

research promising new treatments for patients. Funding and molecular compound information is available now for the initial phase of the recently launched Discovering New Therapeutic Uses for Existing Molecules program. This NIH/industry collaboration will match researchers with 58 compounds to test ideas for new therapeutic uses. Since the start of the program in May the total number of compounds the companies are making available has more than doubled. Abbott, Bristol-Myers Squibb Company, GlaxoSmithKline, Janssen Pharmaceutical Research & Development, and Sanofi have joined Pfizer, AstraZeneca, and Eli Lilly and Company in this innovative approach to research.

The NIH's new National Center for Advancing Translational Sciences (NCATS) created the Therapeutics Discovery program to help re-engineer the research pipeline. By crowdsourcing compounds that already have cleared several key steps in the development process, including safety testing in humans, scientists nationwide

have the opportunity to contribute their expertise to advancing these resources for new disease therapies. The 8 participating companies will provide their compounds and related data, which were determined by the NIH to meet specific eligibility criteria. For example, each compound must have advanced to clinical studies but been unsuccessful in its original therapeutic indication or not pursued for business reasons. Preliminary information about the compounds, including mechanism of action, route of administration, and any limitations in use based on safety and tolerability, are available at <http://ncats.nih.gov/therapeutics-directory.html>.

"Each company participating in this innovative collaboration has made substantial research and development investments to advance these compounds to the point where they can be used in clinical studies," said Kathy L. Hudson, PhD, NCATS acting deputy director. "If researchers funded through this effort can demonstrate new uses for the compounds, they could significantly reduce

the amount of time it takes to get a treatment to patients in need." For the pilot phase of the program in fiscal year 2013, NCATS will provide up to \$20 million to fund 2- to 3-y staged, cooperative agreement research grants. If specific milestones are met, funded researchers will conduct preclinical validation and clinical feasibility studies in the first stage and proof-of-concept clinical trials in the second stage, to test whether one of the compounds may be effective against a previously unexplored disease target. The pilot phase also is intended to test the utility of the newly created template agreements by reducing the negotiation time that otherwise could delay the research.

Researchers interested in the NCATS Therapeutics Discovery funding must submit a preapplication in response to the NIH Funding Opportunity Announcement at <http://grants.nih.gov/grants/guide/pa-files/PAR-12-203.html> by August 14. For more information, visit [ncats.nih.gov/therapeutics.html](http://ncats.nih.gov/therapeutics.html).

*National Institutes of Health*

## FROM THE LITERATURE

*Each month the editor of Newline 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. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.*

### PET/CT and Melanoma Treatment

Beasley and colleagues from Duke University (Durham, NC) and the

Moffitt Cancer Center (Tampa, FL) reported on June 11 ahead of print in *Annals of Surgery* on the clinical utility of  $^{18}\text{F}$ -FDG PET/CT in evaluating response to treatment or to monitor after treatment in patients with stages IIIB/IIIC extremity melanoma. The prospective study included 97 such patients undergoing isolated limb infusion who underwent whole-body PET/CT before and every 3 mo after treatment. Response Evaluation Criteria in Solid Tumors were used to determine clinical response at 3 mo. Thirty-two patients (33%) had complete responses on histology at 3 mo after therapy. PET/CT correctly identified 59% (19) of these but found residual metabolic activity in the extremity in the remaining 41% (13). For patients who were classified as complete responders by both PET/CT and histology, the 3-y disease-free rate was 62.2%, whereas this percentage was only 29.4% for

those histologic complete responders who had been found to have residual metabolic activity on PET/CT. When used for surveillance of recurrence outside the field of treatment, PET/CT correctly identified the 52% (51 patients) of all participants who developed distant disease, at a median time of 212 d after pretreatment imaging, leading to early resection in almost half of such patients. The authors noted that although PET/CT is not accurate in identifying all patients who have histologic complete responses after isolated limb infusion, it appears to "identify a subgroup of patients whose regional progression-free survival is markedly worse." In addition, they concluded that "PET/CT appears to be an excellent method for surveillance in stage IIIB/IIIC patients after isolated limb infusion with ability to identify surgically re-

sectable recurrent disease in these high-risk patients.”

*Annals of Surgery*

### PET Tracer for $\tau$ Tangles

In an article e-published on June 8 ahead of print in the *Journal of Alzheimer's Disease*, Zhang et al. from Siemens Molecular Imaging, Inc. (Culver City, CA) reported on a highly selective and specific PET tracer for imaging of  $\tau$  pathologies. The authors described the process of testing more than 900 compounds to identify  $^{18}\text{F}$ -PET tracers with binding affinity and selectivity to  $\tau$  tangles. In *in vitro* studies, the compound identified as  $^{18}\text{F}$ -T808 showed a high level of binding affinity as well as selectivity for  $\tau$  aggregates over amyloid- $\beta$  plaques. In initial small animal studies, the compound showed rapid uptake and washout in rodent brains. The authors concluded that this research suggests that “ $^{18}\text{F}$ -T808 possesses suitable properties and characteristics to be a specific and selective PET probe for imaging of paired helical filament  $\tau$  in human brains.”

