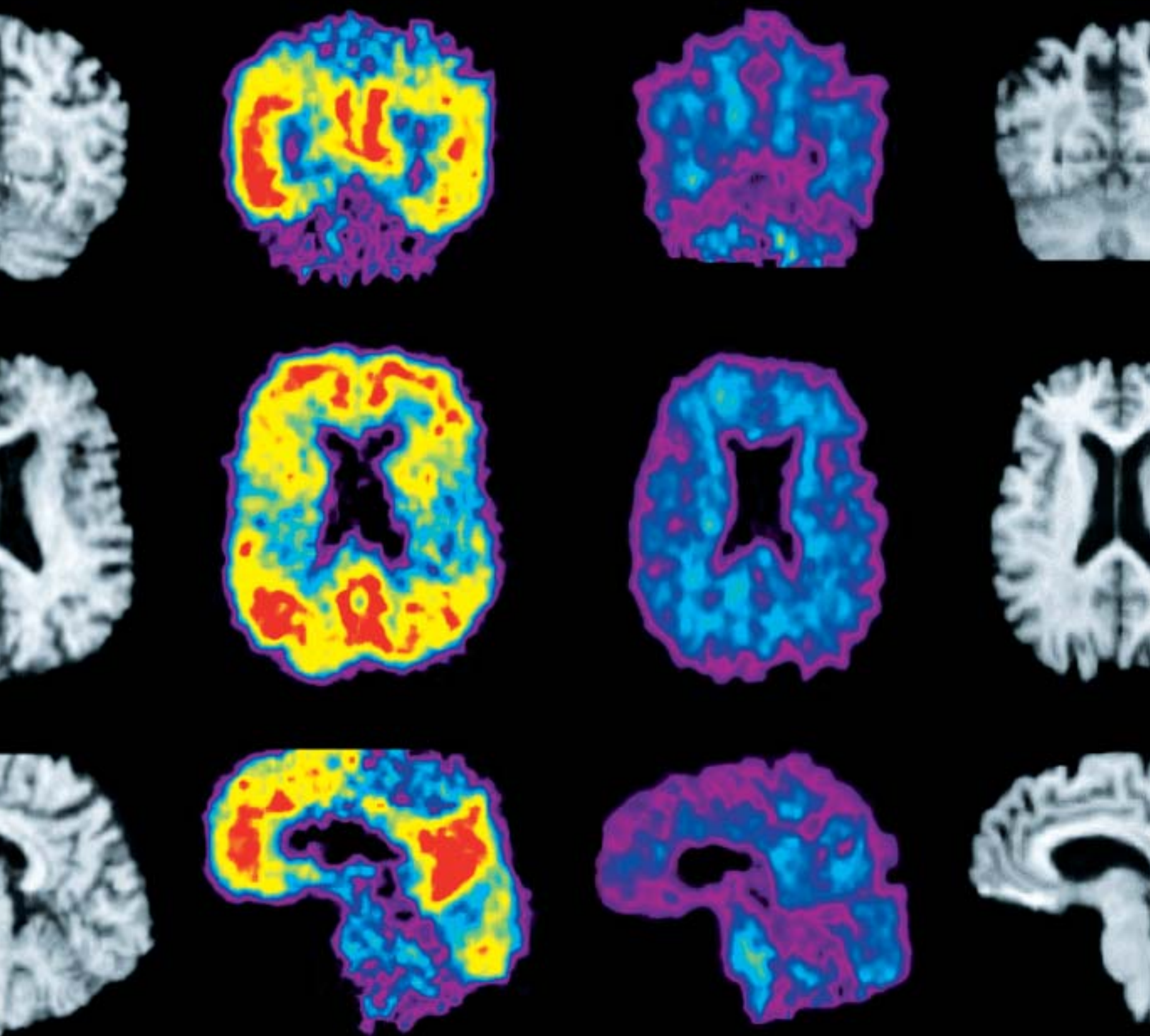


Explorations and revelations taking place at the medical school



For the first time, amyloid plaque can be detected in the brains of living people with Alzheimer's disease—using PET scans of patients injected with Pittsburgh Compound B (PIB), which binds to the plaque. The PET scan on the left shows an Alzheimer's patient with red and yellow areas of PIB accumulation, while the scan on the right, of a normal control, shows no PIB buildup. The difference cannot be detected in MRIs from an Alzheimer's patient (outer left) and normal control (outer right).

SEEING ALZHEIMER'S

COMPOUND MAKES THE DISEASE VISIBLE IN LIVING PATIENTS

BY KRISTIN OHLSON

In the early 1900s, a German neuropathologist named Alois Alzheimer began to work with a patient in her early 50s who had both cognitive and behavioral aberrations. After she died, Alzheimer examined her brain tissue and found gooey clumps of protein among her nerve cells. It was a momentous discovery, suggesting that the woman's mental disorder might have a physical cause.

