The changing landscape for licensing lab mice

As methods to create new mouse models advance, protecting the intellectual property those animals represent is getting more complicated.

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Scottish scientist Roland Wolf has been working for the past 10 years to make a mouse model that metabolizes drugs the way humans do. It has been an ambitious project, Wolf says, one that has involved deleting 35 mouse genes that make the cytochrome P450 enzymes that are essential for drug metabolism, and then replacing them with their human counterparts.

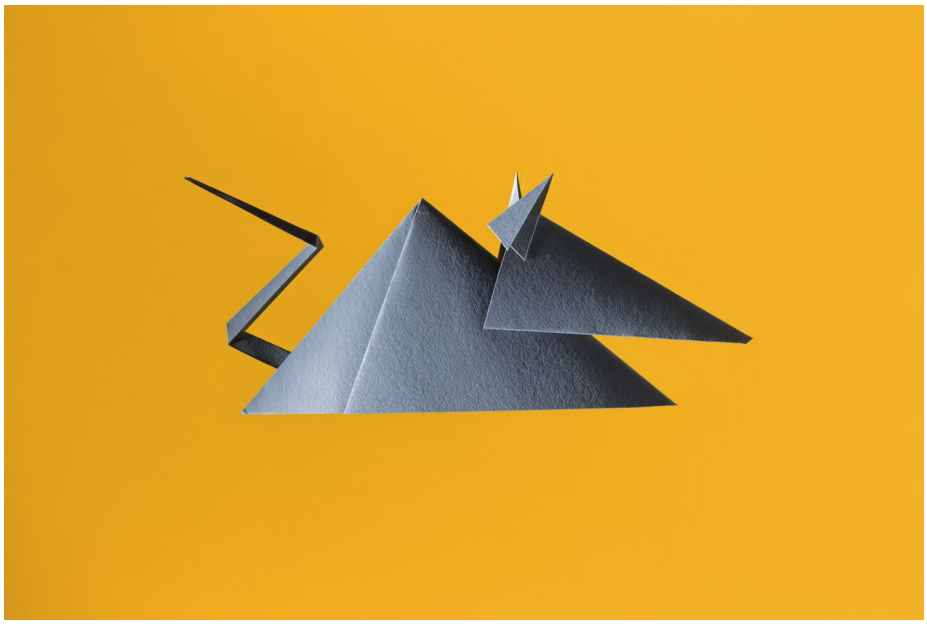
Wolf, professor of pharmacology at the University of Dundee, outsourced the development of the humanized mouse to model developers at Taconic Biosciences. Over that decade of work, the company secured the intellectual property rights it needed, allowing Taconic researchers, for example, to use the popular technology Cre-Lox to complete the necessary gene deletions and replacements.

Wolf will use the mouse and take credit for any publications that come from his studies with it, while Taconic will license it out to other scientists and drug companies for research. Taconic will not, however, patent the final mouse.

The creation of that one mouse demonstrates many of the complexities involved in navigating intellectual property around animal models. Several leading health agencies, led by the National Institutes of Health (NIH) and including many foundations that fund research in specific diseases, have pushed for more open sharing of models to advance drug development, and that has helped loosen the IP red tape to some extent.

At the same time, new technologies like the gene editing system CRISPR-Cas9 are making it easier and faster for researchers to develop innovative animal models. That only makes it more important for researchers who want to create new models—or license them from someone else—to master the basics of the IP surrounding research animals.

"The last three years has been a period of much more rapid change than the previous decade or even two were," says Megan MacBride, director of commercial models at Taconic. "If [new technology] makes it easier to develop an animal model and faster to distribute it, awesome. It will accelerate medical discoveries. But it's also more challenging from an IP perspective."



Mouse paperwork: Distribution agreements vary depending on the parties involved, but they're important for protecting the intellectual property of a new mouse model. Credit: Merton Gauster/ The Image Bank/ Getty

Distribution deals

Although some technologies used to make rodent models may have some degree of patent protection (Box 1), the animals themselves are almost never worth patenting. That's because it's not really necessary; any researcher who develops a sought-after rodent model already has control over the know-how and materials. What's more, MacBride says, "you don't want to spend a lot of money on patent lawyers, because you won't make it back."

