Focal Spot, Spring 2009

Follow this and additional works at: https://digitalcommons.wustl.edu/focal_spot_archives

Recommended Citation
Focal Spot, Spring 2009. Bernard Becker Medical Library Archives. Washington University School of Medicine, Saint Louis, Missouri

This Book is brought to you for free and open access by the Focal Spot at Digital Commons@Becker. It has been accepted for inclusion in Focal Spot All Issues by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.
In the early 1960s, digital computers were massive and expensive. For biomedical researchers, the computers were neither accessible nor compatible with their scientific needs. A group at Massachusetts Institute of Technology’s (MIT’s) Lincoln Laboratory set out to build an all-purpose, inexpensive, research-friendly module. The National Institutes of Health (NIH) recognized MIT’s design as an important research tool and encouraged research teams nationwide to submit proposals for projects to evaluate the Laboratory Instrument Computer (LINC, as MIT’s design was called) as a lab tool. In all, 12 grants—which included funds to build a LINC—were awarded; Washington University in St. Louis was among the recipients.

Eventually, as technology evolved and computers became smaller, faster, and less expensive, LINCs were phased out, often relegated to the trash heap. Of the 50 LINC machines eventually built, only a handful survived—and one of them is being restored and will be permanently displayed at the Washington University Medical Center.

Photographs by Kimberly Kania.
Let there be...bioluminescence

Scientists in the Molecular Imaging Center have a new way to identify cell inflammation before a tumor forms—that old crime-scene standby, luminal, and its reaction to an immune system bleach.

Unlocking the secrets of Alzheimer’s disease

Nuclear medicine physicians are using positron emission tomography in several collaborative studies to detect Alzheimer’s disease before the onset of cognitive symptoms.

Imaging the behavior of cancer cells

Researchers in MIR’s Radiological Chemistry Lab have developed a new approach—positron emission tomography and sigma-2 receptors—to directly visualize the behavior of cancer cells.

CRMO—imaging is key to accurate diagnosis

Multimodality imaging is helping to diagnose and assess chronic recurrent multifocal osteomyelitis, an autoinflammatory disease affecting children and young adults.

A paradoxical view of cancer

Collaborative research has made a marked contribution to the cure of advanced breast cancer—a novel way of assessing the best treatment for patients who have exhausted most available therapies.
WUSM among nation’s top schools

In the 2009 U.S. News & World Report rankings of graduate and professional programs, Washington University School of Medicine was named third among the country’s top 10 research-oriented medical schools—tied with the University of Pennsylvania. The top spot went to Harvard University, second to Johns Hopkins University. The University of California, San Francisco was ranked fifth, with Duke University, Stanford University, the University of Washington, and Yale University tied for sixth place. For the eleventh consecutive year, WUSM was named number one in student selectivity (based on college grade-point averages and MCAT scores).

Bhalla gives AΩA lecture

Sanjeev Bhalla, MD, associate professor of radiology and chief of Cardiothoracic Imaging, was selected by the Washington University School of Medicine students as the 56th Annual Alpha Omega Alpha lecturer. He holds the honor of being one of two faculty members to have been selected twice as lecturer. Bhalla presented “Lights along the path: getting the most education in residency.”

The Alpha Omega Alpha Honor Society, established 107 years ago at the College of Physicians and Surgeons in Chicago, is considered the most prestigious honor society in the medical profession and has more than 50,000 members nationally. The Washington University chapter was organized in 1905.

CMS expands coverage for PET

The Centers for Medicare & Medicaid Services (CMS) announced in April that it would cover costs for positron emission tomography (PET) scans used to support initial diagnosis and treatment for most solid tumor cancers. CMS also expanded coverage for the use of PET scans for follow-up testing for cervical and ovarian cancer and myeloma. Eight other types of cancer continue to be covered: breast, colorectal, esophageal, head and neck, lymphoma, melanoma, non-small cell lung, and thyroid. Follow-up testing of all other cancers continues under the CMS coverage with evidence development (CED) policy.

The CMS decision was fueled by clinical results of the NOPR (National Oncologic PET Registry) study, a nationwide CED effort that helped to prove the effectiveness of PET in diagnosing, staging, restaging, and monitoring treatment for many cancers. Sponsored by the Academy of Molecular Imaging and managed by the American College of Radiology (ACR) and the ACR Imaging Network, the NOPR began accruing patients in May 2006. Mallinckrodt Institute’s Barry Siegel, MD, a key advocate for and organizer of the NOPR, serves as cochair of the NOPR working group. To read more about this expanded coverage, go to www.cms.hhs.gov. In the search box, type “PET coverage for cancer.”
Street earns RSNA R&E award

Mandie Street, ARRT, clinical research coordinator, received a Radiological Society of North America (RSNA) Research and Education Foundation award for her project "Using six sigma techniques to reduce radiation dose," which will assess progress in optimizing radiation exposure during pediatric fluoroscopy procedures. The award of up to $10,000 is sponsored by the Association of University Radiologists, the Association of Program Directors in Radiology, and the Society of Chairmen of Academic Radiology Departments. James Duncan, MD, PhD, associate professor of radiology, serves as Street’s mentor for the project.

Welch corecipient of cancer fund grant

Michael Welch, PhD, professor of radiology, of chemistry, and of molecular biology and pharmacology, and John-Stephen Taylor, PhD, professor of chemistry, received the first research grant awarded by the Kay Yow/Women’s Basketball Coaches Association (WBCA) Cancer Fund and the V Foundation for Cancer Research. The $100,000 award will fund the Siteman Cancer Center research project “Targeted nanoparticles optimized for breast cancer diagnosis and therapy.” The award was presented during the NCAA Women’s Final Four weekend in St. Louis.

Kay Yow, North Carolina State University women’s basketball coach and breast cancer patient who died recently, created the Kay Yow/ WBCA Cancer Fund in 2007 to fund research of women’s cancers and to assist underserved women. The V Foundation for Cancer Research was established in 1998 by ESPN and the late Jim Valvano, North Carolina State University basketball coach and ESPN commentator.

Faculty receive honors

Maurizio Corbetta, MD, professor of neurology, of radiology, and of anatomy and neurobiology, was one of five recipients of the Washington University School of Medicine Distinguished Investigator Award. The award is among the Distinguished Faculty Awards presented annually to recognize outstanding achievements in clinical care, community service, research, and teaching.

Emily Smith, MD, assistant professor of radiology, was one of two honorees who received the WUSM Alumni/Faculty award. She earned a WUSM medical degree in 1968 and completed a diagnostic radiology residency in 1972. In addition to serving on the Mallinckrodt Institute faculty for the past 35 years, Smith is an Eliot Society Patron and has chaired the WUSM Annual Fund for 11 years.

Pamela Woodard, MD, associate professor of radiology and cohead of Cardiac CT/MR, was elected a fellow of the American College of Radiology (ACR), one of the highest honors ACR can bestow on a radiologist, radiation oncologist, or medical physicist. The convocation ceremony was in May at the ACR’s 86th Annual Meeting and Chapter Leadership Conference.
On summer nights, children chase after fireflies, trying to capture these fascinating insects that generate their own blinks of light.

Then there’s David Piwnica-Worms, MD, PhD, professor of radiology and of developmental biology. He exploits firefly-like chemistry to capture glowing images of disease in living mice. What he’s seen lately on his computer screen leaves him as astonished as a child.

A molecule called luminol—cousin to light-producing luciferin in fireflies—shines blue when it reacts with an immune-system bleach that causes tissue inflammation. Using this type of bioluminescence, Piwnica-Worms and his research team have spotted the subtlest beginnings of inflammation in the tail of a mouse—not detectable by sight or palpation—only to watch it morph into a tumor four weeks later. “We were amazed that we could show inflammation starting long before the tumor formed,” says Piwnica-Worms, director of the Molecular Imaging Center (MIC) at Washington University.
His team published its findings on bioluminescence imaging of inflammation earlier this year in the journal Nature Medicine. It marked the latest development in a molecular imaging technique that Piwnica-Worms has honed over the past 10 years, a technique that in some applications could someday outshine such stalwarts as magnetic resonance imaging (MRI). With every new finding, Piwnica-Worms demonstrates the versatility of bioluminescence imaging, which is already helping to develop new drugs and may someday spot potential blood clots and even guide the hand of cancer surgeons.

