

Opening up the Ivory Tower

Big pharma is increasingly looking to academia for new drug leads and technologies; meanwhile universities are being forced to look beyond the National Institutes of Health (NIH) for funding. This mutual attraction-out-of-necessity is helping to forge new bonds between industry and academia.

The notion of a blockbuster drug that generates more than \$1 billion in revenue a year for a big pharma company is waning. Both the business model that produces these monster money-makers as well as the technology underlying drug R&D appear to be positioned to make blockbusters a by-product rather than a goal of a changing system. “Pharma is not depending on the blockbuster, they moved away from that strategy,” says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development in Boston. In addition to the expense of developing drugs with broad indications for large patient populations, the same type of drugs tend to hit the marketplace at the same time, creating a horse race between companies that escalates marketing costs, says Kaitin. And against the odds, if a drug does become a blockbuster, “the company becomes in an unhealthy way reliant upon that product,” he says. Additionally, “when the drug goes off patent, the company suffers.” Points out Simon Goodall, leader of Boston Consulting Group’s (BCG) biopharmaceutical R&D practice, “Obviously, if you can I.D. and develop a blockbuster, it’s still valuable for a portfolio... But the business model itself is breaking down. Nobody has the answer yet. You can’t point to a company that has the new business model.”

The pressure to change business models is also being driven by what lies ahead: loss of patent protection for some notable blockbusters following the examples of Zolofit (Pfizer) and Pravachol (Bristol-Myers Squibb) and potentially fewer new molecular entities or NMEs—molecules containing no active moiety

with physiological/pharmacological action that is already approved by the US Food and Drug Administration (FDA). Indeed, between 2002 and 2005 there were 87 NMEs approved by the FDA, compared to 116 from 1998–2001 and 142 from 1994–1997. Almost \$40 billion in revenue for the top pharmaceutical companies is at risk due to patent expiration in 2010 alone, according to BCG. And for the period 2011–2015, the dollar loss due to patent expiration is estimated at ~\$28 billion annually.

In the past, big pharma would have turned to biotech to pump up its slowing pipeline of new drugs. It is still doing so, but the pickings are getting slim as companies with promising therapeutics and technologies get spoken for. This is a “problem, as more companies are bidding for fewer and fewer assets in biotech, it’s not sustainable,” says Robert Ruffolo, president of R&D for Wyeth Pharmaceuticals in Collegeville, PA. “Big pharma is paying lots of money, and it can’t fill a pipeline by doing so, it’s too expensive.”

At the same time, biotech itself is changing. “Biotech in the 90s was the middleman,” says James Wells, director of the small molecule discovery center at the University of California, San Francisco (UCSF). “But the middlemen have gone away. Middlemen became pharma, it’s now bio-pharma. Biotech is so product-driven right now. Now companies pitch to investors about development-specific assets: develop for two years, sell and it’s over. It’s almost like the business model in motion pictures, you create this little company for two years, you create a picture, it’s out and it disbands.”

Wells, formerly a senior scientist at Genentech and president of Sunesis Pharmaceuticals, doesn’t necessarily think this is bad for biotech. “The market will tell,” he says. “Maybe nothing is wrong with that, though [it opens] an early-technology void.” To fill that void, both big pharma and biotech are looking more intensely to academia. “There is competition between biotech and pharma for university technology,” says Paul Pospisil, a managing partner in Aduro Capital, a venture capital firm in New York City. Biotech has always gone to academia for technology and drug leads, says Pospisil, but what has shifted now is that “pharma is willing to take on academic research earlier than it would have maybe 15 years ago, when it would take up where biology was already well established.”

Buried Patent Treasure

Between 2000 and 2005, university and institution invention disclosures by respondents to a US licensing survey increased steadily from ~12,000 to more than 17,000, according to the Association of University Technology Managers (http://www.autm.net/pdfs/AUTM_LS_05_US.pdf). New patents filed also rose from ~6,000 in 2000 to ~10,000 in 2005.

“There’s a lot of insight left on the table at academic labs” with the potential for contributing to new drug leads or technology, says Merv Turner, senior vice president for worldwide licensing and external research at Merck. Since 2000, the public markets have ceased to be an exit strategy for biotech companies, so they are looking to mergers and acquisitions with pharmaceuti-

cal companies to build equity value, Turner says, and as a result venture capitalists are no longer focusing their funds on early-stage drug discovery. "So for academic researchers it is harder to see their innovations reach development."

To tap into this trend, Merck is developing a system of scouts based in Boston, San Diego, Japan, and the UK. "Five years ago my job didn't exist," says Reid J. Leonard, a scout and executive director for licensing and external research at Merck Research Laboratories in Boston. "We are looking for opportunity extensions of our science outreach for licensing, organized around geography rather than therapeutic area. What I do is very similar to what a person with my background would do in a venture capital firm. I really am the first part of engagement on novel opportunity."

