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Licensing Transgenic Mice: A Short Tutorial

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I. INTRODUCTION

Transgenic mice are phenomenal research tools, which are of interest to both industry and academic researchers. Many technology transfer offices will be faced with the challenge of licensing transgenic mice. In this paper we hope to illustrate some of the unique issues that arise in licensing transgenic mice and to provide some strategies for successful commercialization. We will discuss patent and licensing options and provide some examples from our own experience in transgenic mouse licensing at the Massachusetts Institute of Technology.

II. TRANSGENIC MOUSE MODELS—WHAT ARE THEY AND WHAT ARE THEY GOOD FOR?

Genetically altered mice are valuable research tools for the biotechnology and pharmaceutical industries, and for academic scientists, primarily because they serve as mammalian models of human disease. Mice that are missing a known gene can provide important insights into the gene's function in a living animal, thereby confirming theories about the role of the gene. Transgenic mice can be used commercially to validate drug targets by helping researchers

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determine whether a specific gene is involved in a disease. The researchers can then determine whether the gene (or its protein) is a good target for their drug-screening efforts. Transgenic mice can be used as a means of obtaining critical pre-clinical information about the efficacy and toxicity of candidate pharmaceutical compounds. The expense of caring for and maintaining large colonies of animals make transgenic mice impractical for high-throughput drug screening.

What are transgenic or knock-out mice and how are they made? The term transgenic mouse is the colloquial term for any genetically engineered mouse. In scientific terms, a transgenic mouse is a mouse that has a foreign gene added to all of its cells. A knock-out mouse is a mouse that has had a specific gene deleted (or made inactive) in all of its cells. The making of a transgenic mouse is a long and laborious process that can take up to a year. First, the genetic change is engineered in a single mouse embryonic stem cell—an undifferentiated cell that has the potential to turn into any cell in the body. The altered stem cell is then added to an early-stage mouse embryo that is implanted into a surrogate mother. The researchers will then breed the progeny of these mice for several generations to obtain mice that have the genetic alteration in all of their cells.

III. LICENSING

A. Important Issues in Licensing Mice

1. Is it necessary to file a patent application?

In addition to the usual factors that need to be weighed in deciding whether or not to file a patent application (e.g., whether or not the investigator has published, market size, etc.), there are factors specific to transgenic mice that should influence the patenting decision.

Ever since the landmark decision in 1988 granting a patent to Harvard University for the transgenic mouse now known as “Oncomouse,”¹ it is possible to obtain patent protection for a genetically engineered mammal. However, the patent office no longer grants patents that are as broad as the Oncomouse patent, which claims any non-human mammal containing any activated oncogene sequence. The prosecution of transgenic mouse patent applications is complex and, therefore, very expensive. Thus, while it is possible to get a patent issued, it will be costly and claims will be limited to a mouse in which a particular gene has been inactivated or added.

What is the value of a patent on a transgenic mouse? If the mouse will be used mainly as a research tool, either in academic or industrial labs, it is not necessary to patent it in order to gain value, even after publication. Because of the difficulty involved in developing a transgenic mouse, most companies are willing to pay for a license to an existing mouse rather than use their resources to duplicate work a university researcher has already done. Because the university (with the cooperation of the investigator) controls access to the materials (i.e., the mice), it is possible to receive significant licensing revenue without a patent.

The usual reason under the Bayh-Dole Act² for filing for a patent on a university invention is to induce investment in product development. Because the mice are most often used in research and do not need further development, this reason is generally not applicable. In addition, the royalties gained from licensing mice are not usually enough to justify the expense of a patent.

However, there are always exceptions. If the mouse model could serve as a standard toxicology test for

the pharmaceutical industry, the model is likely to have significant sales, and a patent might be worthwhile. For example, researchers at the National Institute of Environmental Health Sciences have proposed that using two transgenic mouse strains that are prone to tumors can reduce the test time for pharmaceutical toxicology testing from two years to six months.³ The FDA is considering accepting these data in lieu of the standard two-year rodent assay. The time savings will be of significant value to the pharmaceutical industry.

2. Whose mouse is it? Determining ownership.

It is necessary to determine whether a single academic institution wholly owns the mouse model. Did the investigator use materials from another institution? Were there any restrictions on the use of the materials? Is this mouse the result of a cross of two mice where the same institution did not fully own both parents? It is important to check any existing Material Transfer Agreements before deciding on a licensing strategy.

