NEWS

The Hunt for a New Drug: Five Views From the Inside

The world of drug discovery in big pharma can seem pretty mysterious to outsiders. But some patterns are visible from the inside.

Waiting for his lunch to arrive, Graeme Bilbe wants to make sure that the reporter on the other end of his cell phone understands how hard it is to discover a new drug. The U.K.–born, Basel, Switzerland–based head of global neuroscience research at Novartis is dining in southern California with a former pharma colleague, Tamas Bartfai, now chair of the department of neuropharmacology at the Scripps Research Institute in La Jolla, California. The hors d’oeuvre is a lecture on the industry’s staggering attrition rates.

“How many ideas do you think you need [to develop a drug]?” demanded Bilbe, who’s been with Novartis since 1989. “Take a guess. One thousand? Ten thousand? You need at least that many, if not more. The chances that any of those ideas will ever become a drug are vanishingly small.”

Those mind-boggling numbers color everything about research in big pharma and make this research sector distinct from any other area of industrial research. Very few pharma scientists actually work on products. Instead, the vast majority toil at a much more basic level, looking for potential targets, synthesizing compounds that might act on those targets in a way that would be therapeutic, and then making the compound “druggable.” “I have never worked on a successful drug,” confesses Derek Lowe, a medicinal chemist with 16 years in the industry who writes what may be the only Web log (blog) dedicated to pharmaceutical research (www.corante.com/pipeline). “ Heck, I haven’t worked on anything that anybody with a disease has ever put in their mouths.”

The research environment has also been reshaped dramatically in the past decade or so by mergers, which can abruptly shift a researcher’s focus onto a whole new area of study. And unlike research on a new computer chip or a more efficient engine, the output from pharma research labs is not so easy to measure (see p. 726).

The world of big pharma research is shrouded in a culture of secrecy that goes well beyond the specific compounds and targets a company is working on. Here’s how an otherwise candid Lex Van der Ploeg, head of Merck’s new research lab in Boston (see sidebar, p. 723), puts it when asked about his productivity goals. “If I told you that this lab was going to generate, say, eight lead candidates this year, then our competitors could look at the number of people we employ and figure out how many people it takes us to develop a candidate compound,” he says. “Then they would compare it to how many it takes them. And if we’re lower, they’d try to figure out why, and what they can do to become more efficient. That would give them a competitive advantage.”

Knowing where they stand is an all-consuming interest for pharma executives. As a result, investment analysts and corporate consultants churn out reams of reports each year on industry trends, from early-stage alliances with biotech companies possessing intriguing compounds to the latest technology “platforms” that can improve efficiency. The documents are sprinkled liberally with breathless predictions about how these trends “will change everything.”

Most of the time they don’t, of course. In the meantime, however, these big-picture studies provide little idea of what the view is like from inside the industry’s labs. From the scores of scientists and research managers we interviewed for this special section, we have chosen five individuals whose stories provide glimpses of how those big trends trickle down to the labs and computer workstations around the globe that represent ground zero in the hunt for new drugs.

A view from the bench: Change as a constant
Eric Gulve joined big pharma in 1993 in hopes of ameliorating the ravages of diabetes. A research assistant professor at Washington University in suburban St. Louis, Missouri, Gulve became part of a team at G. D. Searle (the pharmaceutical arm of Monsanto) that was just beginning to tackle insulin resistance in type 2 diabetes. Since then, he’s worked on cholesterol metabolism for Monsanto, cardiovascular diseases for Pharmacia, and then diabetes again for Pharmacia. Today he’s with Pfizer, seeking potential targets to treat two forms of cardiovascular disease, thrombosis and hypertension.

Although he’s worked for three companies in 12 years, Gulve is no hired gun. He hasn’t even changed his commute to work. Rather, the 46-year-old physiologist has spent his entire pharma career in the same four-story industrial lab in the St. Louis suburb of Creve Coeur. The job changes were the result of three corporate mergers, culminating in Pfizer’s $53 billion acquisition of Pharmacia in April 2002. Those mergers triggered top-down reviews of existing research, followed by projects or entire areas of therapeutic research being cancelled or

Growth industry. Today’s Pfizer is built upon a decade and more of dealmaking.
Boston Means Business for Drug Companies

**BOSTON, MASSACHUSETTS—**Asked why he robbed banks, Willie Sutton is said to have responded: because that’s where the money is. After more than a century, big pharma is following that logic by setting up shop here amid what may be the world’s largest concentration of biological brainpower.

