphy before parathyroidectomy. In addition to histology and immunohistochemistry, tumor size and volume were measured, and these data were compared with the 64 positive and 14 negative scan results. Smaller adenomas (<0.5 cm3) were more likely to be sestamibi negative than larger lesions. Of the 14 adenomas with negative imaging, 10 showed strong P-gp membrane positivity, and 45 of 64 lesions with a positive scan showed no P-gp membrane expression. The authors concluded that these data suggest “inhibition of the P-gp transmembrane pump using MDR modulators may therefore improve the sensitivity of sestamibi scintigraphy.”

British Journal of Surgery

Modulating Myocardial Metabolism in Diabetes

Peterson et al. from the Washington University School of Medicine (St. Louis, MO) reported on October 3 ahead of print in Diabetes on a study designed to test the hypothesis that myocardial glucose and fatty acids can be manipulated in individuals with type 1 diabetes by altering plasma free fatty acid and insulin levels. The authors quantified myocardial oxygen consumption as well as glucose and fatty acid metabolism in 4 groups: non-diabetics and euglycemic, hyperlidelmic, and hyperinsulinemic/euglycemic clamp diabetics. All participants underwent 18F-FDG PET imaging. In general, patients with type 1 diabetes had higher myocardial oxygen consumption and lower glucose utilization rate/insulin than did healthy participants. Glucose utilization in these patients also increased with increasing plasma insulin and decreasing free fatty acid levels. Myocardial fatty acid utilization, oxidation, and esterification rates as well as the percentage of utilization accounted for by esterification increased along with increasing free fatty acid. Increased plasma insulin levels decreased myocardial fatty acid esterification rates but increased the percentage of fatty acids going into esterification. The authors concluded that the myocardium in individuals with type 1 diabetes has increased myocardial oxygen consumption and insulin resistance during euglycemia, and the results of this study suggest that myocardial glucose and fatty acid metabolism in these individuals respond to changes in plasma insulin and plasma FFA levels. This suggests that “insulin and plasma free fatty acid levels can regulate the intramyocardial fate of fatty acids in humans with type 1 diabetes.”

Diabetes

Functional Neuroimaging of Anxiety

In an article published in the October issue of the American Journal of Psychiatry (2007;164:1476–1488), Etkin and Wager of the Stanford University School of Medicine (CA) reported on the functional neuroimaging of anxiety in a meta-analysis of emotional processing in posttraumatic stress disorder (PTSD). The authors searched the literature to identify common and disorder-specific functional neurobiological deficits in several anxiety disorders, including patients with PTSD, social anxiety disorder, or specific phobias, and healthy individuals who had undergone fear conditioning, as assessed by PET and functional MR imaging. The analysis included studies that compared negative emotional processing with baseline, neutral, or positive emotional conditions. Patients with any of the 3 disorders consistently showed greater activity in the amygdala and insula than matched comparison subjects. A similar pattern was observed during fear conditioning in healthy subjects. Hyperactivation in the amygdala and insula were more frequently observed in social anxiety disorder and specific phobia than in PTSD. Only patients with PTSD showed hypoactivation in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex structures associated with the experience and regulation of emotion. The authors noted the advantages of this type of meta-analytical review in identifying common brain mechanisms in anxiety disorders and normal fear. They added that the results suggest that the mechanism for symptoms of emotional dysregulation in PTSD extend beyond an exaggerated fear response and, therefore, may require different therapeutic approaches.

American Journal of Psychiatry

111In-Peptide for Breast Carcinoma Targeting and Imaging

Kumar et al. from the University of Missouri–Columbia and Harry S. Truman Veterans Hospital (MO) reported in the October 15 issue of Clinical Cancer Research (2007;13:6070–6079) on an evaluation of the cellular targeting and tumor imaging properties of a novel ErbB-2–avid peptide in human breast carcinoma cells and in breast carcinoma–xenografted mice. The authors describe preliminary studies of the ErbB-2–targeting peptide KCCYSL and its alanine-substituted counterparts for the extracellular domain of purified recombinant ErbB-2. Binding of the KCCYSL peptide to breast and prostate carcinoma cells was confirmed by confocal microscopy. In vivo biodistribution and SPECT imaging studies of 111In-DOTA(GSG)KCCYSL were then performed in MDA-MB-435 human breast tumor–bearing severe combined immunodeficient mice. The radioabeled peptide was stable in serum and showed rapid tumor uptake at 15 minutes after injection and extended retention with rapid whole-body disappearance. The authors concluded that “the 111In-DOTA(GSG)-KCCYSL peptide has the potential to be used as a tumor-imaging agent and a vehicle for specific delivery of radionuclide or
cytotoxic agents for tumors overexpressing ErbB-2.”