3. Bailment.

Bailment is a concept used in licensing unpatented biological materials. The owner of the material uses bailment to protect the owner's rights to the progeny and derivatives of the material, distinguishing it from a sale, which would grant the buyer unlimited rights to use of the material. Bailment is covered in detail in the *AUTM Journal* paper by P. Martin Simpson, Jr.⁴

The following wording is included as a section in the termination clause of the M.I.T. Tangible Property License Agreement to protect the institution's ownership rights.

“Upon termination, LICENSEE will return or destroy the

TANGIBLE PROPERTY and such destruction shall be confirmed in writing.”

(See Appendix A for the full text of this agreement.)

4. Cre-lox and Oncomouse.

There are some potentially blocking patents of which a licensing professional should be aware. We discuss some patents below that are being enforced that affect the licensing of transgenic mice. Our discussion is not meant to be a comprehensive list of all potential roadblocks; remaining alert to all issues that might arise is critical.

- a. *Cre-lox*. *Cre-lox* is a very powerful and widely used technology that allows site-specific recombination of DNA. A researcher can flank a known gene with lox DNA and contact the lox site with Cre to mutate the flanked DNA and inactivate that known gene. This tool gives researchers the ability to knock-out specific genes thereby creating knock-out mice. The *Cre-lox* patent (USPN 4,959,317)⁵ is owned by E.I. DuPont de Nemours and Company (DuPont).

For many years, DuPont asked that universities sign a license agreement in order to use the *Cre-lox* technology and to transfer *Cre-lox* mice to other academic labs. Many universities found the terms of the license agreement unacceptable and did not sign. Consequently, transfer of important *Cre-lox* materials between academic labs was limited and research was impeded. Then on July 1, 1998, DuPont signed a landmark agreement⁶ relating to the *Cre-lox* technology with the National Institutes of Health (through the Public Health Service) and Jackson Laboratories (referred to as Jackson Labs hereafter).⁷ The

agreement stated that any researcher affiliated with or receiving support from NIH may use the Cre-lox technology for noncommercial purposes without a license from DuPont. Further, the mice may be distributed to other academic labs and investigators for academic research under a Material Transfer Agreement (MTA) (the terms of which are included in the agreement). The recipient institution may not further distribute the mice without a license from DuPont. If the researcher wishes to distribute the Cre-lox mice to a for-profit company, the commercial entity must first obtain a commercial research license from DuPont for a fee. Further restrictions on academic researchers include: (1) they may not use the Cre-lox technology to create a library of mouse embryonic stem cells, (2) they may not use the Cre-lox technology in higher plants or for agricultural applications, and (3) they may not use the Cre-lox technology on any industrially sponsored research projects.

Importantly, this agreement allows universities to freely license novel discoveries made through the use of the Cre-lox technology (such as functions of novel genes, drugs discovered through the novel genes, etc.) without accounting to DuPont. In addition, DuPont will not take any part of the fees the universities receive for licensing the Cre-lox mice (provided the for-profit licensees have taken a license with DuPont).

Jackson Labs has agreed to serve as a repository for Cre-lox mice and to abide by the DuPont restrictions. As such, Jackson Labs will send out Cre-lox mice to academic institutions under an appropriate MTA, and will only send Cre-lox mice to companies that have signed a license with DuPont.

- b. *Oncomouse*. In 1984, Harvard University received the first patent on a transgenic animal, which has come to be known as Oncomouse. Harvard obtained very broad claims, the broadest of which is “any transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.”⁸ Later patents cover the cells derived from these animals.⁹ The patents are exclusively licensed to DuPont as a consequence of having sponsored the research at Harvard that led to the Oncomouse.

For years DuPont asked that academic labs take a license to the Oncomouse patent. The DuPont agreement restricted noncommercial use of all tumor-prone transgenic mice and restricted the transfer of these mice between academic labs. As in the case of the Cre-lox patents, many universities found these terms unacceptable. On January 18, 2000, DuPont signed an agreement¹⁰ with NIH similar to the Cre-lox agreement. Academic researchers can now use the Oncomouse technology without license from DuPont for noncommercial research and can transfer the mice to other academic labs under an MTA. If universities wish to license transgenic mice (or cell lines) that fall under the Oncomouse patents, they must notify the commercial entities of the Oncomouse patents, notify DuPont of the request, and the commercial entity must obtain a license from DuPont. In addition, at DuPont’s request, the university must provide a reasonable number of mice to DuPont at no cost. Further limitations are that non-profit institutions may not use the Oncomouse to test compounds for any commercial purpose, to produce products for any

commercial purpose, or in any industrially sponsored research.

As in the Cre-lox agreement, universities are not required to share licensing fees with DuPont (as long as the commercial entity has signed a license with DuPont), and DuPont is not asking for a share of licensing revenue received for discoveries made using the mice.