Two of the world’s biggest drug companies, New Jersey-based Merck and Connecticut-based Pfizer, have opened small outposts to supplement their global R&D networks and put company turnaround artists in charge of them. A third company, Novartis, has gone even further by relocating its main research facility, the Novartis Institutes for Biomedical Research (NIBR), in a spectacularly remodeled former candy factory and two other buildings adjacent to the Massachusetts Institute of Technology (MIT) and picking an industry novice to run it. The 1000-strong scientific work force assembled in the past 2 years represents a serious bid by the Swiss-based company to find the sweet spot in drug discovery.

“Our kickoff career fair attracted more than 2000 people, and it was a fabulous opportunity to meet and greet leading scientists and business leaders,” says Lynne Cannon, vice president for human resources at NIBR. “That would have been difficult to do in Groton [Connecticut, the site of Pfizer’s largest lab] or Princeton, New Jersey.”

Boston may be the cradle of American independence, and Cambridge the home of the country’s oldest and most prestigious university, but until the past few years the region wasn’t even on the map of big pharma. Area academics with backgrounds in molecular biology had formed many biotechnology companies, some of which aspired to become the next big pharma. However, the nation’s chemical-based drug industry was confined to the mid-Atlantic region and the Midwest.

Pfizer made the first move in 1999, opening up a Discovery Technology Center in Cambridge that offered the latest technology to drug discovery scientists throughout the company. Last year, officials expanded the center’s mission to the entire pipeline of drug development and plucked Phil Vickers from the company’s ranks to run it. A 45-year-old biochemist who enjoys a challenge and a change in scenery, Vickers was born in England, received his Ph.D. at the University of Toronto, and did a postdoc at the National Institutes of Health in Maryland before joining Merck’s Frost laboratory in Montreal in 1988. He came to Pfizer in 1994 and earned his stripes in a series of management posts on both sides of the Atlantic.

Perched on the edge of the MIT campus, the renamed Research Technology Center aims to satisfy Pfizer’s need for technological support by mixing in-house expertise with the skills of local academics and start-up companies. Vickers says his youthful but growing shop—he plans to add 25 scientists to the current 110-person roster by the end of the year—“offers the attributes of a biotech with the resources of a big pharma.”

Despite running an operation almost 10 times the size of Pfizer’s, Mark Fishman describes NIBR in similar terms. A molecular cardiologist who had pioneered the use of zebras to gene discovery at Harvard Medical School (HMS) and Massachusetts General Hospital, Fishman is hoping to “functionalize the genome” by applying it to diseases where the biological mechanism is already understood. The lab’s location—the region has supplied more than half the institute’s talent, not to mention an ever-widening network of academic collaborations—provides an added boost, he says.

Already, Fishman has raided HMS to find global heads in cardiovascular research and modeling disease. He’s also tapped biotech and pharma for chiefs in oncology, molecular pathways, and discovery chemistry, luring them with the prospect of painting on a fresh canvas. “We’re getting who we want, and almost nobody has left,” he crows.

Across the Charles River and adjacent to Boston’s medical complex sits Merck’s Edward M. Scolnick Research Laboratory. Named in honor of its former research chief, the new 12-story, glass-faced lab opened last fall, and its site head, Lex Van der Ploeg, is busily recruiting talent. Van der Ploeg, 50, a specialist in infectious diseases who joined Merck in 1991, took on the challenge after a year spent shifting the focus of Merck’s San Diego facility from neuroscience to stroke. Soon after he left, however, corporate officials decided to shut the lab and shift some resources to other sites.

His mission is to rev up the company’s efforts in developing treatments for cancer, obesity, and Alzheimer’s disease. He expects to double the size of the basic research team, now 140, by 2007, beginning with oncology and then moving into the neurosciences. “The proximity to talent is terrific, and our success rate is about 90%,” he says about current recruiting efforts. About a quarter of the scientists have migrated from other Merck labs.

—J.D.M.

transferred to another site. During one gut-wrenching transition, Gulve spent weeks interviewing scientists for a revamped department—without knowing whether he would be their boss or even if he would still have a job with the new company.