*Journal of Alzheimer's Disease*

### Characterizing Pediatric PTGC

Shaikh et al. from the Hospital for Sick Children (Toronto, Canada) reported on June 15 ahead of print in *Pediatric Blood & Cancer* on a retrospective review of diagnosis and clinical course in children with progressive transformation of germinal centers (PTGC). The retrospective study included 29 patients (median age at diagnosis, 11.5 y) who were followed for a median of 2.6 y. Of these patients, 13 (45%) had only 1 episode of PTGC and no associated features or identified sequelae, and 5 (17%) had recurrent PTGC. Of the 4 patients (14%) whose PTGC was associated with Hodgkin lymphoma, 1 was diagnosed with PTGC before, 2 concurrently, and 1 after development of the disease. In 7 patients (24%) PTGC was associated with im-

mune disorders. Fifteen (52%) of the total number of patients underwent more than 1 lymph node biopsy. Of interest, PTGCs were  $^{18}\text{F}$ -FDG avid in all 4 patients who underwent PET imaging as part of their diagnostic assessment. The authors' conclusions reinforced current views that PTGC is a nonspecific manifestation of a variety of associated conditions with a small risk of subsequent Hodgkin lymphoma and a likelihood of multiple biopsies for recurrent PTGC. They recommended consideration of immune disorders in patients who present with generalized lymphadenopathy, splenomegaly, immune cytopenias, and/or progression to Hodgkin lymphoma, and added that routine surveillance imaging may not be required. They noted that “Future research should determine the optimal surveillance strategy for patients with PTGC and the indications for repeat biopsies.”

*Pediatric Blood & Cancer*

### SPECT/CT and Diabetic Foot Infection

In an article e-published on June 20 ahead of print in *Diabetes Care*, Erdman et al. from the University of Texas Southwestern Medical Center (Dallas) reported on a study designed to determine the utility of a novel standardized SPECT/CT-based scoring system in patients with diabetic foot infection. The study included chart review and  $^{99\text{m}}\text{Tc}$ -white blood cell (WBC) SPECT/CT image re-analysis of 77 patients (101 involved feet) with suspected diabetic foot infection-associated osteomyelitis. The researchers correlated their Composite Severity Index (CSI) scores with probability of favorable outcomes in each patient, defined as no amputation or readmission after therapeutic intervention over the course of a median 342-d follow-up period. CSI scores (which ranged from 0 to 13) were successful in predicting outcome. A patient with a CSI of 0 had a 92% chance of a favorable outcome, whereas a patient with a CSI of  $\geq 7$  had a  $\leq 25\%$  chance of a favorable outcome. CSI scores were better predictors of outcomes than posi-

tive or negative identification of osteomyelitis by imaging. Extension of antibiotic therapy duration to  $\geq 42$  d significantly decreased treatment failure in patients with intermediate CSI scores (3–6). The authors concluded that “ $^{99\text{m}}\text{Tc}$ -WBC SPECT/CT hybrid image-derived wound infection parameters incorporated into a standardized scoring system, CSI, has prognostic value in diabetic foot infection.”

*Diabetes Care*

### PET and AET Hot Flashes

Joffe et al. from the Massachusetts General Hospital and the Harvard Medical School (both in Boston) and the Indiana University School of Medicine (Indianapolis) reported on June 20 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on research to determine whether  $^{18}\text{F}$ -FDG PET can elucidate the neurobiology of hot flashes in adjuvant endocrine therapies (AET) for breast cancer, specifically whether preexisting neurobiologic traits may predispose some women to hot flashes. The study included 18 women previously without hot flashes who underwent  $^{18}\text{F}$ -FDG PET and structural MR imaging at baseline and after initiation of AET. Concurrent images from the 2 modalities were coregistered to determine whether metabolic activity in the insula, hypothalamic thermoregulatory, and estrogen-feedback regions could predict which women would experience hot flashes. These findings were also correlated with presence of the CYP2D6 genotype. After initiation of AET, hot flashes were reported by 10 (55.6%) women and were detected by imaging in 9 of these. The pretreatment metabolic rate of glucose uptake in the insula, hypothalamic thermoregulatory, and estrogen-feedback regions was lower in women who developed hot flashes. After initiation of treatment, metabolic rate of glucose uptake was reduced even more in the insula in those who developed hot flashes. Insular and hypothalamic metabolic rates of glucose uptake levels were lower in intermediate than extensive CYP2D6 metabolizers. The authors

concluded that “genetic variability in CYP2D6 may underlie the neurobiological predisposition to hot flashes induced by AET.”

