Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. We have added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here.

MOLECULAR IMAGING AND THERAPY

Molecular Imaging and Teratoma Formation

Lee et al. from the Stanford University School of Medicine (CA) reported on August 24 ahead of print in *Cell Cycle* on the use of noninvasive reporter gene imaging to study the relationship between human embryonic stem cell number and teratoma formation in an animal model of embryonic stem cell transplantation. The purpose of the study was to elucidate the mechanisms of teratoma formation, which is currently a significant obstacle to safe clinical implementation of embryonic stem cell–based therapies. The authors used a double-fusion reporter construct of firefly luciferase and enhanced green fluorescent protein driven by a human ubiquitin promoter to stably transduce human embryonic stem cells. Varying quantities of these cells were injected into myocardium or skeletal muscle in immunodeficient mice. Bioluminescence imaging was used to monitor cell survival and proliferation for the following 8 wk. Mice in which no reporter signal was detected after 8 wk were serially assessed to 1 y after transplantation to confirm absence of tumors. Results indicated that minimums of 1×10^5 stem cells injected in the myocardium and 1×10^4 cells injected in skeletal muscle were required for teratoma development. Engraftment and tumor recurrence were also highly dependent on numbers of stem cells injected. The authors concluded that these results suggested that "human embryonic stem cell number may be a critical factor in teratoma formation" and "should yield useful insights to the safe and reliable application of human embryonic cell derivatives in the clinic."

Cell Cycle

Targeted Nanoparticles for Breast Cancer Imaging

Yang et al. from Emory University School of Medicine (Atlanta, GA) reported in the July 15 issue of *Clinical Cancer Research* (2009;15:4722–4732) on the development of a novel targeted iron oxide nanoparticle conjugate that targets cell-surface urokinase-type plasminogen activor (uPA)–receptor overexpression in breast cancer tissues. These amino-terminal–fragment conjugated iron oxide (ATF-IO) nanoparticles were found in in vivo studies to specifically bind to and internalize in uPA receptor-expressing tumor cells. In vivo analysis of the ATF-IO nanoparticles injected into mice bearing subcutaneous and intraperitoneal mammary tumors showed particle accumulation in tumors, with good resolution and detectability using a 3T clinical MR scanner. Tumor targeting specificity of the nanoparticles was confirmed by near-infrared fluorescence imaging. These data and evidence that targeted nanoparticles had relatively low nontarget organ accumulation led the authors to conclude that "uPA receptor-targeted ATF-IO nanoparticles have potential as molecularly targeted, dual-modality imaging agents for in vivo imaging of breast cancer."

Clinical Cancer Research

Visualizing Chemokine Receptor Activation in Pain

Jung et al. from Northwestern University (Chicago, IL) reported in the July issue of the *Journal of Neuroscience* (2009;29:8951–8062) on a novel method for visualizing chemokine receptor 2 (CCR2) activation in vivo in bitransgenic mice in which the CCR2 and its ligand MCP1 (also called CCL2) were labeled with enhanced green fluorescent protein and monomeric red fluorescent protein-1, respectively. CCR2 signaling has been associated with various types of neuropathology, including neuropathic pain, but the mechanisms behind this association have not been elucidated. The generation of these bitransgenic mice made it possible to image CCR2 receptor activation under conditions such as acute inflammation and experimental autoimmune encephalomyelitis. In this study, the authors assessed the status of CCR2 receptor activation in a mouse demyelination injury model of neuropathic pain. They found MCP1-induced CCR2 receptor activation mainly in the peripheral nervous system, including the injured peripheral nerve and dorsal root ganglia. They noted that these results explain the observed rapid antinociceptive effects of peripherally administered CCR2 antagonists under these circumstances, "suggesting that CCR2 antagonists may ameliorate pain by inhibiting CCR2 receptor activation in the periphery." The authors added that the method reported on here for imaging CCR2 receptor activation in vivo has multiple other potential applications.