There’s no way to know if Gulve’s career path is typical. Some scientists remain at one company their entire lives, and others switch jobs often and voluntarily. But mergers have clearly changed the landscape of big pharma in the past decade. Gulve’s current employer, with $52 billion in sales last year, has become the industry’s leader thanks to its ingestion of Warner-Lambert in 2000 and Pharmacia, each of which in recent years had swallowed smaller fish such as Parke-Davis, Upjohn, Monsanto, and G. D. Searle.

“I’m not complaining about any of the decisions that were made,” he says. “But it is frustrating when you’ve worked so long and hard on a project and still haven’t gotten far enough along to know if your hypothesis is right or wrong. I know that mergers are part of the business. But I hope that I never have to go through another one.”

A view from a loyal critic: The art of drugmaking

Derek Lowe may be unique in the pharmaceutical industry: He’s a medicinal chemist for a big pharma who writes a blog on drug discovery. His column (www.corante.com/pipeline) is an irreverent look at the industry. It’s filled with pinpricking commentaries on the latest clinical results, corporate reshufflings, and...
It’s Still a Man’s World at the Top of Big Pharma Research

For a few years after their company was acquired by Wyeth in 1995, molecular biologist Abbie Celniker and several female colleagues at Genetics Institute in Cambridge, Massachusetts, hoped that the new management might boost their careers. But eventually they came to the opposite conclusion. “There was an established culture [at Wyeth] that said it would be harder to influence our peers. ... Simply put, we didn’t see a career progression unless we learned to play golf and use the men’s room.”

What Celniker, now senior vice president for strategic research at Millennium Pharmaceuticals in Cambridge, had sensed becomes obvious by looking at the leadership rosters of the research divisions of big pharma: Drug discovery is a man’s world. Not one of the chief scientists or heads of research at these companies is a woman. The precious few senior women executives with science Ph.D.s or M.D.s are most often found on the development/business side of the company or holding corporate posts without line responsibilities. Why that’s the case, however, is much less clear. Ask a man and you’re likely to hear that the industry is no different from the rest of society. Then he’ll note that his company is very concerned. “It’s a tough issue that I think about a lot,” says Jonathan Knowles, head of global research for Roche. “I’d like to understand it better.” He’ll also say that things are getting better.

Ask a woman—who by definition has not made it to the top—and her answer will be quite different, although equally nuanced. “The forces keeping women scientists down are more psychological and cultural than legal,” says Joanne Kamens, a project team leader at Abbott Bioresearch Center in Worcester, Massachusetts, and president of the state chapter of the Association for Women in Science. “People still have a problem seeing women as leaders rather than as caretakers and mothers. Men who decide to spend more time with their families also tend to be seen as weaker. But at least they have the option. If the father can’t help out at home, it falls on the women.”

Barrier-free. Novartis’s Lijun Wu makes room for both career and family.

overhyped trends in the business. He’s not embarrassed to describe his own failures, either, including an on-again, off-again attempt to test a hypothesis that stubbornly resists verification.

His daily musings generate 25,000 hits a month. That traffic feeds Lowe’s need for an audience, a hunger that offsets the lack of payment for his labors. “It hasn’t helped my research,” he confesses about the blog, which he started in 2002. “But it’s given me a much broader perspective on the business.” His readers are both colleagues—“insiders write me about how they’ve tried the same things in their labs that I write about”—and outsiders with a voyeuristic streak. “Where else would I get to hear from people saying, ‘When I took that drug you wrote about …’? I’ve also done some historical reading about the fashions that sweep through the industry and the fact that most of them don’t pan out.”

A 1988 chemistry Ph.D. from Duke University, Lowe wanted to teach at a small liberal arts college but couldn’t find the right job. Answering a job ad has led to a career in industry that he says “has worked out pretty well.” He currently works for Bayer but goes to great lengths to separate his dual identities as a researcher and blogger.

Lowe doesn’t hesitate to point out the foibles of the pharmaceutical industry. “We’re not angels. And when we mess up, I say so. If I was rah-rah all the time, nobody would read me.”

Even so, he’s as dedicated to improving human health through modern drug discovery as any pharma bigwig. Taking umbrage at a recent story in Business Week entitled “Biotech, At Last” that paints academic research as nimble and pharma science as hidebound, Lowe writes: “It’s true that many of the basic discoveries that have led to the current biotechnology industry came from academic research. That’s just as it should be. But none of it would have been turned into human therapies without corporate research and development.” And he’s personally offended at the article’s characterization of pharma’s relationship with biotech in the 1980s and 1990s. “Shed away from biotech for years? We pumped uncountable billions into it, much of which we never saw again.”