That said, the model is still valuable to the institution that made it, so it is important for developers of mouse models to spell out use conditions and form legally binding agreements with researchers who wish to access the animals. Those distribution agreements will differ depending on whether the licensee is a non-profit institution or a commercial entity such as a pharmaceutical company.

The most common distribution agreement used for sharing animal models between non-profit institutions, including universities, is called a Material Transfer Agreement (MTA). These agreements specify that the animals will only be used by the recipient and cannot be released without permission from the developer. In addition to those restrictions, developers often add language limiting the ability of licensees to modify the model and then distribute their own version of it.

When a biopharmaceutical company wants to access a model, it's generally provided via a non-exclusive licensing agreement. This type of contract includes the same restrictions as MTAs do, but commercial licenses usually involve up-front fees and annual charges. Hence they can be attractive revenue opportunities for academic institutions. The fees vary, but a typical market rate starts at $25,000 up front, plus an annual maintenance fee of $15,000, says Michael Dilling, director of licensing at Baylor College of Medicine in Houston.

Box 1 | A case of tricky IP

The challenge of protecting the IP around mouse models gets especially tricky when the model in question is designed to generate human antibodies that could then be turned into actual drug candidates.

One high-profile case demonstrated how difficult it can be for developers of antibody-producing models to protect their inventions. Regeneron filed suit against Merus and Ablexis in 2014, alleging that they infringed a patented technology Regeneron used to produce antibody-generating mice. The company later dropped its dispute with Ablexis, but the Merus case made its way to a Federal Circuit court, which invalidated Regeneron's entire patent after ruling that the company had engaged in misconduct during the trial.

Regeneron appealed the decision to the U.S. Supreme Court in May of 2018. The justices declined to take up the case, and Regeneron and Merus settled a few months later, striking a $15 million cross-licensing agreement. The companies disclosed few details about the settlement, stating only that they "granted certain royalty-free rights to each other," while at the same time agreeing not to "exploit the other party's products."

Mastering the basics

Regardless of which type of agreement a developer is using, it's important to include specific language describing the model. Is it a "knockout" or "knock-in" mouse? What is its genotype—the exact genetic change that has been made? It's often helpful to include its phenotype as well, which is a basic explanation of how the model differs from a wild-type rodent. Finally, the licensing document should specify whether the model is a heterozygote, meaning it has one copy of an altered gene sequence and one wild-type sequence, or a homozygote, an animal with two copies of the gene sequence that was changed.

Dilling recommends that inventors of rodent models keep basic templates of MTAs and commercial licenses on hand, and then tailor those according to the requests of individual customers. That will help ease the process of distributing new models.

When it comes to licensing models to pharma companies, Dilling suggests resisting the urge to layer on conditions in the hopes of generating higher revenues. For example, some mouse developers have tried to build language into commercial license agreements that would allow them to receive royalties from any product that results from the use of their model. "That generally doesn't work out really well," Dilling says. To the typical pharmaceutical company, a mouse model is just one of dozens of tools it will use to develop a product and get it onto the market. "If you have royalty obligations attached to those, that makes it unnecessarily cumbersome," Dilling says. "That's why we stick to the market norms of an up-front payment and an annual maintenance fee." It's not always easy to strike the right balance between making a new model available in an efficient manner and making sure it's adequately protected from an IP point of view, he adds, but it is what funding institutions like the NIH expect. "They have guidelines on the distribution of model organisms, and typically what they want to see is useful models to be widely disseminated among researchers," he says.

That said, when a mouse model becomes highly sought-after, sticking with best practices can produce significant financial rewards for academic institutions. Baylor created a mouse that develops prostate cancer by the time its 12 weeks old called TRAMP (Transgenic Adenocarcinoma Mouse Prostate), for example. The college has licensed it to 60 pharmaceutical companies so far, Dilling says.

While managing the complexities associated with distributing animal models can be challenging for academic researchers who are stretched for time and resources, there are plenty of outside resources that can help. There are now several repositories that will house animal models, maintained by agencies like the National Cancer Institute (NCI), as well as distributors, including the Jackson Laboratories (JAX) and Taconic. Baylor has a distribution agreement with JAX, for example, for requests from for-profit companies. The university pays a portion of the licensing fees it receives to JAX.