Journal of Neuroscience

PET Assessment of Novel Therapeutic Nanoparticle

In an article published in the July 7 issue of the *Proceedings of the National Academy of Sciences of the United States of America* (2009;106:11394–11399) Schluep et al. from Calando Pharmaceuticals, Inc. (Pasadena, CA), described the use of PET to investigate the multiorgan pharmacokinetics and tumor tissue accumulation of IT-101, a cyclodextrin polymer–based nanoparticle containing camptothecin. The authors outlined the modification of the nanoparticle by attachment of a ligand and radiolabeling with ^{64}Cu. Mice bearing Neuro2A subcutaneous tumors were injected with the radiolabeled nanoparticles and imaged with PET. A biphasic plasma clearance was identified, with ~8% of the injected dose (ID) cleared rapidly as a low-molecular-weight fraction through the kidneys and the remaining nanoparticles circulating in plasma with a terminal half-life of 13.3 h. Over 24 h, increasing concentrations (up to 11% ID/cm^3) of nanoparticles were seen in tumors. Calculated tumor vascular permeability indicated that most nanoparticles remained intact in circulation and did not disassemble into individual polymer strands. Histologic measurements with confocal microscopy confirmed that the IT-101 particles localized within tumor cells.

Proceedings of the National Academy of Sciences of the United States of America

Probe for MT1-MMP Expression Imaging

Temma et al. from Kyoto University (Japan) reported in the July issue of the *Biological and Pharmaceutical Bulletin* (2009;32:1272–1277) on the development of a radiolabeled probe for in vivo molecular imaging of membrane type-1 matrix metalloproteinase (MT1-MMP) expressed on the tumor cell surface of malignant tumors. The authors described the preparation of a ^{99m}Tc-labeled anti-MT1-MMP monoclonal antibody, in vitro validation studies, and initial imaging studies in rats with implanted breast tumors. After injection of the monoclonal antibody, in vivo biodistribution was assessed. MT1-MMP was found to be highly expressed in all malignant cells, with tumor radioactivity increasing after administration so that at 24 h after injection radioactivity levels in tumor were 3–5 × higher than at 1 h after injection. Radioactivity decreased in other organs over the 48 h after injection, and tumor-to-blood ratios increased to more than 11.3 over the same time period. The authors concluded that "^{99m}Tc-anti-MT1-MMP monoclonal antibody is a promising probe for future diagnosis of breast tumors by in vivo nuclear medical imaging."

Biological and Pharmaceutical Bulletin

THERAPY

Promising Immunohibitory Module

Xu et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on July 7 ahead of print in *Cancer Research* on what was termed the first demonstration of microRNA (miR)-29 modulation of an immunomodulatory molecule. The group has developed and previously described monoclonal antibody (mAb) 8H9, which targets a glycoprotein broadly expressed in human solid tumors, including embryonal tumors and carcinomas (*Cancer Res.* 2001;61:4048–4054), and has shown promise in preclinical and early clinical trials. In the current study, the authors identified 4Ig-B7-H3, a member of the B7/CD28 immunoglobulin superfamily, as the target for mAb 8H9 and investigated B7-H3 expression at the mRNA and protein levels for both human tumors and normal tissues. Using a luciferase reporter assay, miR-29 was found to regulate B7-H3 protein expression. The authors discussed the potential and challenges for implementation of this approach in immune-based therapy of human solid tumors. They concluded that "differential modulation of this key immunoinhibitory molecule in tumor versus normal tissues may advance both cell-mediated immunotherapy and antibody-based targeted strategies using the B7-H3-specific mAb 8H9."