*Clinical Cancer Research*

**MOLECULAR IMAGING ———**

**Mitochondrial Bioenergetic Capacity and Glucose Avidity**

López-Ríos et al. from the Universidad Autónoma de Madrid–Consejo Superior de Investigaciones Científicas (Madrid, Spain) reported in the October 1 issue of *Cancer Research* (2007;67:9013–9017) on the relationship between in vivo tumor glucose uptake in lung carcinomas and the proteomic signature of cellular bioenergetics provided by down-regulation of the catalytic subunit of the mitochondrial H⁺-ATP synthase in the cancer cell. The study included 110 patients who underwent PET imaging. The bioenergetic signature, as determined by immunohistochemical analysis in excised lung tumors, was found to be inversely correlated with tumor glucose uptake on PET. Additional analyses indicated that inhibition of oxidative phosphorylation by incubation of cancer cells with oligomycin triggers a rapid increase in rates of aerobic glycolysis. Cellular expression levels of the β-F1-ATPase protein of mitochondrial oxidative phosphorylation were inversely correlated with rates of aerobic glycolysis in cancer cells. The authors concluded that these results “highlight the relevance of the alteration of the bioenergetic function of mitochondria for glucose capture and consumption by aerobic glycolysis in carcinomas.”

*Cancer Research*

**SPECT/CT of Tumor Oncolytic Adenovirus Propagation**

In an article e-published on October 25 ahead of print in *Gene Therapy*, Merron et al. from the Queen Mary’s School of Medicine and Dentistry (London, UK) reported on small animal SPECT/CT imaging of oncolytic adenovirus propagation in tumors using the human sodium iodide symporter (hNIS) as a reporter gene in wild-type and replication-selective adenoviruses. Viruses showed functional hNIS expression and replication in vitro, and SPECT/CT successfully visualized the kinetics of spread of the different viruses in tumor xenografts. The time required to reach maximal spread was 48 hours for the wild-type and 72 hours for replication-selective viruses, suggesting that genetic engineering of adenoviruses can affect their kinetics in tumors. The authors concluded that “hNIS-mediated imaging of viral spread in tumors may be an important tool for combined anticancer therapies involving replicating adenoviruses.”

*Gene Therapy*

**Real-Time Imaging of β-Catenin Dynamics**

Naik and Piwnica-Worms from the Washington University School of Medicine (St. Louis, MO) reported on October 22 ahead of print in the *Proceedings of the National Academy of Sciences USA* on real-time imaging of β-catenin (a key signaling component of the canonical Wnt signaling pathway as well as an increasingly studied contributor to various pathways that regulate cell adhesion, proliferation, and differentiation) in cells and living mice. The Wnt pathway encompasses a complex network of proteins noted for their roles in embryogenesis and cancer but also involved in normal physiologic processes in adult animals. The authors constructed and characterized the bioluminescent fusion reporters β-catenin firefly luciferase and β-catenin click beetle green luciferase to enable direct monitoring of post-translational stabilization of β-catenin in cells and living animals. Bioluminescent imaging of these reporters provided real-time, noninvasive assessments of modulators of β-catenin stability within cells and enabled monitoring of changes in total β-catenin levels in vivo in intact animals. Additional research enabled simultaneous analysis of β-catenin processing and downstream transcriptional activation. The natural product epigallocatechin 3-gallate was found to block Wnt signaling, independent of β-catenin processing. The authors concluded that these β-catenin reporters “represent a powerful new strategy for identifying in cellulo and in vivo dynamic regulators and mechanism-based therapeutics of signaling pathways mediated by β-catenin stabilization.”