The NCI houses and distributes more than 150 mouse cancer models in its repository, which is based at the Frederick National Laboratory in Maryland. The NCI has awarded several grants to researchers who develop mouse models of human cancers, and it houses and distributes the models free of charge (except for shipping costs).

The NCI created the resource in 1999 and then added a new program called the Oncology Models Forum in 2016 after recognizing the need for cancer researchers to use animal models instead of cell and tissue cultures in basic research, says Nancy Boudreau, chief of the Tumor Metastasis Branch at the NCI. "Scientists are developing a wide spectrum of models that are more advanced than they were in the past. For example, they're putting in part of an oncogene and then breeding those mice out for long periods of time to see the heterogeneity that appears in tumors," Boudreau says. "Or they're trying to recapitulate the human immune system in a mouse, so they can test immuno-therapies. These are the types of mouse lines that should be made available to the research community."

Enter CRISPR

Rapid advances in genetic engineering technologies have made the process of protecting the IP associated with animal models more complex. Further complications can arise when there are multiple patent holders for technologies used to create animal models.

Take the gene editing system CRISPR, for example. Although it can't yet be used for complex genetic manipulations, it has been widely embraced by researchers who want to knock out single genes in mice for experiments. "With CRISPR, what we're seeing is more models being made at the earlier stages of development and discovery because it's cheaper and faster" than older techniques of genetic engineering, says Steve Festin, director of scientific and commercial development at Charles River.

The use of animal models in earlier stages of research can make IP and licensing decisions more difficult. Festin recommends that developers plan ahead, considering all the potential uses of their models and making sure any limitations are spelled out in MTAs and licensing agreements. "Developers are not necessarily generating models with a commercial interest, but at a later point those models could be potentially valuable in the drug discovery process and bringing therapies to market," Festin says. "You need to make those considerations earlier in the process so you're not facing IP and licensing challenges later."

What's more, CRISPR has its own IP limitations. Patents for the technology are held by several institutions, including the Harvard and Massachusetts Institute of Technology's Broad Institute and the University of California at Berkeley. The Broad grants CRISPR usage rights to non-profit institutions without requiring licenses, but other owners of IP associated with the technology might indeed require

that anyone who accesses a CRISPR-created mouse obtain additional rights to it.

Charles River, Taconic and JAX are among the companies that will work hand-in-hand with researchers to develop custom mouse models. That can ease the process of navigating the complex IP landscape.

That was the case for the University of Dundee's Wolf when he partnered with Taconic to make the mouse with humanized drug-metabolism capabilities. The basic patents on the core technology, Cre-Lox, expired long ago. But there are still valid patents that cover some aspects of how Cre-Lox is used, Taconic's MacBride says. For example, there's a patented system that controls inducible gene deletion in which Cre is fused to a portion of the estrogen receptor; the modified Cre deletes a floxed gene upon administration of a drug which binds the estrogen receptor. "The basic Cre-Lox system can be employed by anyone, but these more complicated variants cannot," MacBride says.

For Wolf, having access to Taconic's IP expertise was invaluable. "The program was never stalled because of patents that would have prevented us from using specific techniques or developing particular models," he says.

Indeed, rapid advances in genetic engineering have allowed inventors of disease models to make animals that couldn't be made before—a trend they predict will on accelerate in the future. Mouse developers at JAX, for example, used CRISPR to modify one of its immunodeficient models, NSG, by changing a particular gene right in the oocyte. "Before it could only be done in embryonic stem cells, which had to either be isolated from this mouse line or were very difficult to handle," says Michael Wiles, senior director of technology evaluation and development at JAX.

Even more precise genetic manipulations will be possible with an emerging technology called Cas9 base editors. These tools allow researchers to target and edit specific base of DNA with high accuracy. "About 50% of human diseases are caused by a single base change," Wiles says. "So if you can build a tool that gives you that single base change very efficiently, that helps refine your research."

With each new mouse model, of course, comes new challenges in protecting its IP. Gene editing has brought development costs and timelines down, MacBride says, but it has also lowered the standard rates that model makers can charge for their inventions. Developers who try to charge too much are likely to find potential customers deciding just to make the model themselves. "The ripple effect" of CRISPR and other new technologies in the development of animal models, she says, "has really gone quite far." ❐

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