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 radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of both diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. This month's selection of molecular imaging briefs includes a number of articles on novel particles for imaging, therapeutic targeting, and/or drug delivery, a reflection of growing interest and successes in nanotechnology research.

MOLECULAR IMAGING AND THERAPY

Novel mAb Conjugate for Improved Imaging

Ogawa and colleagues from the National Cancer Institute (Bethesda, MD) have described in several recent articles their work on efforts to develop novel molecular imaging probes that can address the challenges of high background signal in radiolabeled monoclonal antibody (mAb) studies in tumors (see, for example, their work on a "quench and chase" strategy [*Bioconj Chem.* 2009;20:147–154] and a more general description of this fluorophore/quencher-based activatable targetable optic probe [*Mol Pharm.* e-published Jan 21 ahead of print]). In the January issue of *Molecular Cancer Therapeutics* (2009;8:232–239) the group provided a detailed description of the probe, which is made up of multiple self-quenching fluorophores conjugated to a mAb (trastuzumab). Multiple in vitro and in vivo studies have shown that this agent becomes fluorescently "active" only after internalization in the cell; outside the cell, the unbound agent is quenched, resulting in high tumor-to-background ratios. The authors identified a specific conjugate that appears to work well with a single mAb to provide a near-infrared optical agent that activates within specific target tumors with high tumor-to-background ratio and has "considerable potential for clinical translation."

Molecular Cancer Therapeutics

^{18}F-Labeled Nanoparticles for Multimodality Imaging

Devaraj and colleagues from the Massachusetts General Hospital and Harvard Medical School (Boston) reported on January 12 ahead of print in *Bioconjugate Chemistry* on the synthesis and in vivo characterization of an ^{18}F-modified trimodal nanoparticle (^{18}F-CLIO) that shows promise for PET, fluorescence molecular tomography, and MR imaging and for applications that use combinations of these modalities. The particle is described as "cross-linked dextran held together in core-shell formation by a superparamagnetic iron oxide core and functionalized with the radionuclide ^{18}F in high yield via 'click' chemistry." The authors described the advantages of the nanoparticles, including the benefits accrued with ^{18}F radiolabeling.

Bioconjugate Chemistry

Heterofunctional Gold Nanorods for Targeting Breast Cancer Cells

In the January 14 issue of *Nano Letters* (2009;9:287–291), Eghtedari and colleagues from the University of Texas Medical Branch (Galveston), the Mayo Clinic Comprehensive Cancer Center, (Jacksonville, FL), and Fairway Medical Technologies (Houston, TX) described a technique for functionalizing gold nanorods for in vivo targeting of breast cancer tumors. The nanorods were functionalized by attachment of herceptin (HER; a monoclonal antibody that facilitates molecular recognition of breast cancer cells expressing highly specific tumor-associated antigens) and polyethylene glycol (which obscures particles against the reticuloendothelial system in the body). The authors described in vitro studies on stability and functionality of the nanoparticles, as well as in vivo studies verifying accumulation of functionalized gold nanorods within HER2/neu-overexpressing breast tumors in tumor-bearing nude mice. They concluded that these results "support the notions that gold nanorods can be used for molecular imaging of tumor."

Nano Letters

pH-Activatable Fluorescence Probes

Urano, from the University of Tokyo (Japan), and colleagues (including members of the group from the National Cancer Institute who authored the first article in this month's Newsline Literature Briefs) reported in the January issue of *Nature Medicine* (2009;15:104–109) on the development of a newly designed "activatable" fluorescent imaging probe that fluoresces only after cellular internalization by sensing pH changes in the lysosome. The authors described the synthesis of the probe and its conjugation with a cancer-targeting monoclonal antibody. The probe's potential utility was validated in ex vivo and in vivo imaging of human epidermal growth factor receptor type 2–positive lung cancer cells in mice and was found to be highly specific for tumors and to produce minimal background signal. Moreover, only viable cancer cells were successfully visualized. The authors concluded that this "design concept can be widely adapted to

cancer-specific, cell surface–targeting molecules that result in cellular internalization."

