Pharma and academia partner for better health

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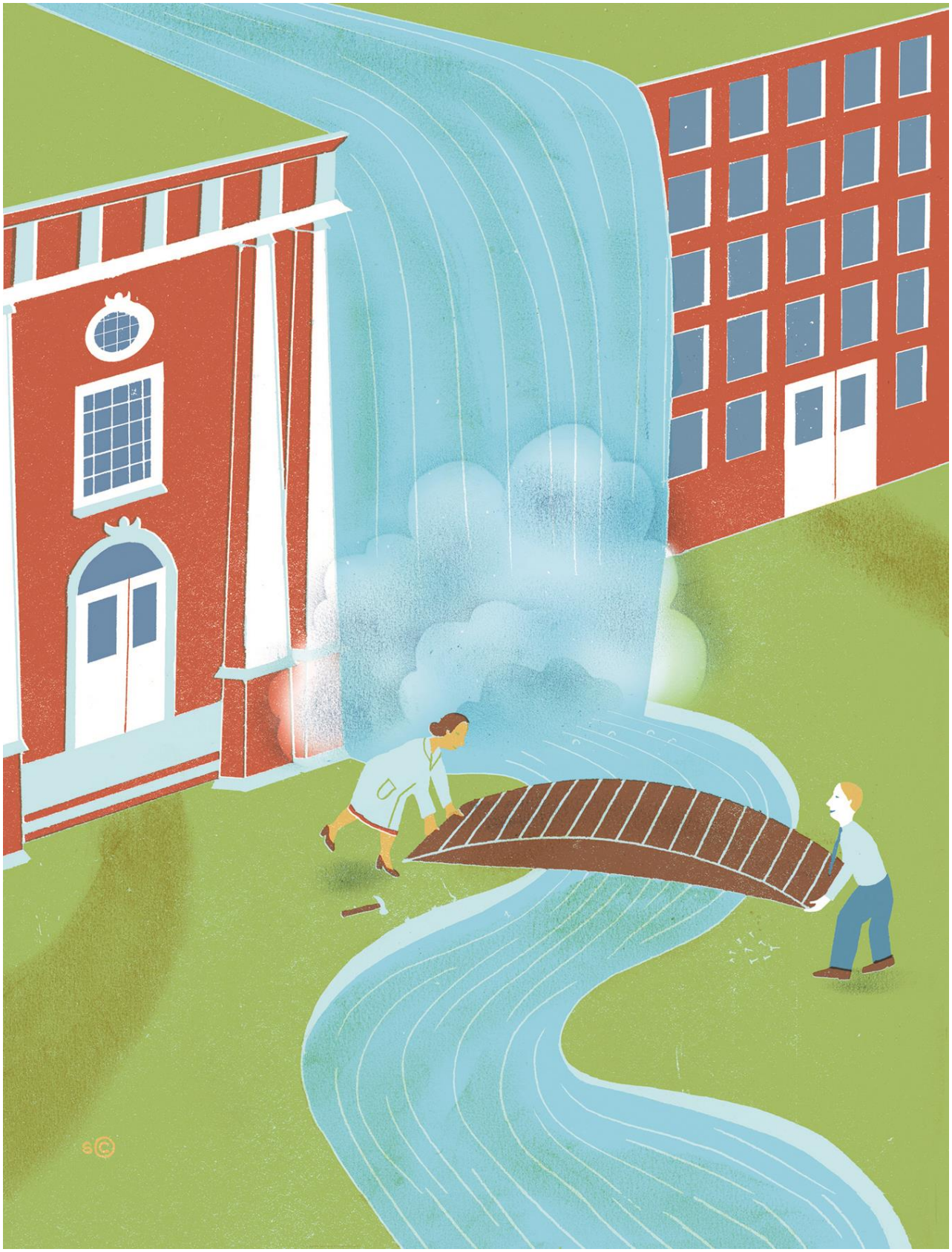
Yale joins forces with the pharmaceutical company Gilead Sciences to search for targets for new and improved cancer therapies.



Illustrated by Sophie Casson

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In 2008 Ruth Halaban, Ph.D., began searching the DNA of melanomas in a quest for genetic clues to skin cancer. The obvious connection between sunlight, ultraviolet rays, and cancer, she said, had been determined through population studies. The genetic causal link remained to be discerned. Halaban hoped—naively, as it turned out—that with about 20 samples she could find a genetic anomaly that would provide that link.