Leonard says that they have concentrated their outreach on licensing and will be expanding to a systemic approach working with academic scientists on biomarkers, target identification and validation, and methodologies for carrying out proof-of-concept studies. Merck, of course, is not alone in their outreach efforts. Novartis, Pfizer, and Amgen have also set up a presence in the Boston area, an ideal location because of its proximity to leading universities and medical centers.

The interest works both ways, especially as NIH funding has remained relatively flat since 2003—the fiscal year 2007 NIH budget is estimated at \$29.2 billion versus \$27.2 billion in 2003 (<http://www.aaas.org/spp/rd/health08p.pdf>). When inflation is factored in, this actually represents a 16% decrease, according to an analysis in the May 2007 *Journal of the American Medical Association* (JAMA 297,1867).

"Academic labs flailing along are looking to how they can move a little further downstream to make themselves more attractive to companies," says Karen Bernstein, editor-in-chief of the biotechnology industry newsletter *BioCentury* based in Belmont, CA. Is it through

"more animal models? More chemistry to present the commercial world with a more fully developed molecule? The answer is not in yet." Traditionally university tech transfer offices push technology toward industry, but the challenge remains to fund post-NIH but precommercial research in the first place, says Isaac T. Kohlberg, chief technology development officer at Harvard University. "How do you bridge this gap so the technology doesn't wind up in death valley?" As big pharma moves toward academia, universities are also reaching out.

Academia's Creative Solutions

One strategy is Harvard's Accelerator Fund, which seeks to raise \$15 million to allocate to translational research. To date about \$5 million has been raised, says Kohlberg, and approximately \$1.25 million is expected to be distributed to five or six projects this year. The funds are raised from philanthropic sources as gifts, says Larry Schlossman, a director at Harvard's office of technology development. Examples of projects eligible for funding include the design and synthesis of small-molecule inhibitors of drug targets, testing of monoclonal antibodies, testing of lead small molecules in animal models of disease, and medicinal chemistry followup of hits from drug target screening assays (<http://www.techaccelerator.harvard.edu/guidelines.php>). Final selection will be made by a committee of venture capitalists, industry executives, and Harvard faculty, says Schlossman.

At Stanford, researchers are taking matters into their own hands and looking for orphan technologies that sit in the tech transfer office but have yet to be claimed by a company. The technologies selected get one year of funding from the university and, perhaps as importantly, says program founder Daria Mochly-Rosen, mentoring by faculty with company experience.

Mochly-Rosen, a professor in the department of chemical and systems biology at Stanford University

School of Medicine, started this so-called SPARK program out of frustration with trying to get companies interested in her protein kinase C research. "Protein kinase C showed it can limit damage to the heart after a heart attack," says Mochly-Rosen. "I thought Stanford was doing a poor job in finding a partner, so I tried. And I found Stanford was doing a good job and industry wasn't interested. It didn't see a kinase as a drug."

She ended up founding her own company, KAI Pharmaceuticals, where she worked for a year. Upon returning to Stanford, she wanted to use her newfound industry insight to help fellow academic researchers. If a new drug target or technology "doesn't look like, smell like, or walk like a duck," then industry is reluctant to develop it, says Mochly-Rosen. So the goal was to pick promising but neglected technologies and work with the investigators to give them more company appeal. Mochly-Rosen asked people from industry to whittle down approximately 470 unlicensed patents from Stanford's office of technology licensing to 40, and then six. She called the investigators. "We didn't expect faculty [to work on the technology], only post docs, but we were surprised, there is faculty, too, on every project."

SPARK projects include a hepatitis C treatment, antiaging drug discovery, protease-based diagnostics and therapeutics, diagnostics for kidney transplant rejection and pancreatitis, and targeting of the unfolded protein response for treating cancer. Mochly-Rosen calls SPARK an experiment, and the odds against a company picking up one or more of the six projects are very high. But "via teaching criteria, we are already successful," she says. "As a university, we teach a lot of scientists to be academicians but many of our students wind up in industry and we don't train them. People are leaving [SPARK] with what they hadn't learned before." One example is a drug package insert that accompanies prescrip-

tion medication and offers pharmacological and clinical information, which Mochly-Rosen asked the researchers to write. "It made them realize that industry is working from the end. This is very different than the academia hypothesis-driven" approach, she says.

Craig Garner, a developmental neurobiologist at Stanford, was approached by Mochly-Rosen. His research focuses on manipulating inhibition associated with the neurotransmitter GABA as a cognitive treatment for Down's syndrome. "Over a year ago, we wrote a use patent and sent it out to more than 150 companies. One said it was interested but wanted even more basic information; they liked the idea but wanted to decrease risk." SPARK mentors reviewed his material and worked with him to position it for industry. "The faculty are not really aware of what biotech wants," says Garner. As a result, the research is "seldom placed in a format to allow [industry] to say ahh, this is one for me." The patent had a "first exposure through the office of technology licensing, and this was not in a way the community saw was important," he says. SPARK, as well as subsequent publication and media coverage, broadened the exposure, and six additional companies expressed interest.

