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Big Pharma Finds a Home on Campus

As drug companies scale back spending on R&D, academic research takes on financial risk



Joon Powell for The Chronicle

P. Jeffrey Conn co-directs Vanderbilt U.'s Center for Neuroscience Drug Discovery, which has attracted top researchers from pharmaceutical companies.

By Goldie Blumenstyk

Nashville

P. Jeffrey Conn left a full professorship for a job in Big Pharma 11 years ago because he saw no path in academe to turn his novel idea for treating Parkinson's disease into an actual drug. Now he and a corps of scientists are closing in on a molecule that could bring relief to the millions suffering with the condition's debilitating tremors and paralysis.

But the screening, testing, formulating, and reformulating that brought Mr. Conn's team to this point didn't happen in a lab at a multinational pharmaceutical company—he left his job at Merck & Company after just three years—nor at a venture-capital-backed biotech firm. It's advancing in the laboratories of Vanderbilt University, one of a growing number of universities now taking on the high-stakes work of drug discovery.



Vanderbilt U.

A nuclear magnetic-resonance spectrometer, which will be used by drug researchers to evaluate protein structures in their efforts to devise medically useful compounds, is put into place at Vanderbilt.

This academic pursuit of new medicines, fueled at Vanderbilt and several other institutions by big-dollar research

collaborations with pharmaceutical companies like Johnson & Johnson, Pfizer, AstraZeneca, and Gilead Sciences, has put research universities at the heart of what one AstraZeneca executive calls "a new economy of drug discovery," one that shifts some of the responsibility, along with some financial peril, away from industry and onto academe.

Converging financial realities drive the shift. Drugs like Lipitor, Plavix, and Gleevec, collectively worth hundreds of billions in annual sales, will lose their patent protection between now and 2015. The pharmaceutical industry, which has laid off thousands of researchers during the past several years of mergers and consolidation, is scrambling for new medicines to fill its sales funnel.

The biotech industry, once a major source of new drugs for Big Pharma, is being squeezed by its own financial pressures.

Universities, meanwhile, realize that they need alternatives to the federal government for research support. And they face growing pressure from politicians and patient groups to demonstrate that the billions in philanthropic and taxpayer dollars flowing into their labs can produce cures.

"All of this is either a perfect storm or a new opportunity," says John Reid, director of global alliance management at AstraZeneca, who oversees its 18-month-old, seven-figure collaboration with the University of Pennsylvania, where neuroscience researchers are trying to develop a drug to treat Alzheimer's disease.



The new activity raises many new ethical and practical questions, and not only the obvious ones concerning the increasing potential for conflicts of interest. Are universities any more likely than the drug companies to succeed in finding useful new drugs? If the financial risks of drug

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No one at Vanderbilt is about to turn down a financial windfall from drug discoveries, but officials say basic research is still key. "These programs would have never survived in another setting," says Mr. Conn.

discovery have become too great for giant multinational companies, is it really practical and timely for universities to take them on? Are universities delving into drug discovery with unrealistic expectations of a big payday? And more broadly, will having universities, with their public mission, more integrally involved in drug discovery make it any more likely that new drugs are affordable to people in the developing world, or for that matter, even here in the United States?

Proponents of this new role for universities say involving top-flight academics more directly in the drug-discovery process could result in more innovative and more effective drugs. And as university researchers shepherd a molecule scientifically beyond the very earliest stages of its path to becoming a drug, they can also make it more valuable when it comes time for the institution to license it to a company.

But entwining academic research with the pharmaceutical industry has its own special risks, notes Susan Solomon, who heads a nonprofit stem-cell bank in New York City that works with many university scientists. The companies' research priorities can shift quickly due to competitive and financial pressures. And sometimes a research group's rights to its own findings and data can get tied up if the company drops the project or plays it down in favor of a more promising one. "If they change their mind and they don't want your thing, you're stuck," Ms. Solomon says.

And even relationships that do produce new medicines pose the potential for problems, note some drug-industry skeptics. Donald W. Light, who has written critically about the health risks and high costs of prescription drugs, for one, warns that unless universities are careful, they could find themselves simply becoming "full partners in a system that leads to 85 percent of all new drugs being little or no better" than the existing one, or worse, helping to create drugs that he says too often come onto the market without adequate testing for side effects. "If universities are setting out to maximize profits on discoveries," says Mr. Light, "then like companies, they become corporatized and become more likely to emphasize benefits and downplay harms" of new drugs.

Big Investment, Big Payoff?

Across the country, academic researchers are taking on a role that was once the purview of the research divisions of Big Pharma and the biotech industry. Only a few, however, have gone as far as Vanderbilt has in developing in-house expertise and facilities.

Since the late 1990s, Vanderbilt has invested about \$50-million of its own money to develop the scientific infrastructure and recruit the personnel that now make possible the work of the program that Mr. Conn co-directs, the Center for Neuroscience Drug Discovery. It aims to develop drugs to treat autism and schizophrenia as well as Parkinson's. The full-time equivalent of 100 researchers and technicians work with the kind of equipment for screening, synthesizing, and purifying compounds that until recently would have been found only in drug-industry settings.