Nature Medicine

Silver Particles for Single Molecule Detection on a Cell Membrane

Zhang and colleagues from the University of Maryland School of Medicine (Baltimore, MD) reported on December 29 ahead of print in *Analytical Chemistry* on the preparation of Cy5-avidin conjugate-bound silver nanoparticles as fluorescence molecular reagents for quantitative single-molecular imaging on cell surfaces. When the nanoparticles were conjugated with and bound to biotin sites on the surfaces of PM1 cell lines, confocal microscopy scanning showed that the complexes could be visualized as isolated emission spots distinct from the cellular autofluorescence. As the amount of avidin-silver complexes on the cell surface increased, emission intensity increased, but the duration of the emissions decreased. Using quantitative regression curves based on the amount of avidin-metal complex on the cell surface and the emission intensity or lifetime over the entire cell image, the authors are working to develop an approach "that can be used to quantify the amount of target molecules on cell surfaces using the cell intensity and lifetime images at the single cell level."

Analytical Chemistry

Biodistribution of Quantum Dots in Living Mice

In the January issue of *Small* (2009;5:126–134), Schipper and colleagues in the Molecular Imaging Program at Stanford University (Palo Alto, CA) reported on the influence of particle size, PEGylation, and surface coating on the quantitative biodistribution of near-infrared–emitting quantum dots in mice. Among the techniques used in the study were serial micro-PET imaging with region-of-interest analysis, transmission electron microscopy, and inductively coupled plasma mass spectrometry. The studies in mice showed that PEGylation and peptide coating slowed quantum dot uptake into the organs of the reticuloendothelial system, liver, and spleen. Smaller particles cleared more quickly from the renal system. Peptide-coated particles were cleared from the liver faster than physical decay alone would predict. The authors noted that "renal excretion of small quantum dots and slowing of reticulendothelial clearance by PEGylation or peptide surface coating are encouraging steps toward the use of modified quantum dots for imaging living subjects."

Small

Glyconanoparticles for Presymptomatic Imaging in Brain Disease

van Kasteren and colleagues from the University of Oxford (UK) reported in the January 6 issue of the *Proceedings of the National Academy of Sciences of the United States of America* (2009;106:18–23) on the design, construction, and in vivo application of carbohydrate-functionalized nanoparticles that facilitate direct MR detection of the endothelial markers E–/P– selectin in acute brain inflammation. Results of initial studies indicated that these glyconanoparticles display multiple copies of the natural complex glycan ligand of selectins. The resulting sensitivity and binding selectivity may allow acute detection of disease during stages of initial recruitment of leukocytes in inflammation, currently not detectable by conventional imaging technique nor in symptom-based diagnoses.

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

THERAPY

Extradomain B Fibronectin–Targeted RIT

In an article e-published on January 8 ahead of print in *Blood*, Sauer et al. from the Charite-Universitatsmedizin (Berlin, Germany) reported on a study evaluating the presence of extradomain B (ED-B) fibronectin in biopsies from more than 200 patients with Hodgkin's disease, non-Hodgkin's lymphoma, and myeloproliferative diseases. A number of previous studies have correlated expression of ED-B fibronectin with angiogenic processes and suggested that it is exclusively observed in tissues undergoing growth or extensive remodeling, making ED-B fibronectin a potential target for radioimmunotherapy (RIT). In the current study, the extent of vascular ED-B fibronectin expression in lymphoma tissues was positively correlated with grade of malignancy and was enhanced in lymph nodes with severe lymphadenopathy and in some hyperplastic tonsils. Scintigraphy with a ^{131}I-L19 small immunoprotein showed localization in lymphoma lesions in 2 patients, and RIT with the same radiolabeled protein in 2 patients with relapsed Hodgkin's lymphoma resulted in sustained partial response. The authors concluded that these results suggest ED-B fibronectin "as a promising target for antibody-based lymphoma therapies."