Other programs designed to connect academia more closely with industry include those at The Scripps Research Institute in La Jolla, CA and the J. David Gladstone Institutes in San Francisco, both of which have made exclusive licensing deals with pharmaceutical companies, says UCSF's James Wells. The Gladstone, for example, has a collaboration and licensing agreement with Merck for the research and development of drugs to treat neurodegenerative diseases, such as Alzheimer's disease, that are linked to ApoE-associated mechanisms. Merck receives worldwide exclusive license to research, develop, and commercialize compounds resulting from the collaboration; Gladstone receives a \$3.25 million upfront pay-

ment, milestone fees, as well as an annual licensing fee and royalties on any marketed product stemming from the agreement.

Wells also points to the Broad Institute in Cambridge, MA, a collaboration between MIT and Harvard, as adopting some lessons from industry to apply genomic research to medical problems. "In a way, [the Broad is] set up like minipharma," says Wells. "They have functional departments like an academic institution but are matrixed around project areas and grants like pharma." BCG's Simon Goodall points to the Myelin Repair Foundation in Saratoga, CA as another research model merging industry and academic approaches to move basic research from the lab to the clinic, in this case focusing on treatments for multiple sclerosis. The nonprofit foundation pools the research efforts of scientists from Stanford, McGill, Case Western Reserve, Northwestern, and the University of Chicago while aggressively managing the intellectual property to apply for patents and engage in early discussions with pharmaceutical companies with the goal of accelerating discoveries toward the clinic.

Technology Creates Suitors

Technology itself is also forcing academic and private for-profit labs into relationships.

"We used to be able to bring new technology into our own labs—cloning and genetic manipulation," for example, says Joan Brugge, professor and chair of the department of cell biology at Harvard Medical School. "But now it is so advanced: imaging and microscopy and engineering approaches" that collaborations need to move beyond traditionally associated groups. "The interactions [with companies] were much more service-oriented" ten years ago, adds Brugge. "Now interactions are [more] about discovery... [and] a dynamic exchange of ideas."

Kenneth Kaitin at Tufts points out that genomics and personalized medicine are also pushing organizations

together. One example is The RNAi Consortium (TRC), a public-private partnership formed in 2005 by the Broad Institute and including companies such as Bristol-Myers Squibb, Eli Lilly, and Novartis. TRC aims to create a shared library of small hairpin RNAs to target 15,000 human genes and 15,000 mouse genes. This ambitious 3-year plan costing \$18 million is partly financed by contributions of \$3.6 million from company member organizations (http://www.broad.mit.edu/genome_bio/trc/). "The move in industry is away from broad-based indications to stratified medicine. To do so, [industry] needs access to technology traditionally not available" to them, says Kaitin. "Much of it is going on in government and academic labs, so it is critical for industry to get in there."

Another example is the public-private Biomarkers Consortium (http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml), backed by the NIH, The Foundation for the NIH, the FDA, and the Pharmaceutical Research and Manufacturers of America (PhRMA). The partnership includes many of the world's largest pharmaceutical companies and is based on the sharing of data and intellectual property in order to identify and validate biomarker tools and discoveries in areas including cancer, neuroscience, and metabolism. "The science is driving us to less of a whole population approach and more [of a] niche approach," as exemplified by the humanized monoclonal antibody Herceptin, says Marie Vodicka, PhRMA's assistant vice president for biologics and biotechnology in Washington, DC. "Companies have to keep up with the advances in science. The science will dictate the drugs. Pharma is evolving."

An Opportunity for Crosspollination

Although people in industry and academia acknowledge this mutual need and talk up its benefits, others are not entirely convinced. "The official lie is people like collaborations, but really if you see a collaboration, it is success by necessity," says Paul Pospisil. It is "an alignment of different interests." It may even be

an opportunity to poach talent. “The relationship between big pharma, biotech and academia is that they are all competing for the best people,” says Charlene Ledbetter of LedbetterStevens, a life sciences executive search firm in New York City. “They are out-and-out competitors” for talent, with academia

luring people with cutting-edge tools, biotech with equity, and big pharma with relative job security, she says.

But partnerships may also enhance productivity of members of different teams. “To get people to be broader and innovate is to get them out of their setting,” says Ginger L. Gregory,

global head of human resources for Novartis Institutes for BioMedical Research in Cambridge, MA. It offers them the chance “to get out of their therapeutic setting, magnified by getting them out of industry into an academic lab” and vice versa, says Gregory, allowing crosspollination in both spheres.

Ken Howard Wilan

Boston, MA

DOI 10.1016/j.cell.2007.05.032