Genetically-engineered models: the value of precious GEMs

Genetically-engineered animal models (GEMs) are critical tools for drug discovery and development, but intellectual property (IP) concerns can complicate access. As pharma and biotech increasingly outsource R&D activities to universities, careful scrutiny is required to ensure adherence to IP restrictions on research tools across those collaborative activities. As demonstrated by recent high-profile lawsuits, the stakes are higher than ever for all parties.

By Dr Megan M. MacBride

Despite improvements to *in vitro* assays, animal models are a critical part of preclinical drug discovery and development and will remain so for the foreseeable future. In particular, GEMs are specialised reagents with value across R&D stages. These tools often have significant upfront costs to generate and characterise, but awareness of their value for research and/or commercial applications, and of the intellectual property associated with GEMs, may vary among researchers, particularly in academia.

What are GEMs?

GEMs are animals which have a genetic alteration artificially introduced by humans. Most commonly these are mice and rats, but advances in transgenic technology over the past decade have made possible the development of genetically-engineered zebrafish, pigs and even non-human primates. Examples of genetic alterations carried by GEMs are gene deletions, added sequences such as reporter genes, or replacement of a native gene with the human version. A wide variety of techniques exist to make GEMs, and quite sophisticated mutations can be made. According to the International Mouse Strain Resource (IMSR), more than 200,000 genetic modifications have been made in mouse embryonic stem cells, so the number of existing GEMs across all animal species and transgenic technology types is significant.

Over time, use of GEMs has increased significantly, with the proportion of standard strains (non-genetically-engineered normal laboratory animals) used falling. While standard strains remain widely used, GEMs permit different types of experiments. For example, when it comes to development of biologic drugs, GEMs with humanised target proteins can permit study of the human drug rather than use of a surrogate in preclinical studies. Data from the UK Home Office compiled by the organisation Understanding Animal Research demonstrates this trend toward greater use of GEMs and decreased use of standard strains (**Figure 1**).

From freely shared to strings attached

Unlike some other types of research tools, GEMs are self-propagating. A single breeding pair of genetically-engineered mice can start a colony which produces scores of mice within just a few

