Pschiatrist William Klunk no longer recruits patients to participate in his studies of Alzheimer’s disease. He’s not allowed. And like his collaborator, radiochemist Chester Mathis, if he wants to review raw research results, he must be attended by a colleague to vouch both for his integrity and that of the data. Each is also barred from serving as a principal investigator—or supervising anyone who does—of protocols involving human or animal studies related to research the pair has pursued since 1994.
Neither has run afoul of the law or even common decency. In fact, each is at the top of his career. Klunk is a professor of psychiatry in the University of Pittsburgh School of Medicine, codirector of the University of Pittsburgh Alzheimer Disease Research Center, and director of the Laboratory of Molecular Neuropharmacology at Western Psychiatric Institute and Clinic. Mathis is director of the UPMC Positron Emission Tomography Center and professor in the Department of Radiology in the School of Medicine.

The prohibitions that constrain how Klunk and Mathis conduct their quest for better tools in the fight against Alzheimer’s owe, quite simply, to Pitt’s commitment to integrity amidst the increasingly complex relations between academic medical centers and an array of business interests. Until 1980, research on college campuses rarely translated to commercial innovation, and there just wasn’t much to worry about in the way of conflict of interest. Then Congress changed the laws governing the intellectual property that emerges from federally funded research.

Between 1996 and 2007, university patent licensing had a $187 billion impact on the U.S. gross domestic product and created 279,000 new jobs through such ventures as Google, FluMist, and the hepatatis B vaccine. Closer to home, the Pittsburgh Life Sciences Greenhouse, a public-private partnership founded by Pitt, Carnegie Mellon University, UPMC, the Commonwealth of Pennsylvania, and a number of local foundations, has provided office and laboratory space and an array of business interests. Until 1980, research on college campuses rarely translated to commercial innovation, and there just wasn’t much to worry about in the way of conflict of interest. Then Congress changed the laws governing the intellectual property that emerges from federally funded research.

In the three decades since, the biotechnology sector has ballooned into a $55 billion-a-year industry. That cash infusion has fueled intensive research and innovation in an era of shrinking federal funding and simultaneously introduced a tangle of ethical concerns as academic researchers navigate the process that turns innovations at the bench into the drugs, devices, and health care services central to care at the bedside. It has also raised the stakes on marketing to clinicians, who were once relatively insulated from industry-funded promotions, blandishments, and lucrative consulting opportunities.

Klunk and Mathis developed Pittsburgh Compound B (PiB), the underpinning of a strategy now in Phase III trials to image amyloid plaque—the hallmark of Alzheimer’s—in the brains of living patients. Previously, the only way to confirm the existence of plaque in a patient was at autopsy. PiB makes the plaque visible in a positron emission tomography scan, meaning a patient may be able to benefit from early-stage diagnosis and intervention. In 2004, GE Healthcare—which manufactures and sells PET scanners—acquired licensing rights to the multiple patents held by Klunk and Mathis with the University of Pittsburgh.

If GE’s resulting product garners the requisite federal approvals—expected in 2011 at the earliest—it promises to transform detection and treatment of a debilitating condition that affects 5.3 million people in the United States. Already, research based on Klunk and Mathis’ work has revealed new insights into the progression of the disease and has been used to test the effect of experimental therapies. Initial proceeds from the licensing agreement have also supplemented the scientists’ salaries, augmented their research budgets, and provided Pitt with discretionary funds.

“The best thing that can happen is for the stuff you work on to be successful,” says Mathis, noting that the prospect of seeing research translated into new treatments can be a powerful motivator for basic scientists and clinicians alike. “Yet the more successful it is, potentially the more conflicts of interest it creates,” he says. “The University has to be very careful, demonstrating that we don’t have a chance to misuse humans or animals or the data that derive from them for our own personal gain.”

Ultimately, says Mathis, he’s happy to submit to the policies and regulations that manage conflict of interest and maintain transparency, if that’s what it takes to see his work with Klunk improve the quality of care for people with Alzheimer’s. “It’s burdensome, but necessary,” he says. “It’s the price we have to pay.”

Mathis was a newly minted PhD in chemistry in 1979 when an audit by the U.S. Comptroller General revealed that just 5 percent of some 28,000 federally funded discoveries were under commercial development. Unlike industry-funded research and development departments, academic researchers simply published their findings to further the collective research enterprise; patents for their work reverted to the government. Such scientists rarely accrued fame or fortune in the process, and neither did anyone else. If a business hoped to protect its investment with a license while developing intellectual property generated on campus, it had to sort through a tangle of more than two dozen federal agencies, each with its own unique policies. As a result, few bothered.