Blood

Enhancing Prostate RIT

Kelly et al. from the Ludwig Institute for Cancer Research Melbourne Centre for Clinical Sciences (Australia) reported in the January 1 issue of *Prostate* (2009;69:92104) on the biodistribution and therapeutic efficacy of ^{177}Lu-anti-Lewis Y monoclonal antibody hu3S193 (^{177}Lu-hu3S193) radioimmunotherapy (RIT) as enhanced by either epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor AG1478 or docetaxel chemotherapy in mice bearing prostate cancer xenografts. The researchers investigated the cytotoxicity of the compound in vitro and in vivo, assessed biodistribution and localization in vivo, and conducted a dose escalation study to determine efficacy and maximum tolerated dose. In addition, either AG1478 or docetaxel

chemotherapy was administered at subtherapeutic doses in conjunction with RIT in the xenografted mice. ^{177}Lu-hu3S193 administration was found to result in significant induction of cytotoxicity and apoptosis in the in vitro studies, with in vivo biodistribution showing specific targeting of prostate cancer xenografts. ^{177}Lu-hu3S193 RIT caused specific and dose-dependent inhibition of prostate cancer tumor growth. The addition of either the EGFR inhibitor or docetaxel chemotherapy significantly improved efficacy. The authors concluded that "^{177}Lu-hu3S193 RIT is effective as a single agent in the treatment of Lewis Y positive prostate cancer models," and "the enhancement of RIT by AG1478 or docetaxel indicates the promise of combined modality strategies."

Prostate

Differential Gene Expression Triggered by ^{213}Bi Immunoconjugates

In an article e-published on January 13 ahead of print in *Investigational New Drugs*, Seidl et al. from the Technische Universität München (Germany) reported on studies to elucidate molecular function and biological responses of HSC45-M2 gastric cancer cells to immunoconjugates made up of the α-emitter ^{213}Bi and the monoclonal antibody d9MAb. These immunoconjugates have been found to efficiently kill tumor cells in a nude mouse model of peritoneal carcinomatosis. In this study, whole genome expression profiling of the cells was performed, and the cells were incubated with lethal doses of ^{213}Bi-d9MAb. Validation of microarray analysis indicated the genes that were downregulated and those that were upregulated. Three of the consistently upregulated and 3 of the consistently downregulated genes had not previously been associated with any biological processes or molecular functions. The authors concluded that "these findings revealed interesting new targets for selective elimination of tumor cells and new insights regarding response of tumor cells to α-emitter exposure."

Investigational New Drugs

Zevalin in Early-Stage Ocular Adnexal Lymphoma

Esmaeli and colleagues from the University of Texas M. D. Anderson Cancer Center (Houston), the Auxilio Mutuo Cancer Center (San Juan, Puerto Rico), and Biogen-Idec Inc. (Cambridge, MA) reported on January 15 ahead of print in *Annals of Oncology* on a study of the efficacy and side effects of ^{90}Y-ibritumomab tiuxetan as a front-line treatment in patients with early-stage extranodal indolent lymphoma of the orbit, conjunctiva, or eyelid. The study included 12 patients (7 women, 5 men) with stages I–E extranodal indolent lymphoma of the ocular adnexa (9 with mucosa-associated lymphoid tissue lymphoma, 3 with grades 1 or 2 follicular lymphoma of the orbit) who were enrolled in a prospective trial of rituximab followed by the ^{90}Y-ibritumomab tiuxetan regimen. All patients underwent pretherapy imaging for biodistribution studies, and 3 underwent subsequent SPECT/CT to estimate radiation dose to orbital and ocular tissues. Responses to therapy were monitored. Within 3 mo of treatment, 10 patients had complete responses and 2 had partial responses. Six mo later, 1 of the partial response patients had a recurrence in the upper eyelid, underwent external-beam radiotherapy, and experienced disease progression in the orbit. Over a median follow-up period of 20 mo, no cases of extraorbital relapse were noted. Although all 12 patients experienced grade I or II transient pancytopenia during the first 3 mo after the ^{90}Y-ibritumomab tiuxetan regimen, no grade III or IV myelosuppression was seen. Results from the 3 patients who underwent SPECT/CT indicated that estimated absorbed radiation doses to orbital soft tissues were $<$3 Gy, more than 10 times lower than radiation doses with external-beam radiation therapy. The authors concluded that "rituximab followed by ^{90}Y-ibritumomab tiuxetan is an effective and safe front-line treatment for early-stage extranodal indolent B-cell lymphoma of the ocular adnexa."