When bleach is spilled

Piwnica-Worms has literally taken his scientific cues from the humble firefly. In earlier research projects, he and his team extracted the firefly gene that makes an enzyme called luciferase and introduced it into lab mice, often in the role of a “reporter” gene. They once added the gene to the DNA of a strain of mice so the animals could make their own luciferase. The mice were then injected with a common cold virus that was genetically engineered to turn on the luciferase gene. The mice also received a dose of luciferin, a firefly compound that glows when it encounters luciferase. When investigators put the live mice under a special camera in a light-free box, they could identify tissues infected by the virus, since it triggered the production of luciferase wherever it spread, and the luciferase, in turn, reacted with the luciferin.

MIC researchers have used this luciferase-luciferin combo in other ways to illuminate gene expression and protein function in disease processes. As a result, they’ve learned how to use this form of bioluminescence to screen various compounds for drug candidates and to test the efficacy of experimental drugs in mice.

The experiment described in Nature Medicine achieved bioluminescence with luminol, a man-made version of luciferin. It’s the ingredient that makes glow sticks glow, but luminol is put to a gruesome task in law enforcement. Because it reacts with blood to produce a blue light, detectives routinely spray crime scenes with a solution containing luminol and hydrogen peroxide to detect blood stains that otherwise might escape notice. Medical detectives have turned to luminol as well, in part because it appears to be safe to use in human experiments, although further research is needed to bear that out.

The focus of the Nature Medicine study was myeloperoxidase, or MPO, a key protein found in two immune cells called neutrophils and macrophages. Such cells are programmed to swallow an intruder such as a bacterium, enclose it in a sack-like structure called a phagosome, and inject the phagosome with MPO and hydrogen peroxide. The MPO then produces hypochlorous acid to destroy the cocooned invader. “Hypochlorous acid is basically a type of bleach, and bleach is a great antiseptic,” says Piwnica-Worms, the study’s senior author.

The bleach helps mice as well as humans stave off bodily insults, but during an autoimmune response, it doesn’t necessarily stay confined to the phagosomes and that’s what contributes to inflammation at its destructive worst. “You have a big battle that gets out of control,” says Piwnica-Worms. “The neutrophils and macrophages are spilling bleach on the body’s own tissues.”

MPO catalyzes other loose cannon molecules such as tyrosyl radicals that damage invader and host alike. This havoc isn’t good, because inflammation is a precursor to a wide variety of disorders linked to the immune system—rheumatoid arthritis, atherosclerosis, renal glomerular injury, pulmonary fibrosis, Alzheimer’s disease, Parkinson’s disease, and certain cancers. So analyzing the bleach production of MPO has enormous potential for studying and treating these diseases.
LET THERE BE...

bioluminescence

Earlier studies at other research centers have observed luminal-bioluminescence in MPO-produced hypochlorous acid in test tube experiments and extracted whole blood. Shimon Gross, PhD, lead author of the Nature Medicine article and a former post-doctoral fellow in the MIC, wanted to see if luminol would shine when it penetrated the phagosomes of immune cells in living animals and reacted with bleach there. Enter the lab mice.

“Gene-knockout” mice prove a point

The luminol experiment involved two sets of mice. One set was normal, as mice go. The other group was genetically engineered so that the gene responsible for creating MPO was turned off. In other words, neutrophils and macrophages in these “gene-knockout” mice couldn’t manufacture hypochlorous acid. Thus, if MPO was the primary source of the observed bioluminescence, then the MPO gene-knock-out mice should not glow.

Both sets of mice had the same disorders involving inflammation. Some had dermatitis, others had arthritic ankles. Still others were genetically engineered so they were prone to develop tumors, often at the site of a bite or scratch. MIC researchers took bioluminescent snapshots of them on a daily or weekly basis, depending on the disorder. Each imaging session was preceded by a luminol injection.

Piwnica-Worms was gratified to see the blue glow of scientific confirmation. Bioluminescence imaging detected inflammation in normal mice, but not in those lacking MPO. What caused the bioluminescence in particular was the highly concentrated bleach inside the phagosomes of immune cells. In contrast, hardly any bioluminescence materialized in conjunction with eosinophil peroxidase, or EPO, a protein similar to MPO that’s found in immune cells called eosinophils. EPO creates its own weapon—hypobromous acid—to destroy microscopic trespassers, and while this acid makes luminol glow in a test tube, it didn’t do that in vivo in the MIC experiment. Because eosinophils squirt their acid at foreign bodies without first engulfing them, “the relative concentration of the reactants is too low to elicit significant bioluminescence,” notes Gross.

Viva in vivo

The MIC research on luminol-bioluminescence underlines the value of diagnostic imaging that can monitor the course of disease in vivo and noninvasively over weeks and months. That doesn’t happen with traditional ex vivo research techniques, explains Piwnica-Worms. “You’d sacrifice a mouse to study inflammation in a tissue sample, for example, but you’d never know whether that inflammation would lead to cancer two months later.”

By eliminating the need to continually sacrifice lab mice, in vivo imaging allows investigators to use fewer of them, reducing costs. In addition, statistical results are tighter, he says. “Each mouse is compared to itself over time.”

Other imaging techniques can monitor diseases processes in vivo, but luminol-bioluminescence outperforms them in several respects. One advantage is greater sensitivity to low-level inflammation as measured by signal-to-noise ratio. In bioluminescence images of one type of tissue inflammation described in the Nature Medicine study, this ratio exceeded 3000.
When MRI and single photon emission computed tomography (SPECT, a nuclear medicine imaging technique based on gamma rays) were used, it dropped to 1.7 and 2.6, respectively.

Due to its relative simplicity, luminol-bioluminescence imaging also is a speedier way to obtain biological images. “We can process two hundred mice in a single afternoon to fully characterize a biochemical or drug action,” says Piwnica-Worms. “We are fans of all modalities, but MRI and PET [positron emission tomography] are limited by their throughput rate. It’s a great day if we get four mice done.”

Luminol-bioluminescence imaging, as it stands now, has one significant disadvantage that would hamper any future application with human subjects—it can’t see very deep inside the human anatomy. The light emitted by luminol can only travel up to one centimeter or so before it’s absorbed by tissues and rendered undetectable.

Consequently, the technique currently would work just for the skin, and tissues and blood vessels near the surface, such as the carotid arteries. In contrast, MRI, SPECT, and PET probe the entire body.

However, Piwnica-Worms says it’s possible to take bioluminescence imaging deeper by attaching the necessary fiber-optic tip to a scope. “You could snake the scope inside arteries, the colon, or the lungs,” he says. He’s also hoping to redesign the luminol molecule so that it emits not a blue light, but a red one. Due to its longer wavelength, a red light could travel two or even three centimeters before being absorbed by the body.

No cancer left behind?

For Piwnica-Worms, a little bioluminescence goes a long way. Every new discovery invariably suggests a dozen more experiments. “Sometimes you have more ideas than hands to execute them,” he jokes.

The recent findings on MPO and inflammation are no exception to the rule. He sees numerous possibilities for basic bench research. “With genetic engineering, you could remove the MPO from neutrophils but retain it in macrophages—or vice versa—and study their exact roles in the immune system,” says Piwnica-Worms. “You might be able to determine which cell is dominant in specific diseases processes.”

Luminol-bioluminescence also promises to report on the efficacy of experimental drugs—exactly when they begin to reduce inflammation, and what dosages and intervals work best. “The technique gives us a new metric,” he says.

Someday, clinicians may study pictures of lit-up tissue to guide treatment of their patients. Take plaque buildup in the carotid artery, for example. “Not all plaques are alike,” says Piwnica-Worms. “Some are what we call active plaques, because they contain activated neutrophils and macrophages that are making bleach. As compared to inactive plaques, they’re more likely to become thicker, form a complete clot, and cause a stroke. Bioluminescence could tell us whether a carotid plaque is active or not.”

Likewise, luminol-bioluminescence may eventually help cancer surgeons figure out where they should make an incision with their scalpel. “Certain cancers cause inflammation in surrounding tissues,” says Piwnica-Worms. “Bioluminescence imaging could help physicians to visualize the inflammation and get a better idea about the tumor’s margins. They’d be less likely to leave any cancer behind.”