A career-eye view: A taste of industry

What’s a postdoc doing in pharma? Scottish-born David Dornan has spent nearly 3 years at Genentech, which has a 30-year-old policy of seeking out promising young scientists to pursue basic research. And although the company has a rule that its postdocs don’t move into permanent positions, Dornan sounds like someone whose career aspirations may have been altered by working at the South San Francisco, California, biotech giant.

“My future? I think of it every day,” says the 27-year-old Dornan, who earned his Ph.D. in molecular oncology at the University of Dundee, U.K. “And the longer I’m here, the more difficult it is to envision becoming an academic.”

A member of a team led by Genentech’s head of oncology V. M. Dixit, Dornan was a co-author of papers in Science and Nature last year that describe the group’s work on how cancer-related proteins are degraded by the ubiquitin system. And although the work is fundamental science, Dornan has also been bitten by the drug discovery bug. “We found something that could be a therapeutic, and we have a unique chance to put it into development. It depends on the next phase. And if it works, we’ll be handing it off to the chemists. The point is that it’s possible.”

Dornan is realistic about his chances of staying on the West Coast. “California is great, but you have to be willing to go where there’s a job.”

A view from a distance: Landing on her feet

When Myrlene Staten saw the job ad in the New England Journal of Medicine in 1989, she thought it could have been written just for her. “Roche wanted a junior faculty member with clinical experience in metabolic diseases,” she recalls. Her work as an endocrinologist at Washington University in St. Louis made her a perfect fit, she realized, and before long she had moved from Missouri to New Jersey to help the company develop drugs for obesity and diabetes.

It was the start of a 15-year odyssey through big pharma that she recalls with mixed emotions from her current post at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, where she runs a program to encourage academics and small companies to develop new therapies for type 1 diabetes. After 4 years at Roche, she moved to Lederle, which was soon bought by Wyeth. In 1995, she headed out west to Amgen, where she was part of the team doing...
Ljun Wu, a 41-year-old unit head within the cardiovascular group at the flagship Novartis Institute for Basic Research (NIBR) in Cambridge, Massachusetts, remembers being asked as a graduate student if her decision to get married meant that she planned to drop out of the program to have a family. Several years later, after becoming pregnant with the first of her two children, colleagues told her that her bosses at Millennium were wondering if she’d return after giving birth. “My career was going well, and they didn’t ask me directly. But I think it’s unfair; they wouldn’t have wondered that about a man.”

Wu doesn’t understand why any employer would care whether she even has a family. But most pharma executives acknowledge that family responsibilities do matter. “One possible reason [for the hesitation] of women is that any senior position requires a huge commitment,” says Knowles. “It would be difficult for someone to do that type of job while also looking after a home and small children.”

Amen’s research chief Richard Perlmutter offers similar thoughts. “I’m reluctant to generalize about gender differences,” he says. “At the same time, you can’t get around the fact that the burden of early child rearing may be a career breaker [for some women].”

That burden can show up in subtle ways, notes Lynne Cannon, vice president for human resources at NIBR. “It’s not just a question of having the door open to women,” she says. “Sometimes it’s about how the door gets opened. If I can’t stay until 8 p.m.—when a lot of decisions get made—because I have to pick up my kid at 6 from daycare, then I may miss out on something important.”

Many pharma companies have recently begun to identify and assist women scientists who want to move up the corporate ladder. Novartis has a “women to watch within the lab” program, Cannon says, to provide ongoing career guidance and support for outstanding women. “Mentoring is great,” says Cannon, “but there’s a danger if you attach yourself to one person and that person leaves.” Although that’s true for men, too, the dearth of women makes any loss of support costly.

Wyeth has a similar program for top-performing women, says Robert Ruffolo, president of research and development, that’s modeled on a gender-blind program for the top 1% of its researchers. Gail Cassell, vice president for strategic planning for Eli Lilly, says that the Indianapolis, Indiana–based company offers a variety of programs for women scientists, from tips on how to ask for a promotion to networking with colleagues in other fields.

None of the programs has run long enough to accumulate meaningful data, however. And it’s not clear that company executives have thought in much detail about what they want to achieve. “We don’t know what enough is,” Ruffolo admits. “But we consider it a win as long as we’re attracting more women and minorities each year than are leaving the company.”

--J.D.M.