Are Intellectual Property Rights Hampering Cancer Research?

In 1988, Harvard Medical School was awarded the first of three patents for creating the first transgenic mouse that would develop a human cancer. The mouse soon became known as the “OncoMouse” and was, at the time, considered pioneering technology by the U.S. Patent Office. The achievement occurred in the laboratory of Philip Leder, M.D., with funding from E. I. DuPont de Nemours & Company; as a consequence, Harvard gave DuPont certain exclusive rights to the resulting intellectual property. The patents, issued between 1988 and 1999, cover the animal itself, the process of making it, and methods of using it.

Since then, many variations of the OncoMouse have been created—some through technology similar to that used by Leder, which basically involves the insertion of human oncogenes into a single-cell mouse embryo that will be expressed in specific tissues, and others through quite different methods. The latter has led to disputes with DuPont about whether these mice should be covered by the patent.

But in general, DuPont has maintained an iron grip on the technology such that high-priced licenses must be obtained from the company when investigators use transgenic mice for cancer research and wish to test drugs on them. The latter may involve either academic–industry collaboration or research within a for-profit company. In either case, the for-profit company must obtain a costly license, reportedly sometimes ranging into the millions of dollars. Academic or other non-profit institutions doing only basic research, including the development of new mouse models, may now obtain licenses at no charge, although some restrictions are imposed. More than 170 of these free academic licenses for several OncoMouse models have been given out, according to William Cotreau, senior patent counselon for DuPont.

At the recent 24th Congress of the International Association for Breast Cancer Research (IABCR) held in Sacramento, the scientific focus was on the use of preclinical models of human breast cancer, which involves attempts to test the effects of various therapies, primarily drugs, in mice—such as the OncoMouse and other mammals (mostly mice) genetically engineered to develop human breast cancers.

However, center stage of the meeting was occupied not by the many exciting research presentations, but instead by sometimes heated discussions of intellectual property rights to these mice.

“We believe that within these mice is the answer to breast cancer,” said Robert D. Cardiff, M.D., Ph.D., professor of pathology at the University of California at Davis Center for Comparative Medicine and director of the meeting. “If we can now engage the people who are going to deliver treatment—industry, the private sector—we can eradicate breast cancer.”

The biggest problem comes with for-profit companies that develop most of the drugs. Academic investigators or researchers at the National Institutes of Health may try to forge an agreement with a pharmaceutical or small biotechnology company to test one of the company’s drugs for efficacy in treating a human cancer growing in a transgenic mouse.

If results are encouraging, the company generally will want to do its own research using the same mouse model with the hope that it can eventually get the drug to the market, but this means that the company will have to pay DuPont what many feel are exorbitant fees for a license to the transgenic technology. (Harvard gets a portion of this money.) Some large pharmaceutical and biotechnology companies have already obtained such a license; for example, via this mechanism the Genentech/Hoffmann-LaRoche agent Herceptin was tested in an OncoMouse model and was brought to market for the treatment of some breast cancers. However, many other companies are often either unwilling or financially unable to obtain such licenses, so the companies decline to allow academic investigators to test their drug, and the research plan sinks.

“Companies won’t share drugs if you’re working with [mice genetically engineered to develop a human cancer],” said Cardiff. “They don’t want their drug validated or in any way tested with such mice for fear DuPont will find out, reach through [the research agreement between the academic researcher and the company], and want royalties.”

One exception occurs if a commercial entity decides to provide its drug free to an academic or government investigator “and not position itself to take commercial advantage or state [intellectual property] rights,” Cotreau said at the IABCR meeting. “That activity can then be performed under the terms of the free license.”

In a recent statement, DuPont said that it “does nothing to hinder or to delay cancer research.”

A few years ago, all investigators—academic and non-academic—who were using transgenic technology were required to pay licensing fees to DuPont. But in January 2000, the Public Health Services (PHS) and DuPont signed a memorandum of understanding. The agreement allows PHS researchers to use transgenic technology without a license as long as there is no commercial purpose or direct benefit to a for-profit institution. PHS investigators can also transfer these mice to other academic scientists as well as to for-profit scientists, but the latter must obtain a license.

The agreement was also intended to pertain to institutions that receive funding from the PHS, but in a number of instances, universities have found such negotiations difficult.

“NCI’s mandate and our mandate is that we want to do more than basic research,” said Teri Melese, Ph.D., associate director for technology at University of California at San Francisco Comprehensive Cancer Center.
“In our own mouse models of cancer program we want to do translational research, which entails coming to some agreement with the private sector. But unless the primary [transgenic] tumor models become accessible to the community, they will never become the gold standard for preclinical models that they have the potential to be. This is the age of chemical genomics and using compounds to trace pathways.”

Transgenic Mice as a Preclinical Model

Another problem is that neither pharmaceutical companies nor the U.S. Food and Drug Administration have generally adopted mouse models of human cancer as a standard for testing drug efficacy in cancer. In use instead are tests on xenografts—which commonly involve implantation of human cancer cells that have been growing in culture into an immunodeficient mouse—or simply tests on such cell lines themselves. Some researchers scoff at these tests, which are inexpensive and give results quickly, as outdated technology.