In 1980, the bipartisan University and Small Business Patent Procedures Act—known as the Bayh-Dole Act, in honor of senators Birch Bayh of Indiana and Robert Dole of Kansas, its cosponsors—turned the tables. Bayh-Dole mandated that colleges and universities patent and promote the commercialization of innovations sparked by federally funded research. In effect, the law assigned to federal grant recipients the same financial incentives for commercialization long enjoyed by industry-funded scientists—the 20-year head start afforded by patent protection that makes capital investments in the commercialization process more likely to pay off.

“[Academic medical centers] can discover things from now to doomsday, but we don’t know how to put them in bottles and market them.”
The route from lab to market—where a device or drug can actually help patients—involves a tightrope walk to avoid conflicts of interest.
Pitt's policy bars pharmaceutical sales reps from patient-care areas, prohibits free meals and gifts from industry, imposes narrow limits on faculty consulting arrangements, and bans ghostwriting (specifically, the practice that conveys a faculty member's creditability to industry-funded and authored publications). The policy also raised the bar for clinical researchers whose findings might have personally lucrative implications by imposing new checks and balances throughout the process of experiment design, data collection, and analysis.

“I've heard it said that Bill and I are the poster children for conflict of interest at Pitt,” says Mathis. “I think they mean it in a good way. We have conflicts; we're required to manage those conflicts. Some things you can't do; many things you can.”

In 2008, the American Medical Student Association awarded Pitt its Paul R. Wright Excellence in Medical Education Award in recognition of the new policy. The next year, Pitt was among nine of the nation's 149 medical schools to receive an A on AMSA's scorecard evaluating conflict of interest policies.

“The implementation went relatively smoothly, considering that we were changing our culture,” says Vice Chancellor for Research Conduct and Compliance Randy Juhl, who cochaired with Barnes the committee that wrote the policy. “That's always a difficult thing to do.”

Early fears that industry might retaliate in the wake of the new policy by curtailing its involvements with Pitt haven't been borne out, says Barnes. Although support for continuing medical education is likely to keep falling—because of mergers and consolidations that have cut the availability of funds, as well as concerns about the undue influence they leverage—faculty continue to consult and industry-sponsored trials persist. “I don’t see that we have really jeopardized any of the valid opportunities as a result of these policies,” she says. “What has gone away are the personal gifts, visits from representatives.”

The Kohl-Grassley Physician Payments Sunshine Act, as appended to the health care reform bill, requires industry to post online details of all direct physician payments with a value of more than $100. Already, Merck, Eli Lilly, Pfizer, and other pharmaceutical companies have signed corporate integrity agreements with the Department of Justice that mandate the creation of Web sites along the same lines. Device manufacturers Medtronic and Zimmer made similar disclosures in 2007 in the wake of a Justice Department inquiry, and many academic medical centers now also host similar Web sites. Pitt administrators have kept a close eye on such efforts but haven't yet implemented policies to govern the public disclosure of relationships between faculty and industry. “We want to make available completely accurate information,” says Barnes. “If you look at the sites, they have a lot of disclaimers—we're not so sure about the accuracy. From our perspective, it's somewhat premature.”

Overall, says Barnes, Pitt's approach to managing conflict of interest has been unique, both for its breadth and the administration's sustained commitment to enacting the policy. Consequently, her current focus is on evaluating that process and publishing the findings to guide other academic medical centers.

“The fact that we could develop a policy and garner the support of the leadership and other key stakeholders is extremely important,” she says.

So what does the future of industry partnering look like for an American medical school?

That's becoming increasingly difficult to predict. Yet, a nimble, entrepreneurial approach to funding research and navigating the commercialization process will be vital for universities as the intellectual-property landscape shifts in response to health care reform, the Kohl-Grassley Physician Payments Sunshine Act, and emerging case law.

Six months before Congress passed Bayh-Dole in December 1980, the U.S. Supreme Court ruled that living organisms could be patented, launching a new era in agribusiness and biotechnology. In late March of this year, a U.S. district court judge issued a landmark decision invalidating gene patents jointly held by the University of Utah and Myriad, a company launched by a former Utah faculty member who developed a screening test for an associated mutation that increases the risk for some types of ovarian and breast cancers. The ruling, which was celebrated by the American Medical Association, sent shock waves through the world of biotechnology. Its implications—and the expected appeals—will take years to percolate through the legal system, as well as the industry and the economy. Meanwhile, a second patent case before the U.S. Supreme Court promises to further define the intellectual-property landscape.

Whatever the future holds, it shouldn't hurt...
Pitt that inventive partnering has become part of its culture. The collaborative spirit that yielded Pitt’s conflict of interest policy has infused the University and the medical school’s recent history. Administrators have inked partnerships with Intel, the nonprofit Rand Corporation think tank, Carnegie Mellon University, the Carnegie Museums of Pittsburgh, and even the Pittsburgh Zoo. UPMC, meanwhile, has built formal alliances with GE Healthcare, IBM, Alcatel-Lucent, and the Italian government, among others. Many of these partnerships focus on research, but they also are about delivering clinical care, updating operations, broadening graduate school offerings, and giving med students other class electives and opportunities for scholarship.

