

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.

DIAGNOSIS

Focus on Brown Fat

Brown adipose tissue, the subject of more than a dozen articles in *The Journal of Nuclear Medicine* since 2002, was the focus of international media attention after 3 articles published in *The New England Journal of Medicine* were featured on page 1 of the April 8 *New York Times* under the headline “Calorie-Burning Fat.” All 3 studies used PET or PET/CT to explore the distribution and functional qualities of brown fat in healthy adults.

Virtanen et al. from the University of Turku (Finland) (*N Engl J Med.* 2009;360:1518–1525) reported on PET studies that indicated that cold-induced glucose uptake was increased by a factor of 15 in paracervical and supraclavicular adipose tissue in 5 healthy adults. Subsequent protein, morphologic, and biochemical analy-

ses of fine-needle biopsies of these tissues confirmed the presence of substantial amounts of metabolically active brown adipose tissue in the participants.

Cypess et al. from the Joslin Diabetes Center (Boston, MA) (*N Engl J Med.* 2009;360:1509–1517) performed a review of 3,650 ¹⁸F-FDG PET/CT scans performed for various indications in a total of 1,972 adults (1,013 women, 959 men), looking for the presence of substantial (>4 mm in diameter) deposits of brown adipose tissue. The criteria for identification as brown fat included density on CT consistent with that of adipose tissue and a maximum standardized uptake value of at least 2.0 g/mL on PET. Biopsy specimens were obtained from the neck and supraclavicular region in patients undergoing surgery. The authors found that PET/CT identified substantial deposits of brown fat in an area from the anterior neck to the thorax. Analysis confirmed the presence of UCPI, the marker for brown adipose tissue, in these biopsied specimens. PET/CT scans were positive for brown fat in 76 women (7.5%) and 30 men (3.1%). Women on average had larger brown adipose tissue masses and higher tracer uptake on PET. The probability of detection of brown adipose tissue was inversely related to age in years, outdoor temperature at the time of the scan, β -blocker use, and (among older patients) body-mass index (BMI). The researchers concluded that not only is PET/CT a useful approach in noninvasively quantifying brown adipose tissue in adults, but the fact that the amount of such tissue is inversely correlated with BMI, especially in older people, suggests “a potential role of brown adipose tissue in adult human metabolism.”

Van Marken Lichtenbelt et al. from the Nutrition and Toxicology Research Institute Maastricht (The Netherlands) (*N Engl J Med.* 2009;360:1553–1556) reported on a systematic examination

of the presence, distribution, and activity of brown adipose tissue in lean and obese men during exposure to cold temperatures. The study included 24 healthy young men (10 lean individuals with BMI < 25; and 14 who were overweight or obese with BMI \geq 25). Each participant underwent PET/CT imaging at 22°C (“room temperature”) and at 16°C (“mild cold exposure”), and body composition and energy expenditure were assessed in each setting by dual-energy x-ray absorptiometry and indirect calorimetry, respectively. The researchers observed brown fat activity in 23 of the 24 participants (96%) during cold exposure but not under thermoneutral conditions. This activity was significantly lower in overweight or obese individuals. BMI and percentage of body fat were inversely correlated with the amount of brown adipose tissue, whereas resting metabolic rate was directly correlated with brown fat amounts. The authors concluded that these results suggest that “brown adipose tissue may be metabolically important in men, and the fact that it is reduced yet present in most overweight or obese subjects may make it a target for the treatment of obesity.”

New England Journal of Medicine

Imaging in Genetic Risk for AD

Reiman et al. from the Good Samaritan Regional Medical Center (Phoenix, AZ) reported on April 3 ahead of print in the *Proceedings of the National Academy of Sciences of the USA* on the results of a study using PET with Pittsburgh Compound B (PiB) to characterize the relationship between fibrillar β -amyloid burden and a predisposition to Alzheimer’s disease (AD) in cognitively normal older individuals at 3 levels of genetic risk for the disease. The study included 28 individuals with a mean age of 64 y with reported family histories of AD, divided into groups with: 2