*Proceedings of the National Academy of Sciences USA*

**Molecular Imaging of Collagen in Atherosclerosis**

Megens and researchers from the Netherlands reported in the October–December issue of *Molecular Imaging* (2007;6:247–260) on an investigation of collagen imaging in intact, viable healthy and atherosclerotic arteries using the fluorescent-labeled collagen-binding protein CNA35 and 2-photon laser-scanning microscopy. For the ex vivo portion of the study, CNA35 was conjugated with fluorescent Oregon Green 488 (CNA35/OG488) and injected into mounted viable muscular (uterine), elastic (carotid), and atherosclerotic (carotid) arteries and fresh arterial rings. Images of CNA35 labeling from 2-photon microscopy were compared with collagen type I, III, and IV antibody labeling in histologic sections. CNA was found to strongly label collagen in the tunica adventitia, media, and intima of muscular arteries. In healthy elastic arteries, the tunica adventitia was strongly labeled, but labeling in the tunica media and intima was prevented by endothelium and elastic laminae. The affinity of CNA35 for type I, III, and IV collagen in arteries was confirmed at histology, and strong CNA labeling was seen in atherosclerotic plaques. For the in vivo portion of the study, CNA35/OG488 was injected intravenously in healthy mice and in an atherosclerotic mouse model. The fluorescent protein only minimally labeled the tunica intima of healthy carotid arteries, but atherosclerotic plaques showed high uptake. Imaging results in organs suggested endothelium as a limiting barrier for in vivo uptake of this tracer. The authors concluded that...
“CNA35/OG488 is a good molecular imaging agent for atherosclerosis.”

**Molecular Imaging**

**Functional Imaging of Tumor Fibroblasts**

In an article published in the October 1 issue of *Cancer Research* (2007;67:9180-9189), Granot et al. from the Weizmann Institute (Rehovot, Israel) reported on in vivo MR and optical imaging of the systemic recruitment of fibroblasts to the angiogenic rim of ovarian tumors in vivo in a mouse model. Building on previous research, the group prelabeled fibroblasts with biotin-bovine serum albumin–gadolinium diethylenetriaminepenta-acetic acid or iron oxide particles for MR imaging and near-infrared and fluorescent vital stains for near-infrared and 2-photon microscopy. The prelabeled fibroblasts, administered intraperitoneally to CD-1 nude mice, were followed in vivo by both MR and optical imaging over several days. The imaging showed extensive fibroblast recruitment into the stroma of remote subcutaneous human epithelial ovarian carcinoma tumors. Optical microscopic imaging showed alignment of these fibroblasts in the outer rim of the tumor, colocalizing with the angiogenic neovascularature. These angiogenic vessels remained confined to the stroma tracks within the tumor and did not penetrate the tumor nodules. The authors concluded that these results “provide dynamic evidence for the role of tumor fibroblasts in maintenance of functional tumor vasculature and offer means for image-guided targeting of these abundant stroma cells to the tumor as a possible mechanism for cellular cancer therapy.”

**Cancer Research**

**Imaging Musculoskeletal Bacterial Infections**

Diaz et al. from the Howard Hughes Medical Institute and John Hopkins University Hospitals (Baltimore, MD) reported in the October 10 online issue of *PLoS ONE* on a study using $^{124}$I-FIAU PET/CT imaging suspected musculoskeletal bacterial infections. The study included 8 individuals with suspected infections and 1 healthy volunteer, each of whom underwent $^{124}$I-FIAU PET/CT imaging. At 2 hours, all patients with proven musculoskeletal infections showed positive uptake at the infection sites, with no adverse effects noted. This technique is based on the fact that bacteria have a thymidine kinase substrate specificity that is distinct from that of the major human thymidine kinase and can be visualized with $^{124}$I-FIAU. The authors concluded that $^{124}$I-FIAU PET/CT is a promising new method for imaging bacterial infections” and appears to provide improvements on current infection imaging techniques, which lack specificity in musculoskeletal infections.