All of this, of course, is scientific speculation, but Piwnica-Worms and his research team have been converting speculation about bioluminescence imaging into a growing body of knowledge. So he continues chasing after the luminous evidence, out there like a cloud of fireflies.
For years, physicians made the official diagnosis of Alzheimer’s disease (AD) in the pathology laboratory, after a patient had died. Imaging methods simply did not work in living patients. While high-resolution magnetic resonance imaging (MRI) detected many other diseases in the brain, it could not firmly indicate AD.

“Then something happened that surprised a lot of people,” says Mark Mintun, MD, professor of radiology and of psychiatry. The ability to image amyloid plaques, a hallmark brain lesion of AD, dramatically changed that landscape — and PET [positron emission tomography] has made that possible.”

Mintun and his team are using PET, combined with exciting new radioactive tracers, in a series of studies all focused on one aspect of the disease: how to detect AD in its earliest stages before cognitive symptoms have become evident. Even then, amyloid plaques (the sticky protein deposits that are implicated in the development of the disease) have begun to form in the brain, but the patient shows no outward signs of illness.
we could identify the pathology of Alzheimer's disease in someone's brain before symptoms occur, that would mean that we could diagnose—and potentially treat—the disease before many brain cells had died," says Mintun. "Multiple treatments are being tested for their ability to alter these amyloid plaques. But right now, no one gets these experimental drugs unless they are showing quite a few symptoms."

In doing this research, Mintun and his team are working with a number of groups at Washington University, especially the Alzheimer's Disease Research Center (ADRC), internationally renowned for its clinical evaluation of patients with AD. They also have strong ties to basic researchers such as David Holtzman, MD, professor of neurology and a world leader in defining biochemical changes that characterize the onset of the disease.

"We hope that PET can continue to be a bridge between the biochemical hypotheses and all the great ideas generated in a lab such as David Holtzman's, and test them in the rigorous research environment of John Morris [professor of neurology]," says Mintun. "It's a marriage made in heaven."

**Imaging preclinical disease**

Already, scientists know that AD, especially at onset, progresses very slowly. But once it starts, it is implacable, killing brain cells and eventually causing a host of cognitive symptoms such as memory loss, poor judgment and disorientation. The incidence of AD increases rapidly with age, rising to some 40 to 50 percent of the 80-year-old population.

Through earlier PET studies, researchers also know something else: that 25 to 30 percent of people aged 70 and older have some amyloid plaques in their brains. But researchers don’t know whether the presence of these plaques means that a patient will inevitably develop AD.

“We predict that people with amyloid plaques have a higher risk of developing Alzheimer's disease, and the people without plaques have a lower risk,” says Mintun. “Now we are hoping to see over time whether that is true.”

In a 2006 study, published in the journal *Neurology*, Mintun and nine colleagues took a first step toward making that determination. They tested 41 subjects without dementia, using PET together with an imaging tracer (developed in 2005 at the University of Pittsburgh) called "Pittsburgh Compound-B" or "PIB." When it was injected into a vein, PIB circulated into the brain, sticking to amyloid plaques. Researchers could then see the plaques on PET scans.
But that research led to further questions: Over time, would these plaques continue to develop? More importantly, while most patients with plaques will likely develop AD, is there a subgroup that remains free of dementia?

In new studies, funded primarily by the National Institutes of Health and by the ADRC, Mintun and others are exploring these questions. With the ADRC, they are identifying more than a hundred subjects aged 65 and older who show no evidence of dementia. Using PIB made in Mallinckrodt Institute’s Radiological Chemistry Lab, they will scan each volunteer annually, and every year the ADRC will conduct the dementia evaluation.

Volunteers are not told whether they have plaques, and since the results are all coded, no examining physician knows either. “If you were told you have plaques that may cause Alzheimer’s disease, you might start doubting yourself,” says Mintun. “Am I remembering correctly? Maybe I’m losing my memory. It’s much better if it’s a blind study.”

Researchers hope to attract as many volunteers as possible and then to observe them for five to 10 years, tracking which ones develop AD and correlating those findings.

Rows of color images are PET scans of a volunteer who received an injection of C11-labeled PIB. Shown are horizontal slices of the brain, from the bottom of the brain (left) to the top (right). Each PET scan is matched to MRI images (black-and-white rows beneath each colored PET scan) of the same person. Top row: a volunteer with dementia of the Alzheimer’s type (DAT) has high uptake (indicated by red and yellow) because of binding of the PIB to amyloid plaques. Third row: PET scan of volunteer who is cognitively normal has only background levels of PIB in the brain.
with plaque development. Perhaps they will discover, says Mintun, that 100 percent of those with plaques eventually develop the disease. But if 80 percent of those with plaques get the disease while 20 percent do not, that leads to other intriguing questions.

“Do these people have a different diet? Are they on some medication, maybe for cholesterol? Is it because they do crossword puzzles or exercise? Is it because they don’t have diabetes or heart disease?” asks Mintun. “What are the reasons why someone would develop these plaques in the brain and yet seem to hold off Alzheimer’s disease for a long time?”

More than 20 new treatments aimed at clearing these plaques or preventing them from developing in the first place are currently wending their way through clinical trials. Not only must pharmaceutical companies test the drugs’ efficacy, but they also have to ensure that patients don’t experience intolerable adverse effects. Still, says Mintun, there is strong hope that effective new drugs are on the horizon.

Ideally, he says, physicians would like to stop the disease in its tracks before—not after—memory loss and other symptoms have occurred. So this study is of immense importance to the future treatment of AD.

“I use the analogy of someone who has heart disease, with plaques in the coronary arteries,” says Mintun. “All of a sudden that person has a heart attack that causes permanent muscle damage; at that point, if the plaques are removed, it won’t reverse the damage. Amyloid in the brain may be

kicking off a series of events that cause the brain cells to die. After they begin dying, removing the amyloid might not be as helpful as if you could start the process earlier.”

Looking at the hippocampus

While amyloid plaques are one problem in the brains of patients with AD, researchers are also investigating whether there are others. Mintun is working with a Washington University group led by Denise Head, PhD, assistant professor of psychology, to examine the hippocampus, a highly sensitive part of the brain associated with memory and emotions. It appears that in patients with AD, the hippocampus loses cells and begins to shrink as part of the disease process.

“So Doctor Head argued that if people with amyloid plaques develop the disease so early that you can’t clinically see it, maybe they also had very early loss in the hippocampus,” says Mintun. “It turns out that these patients have a normal hippocampus volume, but they are in the low end of the normal range and significantly different from people lacking plaques. Further, their hippocampus volume is going down every year.”

This downward trend tallies with the results of cognitive testing done by Martha Storandt, PhD, professor of psychology, on patients who are amyloid-positive and those who are amyloid-negative, as identified through +PIB/PET. Among those who are PIB-positive, their cognition—though still within the normal range—is trending slowly downward year by year. People without plaques varied slightly, but overall their cognition held steady.
Some brain regions may show amyloid plaques earlier than others. Right: an average of PIB PET scans of volunteers who were cognitively normal; scans created by subtracting background activity. Left: correlating average MR image to show anatomy. When processed in this way, PET image shows in stark contrast specific areas of brain (outlined in red) that have subtle, but abnormal, amyloid binding of PIB. Identification of such brain regions may help to increase sensitivity in detecting amyloid plaques in the earliest stage.

$K_D = 4.7 \text{ nM}$

$BP = DV_{ratio-1}$

$\beta$-Amyloid Plaque Imaging with PET at Washington University

- 10mCi.v. & 60 min dynamic 3D scan

Logan method with cereb input

MRI-guided ROIs

The hippocampus is also closely linked to other parts of the brain through neural networks. Yvette Sheline, MD, professor of psychiatry, also working with Mintun, decided to see whether the interaction of the hippocampus with these areas (its “functional connectivity”) is impaired in people with symptoms. Using a functional MRI method developed by Marcus Raichle, MD, professor of radiology and of neurology, and chief of the Institute's Neuroimaging Lab, they have been studying the “resting state connectivity” of the brain in patients with AD and in people with no cognitive impairment. Not surprisingly, the people with AD showed vastly different connectivity from those who did not have the disease.

Using PIB and PET, they have taken that latter group of non-impaired people and separated them into those with plaques and those without. Now they are testing each of these groups using functional MRI to see whether there are connectivity differences. “And sure enough,” says Mintun, “they had a subtle but very clear decrease in the connectivity of their hippocampus to other areas of their brain.”