copies ($n = 8$), 1 copy ($n = 8$), and no copies ($n = 12$) of the apolipoprotein-E (APOE) $\epsilon 4$ allele. Dynamic PiB PET imaging results and region-of-interest analyses were used to assess cerebral-to-cerebellar PiB distribution volume ratios, reflecting fibrillar β -amyloid burden. Fibrillar β -amyloid was found to be significantly correlated with APOE $\epsilon 4$ carrier status and $\epsilon 4$ gene dose in cortical, frontal, temporal, posterior cingulate–precuneus, parietal, and basal ganglia regions of interest. The authors concluded that these findings suggest that fibrillar β -amyloid burden in cognitively normal older people “is associated with APOE $\epsilon 4$ gene dose, the major genetic risk factor for AD.” They called for additional studies of fibrillar β -amyloid burden in individuals with different kinds and levels of AD risk as well as studies to determine how and whether fibrillar β -amyloid interacts with other risk factors, with dual goals of more precisely predicting cognitive decline and transition to clinical AD and validating the role of fibrillar β -amyloid imaging in therapeutic interventions.

Proceedings of the National Academy of Sciences of the USA

APOE Genotype, β -Amyloid, and Atrophy in AD

Drzezga et al. from the Technische Universität München (Germany) reported on April 1 ahead of print in *Neurology* on another study of relationships between apolipoprotein-E (APOE) genotype and levels of β -amyloid plaque load and gray matter volume in patients with Alzheimer’s disease (AD). The study included 32 patients with moderate AD, who were assigned to 2 age-, education-, and degree of impairment–matched groups of carriers and noncarriers of the $\epsilon 4$ allele. Each participant underwent both ^{11}C -Pittsburgh Compound B (^{11}C -PiB) PET imaging to assess cerebral β -amyloid plaque and cranial MR imaging to quantify gray matter volume and correct for partial volume effects in the PET data. Comparisons were made with data from healthy

individuals. Patterns termed “AD typical” for ^{11}C -PiB retention and atrophy were found in both carriers and noncarriers of the $\epsilon 4$ allele. Significantly greater and more extensive tracer uptake was seen in carriers in the bilateral temporoparietal and frontal cortex. Additional analyses showed that higher $\epsilon 4$ allele frequency was associated with greater temporoparietal β -amyloid plaque deposition. No relationship between genotype and gray matter atrophy was identified. The authors concluded that the $\epsilon 4$ -positive APOE genotype “not only represents a risk factor for AD, but also results in higher levels of β -amyloid plaque deposition in $\epsilon 4$ -positive patients with AD compared to age-matched $\epsilon 4$ -negative patients with similar levels of cognitive impairment and brain atrophy.” They cited the potential role of β -amyloid plaque imaging for patient selection and monitoring in anti-amyloid therapy trials.

Neurology

SPECT in Secondarily Generalized Tonic–Clonic Seizures

In 2 publications released in April, researchers from Yale University School of Medicine (New Haven, CT) reported on a study using SPECT to investigate brain regions and cerebral blood flow (CBF) in patients with secondarily generalized tonic–clonic seizures. The study included 59 events in 53 patients. In an article in the April issue of *Brain* (2009;132:999–1012), Blumenfeld et al. analyzed SPECT images to identify the cortical and subcortical regions most often affected during the partial seizure phase before generalization, during the generalization period, and postictally. Focal CBF increases were seen in the temporal lobe before generalization. During generalization, focal CBF increases were seen in individual patients in different regions of the cerebral cortex. Group analysis showed that the most consistent increase in this period occurred in the superior medial cerebellum, thalamus, and basal ganglia. A marked and

progressive CBF increase in the cerebellum was seen in the postictal phase, with spread to the bilateral lateral cerebellar hemispheres. CBF increases were also seen in the midbrain and basal ganglia, with decreases in the frontoparietal association cortex, precuneus, and cingulate gyrus during and after seizures. Additional analyses and correlations with patient behavior indicated the “network of cortical and subcortical structures that are most consistently involved in secondarily generalized tonic–clonic seizures.”

In an article published on April 1 ahead of print in *Brain*, Varghese and the same group of Yale researchers reported on the clinical application of these imaging techniques in the 53-patient group. The authors analyzed ictal SPECT images of secondarily generalized tonic–clonic seizures obtained during epilepsy surgery and compared these findings with baseline interictal SPECT images. They found that in the pregeneralization and generalization phases, ictal SPECT showed significantly more regions of CBF increases in these seizures than in partial seizures without secondary generalization. The result was that 50% of the time it was not possible to pinpoint a single region of seizure onset with ictal SPECT in secondarily generalized seizures. CBF increases on ictal SPECT, however, were useful in identifying the hemisphere (left versus right) of seizure onset in 84% of patients. In 80% of those individuals in whom ictal SPECT pointed to a single unambiguous region of CBF increase, this identification was correct. The authors concluded that these and other findings suggest that “with appropriate cautious interpretation, ictal SPECT in secondarily generalized seizures can help localize the region of seizure onset.” Moreover, enhanced understanding of the networks involved in generalized tonic–clonic seizures can elucidate the underlying causes of behavioral changes associated with these seizures and identify targets for improved therapies.