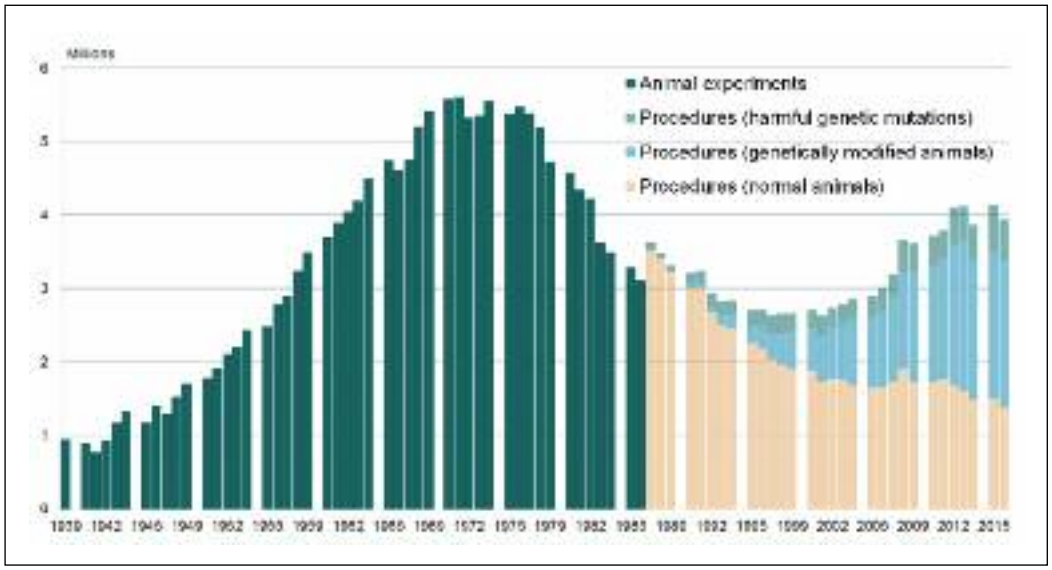

Figure 1
Credit: Understanding Animal Research

months. The development and use of well-defined laboratory mouse strains started in the early 1900s, and mouse geneticists routinely shared mouse strains freely with colleagues through the 1960s. With the advent of transgenic technology starting in the 1970s, the number of mouse strains available began to increase exponentially. The field has gone from hundreds of available strains (all generated using traditional breeding techniques) to hundreds of thousands (most generated using transgenic technology). With the identification of valuable mutant strains, the transfer of mouse and rat strains from institution to institution became more complicated.

From basic research to bioreactor

Most GEMs are used in basic research. Knocking out a gene provides a way to study the function and importance of that gene. Adding a reporter permits functional tracking, whether for gene expression or of the physical location of certain cell types. But GEMs can also be used as bioreactors to create new drugs. Mice and rats which produce human monoclonal antibodies can serve as bioreactors to generate new biologic drugs which can be evaluated and advanced into clinical development. Several different companies have developed such mouse systems, including Ablexis LLC, OMT, Inc (now Ligand Pharmaceuticals, Inc), Regeneron Pharmaceuticals, Inc and Trianni, Inc. For mouse models that produce clinical drug candidates, the intellectual property is complex and the licensing value and use restrictions are correspondingly high. With such a range in value from basic research tools through models which generate lead drugs, a range of distribution mechanisms is appropriate.

Distribution terms between individual institutions

GEMs are typically distributed under some type of legally-binding agreement. This is often a Materials Transfer Agreement (MTA), but other types of licences may also be used.

Material Transfer Agreements (MTAs)

GEMs are commonly shared between non-profit researchers under MTAs. MTAs are legally binding agreements that govern the terms under which biological materials such as GEMs, cell lines and antibodies are shared and used. These agreements are typically between two parties, a provider and a recipient, but may have more parties if additional IP rights are involved or in cases where collaborative research is performed across multiple recipient institutions. MTAs between non-profit institutions usually have the following restrictions:

- Materials are provided for use NOT in humans.
- Materials are only for non-for-profit research use by the named recipient researcher.
- Materials may not be further distributed by the recipient organisation without written permission from the provider.

Other items which may or may not be addressed in MTAs include the following:

- Further distribution of modifications made to materials by recipient.

- Authorship on publications using the material.
- Grantback of rights to modified materials

MTAs may restrict use of transferred material to a defined research scope and may have an expiration date, after which material must be destroyed by the recipient.

Licence agreements

GEMs may also be distributed under commercial licences, for example, when a pharmaceutical or biotech company requests access to a model made at an academic institution. Such licences typically carry upfront and/or annual maintenance fees and grant rights for commercial use such as drug discovery and development.

Distribution terms from commercial animal vendors

GEMs are now widely available from several non-profit repositories as well as commercial animal vendors. Terms of use vary by source. Non-profit repositories commonly use MTAs. By way of example, The Jackson Laboratory distributes many GEMs under a set of relatively simple terms of use, but access to certain other models is predicated on first negotiating and obtaining a licence from one or more third parties which have an IP interest for that model. Taconic Biosciences distributes its most popular GEM products under a simple label licence, which is a concept taken from software 'shrink-wrap' licences. These terms are deemed accepted upon purchase, and this type of label licence can greatly speed up acquisition of GEMs since no negotiation or signatures are required prior to purchase.

Tracking and compliance problems can lead to severe consequences

Negotiation and execution of MTAs take up significant time at most university technology transfer offices. Professional licensing officers focus on protecting their institutions and obtaining materials needed by their scientists, and tech transfer offices may have complex systems in place for negotiation and tracking of agreements. Unfortunately, the academic researchers actually using the materials transferred under such agreements may forget what they have agreed to. Examples of compliance problems include:

- Use of materials in work which is beyond the scope of permitted research as defined in the MTA.
- Neglecting to renew an expired agreement, despite continued use of the transferred material.
- Unpermitted transfers of material to third parties.