Several top scientists from pharmaceutical companies have joined Mr. Conn, including the co-director, Craig Lindsley, also formerly of Merck, and J. Scott Daniels, a recent émigré from Pfizer who oversees pharmacokinetics, the science of how molecules interact in the body, a mainstay of any commercial drug-development program.

The Vanderbilt researchers are pursuing experimental approaches that "were considered 'not druggable' by industry," says Mr. Conn, who is a professor of pharmacology. They are following it up with scientific work that advances ideas farther along the development pipeline than has traditionally been the case for academic labs—not quite developing the pills that a company will eventually sell but, as Mr. Conn describes it, developing a knowledge base for a "druggable" molecule. (Long before it goes into human clinical trials, a compound must pass a battery of cellular and animal-based tests to show that it can both hit its intended target without excess toxicity and retain its chemical potency and stability.)

Other institutions pursuing drug discovery follow different approaches. "What's new is the systemization of it," says Stephen V. Frye, himself a former head of medicinal chemistry at GlaxoSmithKline, who now leads the drug-discovery center at the University of North Carolina at Chapel Hill. Thirty-three of the 56 academic-based drug-discovery centers that responded to Mr. - Frye's recent survey about their priorities and financing were founded within the past six years.

Skeptics question the appropriateness of universities' taking on the costs of drug discovery. But proponents like Mr. Frye say it's a logical step. Drug discovery is more perilous for industry because companies need to make a profit, he says. But in an academic environment, it can yield new knowledge and other kinds of results that are also of value. "There's a different risk equation," he says.

Academic medical centers have long conducted clinical trials on drugs as part of the approval process of the Food and Drug Administration. Some universities specialize in training students in drug manufacturing. And basic-science researchers often identify enzymes or proteins in the body that trigger a disease. Finding that target is the first stage of drug discovery.

But academics haven't typically gone deeper into the science of making and then evaluating how permutations of a molecular compound could actually affect that disease target. The teams of drug-discovery researchers at places like Penn and Vanderbilt are doing just that.

"It's not just finding a target, it's finding a drug," says Michael Cleare, Penn's associate vice provost for research and executive director of its Center for Technology Transfer.

At Penn, researchers work directly with AstraZeneca scientists, sometimes side by side in university-owned laboratories, with the Penn professors focusing on basic science to identify the parameters of what a new drug should do and the company's scientists doing the sophisticated analysis and synthesis to build molecule after molecule to try to accomplish that.

It's a new approach for AstraZeneca, which in 2010 began a four-year plan to cut employment by 8,000, including 1,800 from in-house research and development. Now it's "investing in the best science wherever it may be," says the company's Mr. Reid. "It's a way of sharing risk."

In addition to the sponsorship support, the collaboration includes potential payments of up to \$15-million to Penn if the researchers hit agreed-upon milestones toward the development of a drug. It also includes an unusually flexible license that promises royalties to the university if a drug based on

the researchers' work ever goes on the market, even if the product itself isn't a Penn invention. AstraZeneca is expected to announce similar collaborations with other universities by this fall.

Penn calls its AstraZeneca relationship an "integrated partnership," differentiating this style of university-industry collaboration from prior models that weren't as outcome-focused.

A giant deal between Gilead Sciences and Yale University for developing cancer-fighting therapies, which guarantees at least \$40-million in research support to Yale researchers over the next four years and as much as \$100-million if the arrangements run for 10 years, also is designed to result in jointly developed drugs.

"The intensity of the interactions" between researchers from the company and the university is what's new, says Jon Soderstrom, managing director of Yale's Office of Cooperative Research. A committee of Yale and Gilead scientists choose which projects will receive support. Then the academics work with corporate scientists on selecting targets and assessing the results. The intellectual-property terms of the Yale deal are not public.

'They're All Desperate'

Before now, pharmaceutical companies felt that they were just "throwing money over the wall" when dealing with universities, says Regis B. Kelly, a molecular biologist and a former executive vice chancellor at the University of California at San Francisco. But now "they're all desperate," he says, and they expect payoffs from their research sponsorships.

UCSF, which has given birth to dozens of successful biotech and drug companies (a former top executive at Genentech is the chancellor) has been a magnet for the pharmaceutical-industry partnerships. It has two drug-discovery sponsorships with Sanofi-Aventis, plus an agreement with Bayer HealthCare to encourage future collaborations with minimal red tape.

In late 2010, UCSF was also the first to land a partnership with Pfizer—worth up to \$85-million over five years—under a new collaborative program that matches company scientists with academic researchers to create new medicines.

Pfizer, which dubs the model "science outside our walls," has since announced two additional Centers for Therapeutic Innovation, one involving major research universities in New York City and the other for universities in Boston. For researchers in these programs, Pfizer grants access to some

of its proprietary scientific technology to speed the development of drugs, and liberal terms for intellectual property and rights to publish results of research.