Brain

Selective Odor Identification Deficits and DAT Activity

In an article e-published on March 27 ahead of print in *Parkinsonism and Related Disorders*, Chou and Bohnen of the University of Michigan (Ann Arbor) reported on a study using ^{11}C - β -CFT PET to explore the relationships between cerebral dopamine transporter (DAT) activity and selective deficits of odor identification in Parkinson's disease (PD) and Alzheimer's disease (AD). The study included 44 patients with PD (13 women, 31 men; mean age, 59.3 ± 10.1 y; all with PD for >1 y; none with evidence of dementia) and 44 healthy age- and gender-matched individuals. The University of Pennsylvania Smell Identification Test (UPSIT), with 10 odors developed for AD studies, was administered to all participants. A subset of 29 PD patients also underwent ^{11}C - β -CFT PET imaging to assess dopamine transporter binding in the hippocampus, amygdala, and ventral and dorsal striatum. UPSIT scores were significantly lower in the patient groups than in controls. Test performance in the PD patients did not correlate with DAT activity. The authors concluded that the fact that the "supposed AD-selective" hyposmia scores in PD did not correlate with cerebral DAT binding "may reflect a nondopaminergic olfactory mechanism."

Parkinsonism and Related Disorders

PET and Indolent Dorsal Midbrain Tumor

Yamaguchi et al. from Hokkaido University and Sapporo Asabu Neurosurgical Hospital (Hokkaido, Japan) reported in the April issue of the *Journal of Neurosurgery. Pediatrics* (2009;3:270–275) on the use of ^{18}F -FDG and ^{11}C -MET PET to evaluate the biological behaviors of dorsal midbrain tumors. The study included 4 children (3 boys, 1 girl) who presented with such tumors (diagnosed by MR imaging) and obstructive hydrocephalus. Each patient underwent endoscopic third ventriculostomy to relieve the hydro-

cephalus. No additional surgical procedures were performed, although patients received various treatment regimens. Three patients underwent both ^{18}F -FDG and ^{11}C -MET PET within 6 mo of ventriculostomy, and the fourth patient underwent PET imaging 10 y after the procedure. In all 4 patients, ventriculostomy was successful in relieving clinical symptoms. Gliosis or glial proliferation was identified in 1 patient and possible low-grade glioma in 2 patients. All tumors appeared hyperintense on T2-weighted MR images, but their appearance on T1-weighted images was variable, with partial lesion enhancement in 2 patients. PET, however, was unequivocal, and showed uptake of either ^{18}F -FDG or ^{11}C -MET no higher than that in a normal brain. The authors concluded that PET was successful in identifying the nontumorous character of indolent dorsal midbrain lesions and that "PET studies may be more informative and predictive of the biological behavior of dorsal midbrain tumors than a biopsy procedure."

Journal of Neurosurgery. Pediatrics

PET/CT as Predictor in High-Grade Soft-Tissue Sarcomas

In an article published in the April 15 issue of *Clinical Cancer Research* (2009;15:2856–2863), Benz and colleagues from the University of California at Los Angeles and the University of Freiburg (Germany) reported on a study designed to determine whether tumor tracer uptake on ^{18}F -FDG PET/CT can predict histopathologic treatment responses in high-grade soft-tissue sarcoma after a single cycle of neoadjuvant chemotherapy. The study included 50 patients with resectable high-grade soft-tissue sarcoma scheduled for neoadjuvant therapy and subsequent tumor resection. Each participant underwent PET/CT before (baseline), after the first cycle (early follow-up), and after completion of neoadjuvant therapy (late follow-up). Results from histopathology of resected specimens were obtained for

comparison with tumor tracer uptake on PET/CT. Patients with $\geq 95\%$ pathologic necrosis were classified as treatment responders. At early follow-up, tracer uptake was found to decrease significantly more in 8 responders than in the 42 nonresponders. Between baseline and early follow-up, all responders and 14 of the 42 nonresponders had a $\geq 35\%$ reduction in standardized uptake values. Defining this $\geq 35\%$ reduction in tracer uptake as an early metabolic response threshold resulted in sensitivity and specificity of ^{18}F -FDG PET for histopathologic response of 100% and 67%, respectively. CT did not add to response prediction value. The authors concluded that "a 35% reduction in tumor FDG uptake at early follow-up is a sensitive predictor of histopathologic tumor response" and that "early treatment decisions, such as discontinuation of chemotherapy in nonresponding patients, could be based on FDG PET criteria."