For one thing, researchers now know that having a blood supply is very important to tumor growth as is having a competent immune system.

“Companies believe they have to do things quickly in order to maintain and get their drug on the market before a competitive drug,” said Lewis Chodosh, M.D., Ph.D., associate professor in cancer biology at the University of Pennsylvania School of Medicine. “It’s rare to find a company using genetically engineered mouse models. Pharmaceutical companies don’t want to use survival or [continued presence of tumors] as an end point. They want to use growth of cells in a plastic tube implanted subcutaneously in a mouse over a 4-day period as an end point. You can get a number from that, but what does it have to do with how human cancers behave?”

“If companies use what many scientists consider to be inferior ways of testing drugs, we all lose,” said Bob Erwin, chairman of the board of a small biotechnology company in California and director of a nonprofit cancer advocacy organization. “The majority of compounds that come to clinical trials don’t make it because they haven’t been tested adequately preclinically”—referring to research that can weed out drugs that look promising but are destined to fail in clinical trials because they are not appropriately targeted to genes or biologic pathways that play major roles in cancer.

To be sure, there is disagreement on whether these genetically engineered mouse models are true models of human cancer and can essentially be used as surrogate patients in preclinical studies.

Jeff Green, M.D., head of the transgenic oncogenesis group at the National Cancer Institute’s Center for Cancer Research, believes they are unquestionably valuable but is not yet certain whether they have better predictive value than the traditional xenograft models. “My concern is that we won’t know the answer unless we have access to drugs and are given the ability to test many of these compounds in the genetically engineered mouse models,” Green said. “They may not be, or they may be under certain circumstances or for certain tumor types, although I think many in the field believe they are better in many instances.”

According to Cheryl Marks, Ph.D., scientific program director of NCI’s 4-year-old Mouse Models of Human Cancers Consortium, “with the gene targeting that is taking place in the newest iterations of mouse models, the biology is highly reminiscent of human disease. We try to ask whether, if a particular gene is turned on in the mouse, that’s necessary for the development of a disease that looks like human cancer. If so, would turning this gene off be sufficient for therapy? That’s not something the pharmaceutical companies have been doing.”

Green said that there is tremendous frustration and resentment on the part of many investigators who “have developed very relevant models for this type of translational testing and who are blocked from trying the latest and most innovative therapies.” And it doesn’t necessarily have to be a compound. “I couldn’t develop an agreement with a company that does gene therapy for antitumor purposes—designed to induce the synthesis of endogenous proteins. When the company started to explore a license with DuPont, it decided it could not afford it. So those series of experiments which perhaps could be directly translated to patients were never initiated.”

At the IABCR meeting, a prominent researcher said that after his laboratory and his university had tried and failed to get particular drugs for testing in mouse models from a well-known pharmaceutical company, his laboratory simply asked the institution’s synthetic chemists to make the compound. “Then we went ahead, did our experiments, and discovered things,” he said. “So nowadays we try to forge a good partnership not with companies but with our synthetic chemists. My advice is to get out and make the compound. Forget about these guys.”

Other researchers disclosed that this has not been an isolated practice.

Eventual Solutions?

At NCI and a few other places, comparative studies of the various ways of testing drugs, including mouse models of human cancer, are beginning. The expectation is that testing the drugs on transgenic mice will yield more valid results than the other methods, but this must be proven.

For example, an NCI preclinical models working group is trying to
determine what classes of therapeutic compounds are effective on particular types of transgenic models where the initiating genetic defect is known. Results will be compared with the responses in subsets of patients who have tumors with similar genetic alterations.

In addition, “if enough pharmaceutical companies over the next year start to believe that the transgenic mouse models are an important strategy to use and the current DuPont licenses become an impediment to a major group of companies, large and small, we might be able to sit down and meet with DuPont and sort out what might be a legitimate, reasonable cost in view of their legitimate business rights,” Marks said.

“It’s a matter of sharing the risk [among all parties],” said Melese, pointing to the NCI Pediatric Preclinical Testing Program that recently came up with an agreement between pharmaceutical companies, academic investigators and NCI to speed the testing of possible agents for pediatric cancer by testing those close to phase I adult trials in predefined mouse models of human pediatric cancers.

“When the system itself starts to hinder innovation, that’s a problem,” said Rosemary Rosso, J.D., a board member of the National Breast Cancer Coalition and one of the many breast cancer advocates who attended the IABCR meeting. “It’s too easy and glib to say that just because this is the existing situation and existing legal framework, we can’t try to find better and more innovative ways to deal with it. We would be at a very preliminary stage of breast cancer research if we just stayed with the same ‘patented’ answer and people weren’t willing to ask questions and challenge the conventional wisdom. We need to come up with a system that will work now.”

—Gail McBride