Another pharmaceutical giant, Eli Lilly and Company, has taken a different tack. Having identified its own goals for treating Alzheimer's, diabetes, cancer, and osteoporosis, it invites academic and commercial researchers to submit compounds to the company for screening as possible drug candidates. If the molecule shows promise, Lilly has the first right to negotiate a research sponsorship or license to develop it.

In the two years that the program has been under way, researchers at more than 200 institutions, in 26 countries, have submitted over 30,000 compounds for evaluation. Lilly has struck one deal, with researchers from the University of Notre Dame, for a molecule that shows promise in starving tumors of vital blood flow.

Professional investors are also looking to get in on the trend, in some cases offering financing and scientific advice to university researchers to help them advance potential drug discoveries before trying to license them to pharmaceutical companies.

One such group, a new venture called BioPontis Alliance, promises to evaluate and "pressure test" potential drug candidates from its partner universities with the help of experts recruited ad hoc, and to provide financing for those that show commercial potential. The chief executive, Richard A. Basile, says its model is more suitable to academic-based drug discovery than the typical, riskier approach, in which venture-capital firms finance start-up companies based on early-stage ideas. With BioPontis's approach—financing projects, not companies—"we can kill a technology early" and move on, he says.

Penn, North Carolina, and five other universities have signed nonexclusive agreements with the alliance, which has yet to conclude its first-round fund raising.

A Long Horizon

Vanderbilt's Center for Neuroscience Drug Discovery began as a one-man operation under Mr. Conn, who joined the faculty in 2003. (He got his Ph.D. there in 1996.) Now it boasts an annual budget of nearly \$18-million and is outgrowing its prime home, in three medical-research buildings. About \$11-million of its budget comes from the National Institutes of Health, up from about \$4-million in 2006—a reflection of the federal government's growing willingness to support this kind of translational research in drug discovery.

Most of the rest of the financing comes from foundation grants and industry sponsorships. In 2009 the Johnson & Johnson subsidiary Janssen Pharmaceuticals announced a three-year, \$10-million sponsorship to develop schizophrenia drugs—a deal that could yield an additional \$100-million in milestone payments to Vanderbilt if the work succeeds. The center also has a license with a smaller company, Seaside Therapeutics, which supports its work on an autism drug. Terms of that deal are not yet public.

Vanderbilt's work on a Parkinson's drug, which involves regulating neurotransmitter activity in ways that may be more effective than the traditional focus on dopamine, is financed with \$4.4-million from the Michael J. Fox Foundation. Vanderbilt hasn't yet licensed that drug.

While no one at the university denies the desire for a financial windfall from the drug-discovery program, officials insist that the most significant opportunity the center provides is a venue to pursue novel ideas. "These programs would have never survived in another setting," says Mr. Conn.

For example, a Big Pharma company would have never invested in such an unvalidated approach for treating Parkinson's, he says. (Indeed, Merck didn't do so when he was there.) And "a venture investor wants something to happen in the first year," Mr. Conn says. "I've been here eight years, and we're just now" close to final results with the molecules that he and colleagues will soon put forth as drug candidates for human clinical trials in treating the disease.

The Vanderbilt center counts other measures of success as well. Since 2007 its researchers have filed for more than 100 patents and published more than 140 scholarly papers based on their work. Although the center uses industry processes to advance its work, including high-tech studies that assess how its compounds react in test tubes and in live animals, it doesn't operate like a commercial-contract research organization.

"We're still making basic-science discoveries," says Susan R. Wentz, associate vice chancellor for research. "We're still publishing papers. We're still doing what scientists in academe do."

And Vanderbilt hasn't limited itself to neurological drugs. It's begun a second drug-discovery program, in cancer. That program is headed by Stephen W. Fesik, who left a vice presidency overseeing cancer research at Abbott Laboratories to join Vanderbilt in 2009.

For a while, at least, it appears unlikely that universities' expanding role in drug discovery will result in lower-cost drugs. Although some institutions (not yet including Vanderbilt) sometimes add clauses to their licensing deals to require companies to make their drugs available at little or no cost

in the world's poorest countries, few if any seem to have gone so far as to try to impose general pricing controls.

Even the director of the NIH, Francis S. Collins, says that's not something he'd want the agency to encourage. The costs of health care and drugs are a national concern, he said in a recent interview with *The Chronicle*, but "this is the wrong place to get the leverage" to try to fix that.

Putting price controls on the table during negotiations of a university-industry collaboration, Mr. Collins says, "means there will be no collaboration."

Given the times, it's those collaborations, along with other drug-discovery efforts arising from academe, that will be much in demand. And as Mr. Kelly, of UCSF, contends, it's not just the ailing drug industry that stands to gain. Higher education, not to mention society at large, could benefit, too. After all, governments and benefactors don't give tax money and donations to universities "because they love our beautiful papers," says Mr. Kelly. "If the universities don't do it, who's going to?"