Drug Discovery Gets an Academic Push

As pharmaceutical firms retrench, nonprofit research centers step beyond their initial targets

The drug abiraterone (Zytiga), approved by the Food and Drug Administration (FDA) for late-stage prostate cancer in April and now marketed by Johnson & Johnson, took an unusual route from bench to bedside: The UK Institute of Cancer Research (ICR), which discovered the agent, also helped to carry it through phase I clinical trials.

But that’s not so unusual for ICR’s Cancer Research UK Cancer Therapeutics Unit, where 6 drug candidates have moved to clinical phase I trials over the past year.

The Cancer Therapeutics Unit benefits from having access both to basic cancer researchers at ICR and to clinicians working in the affiliated Royal Marsden Hospital. In addition, with a grant from Cancer Research UK amounting to about £7 million ($11.3 million) a year for 5 years, the group has invested in drug discovery on a large scale.

“Scale is important,” says Paul Workman, head of the Cancer Therapeutics Unit in Sutton. “If you work on only 1 or 2 projects, when most projects fail, you will not get too far.” The grant funds about half the 165 people in the group, including 50 chemists, about 40 of whom are involved in chemical synthesis.

Although ICR’s breadth of attack is the exception rather than the rule among academic biomedical research institutions, it highlights a growing trend for these institutions to broaden their attack beyond basic discovery of drug targets, with funding from both public and private sources.

Traditionally, academics have played a role in target discovery and, to some extent, target validation. “Academic research would focus on different classes of problems, mainly dealing with whether a gene or pathway would be a good target for a drug, and sometimes develop some assays to test these targets,” says Stephen Fesik, a professor at Vanderbilt University Medical Center.

“Compounds developed against these targets would eventually come back to academia as researchers would help set up phase I trials in hospitals.”

But the steps in between—the identification of lead compounds, determining their structures, and carrying out the medicinal chemistry, lead optimization, and preclinical testing—have traditionally been done in industry. “This has now changed,” says Fesik.

The waning of blockbuster drugs, the challenge of personalized medicine, and a weak economy have left the pharmaceutical industry reluctant to take chances on risky projects. Many established companies have slashed their research budgets, and the ranks of biotech companies have been decimated. The resulting gaps in the traditional drug discovery and development pipeline have created needs and opportunities for academic labs to fill in the voids.

Moreover, advances in robotics, high-throughput screening, and database mining have made it easier for academic scientists to participate in various stages of drug discovery and development. And some leading institutes have jumped on the chance to build high-throughput screening facilities and chemistry cores.

Academic researchers now “can test emerging hypotheses in human biology using small molecules and use them in a physiologically relevant context,” says Stuart Schreiber, a Howard Hughes Medical Institute investigator at the Broad Institute of Harvard and MIT in Boston.

“There is a major gulf between what academic researchers do, usually test tube–based observations, and what you need to know to discover a drug,” Schreiber says. “But by doing research in more health-oriented and physiologically relevant ways, academics can help the pharmaceutical industry to make more informed decisions about which targets to use.”

REDEFINING ROLES, REDUCING INDUSTRY RISK

Given the extremely high resource requirements in drug discovery (see “Perils in the Pipeline”), academic centers must pick their shots as they broaden their efforts.

“The reality is that developing drugs is beyond what most academic centers can do,” says Neil Spector, director of Translational Research in Oncology at Duke University’s Comprehensive Cancer Center. “It takes tens of millions of dollars and not just 1 or 2 chemists but whole teams of them. Even the best academic centers don’t have those kinds of resources.”

Carrying out the steps of drug discovery that industry is already doing on its own is not of much value, adds William Sellers, head of oncology research at the Novartis Institutes for Biomedical Research in Boston. Instead, “if academic labs open up entirely new fields and find targets that were not previously druggable, they can motivate a huge amount of research in industry,” he says.