Clinical Cancer Research

THERAPY

RIT in T-Cell Non-Hodgkin's Lymphoma

Gopal et al. from the University of Washington (Seattle, WA) reported on March 30 ahead of print in *Blood* on a study investigating ^{131}I -labeled anti-CD45 targeted radioimmunotherapy (RIT) in both animal (mouse) and human T-cell non-Hodgkin's lymphoma (NHL). After verifying that CD45 was highly expressed on human T-cell NHL patient samples and cell lines, the researchers conducted biodistribution studies of the ^{131}I -anti-human CD45 in human T-cell NHL xenografts in mice. At 24 and 48 h, respectively, 154% and 237% more radioiodine-labeled antibodies than control antibodies were delivered to target tumor sites. Tumor sites targeted with the ^{131}I -anti-human CD45 showed 2.5-, 3.0-, and 3.6-fold higher radioiodine retention at 24 h than nontargeted lungs, liver, and kidneys, respectively. Results were similar in

studies using mouse T-cell NHL xenografts. In mouse studies comparing the ^{131}I -anti-mouse CD45 therapy with that in controls, targeted RIT resulted in improved complete remission rates (75% vs 0%) and progression-free survival (median, 23 vs 4.5 d). The authors concluded that these data “indicate that the high CD45 expression of T-cell NHL allows reliable tumor targeting and disease control supporting anti-CD45 RIT” in this setting.

Blood

MOLECULAR IMAGING

In Vivo Clot Lysis with Immunobubbles and Ultrasound

In an article e-published on April 4 ahead of print in *Thrombosis Research*, Alonso et al. from the University Hospital of Mannheim (Germany) reported on studies of the potential of abciximab immunobubbles to not only facilitate ultrasound imaging of human thrombus but also enhance clot lysis by “sonothrombolysis.” The study included 15 rats in which a partial thrombotic occlusion of the right common carotid artery was induced by catheter insertion of human clot material. Rats were divided into 3 groups to receive intravenously: abciximab immunobubbles, nonspecific control immunobubbles, or saline intravenously over 30 min while also undergoing pulsed 2 MHz ultrasound. Blood samples were taken at baseline and 5, 10, 20, 30, and 60 min after initiation of treatment to assess human D-dimer levels and thereby quantify thrombolysis. The only group that showed a significant increase in D-dimer levels over time was that treated with abciximab immunobubbles and ultrasound. At subsequent histology, thrombi from animals in this group showed clear signs of disintegration, whereas those in the other 2 groups did not. The authors concluded that “2-MHz ultrasound in

combination with abciximab immunobubbles induces thrombolysis without lytic agents.”

Thrombosis Research

Tracking the Pharmacokinetics of Nanoparticles

On April 17 ahead of print in *Molecular Pharmaceutics*, Ali et al. from the Henry Ford Health System (Detroit, MI) and the University of Arizona (Tucson) reported on studies designed to develop a noninvasive assay using MR imaging to track the separate and relative in vivo pharmacokinetics of 2 nanoparticles. Two MR contrast agents that could be selectively detected through paramagnetic chemical exchange saturation transfer (PARACEST) were conjugated to a second- and fifth-generation polyamidoamine dendrimer. Measurements of ratios of the chemical exchange lifetimes of the 2 agents were calculated. Both contrast agents were injected into a mouse model of mammary carcinoma, which resulted in a temporal increase in the CEST effect from each agent in the tumor. The in vivo CEST effects could not be used to quantify the absolute concentrations of each agent within the tumor; however, the ratio of the in vivo CEST effects was used to assess the ratio of the concentrations of the agents. The authors concluded that this result “demonstrated that the relative in vivo pharmacokinetics of 2 nanoparticles may be evaluated using PARACEST MR imaging.”