Cancer Research

Combined ^{131}I-A5B7 Anti-CEA Antibody RIT in Gastrointestinal Cancers

In the July 1 issue of *Clinical Cancer Research* (2009;15:4484–4492), Meyer et al. from University College London (UK) reported on a phase 1 trial of radioimmunotherapy (RIT) with ^{131}I-A5B7 anticarcinoembryonic antigen (anti-CEA) antibody in combination with the vascular disruptive agent combretastatin-A4-phosphate (CA4P) in patients with advanced gastrointestinal carcinomas. The object of the study was to assess dose-limiting toxicity, maximum tolerated dose, efficacy, and mechanism of action of this combination in patients. The study included 12 patients in 2 groups of 6 (mean age, 63 y; range, 32–77 y) with CEAs of 10–1,000 μg/L, no cardiac symptoms, and tumors suitable for bloodflow analysis with dynamic contrast-enhanced MR imaging. An initial dose of 1,800 MBq/m^2 of ^{131}I-A5B7 on day 1 was followed by 45 mg/m^2 CA4P at 48 and 72 h, repeated weekly for up to 7 wk. At the initial dose, 2 of the first 6 patients experienced dose-limiting toxicities (grade 4 neutropenia). The ^{131}I-A5B7 dose was reduced and the amount of CA4P administered was raised for the next group of 6 patients, among whom 2 of 6 experienced dose-limiting toxicities. Ten assessable patients underwent SPECT imaging, which confirmed tumor antibody uptake in all. MR imaging confirmed falls in kinetic parameters in 9 of 12 patients assessed. In 1 patient who had a minor response on CT and reduced serum levels, changes in pharmacokinetic parameters of both ^{131}I-A5B7 and CA4P reached levels expected to produce efficacy. Of 10 patients assessable at 7 wk, 3 had stable disease and 7 had progressive disease. The authors concluded that although this was the first trial reporting a combination of RIT

and a vascular disruptive agent, each of which was shown to function, additional studies are needed to determine optimal dose and timing of CA4P and to address the dose-limiting myelosuppression of the RIT agent.

Clinical Cancer Research

DIAGNOSIS

PET/CT and Preoperative Staging of NSCLC

In July, 2 groups of investigators reported on large studies designed to determine the efficacy of ^{18}F-FDG PET/CT in preoperative staging in patients with non–small cell lung cancer (NSCLC). Fischer et al. from the Rigshospitalet/Copenhagen University Hospital (Denmark) published the results of their prospective, randomized study in the July 2 issue of the *New England Journal of Medicine* (2009; 361:32–39). The study included 98 patients assigned to conventional staging plus PET/CT and 91 assigned to conventional staging alone. Ninety-four percent of patients also underwent medianoscopy. Patients were followed for at least 1 y or until death, with observers tracking "futile" thoracotomies (thoracotomy with pathologically confirmed mediastinal lymph node involvement (stage IIIA [N2]), stage IIIB or stage IV disease, or a benign lung lesion; an exploratory thoracotomy; or a thoracotomy in a patient who had recurrent disease or death from any cause within 1 y after initial imaging). PET/CT results identified 38 patients as having inoperable NSCLC, and conventional staging results identified 18 such patients. In the PET/CT group, 60 patients underwent thoracotomy; the corresponding number was 73 patients in the conventional staging group. In the PET/CT group, 21 of these thoracotomies were classified as futile; the corresponding number was 38 in the conventional staging group. However, the numbers of justified thoracotomies and the survival rates were similar in the 2 groups. The authors concluded that the use of PET/CT for preoperative staging of NSCLC "reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality."

Maziak et al. from Hamilton Health Sciences/McMaster University (Ontario, Canada) reported on July 6 ahead of print in the *Annals of Internal Medicine* on whether whole-body ^{18}F-FDG PET/CT plus cranial imaging correctly upstaged more patients with NSCLC than did conventional staging (abdominal CT and bone scan) plus cranial imaging. The study included 337 patients with confirmed stages I, II, or IIIA NSCLC and a tumor believed to be resectable, who were seen at 8 hospitals and 5 PET/CT centers in academic institutions. Patients were randomly assigned to the PET/CT group (n = 170) or the conventional staging group (n = 167). All patients also underwent CT or MR cranial imaging. Eight patients (3 in the PET/CT group and 5 in the conventional staging group) did not have planned surgery and were not included in the results. The researchers found that disease was correctly upstaged in 23 of 167 PET/CT recipients (13.8%) and 11 of 162 conventional staging recipients (6.8%). Disease was incorrectly upstaged in 8 PET/CT patients (4.8%) and 1 conventional staging patient (0.6%) and was incorrectly understaged in 25 (14.9%) and 48 (29.6%) patients in the respective groups. At 3-y follow-up, 52 patients in the PET/CT group and 57 patients in the conventional staging group had died. The authors summarized their findings: "Preoperative staging with PET/CT and cranial imaging identifies more patients with mediastinal and extrathoracic disease than conventional staging, thereby sparing more patients from stage-inappropriate surgery, but the strategy also incorrectly upstaged disease in more patients."