That is the approach that Fesik and others are taking. “The focus of our work is to take highly validated targets that were not thought to be druggable and find a way to make them druggable,” says Fesik. His group uses a nuclear magnetic resonance (NMR)–based method to identify small organic molecules that bind to sites on a protein, which Fesik developed at Abbott Laboratories before joining Vanderbilt. He is applying the method to discover molecules...
“It was definitely a rude awakening for me to see what the real challenges in drug discovery are and the differences between doing great science and developing treatments,” says Ira Mellman, vice president of research oncology at South San Francisco-based Genentech and former chair of the department of cell biology at Yale Medical School in Connecticut.

Bringing a drug to market typically takes 10 to 15 years, and costs can soar beyond $1 billion. The Pharmaceutical Research and Manufacturers of America has estimated that for every 5,000 to 10,000 compounds that enter the research and development pipeline, only 5 make it to phase I clinical trials and only 1 receives FDA approval.

Once a potential drug target is identified, it must be validated to make sure that tinkering with its function will affect the disease mechanism. Finding a “lead compound” small molecule that interacts with the target in the desired way typically involves screening many thousands of such molecules.

For a lead compound to become a potential drug, it cannot sit in the stomach like a stone, be metabolized by the body before it can produce an effect, or be toxic to animals. The lead compound usually must be optimized to improve its performance.

Having the right expertise in chemistry becomes critical here. “In industry you will find large teams of chemists who have been doing drug discovery for many years. They know how to take a drug and make it soluble in the gut or increase its half-life,” says Neil Spector, director of Translational Research in Oncology at Duke University’s Comprehensive Cancer Center. “It is like going to a doctor who has been around for 30 years and has seen it all.”

With a lead compound in hand, an Investigational New Drug application can be filed with the FDA. If the application receives approval, the investigational drug must progress through phase I, II, and III trials before the company can file a New Drug Application with the FDA.

that bind to the oncogenes K-Ras and c-Myc. “It’s a big challenge but with a potentially high payoff,” says Fesik.

Academic institutions also take on projects that are viewed as too risky for industry. For instance, ICR’s Cancer Therapeutics Unit has identified several possible drug targets that were thought to be too risky, such as PI3 kinase and the heat shock protein Hsp90. “These were targets industry was not initially interested in,” says Workman. “When we first decided to take on Hsp90, people said, ‘You must be joking.’ Now there are 16 to 18 drugs in clinic against this protein. Big pharma is now doing the work, so it is time for us to move on to the next project.”

Additionally, academics can find targets for drugs against diseases that affect small numbers of patients, for which industry may be reluctant to invest resources, or find new applications for known drugs. “A more realistic route to drug development for many academic centers is to take a drug being used for certain indications and, through research, identify additional uses,” says Spector. “This is something industry is not doing because it does not bring in money.”

**PICKING INDUSTRY PARTNERS**

Generally, however, an academic lab must partner with industry to bring a potential drug to clinical trials and file for FDA approval. “The choice of how and when to do it depends on the best way to get a compound to patients as quickly as possible,” says ICR’s Workman. As in the case of abiraterone, his group has taken some projects all the way to phase I trials. Often that was because “industry thought the project was too risky or just because we thought we could do it quickly,” he says.

In other instances, ICR partnered with industry at an early stage—for example, if the group needed access to large chemical libraries to screen for lead compounds or if he thought industry would work faster in optimizing a compound than his group.

At other times, Workman says, he started biotech companies that could take a drug discovery project to a stage where larger companies would be interested. “At that time, venture capital funding was available, and a start-up was a good way to move the projects along quickly,” he explains.

**CREATING ACADEMIC BUY-IN**

Academic institutions also must buy into the notion that drug development is important. “Our performance is viewed under that light,” says Workman. “We are expected to publish strongly and we do, but at the end of the day the goal is to get drugs into the clinic.”

Without this buy-in, academic culture can stand in the way of drug development—an endeavor that requires large, multidisciplinary teams of scientists. “In academia, the reward system relies on publishing papers and getting grants, and people are often faulted for being on multi-author papers,” Spector points out.

Overall, however, “I think it’s tremendous that academic institutions are realizing that translational research and experimental therapeutics are just as worthwhile as basic research,” Spector emphasizes. “It is a great leap forward that we can apply to unmet medical needs.”
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