Molecular Pharmaceutics

$\alpha_v\beta_3$ Function and Dasatinib Treatment

Dumont et al. from the University of California at Los Angeles reported in the April 1 issue of *Cancer Research* (2009;69:3173–3179) on a study evaluating whether ^{64}Cu -DOTA-cRGDFK PET imaging of $\alpha_v\beta_3$ integrin activity can be used to monitor cellular response to the Src family kinase (SFK) inhibitor dasatinib. The study was conducted in severe combined immunodeficient

mice bearing U87MG xenografts. The mice were administered dasatinib or a control vehicle before tracer uptake was assessed by serial ^{64}Cu -DOTA-cRGDFK PET and tumor metabolism was evaluated by ^{18}F -FDG PET. Dasatinib administration was found to significantly (up to 59%) reduce uptake in the xenografts, whereas tumor ^{18}F -FDG uptake showed no significant reduction with dasatinib. Continued dasatinib treatment resulted in significant inhibition of tumor growth. The authors concluded that “ ^{64}Cu -DOTA-cRGDFK may provide a sensitive means of monitoring tumor response to SFK inhibition in $\alpha_v\beta_3$ -expressing cancers early in the course of therapy.”

Cancer Research

Immune Cell Function in Transplant Rejection

Christen et al. from the Brigham and Women’s Hospital (Boston, MA) reported in the April 14 issue of *Circulation* (2009;119:1925–1932) on a study designed to explore the use of molecular and cellular imaging techniques to visualize macrophage host responses in clinical detection of cardiac transplant rejection. Isografts from B6 mice and allografts from Balb/c mice were transplanted heterotopically into B6 recipients, a process known to result in predictable and progressive rejection, leading to graft failure after 1 wk. On d 2 and 6 after transplantation, a fluorescent protease sensor or a magnetofluorescent phagocytosis marker was injected into the mice. The authors created a 3-dimensional functional map of macrophages showing higher phagocytic uptake of magnetofluorescent nanoparticles during rejection on MR imaging and higher protease activity in allografts than in isografts using tomographic fluorescence imaging. In vivo imaging of macrophage response correlated closely with gradually increasing allograft rejection as well as with attenuated rejection in recipients with a genetically impaired immune response. The authors concluded that

“molecular imaging reporters of either phagocytosis or protease activity can detect cardiac allograft rejection non-invasively, promise to enhance the search for novel tolerance-inducing strategies, and have translational potential.”

Circulation

Novel Peptide for Apoptosis Imaging

Maxwell et al. from Washington University School of Medicine (St. Louis, MO) reported in the April issue of *Bioconjugate Chemistry* (2009; 20:702–709) on previous development and biochemical analysis studies of an improved cell-penetrating, caspase-activatable, near-infrared fluorescent (NIRF) peptide for apoptosis imaging. In addition to reviewing the development process, they detailed the biochemical analysis of a second generation probe, KcapQ, with a modified cell-penetrating peptide sequence. This modification resulted in a probe that was more sensitive to

effector caspase enzymes, displayed an unexpectedly higher quenching efficiency between the fluorophore-quencher pair, and was potentially less toxic to cells. In vivo studies, including fluorescence microscopy, indicated that the activated probe localized to apoptotic cells. The authors concluded that “KcapQ represents an improved effector caspase-activatable NIRF probe for enhanced noninvasive analysis of apoptosis in whole cells and live animals.”

Bioconjugate Chemistry

MR and Choline Kinase Targeting in Breast Cancer

In the April 15 issue of *Cancer Research* (2009;69:3464–3471), Krishnamachary et al. from the Johns Hopkins University School of Medicine (Baltimore, MD) reported on pre-clinical evaluation of noninvasive MR detection of lentiviral vector-mediated RNA interference in choline kinase targeting in a human breast cancer xenograft. Concentrated lentivirus ex-

pressing short hair RNA against choline kinase was injected into the tail veins of MDA-MB-231 tumor-bearing female severe combined immunodeficient mice. Optical green fluorescent protein imaging was used to assess transduction efficiency in cells and tumors in vivo as well as choline kinase mRNA and protein levels. Results showed that an 80% reduction in choline kinase mRNA and protein occurred after ~90% transduction efficiency in cells. ¹H MR spectroscopy of cell and tumor extracts showed decreased phosphocholine and total choline levels. In vivo, phosphocholine levels were monitored by ³¹P MR spectroscopy, and results indicated reduced tumor growth and proliferation. The authors concluded that this study indicates the feasibility of the use of lentiviral vectors to target choline kinase in a human breast cancer xenograft and of noninvasive MR spectroscopy to detect this targeting.

Cancer Research