**PLoS ONE**

**PET/CT Target Delineation in NSCLC**

Klopp et al. from the University of Texas M.D. Anderson Cancer Center (Houston, TX) reported on September 26 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics* on patterns of treatment failure in patients treated for non–small cell lung cancer (NSCLC) according to a PET/CT-defined radiotherapy target and evaluated the relationship between standardized uptake values (SUVs) and recurrence after radiotherapy. The study included 35 patients with NSCLC who underwent PET/CT simulation in treatment planning for definitive radiotherapy. Nine to 11 regions of interest (ROIs) were identified for each patient, including primary tumor and regional nodes. For each ROI, maximum SUV, volume, and mean dose were recorded, and follow-up scans were used to evaluate recurrence in each ROI. A total of 353 ROIs were identified in 35 patients. Two patients (5.7%) developed isolated out-of-field recurrences. ROIs were classified as low, intermediate, and high risk according to volume and SUV. All low-risk ROIs with volumes <1.2 cm$^3$ were recurrence free, compared with 73% of intermediate-risk ROIs (volume $\geq$ 1.2 cm$^3$) were found to be 3S193 positive. The screening process yielded a study group of 10 patients who received 4 weekly injections of hu3S193; 5 patients at 10 mg/m$^2$; and 5 at 20 mg/m$^2$. $^{111}$In was used to radiolabel the first and fourth injections, and participants underwent gamma camera imaging. SPECT was used to visualize $^{18}$F-FDG–avid lesions. One patient did not complete the 4-injection series. Four toxicity reactions included grade 2 urticaria, grade 1 vomiting, and grade 2 hypertension after infusion at the higher dose. The authors concluded that “given the strong tumor targeting, particularly at the higher dose, the favorable toxicity profile, and the potential for immuno-modulatory effects, hu3S193 warrants further investigation in SCLC.”

**Journal of Thoracic Oncology**
cm$^3$; SUV $\leq 13.8$) and only 29% of high-risk ROIs (SUV $> 13.8$). Limiting the target volume to predominantly PET-positive disease resulted in a low rate of isolated out-of-field recurrences, for which SUV and volume were predictors. SUV $> 13.8$ was noted as the best identifier of ROIs at the greatest risk of recurrence.

*International Journal of Radiation Oncology, Biology, Physics*

**Image-Guided Adenovirus-Mediated RT of MTC**

In an article published in the October issue of *Human Gene Therapy* (2007;18:916–924), Spitzweg et al. from the Ludwig-Maximilians University (Munich, Germany) reported on a study of the feasibility of image-guided radiiodine therapy of medullary thyroid cancer (MTC) after human sodium iodide symporter (hNIS) gene transfer, using a tumor-specific carcinoembryonic antigen (CEA) promoter for transcriptional targeting. NIS gene transfer was performed in human MTC cell (TT) xenografts, using adenoviral vectors carrying the NIS gene linked either to a cytomegalovirus promoter or a CEA promoter fragment. Functional NIS expression was confirmed by immunostaining and in vivo $^{123}$I gamma camera imaging, followed by application of a therapeutic $^{131}$I dose. TT cell xenografts in nude mice injected intratumorally with 2 dosages of Ad5-CEA-NIS accumulated $7.5 \pm 1.2\%$ ID/g and 12 $\pm 2.95\%$ ID/g, compared with accumulation of $8.4 \pm 0.9\%$ ID/g after application of Ad5-CMV-NIS. Administration of a therapeutic dose of 111 MBq (3 mCi) of $^{131}$I resulted in a significant reduction of tumor growth, associated with significantly lower calcitonin serum levels, as well as improved survival. The authors concluded that “a therapeutic effect of $^{131}$I was demonstrated in vivo in MTC cell xenografts after adenovirus-mediated induction of tumor-specific iodide accumulation by CEA promoter-directed hNIS expression.”

*Human Gene Therapy*

(Continued from page 24N)

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(Continued from page 31N)

any dementia and with AD or vascular dementia in 2002. According to their calculations, 13.9% of Americans ages 71 and older have some type of dementia, 9.7% of Americans in that age group have AD, and 2.4% have vascular dementia. AD accounted for about 70% of all dementia cases among people 71 and older. As in other studies, the ADAMS analysis showed that the prevalence of dementia increases significantly with age. Five percent of people ages 71 to 79, 24.2% of people 80 to 89, and 37.4% of those 90 years or older were estimated to have some type of dementia. The estimated rate of AD also rose significantly with age, from 2.3% of people ages 71 to 79 to 18.1% of people 80 to 89 to 29.7% of those age 90 and older. The ADAMS investigators found fewer years of education and the presence of at least 1 APOE e4 allele, a genetic risk factor for AD, to be strong predictors of AD and other dementias.

The ADAMS and HRS data are made publicly available to researchers seeking to conduct studies about the older U.S. population. For further information about the HRS and ADAMS, visit hrsonline.isr.umich.edu or www.nia.nih.gov/ResearchInformation/HRS.htm.

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