*Journal of Clinical Endocrinology and Metabolism*

## PET and Bevacizumab Treatment

In an article e-published on June 18 in *Neuro-Oncology*, Harris et al. from the University of California Los Angeles described the use of voxel-wise changes in  $^{18}\text{F}$ -FDOPA and  $^{18}\text{F}$ -FLT PET uptake, assembled as “parametric response maps,” to predict responses to bevacizumab treatment in patients with recurrent malignant gliomas. The study included 24 such patients who underwent MR and PET imaging before and at 2 time points after bevacizumab treatment. The researchers found that voxel-wise increases in PET uptake in areas of pretreatment contrast enhancement as defined by MR imaging successfully stratified 3-mo progression-free survival and 6-month overall survival. A decrease in PET tracer uptake was associated with longer progression-free and overall survival, and an increase was associated with shorter progression-free and overall survival. Increased  $^{18}\text{F}$ -FDOPA PET uptake between the 2 posttreatment time points also stratified long- and short-term survivals, but  $^{18}\text{F}$ -FLT did not. The authors concluded that these data suggest that an “increase in FDOPA or FLT PET uptake on parametric response maps after bevacizumab treatment may be a useful biomarker for predicting progression-free survival and that FDOPA PET parametric response maps are also predictive of overall survival in recurrent gliomas treated with bevacizumab.”

*Neuro-Oncology*

## PET/CT and NSCLC Lymph Node Metastasis

Billé et al. from King’s College London (UK) reported on June 11 ahead of print in the *European Journal of Cardiothoracic Surgery* on a study designed to assess the specificity and sensitivity of PET/CT in identifying nodal metastasis and accompanying

histology (adenocarcinoma or squamous cell carcinoma) as well as to characterize factors associated with false-negative findings. The retrospective study included 353 patients with suspected or pathologically proven, potentially resectable non-small cell lung cancer who also underwent PET/CT. A total of 2,286 nodal stations (1,643 mediastinal, 333 hilar, and 310 intrapulmonary) were evaluated on imaging, with final diagnoses of adenocarcinoma in 244 patients and squamous carcinoma in 109 patients. PET/CT had sensitivity, specificity, and accuracy of 53.8%, 91.5%, and 79.1%, respectively, in the adenocarcinoma group and corresponding figures of 87.5%, 81.8%, and 83.5% in the squamous cell group. On a per-patient basis analysis in N2 disease, the sensitivity, specificity, and accuracy of PET were 38.8%, 97.4%, and 85.7%, respectively, for the adenocarcinoma group, with corresponding figures of 81.8%, 91.8%, and 90.8% in the squamous cell group. The mean diameters of false-negative and true-positive lymph nodes in the adenocarcinoma group were 7 and 12.5 mm, respectively, with corresponding figures of 7.4 and 14.7 mm in the squamous cell group. The authors concluded that the “sensitivity of PET/CT in detecting nodal metastasis in patients with adenocarcinoma is too low to avoid any further invasive staging procedure,” and that ultrasound-guided needle biopsy or mediastinoscopy remains necessary in staging patients undergoing lung resection for adenocarcinoma.

*European Journal of Cardiothoracic Surgery*

## REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in June. In an article e-published on June 18 ahead of print in the *Journal of Alzheimer’s*

*Disease*, Villemagne and Rowe from Austin Health and the Mental Health Research Institute of Victoria (Australia) described “Long night’s journey into the day: amyloid- $\beta$  imaging in Alzheimer’s disease.” Al-Hawary and Zimmermann, from the University of Michigan Medical Center (Ann Arbor), provided “A new look at Crohn’s disease: novel imaging techniques” in the July issue of *Current Opinion in Gastroenterology* (2012;28:334–340). In the June issue of *Psychogeriatrics* (2012;12:106–114), Mori et al. from the National Institute of Radiological Sciences and Ehime University Graduate School of Medicine (Shitsukawa, Japan) reviewed “Molecular imaging of dementia.” Créhange et al. from the University of California, San Francisco and the Centre Georges François Leclerc (Dijon, France) published “Management of prostate cancer patients with lymph node involvement: a rapidly evolving paradigm” on June 13 ahead of print in *Cancer Treatment Reviews*. On May 29 ahead of print in *Current Radiopharmaceuticals*, Roesch, from the the Johannes Gutenberg University of Mainz (Germany), described “Scandium-44: benefits of a long-lived PET radionuclide available from the  $^{44}\text{Ti}/^{44}\text{Sc}$  generator system.” Kosuri et al. from the Weill Cornell Medical College (New York, NY) reported on May 28 ahead of print in *Advances in Urology* on a “Review of salvage therapy for biochemically recurrent prostate cancer: the role of imaging and rationale for systemic salvage targeted anti-prostate-specific membrane antigen radioimmunotherapy.” In an article published on June 9 ahead of print in *Brain Imaging and Behavior*, Lin et al. from the Harvard Medical School (Boston, MA) described “Metabolic imaging of mild traumatic brain injury.” Mavridis, from the University of Athens School of Medicine (Greece), provided an overview of “The role of nuclear medicine in the management of patients with glioblastoma multiforme” on May 29 ahead of print in *Current Radiopharmaceuticals*.