In the decades since, autopsy after autopsy has revealed the same gooey clumps—now called amyloid plaque—in the brains of patients with Alzheimer's disease. Researchers have been able to find the plaque easily enough by applying various dyes to post-mortem brain tissue samples. But in living patients, no one has been able to tell whether a person has plaque or to identify any physiologic evidence of the disease.

Until now, that is. In January, scientists at the University of Pittsburgh School of Medicine and at Uppsala University in Sweden announced that they had successfully detected plaque in living patients using a new compound—dubbed Pittsburgh Compound B (PIB)—in combination with positron emission tomography (PET). The discovery, published in the *Annals of Neurology*, offers a huge boost to Alzheimer's research everywhere.

In particular, the compound will prove to be a powerful asset to pharmaceutical companies attempting to develop antiplaque drugs for Alzheimer's patients.

"People have been working on these drugs for a long time, but it has been hard to know if they're effective when you can't see the target of the drugs in a living person," says William Klunk, an MD/PhD

associate professor of psychiatry at Pitt and codeveloper of PIB.

"It's like trying to develop drugs for hypertension without being able to measure blood pressure. You could just wait for the subject to have a stroke, but that's not a very good solution."

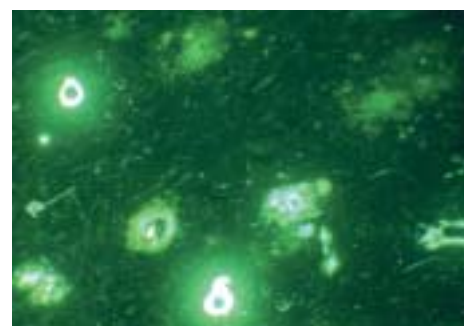
The new compound will allow researchers to diagnose Alzheimer's disease, track the growth of plaque in patients, and see if the new antiplaque drugs are actually having the desired effect.

For the last 15 years, Klunk has searched for a compound that could be used to flag plaque in living patients. Eight years ago, he teamed up with Chester Mathis, a PhD professor of radiology at the medical school. Mathis specializes in developing radiopharmaceuticals—compounds that are injected into the body and temporarily emit radioactive particles that can be captured by PET imaging to reveal anatomical clues.

Working with three classes of dyes used to detect plaque in the lab, Klunk and Mathis tested hundreds of compounds in both in vivo and in vitro studies. They needed a compound that could be safely injected into humans, that would penetrate the protective barrier that keeps most substances from entering the brain, and that would bind to plaque in the brains of diseased patients, while quickly clearing out of nondamaged areas of the brain. When they finally arrived at an effective compound, Klunk and Mathis arranged for human trials in Sweden, while waiting for approval of studies in the United States. They worked with 16 patients who were thought to have mild Alzheimer's disease, based on their clinical history, and nine patients in a healthy control group. Forty

minutes after they were injected, the Alzheimer's patients as a group showed more than twice the amount of PET signal than the average in the control group. The strong signal was a result of plaque binding to the PIB, notes Mathis. The distribution of the signal corresponded well to that seen during autopsies of other Alzheimer's patients.

Three of the 16 displayed lower signals—about the same level as the control group. "When we rechecked the histories of these three, they were all atypical," says Mathis. "Their cognitive impairment was very mild, and they hadn't gotten any worse in two to four years. The implication is that they have some other form of dementia."



Postmortem tissue from an Alzheimer's patient shows amyloid plaque and rings of amyloid around blood vessels.

Klunk and Mathis will soon begin a trial in the United States of 100 healthy elderly people, injecting them with PIB and then doing PET imaging to detect plaque deposits. In those over the age of 75, the odds are about 25 percent of finding some plaque. The researchers will follow up on the participants who test positive to study the progression of the disease. ■

RAPAMYCIN MOONLIGHTS

WHAT MAKES AN IMMUNOSUPPRESSANT A POTENTIALLY
EXCELLENT CANCER DRUG? | BY ROBIN MEJIA

Sometimes a drug ends up being effective in a role its developers never would have expected. Rapamycin may soon prove to be such a drug. Now being tested in phase

suppressors don't generally moonlight as cancer fighters. But it turns out that some tumors are strangely sensitive to the drug. At a dosage so low the rest of the body hardly registers it, rapamycin will stop tumors in their tracks. But studies suggest that only about 50 percent of tumors will be sensitive to the drug. How rapamycin works, and why it will arrest one tumor but not another of the same type, have become hot questions.