But with the sequencing of each sample then costing $2,500—and she also had to sequence a normal sample for comparison—the experiment grew costly. Funding from private foundations helped her launch the project, but Halaban, a senior research scientist in dermatology, soon realized she'd need far more than 20 samples. In the end, the cost of sequencing fell to about $1,400 per sample, and Halaban sequenced almost 150 samples. Her findings led her to a gene called RAC1, which appears mutated in about 9 percent of melanoma tumors. She completed the research in 2012 thanks to a collaboration with Gilead Sciences, and her findings were published online in *Nature Genetics* in July of that year.

"We discovered that *RAC1* is a sunlight signature mutation," said Halaban. "You can say that this is the culprit. This is directly related to sunlight."

Halaban's findings are the fruit of a collaboration between Gilead and the School of Medicine that began in 2011. By studying the genetic and molecular mechanisms underlying different forms of cancer, Yale and Gilead scientists work together to pinpoint new molecular targets implicated in cancer pathogenesis, and to develop agents designed to put a halt to the molecules' rogue activities.

Under an agreement with the School of Medicine, Gilead agreed to provide $40 million over four years to support research to identify novel targets and new drugs for cancer therapy. The collaboration will continue, with evaluations after the fourth and seventh years, through 2021 with a total of up to $100 million in funding over 10 years—the largest corporate commitment in Yale's history. As part of the agreement, Gilead has the option to license potential cancer therapies that result from the collaboration.

Although such collaborations are decades old, in recent years academia has sought new funding sources as the pharmaceutical industry seeks new research collaborators. The industry needs new drugs in its development pipeline, and researchers across the country worry about years of flat spending from the National Institutes of Health, sequestration—which mandates across-the-board federal spending cuts of 8 percent—and declines in funding of research from venture capital. Partnerships between universities and pharma also allow each party to leverage their respective strengths in research and drug development.

Tapping into the best minds

The Yale-Gilead collaboration relies on some of Yale's top scientific minds, technology investments at the West Campus, and the resources of Yale Cancer Center, the Cancer Biology Institute, and Smilow Cancer Hospital. "Through this collaboration," says

Howard Jaffe, M.D. ’82, president and chair of the board of the Gilead Foundation, and a member of the Yale-Gilead joint steering committee, “we’re tapping into some of the best minds on the planet who’ve done it before and are scientifically, technologically, and instinctively better than just about anybody else.”

Indeed, the joint steering committee brings some of Yale’s leading scientists and clinicians to the table to help select and nurture the Yale research projects that receive Gilead funding. Joseph Schlessinger, Ph.D., chair and the William H. Prusoff Professor of Pharmacology, and director of the Cancer Biology Institute on the West Campus, chairs the six-member committee.

“When we find cancer targets that are new, we will work with Gilead on designing drugs, which they can then test in the clinic,” said Schlessinger, whose studies of molecules involved in cell signaling led to the development of many cancer drugs, including two developed by his biotech companies. “This is a tremendous opportunity for Yale and Gilead.”

The Yale half of the steering committee also includes Richard P. Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics, head of the Yale Center for Genome Analysis, and a Howard Hughes Medical Institute investigator; and Thomas J. Lynch Jr., M.D. ’86, the Richard Sackler and Jonathan Sackler Professor of Medicine (medical oncology), director of the Yale Cancer Center, and physician-in-chief of the Smilow Cancer Hospital at Yale-New Haven Hospital.

Three accomplished Gilead scientists round out the steering committee—Jaffe; William A. Lee, Ph.D., senior vice president of research; and Linda Slanec Higgins, Ph.D., vice president of biology.

An old trend revived

The past two years have seen an increase in multimillion-dollar pharma-academia collaborations that focus on discovering drug targets. Notable partnerships include Pfizer and the University of California at San Diego; Sanofi-Aventis and Columbia University Medical Center; and Novartis and AstraZeneca and the University of Pennsylvania.

Since signing with Gilead in 2011, Yale has partnered with several other companies. December 2011 brought news of a collaboration with the Johnson & Johnson Corporate Office of Science and Technology to jointly fund activities at the Yale Molecular Discovery Center on Yale’s West Campus. In May 2012, Yale announced a new partnership with GlaxoSmithKline to identify promising protein-destroying drug candidates in a variety of therapeutic areas. And in February, Yale and AbbVie announced a new collaboration. AbbVie will provide $14.5 million over five years to support research into the molecular, cellular, and genetic underpinnings of autoimmune and inflammatory diseases. In return AbbVie has an option to negotiate a license for any invention made through the collaboration.

In 2002 Yale and Pfizer began a collaboration that led to the creation of Yale's pet Center in 2007.