All of these signals—decreasing cognition, a shrinking hippocampus and deteriorating functional connectivity—may eventually help researchers to establish whether the disease has begun and how far it has progressed. They will also help physicians decide who would most benefit from medication, thus sparing those who do not yet need it from the possible adverse effects of powerful drugs.
Brain Inflammation

Researchers hypothesize that one of the first things to happen in the AD process is the deposition of amyloid plaques in the brain. Then, years later, neurons begin to die. What causes them to die—and why such a long delay? A possible culprit is brain inflammation, and controlling it may be a critical component of helping people with AD.

In a new project, Mintun and his group are partnering with Robert Mach, PhD, head of the Institute’s Radiological Chemistry Lab, to develop better ways of imaging brain inflammation. Mach is trying to produce a new tracer that would bind to the inflamed cells, which would then show up on PET imaging. Though he is building on the foundation of a tracer developed several years ago, we would like to develop a technique sensitive enough to see the types of inflammation that occur in Alzheimer’s disease and then monitor them,” says Mintun. “Does it correlate with the severity of the symptoms or with the number of amyloid plaques in the patient’s brain? Is the inflammation different from one person to another? Does it track with how quickly the cognitive abilities are declining? These are all questions that are difficult to answer without an imaging tool.”

Looking to the Future

As researchers move further into this new realm of experimentation, it is clear that PET provides information that other methods cannot. Using molecular imaging, it can use trace amounts of molecules, noninvasively, to supply unique feedback on biochemical and cellular processes in the human brain. And Mallinckrodt Institute is perfectly positioned to do this PET imaging, with its history as the place where PET was developed and its record of “firsts” in the field, says Mintun, who heads the Center for Clinical Imaging Research.

While it is impossible to predict when clinical breakthroughs may occur, Mintun and his colleagues remain optimistic that major advances will take place within this generation. So many researchers are tackling these problems, from so many directions, that there is a far better understanding now of the mechanism of this terrible disease. And clinical treatments cannot come soon enough, he says, given the suffering of patients with AD and their families.

Mintun illustrates the severity of AD with an anecdote from a presentation he was giving with John Morris: “Doctor Morris asked a room full of people aged fifty and older, ‘How many people here have survived cancer?’ Hands went up. When he asked about heart attacks, again a lot of hands went up,” says Mintun. “But when he asked how many had survived Alzheimer’s disease, no hands were raised. AD is a relentless disease, one-hundred percent fatal. I am cautiously optimistic, but we are not there yet—and a lot of people are suffering.”

Researchers hypothesize that one of the first things to happen in the AD process is the deposition of amyloid plaques in the brain...
Cancer treatment has come a long way but, as most would agree, not far enough. Cytotoxic chemotherapy, which works by damaging divided cancer cells and preventing their reproduction, has been around for nearly 60 years.

More recently, targeted therapies that preferentially bind certain cancer cells have emerged, but they’re typically administered to patients along with cytotoxic drugs. This means a large percentage of patients with cancer are still exposed to highly toxic levels of chemotherapy during treatment and often experience debilitating adverse effects as a result.

Positron emission tomography (PET)—an imaging technique developed at Mallinckrodt Institute in the early 1970s to measure bodily changes at the molecular level—is one of the methods used by oncologists to eliminate some of the guesswork of cancer treatment. While PET is effective at staging cancers and detecting recurrence, current uses provide limited information as to whether a tumor will respond to certain therapies. But now, a new type of PET imaging may provide a more detailed assessment of tumors, thereby helping physicians to plan more effective treatment strategies.

Researchers at Mallinckrodt Institute recently began the first human studies investigating how imaging a certain cell receptor can allow better understanding about the size of a tumor and the likelihood that it will respond to certain treatments.
IMAGING THE BEHAVIOR OF CANCER CELLS

Thus far, the use of PET scanning in oncology has largely focused on a metabolic tracer known as FDG, or fluorodeoxyglucose. When a patient is injected with this radioactively labeled glucose, the PET scanner can detect differences in glucose use between tumors and healthy surrounding tissue. This measurement has proven useful in diagnosing and staging tumors but doesn't provide detailed information for guiding treatment.

A new approach to using PET in cancer imaging involves using radiotracers that measure tumor proliferation at the cellular level. In the Tissue Culture Room, Justin Rothfuss, senior research technician, is using the inverted microscope; Fanjie Chang is at the bio-safety cabinet.

“Thymidine is a good marker of DNA synthesis, but this method doesn’t tell the whole story,” says Robert Mach, PhD, chief of Mallinckrodt Institute’s Radiological Chemistry Laboratory. “Imaging with radiolabeled thymidine analogs underestimates the true number of proliferating cells in a tumor—an important distinction in determining which treatment is best for the patient.”

In search of a method to image cell proliferation, currently most researchers are using radiolabeled thymidine analogs with PET. Tumors undergoing rapid growth and division accumulate radiolabeled thymidine analogs, which can be detected by PET imaging. When these agents are injected into a patient, the PET scanner measures the number of cells that are in a state called “S-phase” (the synthesis phase of the cell’s life cycle). But only a small percentage of cells in a tumor will be in S-phase at any given time. After S-phase, cells continue to go through other phases of growth and division, including a resting period known as the Q-phase (quiescent).

“Looking at sigma-2 receptors to image proliferation is an entirely new approach, something different from what everyone else is doing...”

A NEW APPROACH TO IMAGING TUMORS

Researchers are using a new method to image cell proliferation in tumors, using sigma-2 receptors to directly visualize a tumor’s behavior. Sigma receptors, originally thought to be a subtype of opiate receptors, are now recognized as a class of receptors expressed in normal tissues, including liver, kidneys, endocrine...
Zhude Tu, PhD, research assistant professor of radiology, with the fluoride chemistry system used in the production of radiotracers.

The density of the sigma-2 receptor in quiescent tumor cells is higher than that reported in normal cells, this imaging strategy can also differentiate slow growing tumors from healthy tissue.

**IMAGING THE BEHAVIOR OF CANCER CELLS**

Zhude Tu, PhD, research assistant professor of radiology, with the fluoride chemistry system used in the production of radiotracers.

cling glands, and, to a lesser extent, the central nervous system. "Looking at sigma-2 receptors to image proliferation is an entirely new approach, something different from what everyone else is doing," says Mach, professor of radiology, of cell biology and physiology, and of biochemistry and molecular biophysics.

As they relate to cancer treatment, sigma-2 receptors may be most impressive for their ability to reflect the entire life cycle of cancer cells. This is because the number of sigma-2 receptors in proliferating tumor cells is 10 times higher than the number of receptors in quiescent (resting) tumor cells. This difference in density means that imaging the sigma-2 receptor status of tumor cells can provide an accurate measure of the tumor's overall proliferative status.

Many of today's cancer treatments are risky because of their high toxicities and price tags and, for that reason, physicians would prefer to know ahead of time how effective a particular treatment is likely to be. Sigma-2 receptor imaging may bring them closer to that goal.

As solid tumors grow, even a few millimeters, they outgrow their blood supply. Areas of the tumor are deprived of nutrients and exit the cell cycle, a process that turns them into quiescent, or nongrowing, tumors. Quiescent tumors cells (the "Q" in the P:Q ratio) are more resistant to treatment than are proliferating tumor cells. That doesn't mean they're not dangerous, but rather that they are unlikely to respond to therapies that target rapidly growing cells.

**DETERMINING THERAPIES**

The implications of a method for producing accurate P:Q ratios are rewarding for oncologists and cancer patients alike. Many of today's cancer treatments are risky because of their high toxicities and price tags and, for that reason, physicians would prefer to know ahead of time how effective a particular treatment is likely to be. Sigma-2 receptor imaging may bring them closer to that goal.

As solid tumors grow, even a few millimeters, they outgrow their blood supply. Areas of the tumor are deprived of nutrients and exit the cell cycle, a process that turns them into quiescent, or nongrowing, tumors. Quiescent tumors cells (the "Q" in the P:Q ratio) are more resistant to treatment than are proliferating tumor cells. That doesn't mean they're not dangerous, but rather that they are unlikely to respond to therapies that target rapidly growing cells.