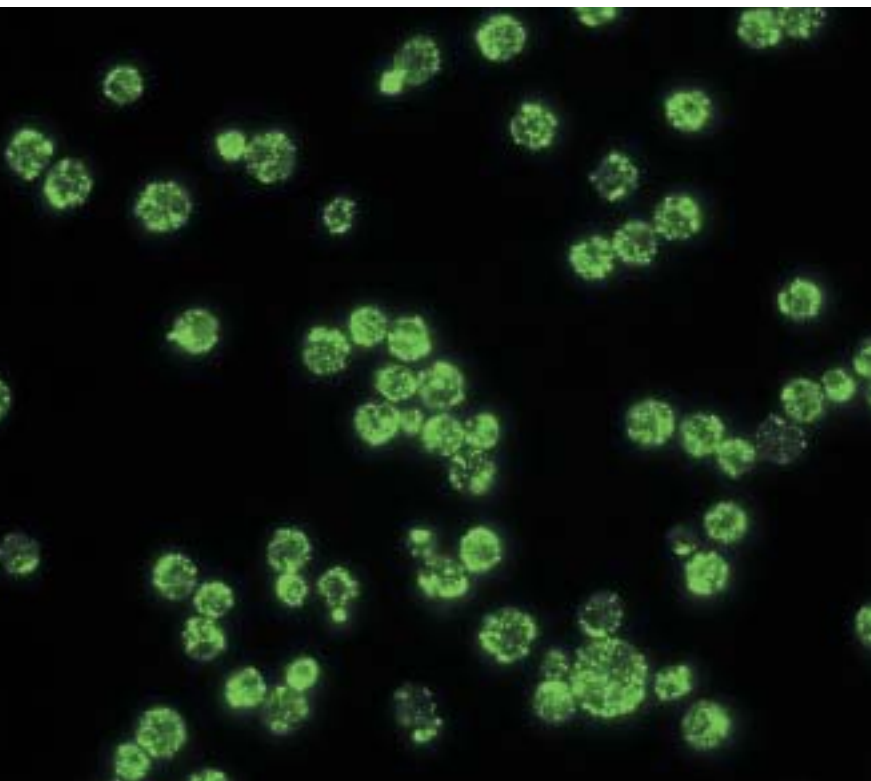
These are questions that intrigue Yu Jiang, assistant professor of pharmacology in the University of Pittsburgh School of Medicine. Jiang studies the Tor pathway, a sequence of molecular actions (rather like a complicated relay) that tells cells when and how much to grow and divide—the very functions that go into overdrive in tumors. It's also one of those nearly universal pathways that reminds us of our con-

Researchers have learned that rapamycin targets the Tor pathway in cancer cells. It's as though the drug makes the tumor think that no nutrients are available—so the tumor stops growing. But scientists don't know all the steps involved in the pathway. Nor do they know how rapamycin brings about the arrested growth of the tumor.

Jiang came to the study of Tor during a postdoctoral fellowship at Princeton. At the time, his research actually focused on protein phosphatases (there are several types), which are important in controlling cell growth. As a postdoctoral fellow, Jiang established that protein phosphatase 2A was part of the Tor cascade. Recently, Jiang published research showing that by inhibiting Tor action, rapamycin also incites protein phosphatase activity. When the phosphatase activity stops, so does cell growth.

But the “million-dollar question,” says Jiang, is how does activating phosphatases stop cell growth? It's a question he'll address in future studies. To learn more about how rapamycin works, he'll also pursue genetic studies in yeast. One by one, he'll “knock out” different components of the Tor pathway, to see if the yeast cells become more or less sensitive to rapamycin.

Jiang is optimistic about the possibilities for the drug. None of the chemotherapy drugs administered to patients today acts through the Tor pathway. And unlike many of these drugs, rapamycin has few side effects. Perhaps rapamycin could be used in combination with other chemotherapeutics, allowing them to be used in lower doses. Or it may even be effective as a stand-alone treatment. “Maybe your immune system will kick in and kill the cancer cells,” says Jiang. Wouldn't that be a twist for a drug also used to repress the immune system? ■



COURTESY Y. JIANG

In these yeast cells, a defective Tor pathway has resulted in abnormal distribution of the protein actin (labeled green). Actin is involved in cell growth; these yeast cells are not growing normally. Yu Jiang studies how the Tor pathway signals cell growth and how the drug rapamycin interacts with the pathway to curtail growth.

II clinical trials against breast and kidney cancer, rapamycin was originally approved as an immunosuppressant—it has been used in kidney transplants for several years.

Rapamycin's potential new role came as something of a surprise. Cancer patients need to boost their immune systems, so immune

connections to the rest of the animal kingdom; apparently, this cascade of actions has been conserved throughout evolution. In just about all organisms, from yeast to humans, the Tor pathway seems to serve as a sensor of nutrient availability, limiting growth in times of starvation.