Such violations can lead to various problems. For example, many MTAs permit use only for internal, non-commercial research. As the interface between academic institutions and for-profit companies changes, with more universities engaging in sponsored research, contract research and even spin-off companies, GEMs and other research tools are sometimes used for commercial purposes in violation of distribution terms. Any tool, including genetically-engineered mouse and rat models, that is transferred under terms which permit only internal non-profit research should not be used in projects involving an external commercial partner without obtaining further rights from the tool provider.

High stakes

A widely-reported dispute between St Jude Children's Research Hospital and the University of Pennsylvania over technology related to chimeric antigen receptor (CAR) T-cell immunotherapy illustrates the risks involved in transfer of valuable research materials. Researchers at St Jude developed a DNA construct for a chimeric T-cell receptor and shared it with Penn under an MTA which permitted only preclinical use and prohibited any commercial use of the provided materials. The Penn researchers developed a new vector which incorporated St Jude's DNA sequence. They failed to credit St Jude in resulting journal articles and Penn licensed CAR-T technology incorporating DNA from the St Jude vector to Novartis. Meanwhile, St Jude patented its CAR T-cell technology and licensed it to Juno Therapeutics. With immunotherapy offering such promise in cancer treatment, anything related to it has enormous value and correspondingly high stakes. Each side filed lawsuits against the other, and in the end Novartis agreed to pay Juno $12.25 million plus milestone payments and royalties to settle the dispute.

The case of the Jackson Laboratory (Jax) versus Nanjing University is another example of a dispute over biological materials and transfer agreements. Jax executed a Use of Strains Agreement with the Nanjing University Model Animal Research Center, which permitted Nanjing to use animal models provided by Jax solely for internal research and restricted further transfer or resale of purchased animals or progeny. Jax alleged that Nanjing was selling progeny of strains provided by Jax and filed a lawsuit against Nanjing in September 2017. This dispute has now gone to arbitration, but purchasers of disputed strains from Nanjing, including a super immunodeficient strain distributed in the US by a

Biotechnology patents relevant to GEMs

Gene targeting technologies	The platform technologies used to make a GEM, such as CRISPR/Cas9 gene editing technology
Methods applied to a model	Use of a technique applied to a GEM, such as application of the drug tamoxifen to induce gene deletion *in vivo*
Specific genetic modifications	Individual genetic alterations can be patented. These patents can sometimes be quite broad and may cover a class of related strains, only some of which may have been made by the patent holder

A single GEM may be covered by multiple patents. The table shows common types of biotechnology patents which may apply to individual GEMs

commercial animal vendor, may rightly be concerned about their use of such GEMs.

In 2014, Regeneron filed a lawsuit against Merus and Ablexis alleging infringement of a Regeneron patent covering technology associated with GEMs that produce partly human antibodies. The Ablexis suit was settled when evidence emerged during discovery that Ablexis specifically designed its mouse model to avoid infringing the patent in question. In a surprising twist, the Federal Circuit court held that Regeneron demonstrated misconduct both during patent prosecution and during the Merus trial and rendered the entire Regeneron patent unenforceable. Regeneron was ordered to pay Merus' litigation costs in the sum of more than $10.5 million. Regeneron has since appealed the decision rendering the patent unenforceable to the US Supreme Court.

Drug companies are increasingly relying on academia as a critical source of outsourced R&D. Schuhmacher, Gassmann and Hinder studied pharma's changing R&D models and found that "73% of the investigated companies were making process changes in R&D", for example, "widening the competence field by progressively expanding collaborations and research partnerships"[1]. While these partnerships benefit both pharma and academia, the risk to pharma created by poor compliance of academic partners with research tool restrictions is non-trivial. As demonstrated above, the cost to defend litigation can be quite large, and revenues of downstream therapeutics developed with problematic IP may be at risk.