**UNCOVERING LIGAND FOR HUMAN TRIALS**

Research on the sigma-2 receptor's role in reflecting cell proliferation goes back to 1995, when Mach and Ken Wheeler, a cancer cell biologist from Wake Forest University, began studying the expression of the receptor in tumor cell cultures in mice. Known as "66 cells," the cells came from a breast tumor line that grows in nutrient-deprived conditions. These cells would grow for four days, exit the cell growth cycle, and go into a resting phase. By observing this process, researchers were able to detect changes in tumor biology between P and Q cells. They found that the presence of sigma-2 receptors was 10-fold higher in proliferating tumor cells than in quiescent tumor cells, and the presence of sigma-2 in quiescent tumor cells was higher than in normal cells. Their research was published in *Cancer Research* and the *British Journal of Cancer*.

Over the past seven years, the Mach research group turned this discovery into an imaging strategy ready to be used in human study volunteers. Since the concept was entirely new, everything had to be created from scratch—no small feat in the world of molecular...
First they needed to find a way to image the receptors with PET scanning, which meant they had to develop a ligand to bind to the sigma-2 receptor. In most research of this type, scientists can choose from a few known ligands, but no such ligand was known for the sigma-2 receptor. After a five-year effort, the research team developed a sigma-2 selective molecule that could be labeled with a radionuclide and tested in animal models of cancer; in the following years, they studied its use in imaging as well as its toxicity and dosimetry (the right amount of the agent to give and get a good picture without causing adverse effects).

The animal studies concluded that radioligands with a high affinity and a high selectivity for sigma-2 receptors have the potential to noninvasively image solid tumor cell proliferation with PET. In addition to providing more information about the tumor itself, the scientists found the new technique yielded superior image quality as compared with other methods. The technique has been licensed by Isotrace Technologies, Inc. and sublicensed to Bayer Schering Pharma AG, which will sponsor the first human clinical trials.

In a study led by Farrokh Dehdasthi, MD, professor of radiology in Mallinckrodt Institute’s Division of Nuclear Medicine, researchers are now trying to reproduce in humans the success found in the animal studies. The initial trials will focus on breast cancer since it’s the type of cell originally validated in animal models, as well as patients with head and neck cancer and lymphoma. Future studies will likely include patients with lung cancer and brain tumors.

“This may be useful for delivering treatments directly to the tumors, potentially triggering the cancer to kill itself…”

Long-range plans include studying this type of imaging for the delivery of toxic agents. “Sigma-two receptors on the membrane, mitochondria, and endoplasmic reticulum are linked to the cell death pathway,” explains Mach. “This may be useful for delivering treatments directly to the tumors, potentially triggering the cancer to kill itself.”

As scientists like Mach expand our ever-growing understanding of cancer, we look forward to safer and more effective treatments. Though it’s likely to be some time before sigma-2 imaging makes it to the marketplace, the dedication that brought us here is what perpetuates cancer patients’ hope for the future.
Nothing is worse for a parent than to have a child in pain and not know what is causing the pain or what to do about it.

Our greatest fears are about cancer, a massive infection, or a progressive chronic disease. Having a doctor rule out those conditions is only one step in determining what is causing your child’s illness.

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disease that mostly affects children and young adults, is slightly more common in girls than in boys (a ratio of 5:1), and typically develops in children between the ages of four and 14 (with 10 being most common). While CRMO is noninfectious and noncancerous, the disease is often misdiagnosed because of its rarity—and that misdiagnosis can lead to multiple bone biopsies and long-term antibiotic therapy.
WHAT IS CRMO?

Geetika Khanna, MBBS, MS, a pediatric radiologist, recently came to Mallinckrodt Institute from the University of Iowa, where she studied CRMO extensively. Her youngest patient was a six-month-old infant. “Typically around the age of ten, these children present with bone pain that seems to move around and sometimes with a low-grade fever,” she says. “With conventional X ray, we may detect a bone lesion and then biopsy it. But there is no infection, only inflammation that occurs in the bone and typically in the long bones close to the growth plates, which can affect a child’s growth if the inflammation is not brought under control. We’re not sure why patients develop this condition, but it seems such as psoriasis and inflammatory bowel disease. Patients typically have debilitating, multifocal bone pain caused by the inflammation. Since the medical community became aware of the disease more than three decades ago, several hundred cases of CRMO have been reported. Because there is no specific diagnostic test for CRMO, it remains a diagnosis of exclusion, making it likely that the number of cases is much higher than reported.

Why people develop CRMO remains somewhat elusive. “The association of CRMO with dermatologic disorders such as psoriasis and inflammatory bowel disease, along with its response to steroids, indicates a possible autoimmune etiology. More recently, a genetic etiology has been suggested, based on observation of the disease in siblings and monozygotic twins,” says Khanna. “Another fact pointing to a genetic cause is Majeed syndrome, an autosomal recessive disorder of CRMO with congenital dyserythropoietic anemia, which is associated with mutations in the LPIN-two gene.”

Geetika Khanna, MD, in the entrance to the Jack Buck Imaging Center at St. Louis Children’s Hospital
CRMO CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

A CASE STUDY

An eight-year-old girl presented with acute onset pain in her left hip. One month after presentation, plain radiographs showed a lytic lesion at the greater trochanter (part of the thigh bone); biopsy revealed nonspecific inflammation. Two years later, the patient developed severe pain in the chest wall. A chest X ray showed an expanded sclerotic right-third rib with permeative lytic areas. Bone biopsy showed nonspecific inflammation. Magnetic resonance imaging of the chest confirmed the inflammatory lesion of the rib and revealed additional vertebral body lesions. A diagnosis of CRMO was suggested, and the patient was started on anti-inflammatory therapy. She has had no major disease exacerbations for two years since starting methotrexate. She continues to have intermittent short-lived episodes of mild bone pain, but they do not interfere with her activities.

MAKING THE DIAGNOSIS

The disease has characteristic findings— including lesions in the metaphyses of long bones (such as in the leg) and the medial clavicle (or collarbone)—and is most often diagnosed by a radiologist due to its typical imaging findings. The metaphyses are the primary site of bone growth in children. Because of their rich blood supply, the metaphyses of long bones are prone to hematogenous spread of infection in children. Hence, a bone biopsy is often required to exclude the possibility of infectious osteomyelitis or a tumor such as histiocytosis.

Other common sites for the disease include the vertebral bodies, pelvis, ribs, and mandible. CRMO is often bilateral and multifocal at presentation. However, because many of the lesions are asymptomatic at any given time, the patient may undergo conven-

OTHER COMMON SITES FOR THE DISEASE

INCLUDE THE VERTEBRAL BODIES, PELVIS, RIBS, AND MANDIBLE.

CRMO IS OFTEN BILATERAL AND MULTIFOCAL AT PRESENTATION.

Classical findings of CRMO as seen in the case study: sclerosis and expansion of the medial clavicle, unilateral sacroilitis, vertebra plana and involvement of contiguous vertebral bodies with sparing of the intervening disc space.
RECURRENT

Radiographs for the painful area, which, without information about other bone involvement, may lead to an erroneous diagnosis. As the imaging appearance of CRMO can mimic other entities like infection and tumors, awareness of other asymptomatic sites of disease can aid the diagnosis of CRMO.

While at the University of Iowa, one of Khanna’s patients was a girl who had undergone multiple surgeries on her jaw and was on long-term antifungal treatment. When Khanna performed more extensive imaging, she found lesions in the girl's clavicle, a classic marker for CRMO, and unique among bone conditions in its involvement of the clavicle.

According to Khanna, magnetic resonance imaging (MRI) can demonstrate associated periostitis, soft tissue inflammation, and synovitis—findings initially believed to be more typical for infectious osteomyelitis rather than CRMO. MRI is more sensitive than conventional imaging in detecting transphyseal spread of disease, which can result in growth deformities and, thus, has prognostic significance.

TREATMENT FOR CRMO

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are the mainstays of therapy, and most patients do quite well on these. For patients who do not respond to NSAIDs, treatment may include steroids, methotrexate, and other immunosuppression drugs, particularly when CRMO is associated with a rash, arthritis, and a high probability of growth deformities.