THE BIG CHILL

BUYING TIME TO SAVE LIVES

BY DOTTIE HORN



CORBIS

A man is rushed in an ambulance to the hospital; he is bleeding internally from a deep stab wound to the chest. His heart is no longer getting enough blood to pump normally. As the sirens wail, the man's heartbeat becomes slower and slower. Just as the ambulance reaches the hospital, his heart stops.

Within five minutes, his brain will almost certainly be damaged. The trauma team starts delivering blood through an IV. Within 30 seconds, they've made an incision, spread apart the ribs, and gained access to the chest cavity. The doctors directly compress the heart. They look for an obvious bleeding site—perhaps a hole in the heart or in the lung—that they can quickly clamp or stitch. They see whether the loose sac that surrounds the heart has filled with blood and might be drained to give the heart the space it needs to work. Maybe there is a problem they can quickly fix. Usually there isn't. Eighty-five percent of the time, a patient in this situation dies. For all the efforts of the emergency department, he is likely to bleed to death, notes Samuel Tisherman, associate professor of surgery and critical care medicine.

But Tisherman and Patrick Kochanek, professor of critical care medicine and director of the Safar Center for Resuscitation Research, aspire to change this reality with an extraordinary new therapeutic strategy. Imagine again the stabbed man whose heart has stopped—doctors open the chest, but the steps they take don't help, and there's no quick problem they can fix. So, the doctors shift gears. They put a catheter into the aorta and flush ice-cold fluid through his blood vessels, until they chill the body to 50–60 degrees Fahrenheit. The cold temperature, they believe, will have a preserving effect, so that cells and tissues and organs will not be damaged even though there is no blood flowing through the body. The goal is to

buy time—time to take the patient to the OR to locate and repair bleeding sites. Then doctors would begin circulating blood again. The blood would slowly warm the body, until it is warm enough to restart the heart, which typically will not beat below 86 degrees Fahrenheit.

This approach was inspired by earlier work by Ronald Bellamy, of the Walter Reed Army Medical Center, and the late Peter Safar, Distinguished Service Professor of Resuscitation Medicine. They imagined putting wounded soldiers in danger of bleeding to death in “suspended animation” to give them time to be transported to a hospital.

Tisherman and his collaborators have experimented with this procedure in anesthetized animals. To simulate a traumatic injury, researchers bleed the animal, cut open its abdomen, injure the spleen, and then stop its heart. For two minutes, no blood flows through the body; then researchers cut open the animal's chest and begin the cooling flush. After the approximate time it would take to get a patient to the OR, they remove the spleen. Animals can remain chilled with no blood flow for up to two hours and be successfully resuscitated—with no apparent damage to the brain. (The researchers test the animal's cognitive abilities after the experiment.)

Already, a similar procedure is the standard of care for some cardiac surgeries. Say a section of the major artery that carries blood to the brain is diseased and needs to be replaced with an artificial segment. For some replacement procedures, surgeons must cease all blood flow. To protect the body, they cool patients to 60 degrees Fahrenheit before the operation. The surgery is fatal 10 to 15 percent of the time. But in patients under 75 who survive, most are able to tolerate no blood flow for 30 to 60 minutes, apparently without cognitive or neurologic complications. (The extent of

complications associated with this procedure has not been studied extensively.)

Tisherman and his group hope to begin clinical trials soon. But where will they find a pool of willing volunteers? Human research normally requires that participants sign an informed consent form, acknowledging that they understand and agree to an experiment. But, when doctors have only minutes to save the life of someone who is unconscious, it is impossible to obtain informed consent from the patient or a family member. A special provision, which allows researchers to obtain an “exception from informed consent,” makes such clinical trials possible.

To be considered for an exception, Tisherman will have to consult with the community. First, he'll inform the community—through advertising or other publicity outlets—about the proposed research. Next, he'll explain the study to a group of community representatives; in deciding whether or not to approve the research protocol, the University's Institutional Review Board considers the group's reactions to the proposed research. Tisherman will also hold a public forum to allow anyone interested to learn about the study, ask questions, and comment.

So far, Pitt's review board has approved six protocols involving the exception from informed consent. One of those studies is being led by Clifton Callaway, assistant professor of emergency medicine; Callaway studies the effectiveness of having paramedics administer the drug vasopressin in cardiac arrest cases.

“We have to weigh the fact that [subjects] didn't give permission to be in this research against the fact that our current technology for treating this disease does not produce many survivors,” says Callaway. “If we don't do this type of work, then we are frozen, and we will never be able to provide better care down the road.” ■