Annals of Oncology

DIAGNOSIS

NOPR and PET Effect on Management

Hillner and other researchers associated with the National Oncologic PET Registry (NOPR) reported in the January 15 issue of *Cancer* (2009; 115:410–418) on the effect of PET on expected management in cancer treatment. Data continue to be collected through NOPR in response to the Centers for Medicare & Medicaid Services "Coverage with Evidence" policy, under which PET and PET/CT are covered for treatment monitoring only when the physician is a part of and submits results to a prospective registry. The NOPR group has previously reported on the relationship between type of cancer and effects of PET and PET/CT on management (*J Nucl Med.* 2008;49:1928–1935) and initial comparative effects of PET/CT and PET alone on management of patients with cancer (*J Clin Oncol.* 2008;26:2155–2161). These findings were extended with new data in the current study, which included results from 8,240 patients who underwent 10,497 treatment-monitoring PET scans (82% to monitor only chemotherapy, 6% to monitor only radiation therapy, and 12% to monitor combined treatments) at 946 centers. The authors compared pre- and post-PET treatment plans. Without PET (pre-PET), management would have been referral to other imaging (53%) to decide about next treatment strategies, ongoing treatment (41%), or biopsy/watching (6%). With the added information provided by PET (post-PET), a change to a different therapy was recommended for 26% and 28% of patients in the imaging referral and ongoing treatment groups, respectively. An addition 16%−19% of scans in these groups led to changes in dose or duration of ongoing therapies. When the post-PET

prognosis was worse (rather than improved or unchanged) than the pre-PET information, changes in management were more frequent. Physicians responding as part of the NOPR questionnaire process indicated that PET enabled 91% of their patients to avoid 1 or more future tests and that the modifications in treatment plans were especially notable and beneficial when PET was used in treatment monitoring in elderly patients with cancer.

Cancer

PET/CT in Suspected Recurrent Ovarian Cancer

Fulham, from the Royal Prince Alfred Hospital (Sydney, Australia), and study panel colleagues from the Australian PET Data Collection Project, reported on January 14 ahead of print in *Gynecologic Oncology* on the results of a large multicenter study of the impact of PET/CT imaging on management in suspected recurrent ovarian cancer. The study included 90 women with suspected recurrence (based on elevated markers, anatomic imaging, or clinical symptoms) of previously treated epithelial ovarian carcinoma. Each patient underwent PET/CT imaging. Referring physicians reported on plans for management before PET/CT, whether the results of PET/CT changed management plans, and the general effect of PET/CT (none, low, medium, or high) on overall management, including 6- and 12-mo patient follow-ups. The addition of PET/CT in these patients' management identified 168 additional lesions not identified by conventional imaging in a total of 61 patients (68%). In 77% of these, the additional lesions were located below the diaphragm and most were nodal or peritoneal. PET/CT changed management in 60% of all patients (changes assessed as 49% high and 11% medium impact). In those patients in whom PET/CT detected more disease than conventional assessments, disease progression was more likely in the following year. In addition to carrying the advantages of positively changing management and identifying more sites of disease than abdominal and pelvic CT, PET/CT was found to be superior in detection of nodal, peritoneal, and subcapsular liver disease in this population. The authors concluded that PET/CT "offers the opportunity for technology replacement in management of suspected recurrent ovarian cancer."