FURTHERING EFFECTIVE DIAGNOSIS OF CRMO

While at the University of Iowa, Khanna worked closely with her rheumatology colleague Polly Ferguson, MD, observing patients and reviewing imaging studies sent from all parts of the country and even some from outside the United States. They compiled case after case of diagnosed CRMO, with all of its variations in individual children. Twenty-five cases of CRMO were referred to the University of Iowa’s Department of Pediatric Rheumatology: 10 boys and 15 girls with an average onset of symptoms at 8.3 years. Khanna and Ferguson found these sites of disease at initial presentation to be the most common: lower extremities.

MRI is more sensitive than conventional imaging in detecting transphyseal spread of disease, which can result in growth deformities and, thus, has prognostic significance.
FUTURE DIRECTIONS FOR CRMO

In September 2008, a National Institutes of Health conference/CRMO workshop was held in Bethesda, Maryland, bringing together international clinical and research experts to define the criteria for diagnosis of this condition and to identify the clinical markers that can be used for future clinical trials. At the conference, Khanna’s presentation focused on using multimodality imaging for diagnosis and scoring of CRMO bone lesions to assess response to treatment. A Washington University colleague, Deborah Novack, MD, assistant professor of pathology and immunology, spoke on the immunological evaluation of CRMO bone lesions. Following the presentations on state-of-the-art technology in all aspects of this disease, conference attendees participated in concurrent workshops focusing on scoring of imaging findings, skin scoring, study entry criteria, rheumatology and rehabilitation endpoints, and biomarkers for inflammation, bone, and GI tract—with the goal of creating a consensus for the development of study inclusion criteria, outcome measures to identify response to treatment, and biomarkers of disease activity. The proceedings from this workshop will be used to develop a multicenter trial for follow-up care of children with CRMO.

CLINICAL PRESENTATION OF CRMO

- History of pain, tenderness, swelling, and limited range of joint motion
- Duration of symptoms: from a few days to several years
- Inconclusive laboratory findings, such as a mildly elevated ESR (erythrocyte sedimentation rate or how fast red blood cells fall through a column of blood) and CRP (C-reactive protein found in blood in response to inflammation), and normal WBC (white blood cell)
- X-ray indication of marrow inflammation in the long bones near physeal plates
- Bone scan or magnetic resonance imaging reveal bilateral, multifocal areas of bone inflammation, even if asymptomatic
- Most common bones affected: the long bones, medial clavicle. Other common sites: vertebral bodies, ribs, and mandible
- Possible other symptoms: skin lesions (eg, psoriasis) and inflammatory bowel conditions (eg, Crohn’s disease)
As the most common cancer in females, breast cancer ranks high as a potential threat to a woman’s vitality. But as physicians and scientists understand more about the nature of breast cancer, new treatments are being discovered and women are living longer even when they have advanced disease. Recently, research conducted at Mallinckrodt Institute of Radiology has made a marked contribution to the race for a cure—a novel way of assessing the best treatment for breast cancer in patients who have exhausted most available therapies. This new approach to a common imaging technique allows doctors to predict a tumor’s response after only a few days of treatment. The insight gained not only helps to guide patients with limited options to the next best treatment choice, but it also unlocks incredible potential for the investigation of new breast cancer treatments that, hopefully, will give women even more time for life.
A PARADOXICAL VIEW OF CANCER

Predicting patients' response to hormone therapy

Dehdashti currently is studying a breast cancer phenomenon called "flare"—breast cancer's paradoxical response to treatment that will eventually be effective. One in 20 women who receive hormone therapy for breast cancer will experience an initial phase of tumor growth, and this is the flare response. It typically indicates that after the initial growth phase, the tumor will respond well to hormone therapy and subside with further treatment. More simply put: If a tumor reacts to the administration of hormones either by growing or shrinking, it must have functioning receptors.

Once doctors know that the hormone receptors are functioning, they can offer the patient a number of hormonally derived cancer treatments that are less toxic and less expensive than traditional chemotherapy. And those women with unresponsive tumors can proceed with therapies that have a better chance of helping their particular tumor. Biopsy can differentiate whether a tumor has receptors, but many tumors with receptors present still do not respond because the receptors are not functioning. And biopsy is often impractical for patients with metastatic disease whose tumors are hard to reach. This leaves the remaining patients and their doctors with a difficult decision: try additional hormone agents or move on to other lines of treatment.

Though clinical flare is helpful in predicting response to treatment, only a small portion of women with breast cancer will experience physical signs of flare, such as swelling or pain at the site of the tumor or tumor metastasis. A larger portion of women will have a response termed "subclinical flare" in which the tumor does have a short period of growth related to treatment, but the patient has no physical indication this is happening. Since it is known that women with any flare reaction tend to respond well to hormone therapy, doctors have looked for a way to detect which women have subclinical flare and should also be treated with continued hormonal therapy.

In her past and current research, Dehdashti is finding new ways to determine the functional status of estrogen receptors, including the ability to use positron emission tomography (PET) to detect the presence of subclinical flare. The idea of imaging flare originated...
from the known effects of tamoxifen, an agent often used to treat hormone-responsive breast cancer. Tamoxifen is a hormone-blocking agent that has pro-estrogen effects for approximately the first seven days it is given to a patient. The initial pro-estrogen phase is then followed by an anti-estrogen effect that is often used to treat women with hormone-responsive breast cancer. “If we can assess the effect of tamoxifen on the estrogen receptor, we can determine the receptor’s functional status,” says Dehdasthi.

Detecting subclinical flare
Dehdasthi is able to visualize a tumor’s response to a hormone challenge by using PET, which detects a growing cancer’s hearty appetite for glucose. A patient is injected with glucose combined with a radioactive tracer (fluorine-18 fluorodeoxyglucose, or FDG), and the PET scanner is able to detect and localize the tagged glucose within the body. PET imaging takes advantage of the fact that rapidly growing cells, like cancer cells, use more glucose than normal cells, and typically a cancer will have an increase in glucose utilization during a growth spurt.

“If we can assess the effect of tamoxifen on the estrogen receptor, we can determine the receptor’s functional status”

By performing a baseline PET scan followed by a repeat PET scan about one week after a patient begins taking tamoxifen, doctors can predict response by comparing the difference in tumor activity on each scan. If the demand for glucose increases just after tamoxifen is introduced, then it is clear that the estrogen receptors are responding and functional. In other words, the patient is experiencing a flare response, known by doctors as “metabolic flare.” In more recent studies, Dehdashti has shown that the flare can be detected after just one day of tumor stimulation with an estrogen drug.

Once the detection of flare determines a patient’s tumor has functioning hormone receptors, that patient can then begin or resume hormone therapy knowing there is a high likelihood the tumor will respond to treatment. If the receptors are shown to be unresponsive by imaging, the doctor knows the tumor is unlikely to respond to a course of hormone therapy and can move on to more aggressive chemotherapies for treatment. The ability to treat a
FDG—PET/CT

BASELINE

SUV = 6.4

24 HOURS AFTER ESTRADIOL

SUV = 8.3

In bottom right image, metabolic flare reaction is shown as a 12% or greater increase in standardized uptake value (SUV), indicating a response to endocrine therapy.

cancer with hormone therapy is advantageous for many reasons:
- Hormone therapy is generally less toxic than chemotherapy.
- The adverse effects are generally better tolerated than those related to chemotherapy.
- The cost of using hormones to treat cancer is significantly less than with other treatments.

Impact on quality of life

Barry Siegel, MD, professor of radiology and of medicine, and chief of Mallinckrodt Institute’s Division of Nuclear Medicine, has collaborated with Dehdasthi in looking at PET’s ability to detect flare. “The results are encouraging,” says Siegel. “Now we must look at survival data and compare outcomes, adverse effects, and cost.”

The next step for researchers is to compare whether the use of PET to predict flare makes a significant difference in the lives of those with breast cancer. “We know it’s good, but is it good enough? We must show not only that this technique can properly predict response, but that it also improves the quality of a patient’s life,” says Siegel.

Matthew Ellis, MB, BChir, PhD, professor of medicine, is enthusiastic about Dehdashti’s work. He is head of the Medical Oncology section at Washington University School of Medicine (WUSM) and director of the Breast Cancer Program at the Alvin J. Siteman Cancer Center at WUSM and...
Barnes-Jewish Hospital. Ellis relies on knowing the functional status of estrogen receptors to provide the right treatment for his patients. “For patients with estrogen receptor [ER]-positive breast cancer, the manipulation of estrogen levels is critical to treatment. But it doesn’t work in everyone, even in the presence of ER-positive tumors. The goal is to predict who will do well.”