Protecting GEM intellectual property

The first patented mammal

In 1980, the US Supreme Court held in Diamond versus Chakrabarty that "A live, human-made micro-organism is patentable subject matter." That case involved genetically-modified bacteria. The first patent on a genetically-modified animal was granted on April 12, 1988 for the so-called 'Oncomouse' developed by Philip Leder at Harvard University. This was but the first of many patents on GEMs in the following years.

Technology titans

A single GEM may be covered by multiple patents. For example, the technology used to generate the genetic modification may be patented. Patents may cover methods used in the model, such as a reporter system. Finally, the actual genetic modification can be patented. Note that patent holders often permit non-profit institutions to use patents either under simple terms or without any licence, but that typically applies only to internal non-commercial use by the non-profit institution and does not permit the non-profit institution to sell, transfer or license any materials covered by the patents or generated using the patented technology.

CRISPR conundrum

The hottest new thing in transgenic technology is CRISPR/Cas9 gene editing. Frequently used to make knockout animals and cell lines, its use is being expanded towards generating other types of mutations such as introducing large segments of foreign DNA. Although CRISPR is not yet capable of the sophisticated genetic manipulations which can be accomplished via embryonic stem cell targeting, its ease of use, greater speed and application to a broader range of animal species have made it the technology of choice for a large proportion of new GEMs.

CRISPR has been rapidly adopted by the scientific community and put to a wide range of uses. As with many high-value technologies, multiple parties claim ownership of CRISPR-related intellectual property, including The Broad Institute, the University of California at Berkeley and others.

Reference

1 Schuhmacher, A, Gassmann, O, Hinder, M. Changing R&D models in research-based pharmaceutical companies. J Transl Med. 14(1):105 (2016).

The Broad Institute explicitly addresses use of its CRISPR IP by non-profit institutions as follows: "No licence is necessary for academic and non-profit use. Non-profit institutions and government agencies do not need to receive a written licence from Broad to conduct internal research, including sponsored research to the extent such research does not include the production or manufacture of products for sale or offer for sale or performance of commercial services for a fee. Further, non-profit institutions and government agencies may transfer materials they generate in the conduct of such internal research to other non-profit institutions or government agencies under the terms of the UBMTA without needing to receive a further written licence from Broad." While Broad grants wide use rights to non-profit institutes, for-profit companies should clearly understand the implication that acquisition of GEMs or other research tools made using CRISPR from non-profit institutions is not permitted without obtaining additional technology rights. They should also understand that the use of such tools in fee-for-service work at non-profit partners may require additional licences from CRISPR IP owners.

Beyond patents

While GEMs can be patented, that is not always the best strategy in terms of commercialisation. Gaining patent protection is expensive and time-consuming and may need to be pursued in multiple countries. From a cost-benefit perspective, inventing institutions may be better served through maintaining control of materials rather than obtaining patents. Licences granted to use of materials rather than patent rights can also yield royalties for extended periods of time. While the US Supreme Court held that collection of royalties after patent expiration is unlawful in Brulotte versus Thys Co, licence agreements predicated on access to materials do not have legal limitations on the royalty period. Many GEMs are distributed under licences which grant access only to materials and know-how, and this can be a very cost-effective way for inventing institutions to realise revenue from such inventions.

So what's a drug developer to do?

Intellectual property around GEMs can feel a bit like a minefield, but with proper due diligence, these important tools can be used without worry. The most important tactic is simply to be aware and ask questions. When contemplating obtaining a GEM or other research tool from a non-profit institution or collaborator, be sure to inquire as to the IP status of the tool. Relevant questions include:

- Where was the tool developed and who developed it?
- Were any materials provided by third parties?
- Under what terms was the animal model or contributing material received?
- What technologies were used to develop the animal model?
- Do you have rights to use the animal model for commercial purposes or only for internal, non-commercial research?

The answers to those questions can identify problems or turn up the need to obtain additional licence rights prior to use in the planned research. Identifying such issues upfront is always preferable to sorting out a larger problem downstream and can insulate your organisation against expensive lawsuits. DDW

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