"The proximity of the clinical research unit Pfizer was building in New Haven made it ideal for Pfizer to partner with the Yale pet Center to achieve its goal of finding out whether the drugs they were developing were hitting the targets in clinical trials," said Roopashree Narasimhaiah, deputy director of corporate and foundation relations in the medical school's development office. Pfizer, the pharmaceutical company, contributed $5 million to establish the center and provides $2 million annually to support pet imaging studies of mutual research interest. In these studies Yale and Pfizer scientists have worked together to determine whether to pursue the development of certain compounds to drugs. "It was not a discovery partnership," said Narasimhaiah. "The aim was not to discover, but to validate compounds that Pfizer was making."

Such alliances between industry and universities may suggest a new trend; but as Jonathan Soderstrom, Ph.D., managing director of the Yale University Office of Cooperative Research, explains, industrial sponsorship of academic research is not new. In fact, it is decades old. In 1982, Soderstrom said, Yale was already receiving almost $4 million in industry-sponsored research. By 1994, that figure had swelled to almost $18 million; the figures held steady between 2001 and 2009, with Yale averaging more than $15 million per year in industrial funding.

Gilead, a company rooted in HIV and hepatitis research, also points to a long history of ties to academia. "We just celebrated the 25th anniversary of an interaction we've had with two universities in Europe that was basically the genesis of the HIV drugs we developed," says Jaffe. "We've always been of the mantra that Gilead itself is only capable of a very minuscule fraction of the potential for innovation in the world, and that we can expand dramatically on that by partnering with the right academic institutions."

This recent spate of corporate agreements reflects a convergence of factors—advances in technology and a need to tap into academic research—that have opened the floodgates for academia-pharma partnerships. The prime force driving both academia and pharma to partner, however, is shrinking funding.

Creative solutions in tough times

Although the NIH budget doubled from 1999 to 2003, it has remained stagnant for nearly 10 years, topping out at $30.6 billion for fiscal year 2012. Early this year the U.S. Congress passed a continuing resolution that maintained NIH spending at that level. As a result, R01 research grants from the NIH have failed to keep pace with biomedical research costs. Despite these years of flat funding overall, however, NIH grants to Yale have been increasing. In the fiscal year that ended in June 2011, Yale received almost $340 million in NIH funding. While Yale in general has benefitted, some labs at Yale have lost funding, causing worry among scientists.

The outlook for 2013 is one of uncertainty. When Republicans and Democrats in Washington failed to reach a budget agreement early this year, sequestration took effect, with an 8 percent reduction in federal spending. A White House report issued last September projected an 8 percent cut in funding for science.

The pharmaceutical industry is likewise going through a difficult time. The cost of drug discovery keeps rising, while many of the blockbuster drugs sustaining big pharma are about to go off patent, with few potential all-stars waiting in the wings. The floundering economy means less venture capital for startup biotech companies, which big pharma has recently relied on to identify drug targets and jumpstart the development of therapeutic agents. Pharma's wellspring of research and development money is also beginning to slow to a trickle due to waning revenue growth, forcing the drug companies to look elsewhere for leads on drug candidates. Out of the search for potential fixes, academia and pharma have looked to each other's complementary strengths, recognizing that together they have the potential for much greater research capacity.

Schlessinger cautioned, however, that the collaboration should not be seen as a replacement for the NIH. Much of the cancer-related research typically supported by NIH grants, he emphasized, "do not fit the goals of the Yale-Gilead collaboration. The collaboration's goals are to identify genetic changes or other molecular alterations that take place in human cancers that can be used to develop novel targeted therapies, including small molecules, therapeutic monoclonal antibodies, or biologicals that selectively block cancer cell proliferation and/or stimulate programmed cancer cell death."

Although the monetary perks of academia-pharma collaborations are obvious—academia gets money for health-related research and pharma has the chance to identify a blockbuster drug that stands to turn a handsome profit—there are other benefits. The two sides need each other.

"The reason taxpayers in this country support $30 billion in biomedical research every year is because of the expectation that it is going to lead to an ability to improve human health," says Lifton. However, there is a catch-22. "We have almost no ability to make new drugs and pharmaceuticals in academia. We rely almost entirely on that happening in the private sector." Toward that end, he says, there needs to be a translation from basic science to clinical development of a drug.

"I have long felt that there's tremendous talent and depth of understanding of biology in academia, and tremendous talent and depth in chemistry in the pharmaceutical industry, and a very inefficient bridge between those two bodies of expertise that is necessary to translate basic discoveries into new therapies," says Lifton. "Unless we have really effective pipelines for communication between academia and industry, we're not going to achieve the realization of turning basic science discoveries into new treatments that are going to benefit the people who are funding the basic research—the taxpayers."