New England Journal of Medicine
Annals of Internal Medicine

PET and the Transition from MCI to AD

Okello and a consortium of colleagues from the Imperial College London (UK), the University of Turku (Finland), Victoria Hospital (Swindon, UK), and Hammersmith Imanet/GE Healthcare (London, UK) reported on July 22 ahead of print in *Neurology* on a study using ^{11}C-PiB PET and other data to assess rates of conversion of amnestic mild cognitive impairment (MCI) to Alzheimer disease (AD) over a 3-y period and to determine whether amyloid deposition can be used as an effective in vivo marker of this transition. The study included 31 individuals with MCI who underwent baseline ^{11}C-PIB PET and MR imaging as well as neuropsychometric assessment and were followed clinically for 1–3 y. Among the PET data assessed were raised cortical tracer binding with region of interest analyses and statistical parametric mapping. Of the total of 31 participants in the study, 17 (55%) had increased ^{11}C-PIB retention at baseline imaging, and 14 of these (82%) clinically converted to AD during the 3-y follow-up period. Half (47%) of these converters progressed to AD within 1 y of baseline imaging and had higher tracer retention values in the anterior cingulate and frontal cortex than did the slower converters. Out of the remaining 14 participants who were negative for tracer retention at baseline, only 1 converted to AD over the study period. The authors concluded that ^{11}C-PiB-positive subjects with MCI are "significantly more likely to convert to AD than PIB-negative patients" and that "in vivo detection of amyloid deposition in MCI with PIB PET provides useful prognostic information."

Neurology

^{18}F-DOPA PET vs. Conventional Imaging in Catecholamine Excess

Fiebrich et al. from the University Medical Center Groningen (The Netherlands), Martini Hospital (Groningen, The Netherlands), and Hamilton Health Sciences/McMaster University (Ontario, Canada) reported on July 21 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a comparison of ^{18}F-DOPA PET with conventional imaging (^{123}I-MIBG scintigraphy, CT, and MR imaging) for

tumor localization in patients with catecholamine excess. The study included 48 patients with catecholamine excess and final diagnoses of pheochromocytoma ($n = 40$), adrenal hyperplasia ($n = 2$), paraganglioma ($n = 2$), ganglioneuroma ($n = 1$), and unknown causes ($n = 3$). All patients underwent ^{18}F-DOPA PET imaging and ^{123}I-MIBG scintigraphy with either CT or MR imaging. A series of laboratory values and assessments were also recorded. PET, CT or MR, and scintigraphy indicated lesions in 43, 32, and 31 patients, respectively, with patient-based sensitivities of 90%, 67%, and 65%, respectively. Lesion-based sensitivities were 73%, 44%, and 48%. The authors found that the combination of ^{123}I-MIBG with CT or MR imaging (93% sensitivity) was superior to the combination of ^{123}I-MIBG with either CT or MR (76%). Whole-body metabolic burden as assessed by PET accurately correlated with plasma normetanephrine, urinary normetanephrine, and metanephrine levels. They concluded that "to localize tumors causing catecholamine excess ^{18}F-DOPA PET is superior to ^{123}I-MIBG scintigraphy and CT/MR imaging.