“Improving clinical research

In addition to its potential for clinical use, the ability of PET to predict the functional status of estrogen receptors in breast tumors is also a great boost to research. Therapeutic agents designed for use on hormonally responsive tumors can be tested on those likely to respond. “This helps us to study the effectiveness of new therapies without fighting the battle against tumors that would be unresponsive anyway,” says Ellis. By eliminating the subset of tumors that wouldn’t respond to any hormone manipulation, researchers can get a better idea of a new agent’s efficacy in the target group of patients with functioning hormone receptors on their tumors.

And it is these newer and more effective agents thought to be, in part, responsible for the improvement seen in breast cancer patients’ survival. Even women with advanced disease are living longer with the treatments available now. As scientists investigate treatments for those who have exhausted their options, new research is bringing hope to those who had none. And the research at Mallinckrodt Institute is already changing the clinical practice across the United States.

Ellis recently collaborated with Dehdashti and Siegel in studying an estrogen regimen for patients with metastatic breast cancer who have become resistant to certain treatments. The investigators suspect that daily estrogen therapy could wipe the resistance slate clean in some patients who have exhausted other options, and that PET could be a useful predictor of likely success in this group of women. Their findings have been submitted for publication.

Risk factors for breast cancer

- **gender**—100 times more common among women than men
- **aging**—risk doubles in women aged 55 years or older
- **family history**—20% to 30% of women with the disease have a family member with the disease
- **race and ethnicity**—Caucasians are slightly more likely to develop the disease than are other races or ethnicities
- **dense breast tissue**—more glandular tissue and less fatty tissue increase risk
- **lifestyle-related factors**—including use of alcohol, being overweight or obese, lack of physical activity

NEW FACULTY
Larry Bretthorst, PhD, research associate professor of radiology, Division of Radiological Sciences.
Monica Shokeen PhD, instructor in radiology, Division of Radiological Sciences.
Thaddeus Wadas, PhD, instructor in radiology, Division of Radiological Sciences.

PROMOTIONS
Barry Edwards, PhD, research instructor in radiology, was promoted to assistant professor of radiology, Division of Radiological Sciences.
David Gierada, MD, associate professor of radiology, was promoted to professor of radiology, Division of Diagnostic Radiology.
Michael Penney, MD, instructor in radiology, was promoted to assistant professor of radiology, Division of Diagnostic Radiology.
Suresh Vedantham, MD, associate professor of radiology, was promoted to associate professor of radiology, Division of Diagnostic Radiology.
Daniel Wessell, MD, PhD, instructor in radiology, was promoted to assistant professor of radiology, Division of Diagnostic Radiology.

JOINT APPOINTMENTS
Jin-Moo Lee, MD, PhD, associate professor of neurology, was appointed associate professor of radiology, Division of Radiological Sciences.
Youan Xia, PhD, professor of biomedical engineering, was appointed professor of radiology, Division of Radiological Sciences.

GRANTS
Carolyn Anderson, PhD, professor of radiology, of molecular biology and pharmacology, of chemistry, and of biochemistry, was appointed associate professor of radiology, Division of Diagnostic Radiology.

Thomas Conturo, MD, PhD, associate professor of radiology, of physics, and of biomedical engineering, as principal investigator, received a $456,000 grant from the U.S. Department of Defense to study “Breast cancer diagnosis and therapy monitoring.” Collaborators for the three-year grant are Erbil Akbudak, PhD, research assistant professor of radiology, and Hsiu-San Lin, MD, PhD, Washington University Department of Radiation Oncology.

Conturo, as subcontract principal investigator, and Rob Paul, PhD, University of Missouri, St. Louis, as overall principal investigator, received a $3.1 million grant from the National Institutes of Health for research on “Neuromarkers of age-related cognitive decline.” Collaborators for the five-year grant are Akbudak, Eren Gultepe, and Amanda McMichael, MS.

Steven Don, MD, associate professor of radiology, received the Society for Pediatric Radiology's 2009 John Dorst-Felix Fleischner Seed Grant of $10,000 for research on “Mathematical modeling of pediatric pulmonary nodules.”

Fred Prior, PhD, research associate professor of radiology, as principal investigator, received a one-year, $1.9 million grant from the National Institutes of Health to fund the project “High performance biomedical imaging computer resources.”

Yuan-Chuan Tai, PhD, associate professor of radiology, as principal investigator, received a $82.2 million grant from the National Cancer Institute, National Institutes of Health, for “A sub-millimeter resolution add-on for animal PET scanners.”

APPOINTMENTS/ELECTIONS
Bennett Greenspan, MD, instructor in radiology, was named editor of the Nuclear Medicine Science Syllabus, 5th edition, published by the American Board of Science in Nuclear Medicine.
Nassir Siddiqi, MD, assistant professor of radiology, was elected chairman of the Continuing Medical Education Committee of the King Edward Medical College Alumni Association. He was appointed to membership of the Society of Interventional Radiology's Standards of Practice Committee, the Publications Advisory Committee, and the Oncology Task Force. He also was appointed to the Washington University St. Louis Institutional Review Board.
**Honors/Awards**

Samuel Achilefu, PhD, professor of radiology and of biochemistry and molecular biophysics, was named session chair of “New activation strategies in molecular imaging” at the 100th Annual Meeting of the American Association for Cancer Research, Denver, Colorado, April 18-22.

Naganathan Mani, MD, instructor in radiology, received the eighth highest score among all physicians who participated in the Korean Society of Thoracic Radiology’s 2008 weekly chest case quiz.

Fred Prior, PhD, research associate professor of radiology, received his fifth year of funding as a Subject Matter Expert for the Cancer Bioinformatics Grid (caBIG) program.

**Lectures**

Samuel Achilefu, PhD, professor of radiology and of biochemistry and molecular biophysics, as Ground Rounds Speaker, presented “Optical imaging: a unique and complementary imaging modality” at Thomas Jefferson University, Philadelphia, Pennsylvania, February 24. He spoke on “Optical techniques of bioluminescence & fluorescence” at the International Symposium on Molecular Imaging and Therapy: Road Map to Modern Medicine, Kuwait University, Kuwait City, March 9-12. He presented “Flip-flopping contrast mechanisms in molecular optical imaging of tumor cells and tissues” as part of the Faculty of Graduate Studies Lecture Series, Loma Linda University, California, April 14.

Carolyn Anderson, PhD, professor of radiology, of molecular biology and pharmacology, of chemistry, and of biochemistry, spoke on “Copper-64-labeled biomolecules for molecular imaging of cancer metastasis” at the Duke University Workshop: Clinical Directions for Molecular Imaging, Durham, North Carolina, March 12, and at Johns Hopkins University, Baltimore Maryland, March 25. She presented “Nuclear and radiochemistry at Washington University in St. Louis” at the MARC VIII Conference, Kona, Hawaii, April 15-10.

Delphine Chen, MD, assistant professor of radiology, spoke on “Imaging intracellular markers of apoptosis” at the Transatlantic Airway Conference, sponsored by Boehringer-Ingelheim, Lucerne, Switzerland, January 22 and 23. She presented “FDG-PET imaging as a biomarker for neutrophilic lung inflammation” as part of the Nuclear Medicine Research Seminar Series, Massachusetts General Hospital, Boston, April 3.

Nirvikar Dahiya, MD, assistant professor of radiology, presented “Acquiring a 3-dimensional ultrasound image: basic principles” and moderated “Nonobstetric applications of a 3-dimensional ultrasound: improving productivity and workflow” at the 2009 Annual Convention of the American Institute of Ultrasound in Medicine, New York City, April 2-5. He spoke on “Ultrasound evaluation of liver transplant and ultrasound evaluation of thyroid lesions” at USCON XVIII, the Annual Conference of the Indian Federation of Ultrasound in Medicine and Biology, Goa, India, April 30-May 3.

**Biello Lecture**

Chaitanya Divgi, MD, professor of radiology, University of Pennsylvania; chief, Nuclear Medicine and Clinical Molecular Imaging, Hospital of the University of Pennsylvania, Philadelphia, was guest speaker for the Twenty-third Annual Daniel R. Biello Memorial Lecture on March 11. He presented “Back to the future in nuclear medicine: developments and integration.”