Gynecologic Oncology

PET Screening for Spine Metastases

Laufer and colleagues from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported in the January issue of *Neurosurgery* (2009;64:107–112) on a study of ^{18}F-FDG PET as a screening test for vertebral metastases in patients with cancer. The retrospective study included the records of 82 patients with solid tumors and hematological spine metastases who underwent a needle biopsy of a spinal lesion and PET imaging within 6 wk of that biopsy. Other data included in the study were biopsy results, MR and/or CT appearance of the biopsied lesion, and long-term clinical follow-up. The mean standardized uptake values (SUVs) averaged 7.1 in lesions with active cancer and 2.1 in benign lesions. ^{18}F-FDG PET proved to be a significantly better predictor of cancer status than CT in lytic or mixed lesions. Using an SUV cutoff of 2 for nonsclerotic lesions, ^{18}F-FDG PET agreed with needle biopsy diagnoses in 100% of patients with histories of solid tumors. The authors concluded that ^{18}F-FDG PET "is an accurate screening test for vertebral metastases in cancer patients" and is especially accurate in patients with nonsclerotic vertebral lesions and a history of solid malignancy.

Neurosurgery

PET and Involved Field Radiotherapy in Lymphoma

In an article e-published on January 12 ahead of print in *Bone Marrow Transplantation*, Hoppe and colleagues from the Memorial Sloan–Kettering Cancer Center (New York, NY) assessed the prognostic value of ^{18}F-FDG PET imaging before involved-field radiotherapy (IFRT) in salvage therapy. The study included 83 patients with chemosensitive relapsed or primary refractory diffuse large B-cell lymphoma who underwent PET imaging after second-line chemotherapy but before high-dose therapy with autologous stem cell rescue. Over a median follow-up of 45 mo, 3-y progression-free survival was 72%, disease-specific survival was 80%, and overall survival was 78%. Patients with positive PET scans had poorer progression-free, disease-specific, and overall survival than those with negative scans. A comparative group of patients who did not receive IFRT had worse progression-free and disease-specific survival than those who did. Those who received IFRT had better local control with fewer relapses than those who did not. The authors concluded that "these outcomes confirm the important prognostic value of FDG PET scans before undergoing high-dose therapy with autologous stem cell rescue" and also suggested that the role of IFRT should be further evaluated.

Bone Marrow Transplantation

^{18}F-DOPA PET and Digestive Endocrine Tumors

Montravers et al. from the Tenon Hospital (Paris), Beaujon Hospital (Clichy), Saint Antoine Hospital (Paris) and the Ambroise Paré Hospital (Boulogne-Billancourt), all in France, reported on January 13 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on the effect ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) PET on management and treatment decisions in patients referred for carcinoid or noncarcinoid digestive tumors. The study included 78 adult patients who were imaged with ^{18}F-DOPA PET as follow-up for histologically documented carcinoid tumor of the ileum (n = 23) or noncarcinoid digestive tumor (n = 26) or to screen for occult digestive endocrine tumors (n = 29). Referring physicians completed

questionnaires on the effects of PET results on management decisions, and clinical follow-up was used to assess the relevance of decision changes to general outcomes and progression. ^{18}F-DOPA PET changed management in 18 of 71 (25%) patients whose physicians responded to the survey. The effect on management was much more marked for gastrointestinal carcinoid tumors (11 of 22, 50%) than for occult endocrine tumors (4 of 25, 16%) or noncarcinoid tumors (3 of 22; 13%). These changes in management were determined to be clinically relevant in all the patients with gastrointestinal carcinoid tumors but in only 75% and 33% of the occult endocrine and noncarcinoid tumors, respectively. The authors concluded that ^{18}F-DOPA PET "appears to be a major tool for the management of carcinoid tumors with excellent diagnostic performances and induced relevant changes in patient management" but was less sensitive and less useful in the management of noncarcinoid tumors.