For scientists, such collaborations have yielded new opportunities, which are perhaps even more important than access to funds. Cross-disciplinary teams have sparked new approaches to both basic investigation and the translation of associated intellectual property into clinical settings worldwide.

“We're not as good with marketing and all that stuff,” says Chang. “You control a bigger piece of the pie, but think of the headaches, all the other enterprises that have dried up and blown away.”

Klunk thinks of licensing PiB to GE Healthcare as akin to sending a child off to boarding school or college.

“As clinician-scientists, we can’t take this technology to its full potential,” he says. “We don't have the skills or funds.”

That reality hasn’t stopped Klunk and Mathis from occasionally second-guessing the process. To make PiB visible in a PET scan, the pair used a carbon-11 tracer, which has a half-life too brief for clinical applications. GE’s first task was to work with Klunk and Mathis to find an alternative tracer. A robust collaboration yielded a fluorine-18 tracer, and the company moved on to the next stage of commercialization. Klunk and Mathis weren’t convinced that the new tracer was ideal and persisted in the investigation using NIH funds.

So far, they haven't found anything better. "If I'd done that, I don't know if it would have worked. There were times we thought we'd be better off if we were controlling everything, but not every decision we'd have made would have been right,” he says. "You control a pretty good idea. But that may change. We haven't given up.”

The decision to proceed with a good-enough compound gained the company at least two or three years in the march to market, says Klunk. “It took us that long to realize maybe we'd never beat it.”

Klunk and Mathis have largely come to terms with the complexities and frustrations of the commercialization process. They realize that biomedicine is a risky and expensive business sector. (The Biotechnology Industry Organization estimates it costs about $1.2 billion to bring a biopharmaceutical to market; about 30 percent make it out of clinical trials.) Yet, it’s worth asking: What if someone in the original research group had brought PiB to market by launching a new company? Klunk says he wasn't the man for the job.

Perhaps the University of Pittsburgh’s highest-profile commercial venture to date is Stentor, a storage, management, and distribution system for digital radiology images. In fact, it was so successful, it inspired UPMC to commercialize some technologies on its own.

The Stentor system was created by Paul Chang, formerly a professor of radiology at Pitt and director of radiology informatics at UPMC. When Chang was recruited to Pitt in 1996, the management of digital radiology images depended on huge, centralized systems vastly more expensive and only marginally less cumbersome than the films they had replaced. “[Stentor] was a traditional research project to demonstrate that one could use more flexible mathematical algorithms to leverage less expensive PCs to use the Web,” says Chang, now professor and vice chair of radiology at the University of Chicago. To test his hypothesis, UPMC installed kiosks loaded with experimental software in emergency medicine, surgery, and a few clinics. “It worked so well, the clinicians preferred to use the prototype rather than the $70,000 commercial work stations.”

What happened next, says Chang, was a “support and management nightmare.” He and his team had the skills to test concepts; they weren’t equipped to sustain their system on the scale of an entire medical center. But it seemed like a great product.

Because Stentor relied only on software development, the project was free of the extraordinary costs and regulatory considerations associated with manufacturing clinical-grade biological materials. So instead of licensing a patent to an existing company with FDA-approved facilities and manufacturing expertise—prerequisites to the commercialization of a pharmaceutical or medical device—UPMC hired a management team and launched the company with help from venture capitalists. The approach preserved Chang’s involvement and an emphasis on the technology’s clinical requirements. The process was ideal, says the MD: “We academics tend to be very good at coming up with ideas, and because we're physicians, we understand workflow and have the domain knowledge to know what's required of tools to take care of patients. We're not as good with marketing and all that stuff.”

The course Stentor took to commercialization was unique at the time, says Chang, and remains rare. UPMC has since taken a page from the playbook of the venture capitalists, whose early-stage investments had yielded rich profits by dedicating more of its own funds to the commercialization of homegrown ventures. (When Philips Electronics purchased the company for $280 million in the summer of 2005, Pitt earned $10.8 million, and UPMC, which had invested $9 million developing the technology, received $45.1 million. Much of the rest went to venture capitalists.) To date, UPMC’s International and Commercial Services Division has invested more than $200 million in 36 companies and committed additional funds to partnerships with firms like IBM, GE, and Alcatel-Lucent.

With Wall Street’s many surprises of late, a medical center’s choice to reinvest funds toward spin-off enterprises that further patient care and its own community’s growth starts to sound like a pretty good idea. —ST