Journal of Clinical Endocrinology and Metabolism

SPECT in Spontaneous vs. Induced Myocardial Ischemia

In an article e-published on June 26 ahead of print in *Peptides*, Fontana et al. from the Ospedale S. Orsola (Bologna, Italy) reported on a study designed to evaluate the effects of repeated episodes of angina and induced myocardial ischemia on plasma nociceptin/orphanin FQ (N/OFQ) levels. N/OFQ is a neuropeptide that binds to the NOP_1 receptor with high affinity but does not interact directly with classical opioid receptors. The study included 41 patients with unstable angina (23 with new-onset severe angina or accelerated angina and 18 with subacute angina at rest) who had experienced repeated spontaneous episodes of chest pain in the week before the study. Each patient underwent myocardial perfusion SPECT with adenosine infusion. The control group included 20 healthy age-, sex-, and cardiac risk factor–matched individuals. N/OFQ levels were found to be significantly higher in patients than in controls, whereas blood pressure and heart rate did not differ significantly between the 2 groups. All of the patients showed transient adenosine infusion myocardial ischemia, but this did not induce chest pain or significantly modify either plasma N/OFQ levels or hemodynamic parameters. These results indicated that unstable angina is associated with a significant increase in circulating N/OFQ levels that is unrelated to intervening transient myocardial ischemia or hemodynamic changes. The authors speculated that this increase is "related to the chest pain repeatedly occurring in the course of coronary artery disease but absent during transient adenosine-induced myocardial ischemia."

Peptides

PET Prognosis in Myocardial Ischemia

Herzog et al. from University Hospital Zurich (Switzerland) reported in the July 6 issue of the *Journal of the American College of Cardiology* (2009; 54:150–156) on a study of the long-term predictive value of myocardial perfusion imaging with ^{13}N-ammonia PET in patients with suspected myocardial ischemia. The study included 256 patients who underwent ^{13}N-ammonia PET to assess perfusion and coronary flow reserve (CFR). Follow-up (5.4 ± 2.2 y) studies were conducted in 245 (96%) participants. After the exclusion of 16 early revascularized patients, the remaining 229 were assigned on the basis of their original PET studies to groups of normal ($n = 103$) and abnormal perfusion ($n = 126$) and normal and abnormal CFR (defined as <2.0). Over the follow-up period, 78 patients had at least 1 cardiac event and 29 died from cardiac causes. Abnormal perfusion was found to be associated with a higher incidence of major adverse coronary events and cardiac death. In patients with normal perfusion, abnormal CFR was independently associated with a higher annual adverse event rate. In a group of patients followed for 10 y, CFR in abnormal perfusion remained predictive throughout follow-up. The authors concluded that not only are perfusion findings in ^{13}N-ammonia PET and CFR strong outcome predictors, but "CFR allows further risk stratification, suggesting a 'warranty' period of 3 y if normal CFR is associated with normal perfusion."

Journal of the American College of Cardiology

Prognostic Factors in ALS

Rusina et al. from the Thomayer Teaching Hospital and Institute for Postgraduate Education in Medicine (Prague, Czech Republic) reported on June 30 ahead of print in the *European Journal of Neurology* on a study designed to identify reliable prognostic factors for patients with amyotrophic lateral sclerosis. The study included 67 patients (42 women, 25 men) who had clinically defined ALS. All participants underwent SPECT imaging; lumbar puncture for levels of τ, hyperphosphorylated τ, and β-amyloid; and a detailed neuropsychological assessment. Neuropathologic and histologic studies were conducted in 20 participants who died during the course of the study. The average survival of participants was 26.8 mo, with an average 12.75-mo delay between first symptoms and diagnostic confirmation. The authors found that higher age at onset, more pronounced physical symptoms, and elevated β-amyloid in the cerebrospinal fluid were associated with shorter survival times. In the 9 patients who died during the study and who had dementia, 6 showed frontotemporal lobar degeneration and 3 showed Alzheimer disease pathology. In the 11 participants who died during the study and did not show signs of dementia, brain tissue showed only changes compatible with a diagnosis of motor neuron disease.