Journal of Clinical Endocrinology and Metabolism

Angiogenesis and Tracer Uptake in NSCLC

Kaira and colleagues from the Gunma University Graduate School of Medicine (Japan) reported on January 9 ahead of print in *Cancer Science* on a study designed to characterize the correlation between PET assessment of uptake of ^{18}F-FDG or ^{18}F-α-methyltyrosine (^{18}F-FMT) and angiogenesis in patients with non–small cell lung cancer (NSCLC). The study included 37 such patients, each of whom underwent PET imaging with both tracers, and standardized uptake values were recorded. These data were then analyzed along with histopathologic assessments of vascular endothelial growth factor (VEGF), CD31, CD34, L-type amino acid transporter 1 (LAT1), and Ki-67 labeling index from resected tumors. Clinical data were also considered in the analysis. High VEGF expression was seen in 30 patients (81%) and was associated with progressively growing microvessel counts. VEGF also correlated with LAT1 expression and Ki-67 labeling index. Clinical factors such as age, gender, disease stage, and tumor size did not correlate with VEGF expression, nor was microvessel density correlated with any other parameters in the study. Although both ^{18}F-FMT and ^{18}F-FDG uptake correlated significantly with VEGF expression, correlations between ^{18}F-FMT and VEGF were more statistically significant. The authors concluded that "the metabolic activity of primary tumors as evaluated by PET study with ^{18}F-FMT and ^{18}F-FDG is related to tumor angiogenesis and the proliferative activity in NSCLC."

Cancer Science

SPECT/CT-Based Lymph Node Imaging in Radiation Treatment Planning

Cheville, from the Mayo Clinic (Rochester, MN), and colleagues from Mayo and other institutions reported on January 17 ahead of print in *Breast Cancer Research and Treatment* on a proof-of-concept study to assess whether a coordinated use of SPECT and CT is sufficiently precise to enhance image-guided radiation treatment planning in ways that could lessen the incidental exposure of critical lymph nodes. The study included 32 women with breast cancer who underwent scanning with a hybrid SPECT/CT scanner (dual-head SPECT + low-dose, single-slice CT) with ^{99m}Tc-sulfur colloid before radiation treatment planning. Data recorded included number of visualized lymph nodes, locations, maximum counts, and total uptake. Lymph node locations were mapped onto the 3D radiation treatment planning system using coordinates derived from the SPECT/CT images. A mean of 3.4 lymph nodes were detected in each patient. Level I and II lymph nodes were detected more frequently in patients who had undergone sentinel node biopsy, whereas more supraclavicular nodes were detected in patients who had undergone axillary dissection. SPECT/CT fusion imaging was found to successfully localize lymph nodes draining the arm after breast cancer surgery. The authors concluded that "these finding suggest that SPECT/CT may be helpful in minimizing incidental lymph node irradiation and in directing breast cancer therapy to reduce long-term morbidity."

Breast Cancer Research and Treatment

High-Resolution Lymphoscintigraphy in Internal Mammary Nodes Assessment

In an article e-published on January 19 ahead of print in *Annals of Oncology*, Spillane and colleagues from the University of Sydney (Australia) reported on an analysis of data on sentinel node biopsy of internal mammary nodes in breast cancer, with a focus on identifying data that could clarify current controversies about techniques for lymphatic mapping, safety of the procedure, and potential benefits to patients. The authors looked at data from 1,754 patients from 2 nuclear medicine department databases and reviewed related literature. They found that high-resolution lymphoscintigraphy showed results in internal mammary node drainage in an average of one-third of cases (53% of medial tumors, 37% of midline tumors, and 24% of lateral tumors). These and other data suggested that internal mammary node mapping provides information that can alter management in up to one-third of cases, especially because these rates of drainage are reproducible and reflect lymphatic density and anatomy of the breast. The authors called for the establishment of collaborative clinical trials to clarify the value of internal mammary node assessment.

Annals of Oncology