Divgi (left) with Barry Siegel, MD, chief, Division of Nuclear Medicine.
Lectures
Continued from page 29

Colin Derdeyn, MD, professor of radiology and of neurology and neurological surgery, presented “Overview of cerebral hemodynamics” at the 9th Annual International Meeting on Cerebral Revascularization, St. Louis, Missouri, January 8; at Radiology Grand Rounds, Department of Radiology, University of Virginia, Charlottesville, March 9; and at the Allegheny Regional Hospital Neuroscience Grand Rounds, Pittsburgh, Pennsylvania, March 25. He spoke on “Intracranial atherosclerotic disease and the SAMMPRIS Trial” at the Cedars-Sinai Neurovascular Symposium, Los Angeles, California, January 10.

Derdeyn spoke on “Natural history of intracranial atherosclerotic disease” at the annual meeting of the Joint Section on Cerebrovascular Disease, San Diego, California, February 17. He presented “Stenting versus Aggressive Medical Management for the Prevention of Ischemic Stroke (SAMMPRIS) Trial update” at the 34th International Stroke Conference, San Diego, California, February 20.


Bennett Greenspan, MD, instructor in radiology, presented “Diagnosis and therapy of hyperthyroidism” at Grand Rounds at the Habif Health and Wellness Center, Washington University in St. Louis, January 14.

Perry Grigsby, MD, professor of radiation oncology, of radiology, and of gynecologic oncology, spoke on “The use of PET/CT for simulation, treatment planning, and IMRT guided therapy for cervical cancer” and “The use of PET/CT in cervical cancer to assess response during therapy, after completion of therapy, and for long-term follow-up” at the 2009 First Multidisciplinary PET/CT Oncology Symposium, San Juan, Puerto Rico, January 31.


Charles Hildebolt, DDS, PhD, professor of radiology and of anthropology, presented “Virtual hobbits and health in Homo floresiensis” at Hobbits in the Haystack: Homo floresiensis and Human Evolution, the Seventh Human Evolution Workshop sponsored by the Turkana Basin Institute, at Stony Brook State University of New York, April 21.

Rebecca Hulett-Bowling, MD, assistant professor of radiology, spoke on “Imaging of pediatric tuberculosis and other infections” at the Queen Elizabeth Hospital, Maseru, Kingdom of Lesotho, Africa, February 16.

Seung Kwon Kim, MD, assistant professor of radiology, presented “Imaging of pediatric tuberculosis and other infections” at the Queen Elizabeth Hospital, Maseru, Kingdom of Lesotho, Africa, February 16.

Robert McKinstry, MD, PhD, associate professor of radiology and of pediatrics, as Radiology Grand Rounds speaker, presented “Imaging of brain injury in newborns and “Neuroradiology cases from the Mallinckrodt Institute of Radiology” at Brigham and Women’s Hospital, Boston, March 31, and at Massachusetts General Hospital, Boston, April 1.
Michelle Miller-Thomas, MD, instructor in radiology, spoke on “Temporal bone imaging” at the University of Texas Health Sciences Center, Houston, March 16.

Nassir Siddiqi, MD, assistant professor of radiology, spoke on “Chemoembolization for liver tumors” at the Nurses Continuing Education Lecture, sponsored by Barnes-Jewish Hospital and the Center for Advanced Medicine, St. Louis, Missouri, March 6. He presented “Venous thromboembolism and IVC filters” at the King Edward Medical College Alumni Annual Meeting, St. Louis, Missouri, March 28.

Barry Siegel, MD, professor of radiology and of medicine, presented “Sponsorship and economics of imaging trials and research billing compliance” and “Practicalities of running a clinical trial” at the Radiological Society of North America Clinical Trials Methodology Workshop, Phoenix, Arizona, January 10-16. He spoke on “PET reimbursement and the National Oncologic PET Registry” and “PET and PET/CT in oncology: monitoring and predicting response to therapy” at the 2009 First Multidisciplinary PET/CT Oncology Symposium, San Juan, Puerto Rico, January 31. He spoke on “Update on reimbursement of PET and the NOPR” and “Cervical cancer” at Advances in Whole Body Fusion Imaging: PET/CT and SPECT/CT, Johns Hopkins University, Baltimore, Maryland, March 13 and 14. Siegel presented the Fifth Annual Maxfield Lecture—“PET reimbursement and NOPR”—and “PET & PET/CT: predicting and monitoring response to therapy” at the 54th Annual Meeting of the Southwestern Chapter, Society of Nuclear Medicine, Houston, Texas, March 20-22. As invited speaker, he presented “PET as a biomarker in early cancer treatment trials” at the City of Hope Comprehensive Cancer Center’s 2nd Developmental Cancer Therapies/Phase 1 Retreat, Pasadena, California, April 4.

Michael Welch, PhD, professor of radiology, of chemistry, and of molecular biology and pharmacology, presented the Fifth Annual Maxfield Lecture—“PET reimbursement and NOPR”—and “PET & PET/CT: predicting and monitoring response to therapy” at the 54th Annual Meeting of the Southwestern Chapter, Society of Nuclear Medicine, Houston, Texas, March 20-22. As invited speaker, he presented “PET as a biomarker in early cancer treatment trials” at the City of Hope Comprehensive Cancer Center’s 2nd Developmental Cancer Therapies/Phase 1 Retreat, Pasadena, California, April 4.

Michael Darcy, MD, “TIPS too long”; “SIR Foundation and SIR: the big picture.”

Focal Spot, Spring 2009
Continued from page 31

William McAllister, MD, “Osteoprotegerin (OPG) deficiency mimicked by a novel 15-base pair tandem duplication in TNFRSF11A encoding RANK: merging the juvenile Paget’s disease and expansile skeletal hyperphosphatasia phenotypes”; c.1250-G, p.N417S is a common American TNSALP mutation involved in all clinical forms of hypophosphatasia (HPP), including pseudo-HPP.”

AMERICAN ROENTGEN RAY SOCIETY
109th Annual Meeting
Boston, Massachusetts
April 26-May 1, 2009

REVIEW COURSES
Sanjeev Bhalla, MD, Course director, “Approach to diagnosis: a case-based imaging review.”

Sanjeev Bhalla, MD, “Cardiovascular imaging: plain film correlates of cardiovascular disease.”

Sanjeev Bhalla, MD, “CTA of the thorax: pulmonary thromboembolic disease, arterial and venous malformations, acute aortic syndromes and postoperative evaluation of the aorta.”

Cylen Javidan-Nejad, MD, “Cardiovascular imaging: chest pain.”

Christine Menias, MD, moderator, “Genitourinary/ OB/GYN (pelvis) imaging papers.”

Christine Menias, MD, “Gastrointestinal imaging: esophagus, stomach, small bowel.”

Christine Menias, MD, “Acute intestinal ischemia and bleeding.”

Pamela Woodard, MD, moderator, “Cardiopulmonary imaging papers.”

Pamela Woodard, MD, keynote, “Cardiac imaging: 2009 update.”

SCIENTIFIC SESSIONS
Cylen Javidan-Nejad, MD, “Truths and myths of CT-guided thoracic biopsies: factors affecting complications.”

Cylen Javidan-Nejad, MD; Thomas Pilgram, PhD, “CT-guided thoracic biopsies: a five-year retrospective study of outcomes.”

EXHIBITS
Kartikeya Kantawala, MD; Nirvikar Dahiya, MD; Kathryn Robinson, MD; William Middleton, MD; Sharlene Teefey, MD, “Virtual cystoscopy using three-dimensional ultrasound: a new dimension in the evaluation of urinary bladder pathologies.”

Christine Menias, MD, “Recent imaging and interpretation advances in diagnostic workup of ovarian cystic lesions.”

Editor’s Note: On page 5 of the Winter 2008/2009 Focal Spot, Volume 39, Number 3, a Certificate of Merit notation should have been shown for this poster presentation: Geetika Khanna, MD; Takashi Sato; Polly Ferguson, MD, “Chronic recurrent multifocal osteomyelitis: a pictorial review.”
Construction of the BJC Institute of Health at Washington University is nearing its targeted completion date of December 2009. The 700,000 square-foot building at the southwest corner of Euclid Avenue and Children’s Place will serve as home base for Washington University’s BioMed 21 initiative to establish a multidisciplinary research environment for the acceleration of scientific discovery into clinical care.

Photograph by Kimberly Kania.