To facilitate new research—rapidly—the Yale-Gilead steering committee has streamlined the funding process. “If someone has an idea, they can bring it to the steering committee and it can be funded two or three days later,” says Lynch. “Even in the best scenario, the NIH funds projects nine months later from when you have your idea. So this really allows us to put resources to problems very quickly.”

Another beauty of the Gilead partnership and others like it is that they not only foster collaboration between academia and pharma, they also encourage collaboration among different medical disciplines on the Yale campus. Under standard operating procedures, an individual investigator receives an R01 grant to locate one small piece of the bigger cancer puzzle. For example, after a geneticist identifies a mutation underlying a particular cancer, advancing that information—and securing the funding to do so—sometimes gets a bit fuzzy.

“One of the real strengths for Yale has been the ability to build teams among clinical investigators who have access to patients and tissue samples; genomics investigators who know how to use those samples to discover genes that underlie specific forms of cancer; and biochemists and cell biologists who know how to go from specific genes and their mutations to assays to determine the consequences of the mutation that has been identified,” says Lifton. “It’s been really catalytic in terms of team-building across disciplines at Yale.”

Halaban concurs. Every Thursday morning, she attends a melanoma board meeting with surgeons, pathologists, medical oncologists, radiologists, and researchers, where the discussion may turn to her Gilead-funded melanoma sequencing project. “To hear clinicians talking about genes, asking me, ‘What did you find out about this gene or that gene?’ is amazing,” says Halaban. “These things were not previously part of routine discussions. But now, the genetics of melanoma, currently mostly *BRAF* mutation status, changed it all.”

Yet another advantage is that the flow of cash promotes other non-Gilead-funded research. “They’ve infused resources that we may not otherwise be able to get, both to expand Yale’s genomic capability and to build other aspects of our infrastructure,” says Patricia Pedersen, Ph.D., associate vice president for development and director of corporate and foundation relations, who played a key role in negotiating the collaboration. “Overall, the Gilead investment has increased our capacity, which was necessary to enable us to deliver results to them. In doing so, it has increased our ability to do more research, apply for more NIH grants, and get other funding.”

Finding the right partner

Although academia-pharma collaborations create synergy through aligned interests and can be highly productive, negotiating the terms of the relationship can be difficult. Each stakeholder holds different core values. Academia prizes public pursuit of knowledge, research grant funding, and intellectual freedom. “We all have academic calendars that

we live on, meaning that we want to get promoted, and for our careers to advance so that we get more grants. That's why we have a never-ending desire to publish," says Lynch.

Both sides are working to eliminate such potential sources of conflict as restrictions on publication, problems with licensing rights, and conflict over control of the intellectual property. "You have to pick your partner well," says Lynch. "It's like a marriage. It's really important that you select a company that fits the university."

"Indeed, Yale and Gilead have established strong links, productive collaboration, and common goals, and function as a harmonious couple," Schlessinger said. Jaffe is an alumnus of the medical school; Gilead Sciences has previously funded faculty research projects; and the Gilead Foundation has supported a needle-exchange program and a mobile health care van in New Haven, so there is a history of camaraderie and collegiality. Adds Pedersen, "The company's leadership is very academically minded." For example, Gilead respects Yale's mission to educate and disseminate information, placing few restrictions on the ability of Yale researchers to publish.

"I think that Yale can feel confident based on our long-standing relationship and Gilead's track record of social responsibility. We have pioneered worldwide access to our HIV drugs, signing deals with 13 different generic manufacturers in India and having a no-profit cost," says Jaffe. "We're different. The major reason is that the people who created the value are still here. We're all scientists or M.D.s. The core senior management of the company has been together over 20 years. We've been able to maintain a certain culture here, and I think that's of benefit for the Yale group."

Given the pressures on both pharma and academia, such alliances seem inevitable.

"I believe that there is great beauty in science, and that's one of the compelling things about being a scientist," said Lifton. "But in addition, there is the expectation that our research will ultimately contribute to improvement in human health. Today, that is almost always going to go through an industry partner. We need to recognize that that's how our system works."

Schlessinger agrees. "Many colleagues from other universities, as well as senior executives of major drug companies, emphasized to me the visionary aspects and the forward looking approach taken by the Yale-Gilead collaboration," he said. "Moreover, as I believe that we are now in a golden age of drug discovery for cancer therapy and treatments for other diseases, we must come up with creative solutions to merge the best that academia and drug companies offer in order to develop new treatments that reduce the suffering caused by such devastating human diseases as cancer."

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