European Journal of Neurology

Pediatric ^{11}C-MET PET

In an article e-published on July 4 ahead of print in the *Journal of Neuro-oncology*, Galldiks et al. from the University of Cologne (Germany) reported on the utility of ^{11}C-methionine PET studies in the differentiation between tumorous and nontumorous lesions in children and young adults with brain tumors. The study included 48 PET scans from 39 patients (ages, 2–21 y) with brain neoplasms. The authors found that differentiation between tumorous (n = 39) and nontumorous brain lesions (n = 9) was possible at a threshold of 1.48 of relative tracer uptake, with sensitivity of 83% and specificity of 92%. Differentiation between high-grade malignant lesions and low-grade tumors was not possible; however, a significant difference in tracer uptake was noted between the histologically homogeneous subgroups of astrocytoma WHO grade II and anaplastic astrocytoma WHO grade III. The authors noted that the radiation exposure and long scan times associated with ^{11}C-methionine PET restrict its use in pediatric patients. They concluded that ^{11}C-methionine PET "might be a useful tool to differentiate tumorous from nontumorous lesions in children and young adults when a decision for further therapy is difficult or impossible from routine structural imaging procedures alone."

Journal of Neurooncology

PET in TBI

de la Cueva-Barrao et al. from the Hospital 9 de Octubre (Valencia, Spain) reported in the July 16 issue of the *Revista de Neurologia* (2009;49:58–63) on a study designed to evaluate the accuracy of ^{18}F-FDG PET as a predictor of long-term disability after severe traumatic brain injury (TBI). The study included 56 patients who had severe TBIs in a long-term rehabilitation program. All patients were assessed with cognitive and functional examinations and underwent PET imaging at the beginning of the study. A physician unaware of the clinical and cognitive assessments performed semiquantitative analyses of PET results. The total number of lesions on PET was correlated with the intensity of the TBI and with clinical data at admission and at 6-mo follow-up. PET showed changes in cerebral metabolism in all patients studied, with the thalamus most often affected. The extent of cerebral hypometabolism on PET was significantly correlated with TBI severity, functional disability, global outcome, and memory and intelligence impairment both at baseline and at follow-up. Despite these correlations and the promising aspects of PET as a "useful tool when studying brain dysfunction after severe TBI," the authors concluded that "clinical variables related to the severity of the TBI still are the best predictors of functional outcome after TBI."

Revista de Neurologia

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carried out under collaborative agreements with academic sites and/or private industry. Project titles and originating laboratories include the Hard X-Ray Nanoprobe from Argonne National Laboratory (IL), a technology that will significantly improve the ability of medical scientists and nanoscientists to study the use of nanocomposites in tissues, cells, and subscellular organelles in new medical imaging techniques and therapies; Compact Gamma Camera from Brookhaven National Laboratory (Upton, NY), a high-resolution nuclear medical probe that can pinpoint the location of cancer tissue in the prostate gland in detail at an early stage; Precision Nanoparticles from Idaho National Laboratory (Idaho Falls), a technology that efficiently produces nanoparticles in uniform and prescribed sizes (1–100 nanometers) using supercritical fluids; the TEAM Electron Microscope Stage from the Lawrence Berkeley National Laboratory (CA), an improvement on 1 of the world's most powerful electron microscopes, enabling atomic-scale imaging in 3D; the GeMini from the Lawrence Livermore National Laboratory (CA), a palm-sized γ-ray spectrometer based on germanium technology; the Artificial Retina from the Lawrence Livermore National Laboratory, 4 other national labs, and 4 academic sites, a device with bioelectronic integrated circuits that transform digital images from a camera mounted on a pair of glasses into electric signals in the eye that the brain uses to create a visual image; the Mass-Independent Kinetic-Energy-Reducing Inlet System for Mass Spectrometers from the Oak Ridge National Laboratory (TN), a system that permits high-resolution mass analysis of large, intact biological molecules without having to break them apart; Ultrasensitive ESI-MS Source & Interface from the Pacific Northwest National Laboratory (Richland, WA), a system that integrates 4 technologies to provide greater sensitivity and precise measurements from mass spectrometry instrumentation while requiring smaller samples; and the Hyperspectral Confocal Fluorescence Microscope System from Sandia National Laboratories (Albuquerque, NM), a system that rapidly finds all emitting fluorescence species of an image, determining their relative concentrations without any a priori information.

The 47th Annual *R&D* 100 Awards will be formally presented at an awards banquet in Orlando, FL, on November 12. A complete list of awardees and their projects is available at: www.rdmag.com/RD100Home.html.

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