B. Structures for License Agreements

There are a variety of ways to structure license agreements depending on the value of the mouse, the potential uses of the mouse, and how broad the distribution will be. Here we present some of the more common ways M.I.T. chooses to structure its licenses.

1. Two-tiered licensing.

“Two-tiered licensing” means distributing the mice to any academic institution under an MTA, but restricting a company’s access to the mice through a fee-based license agreement. This structure serves the purpose of making the mice widely available to academic institutions, while still generating some licensing income for the university and investigator. The mice can be sent directly from the researcher’s lab or can be deposited with a distributor. (We will discuss the advantages of using a distributor below.) The majority of the license agreements at M.I.T. fall into this category.

Academic Institutions

Mice are sent to academic institutions under an MTA, which prohibits the recipient from further distributing the mice but does not restrict breeding or cross-breeding. At M.I.T., we prefer to use the Uniform

Biological Material Transfer Agreement (UBMTA)¹¹ when possible. The UBMTA is a pre-negotiated MTA for transfer of materials between non-profit organizations and it is endorsed by the NIH. If both institutions (recipient and provider) have signed the UBMTA (see AUTM Web site for signatory institutions¹²), investigators may send materials under the Implementing Letter,¹³ allowing for ease of transfer without the need to negotiate the MTA terms. If the recipient institution has not signed the UBMTA, M.I.T. will use the related New Simple Letter Agreement,¹⁴ which is also endorsed by the NIH.

In the event that the UBMTA is not available for use, i.e., both parties have not signed the Master Agreement, the following definition of Material is used by M.I.T. in M.I.T.'s MTA agreement:

“Material” shall mean the _____ mice, and any additional progeny or unmodified derivatives thereof.”

The provider's retention of part ownership of cross-bred mice is accomplished with the following language in the grant of rights section of the MTA:

“Provider retains ownership of any Material included or incorporated within modifications.”

Companies

The mice are sent to companies under the M.I.T. “Tangible Property License Agreement,” which is broader than an MTA but not as comprehensive as a normal patent license agreement (see Appendix A). The most common fee structure used at M.I.T. is a one-time fee, the magnitude of which varies depending on the value of the mouse model. The general range is from \$10,000 to \$100,000. Fees in

the higher end of this range are possible when the model is very valuable or when the company is using the model for validation of therapeutic compounds. When a company is at the point of validating a therapeutic compound, for example, the company has already invested significant amounts of money in developing this family of compounds, thus the additional information that the mouse model can provide to the company is worth a lot. To assess an appropriate fee based on desired use, we always first ask companies what they plan to do with the mice before setting a fee. Because the mouse model at M.I.T. has not enabled the identification of the drug candidate, but rather the validation of its therapeutic value, it has been difficult for companies to agree to reach-through royalties.⁺ We therefore often seek to gain value by structuring the fees on a milestone basis, or over a few years. Most of the time, the fees are on the low end of the \$10,000 to \$100,000 range. This License Agreement prohibits transfer of the mice to third parties, but allows breeding and cross-breeding; however, M.I.T. retains joint ownership of cross-bred mice. This is accomplished by inserting the following language in the GRANT section of the License Agreement:

“Provider retains ownership of any Material included or incorporated within modifications.”

The field of use may be restricted to certain types of research.

⁺ Reach-through royalties refer to royalties on sales of a drug that is discovered or validated using a research tool but that is NOT covered by the claims of a patent held by the research tool owner.

What follows are two examples of M.I.T. licenses that follow the two-tiered model.

Example One. The K-ras mouse was developed by Tyler Jacks and Leisa Johnson at the M.I.T. Center for Cancer Research. It is an important cancer model. This mouse has been licensed to three companies. Because of the mouse's value as a unique therapeutic model, companies have been willing to pay significant fees for access to the mouse. In one license agreement, the license fee is payable over a few years. In another license agreement, part of the fee is payable when the company determines—using the mouse model—that their drug has a significant anti-tumor effect. The investigator distributes this mouse directly from his lab.

Example Two. In 1992, Robert Weinberg and Tyler Jacks developed a transgenic mouse at the Whitehead Institute in which they had knocked-out the p53 gene, which is a tumor suppressor. When the p53 gene is functioning normally, it will cause a damaged cell to die. When the p53 gene is missing, damaged cells do not die, which can lead to tumor formation (hence the healthy p53 is called a tumor suppressor). M.I.T. did not file a patent on this mouse. The p53 mouse is licensed on a two-tiered system, using Jackson Labs as M.I.T.'s exclusive distributor. Companies that request the mice from Jackson Labs are informed of M.I.T.'s ownership and the requirement for an additional license from M.I.T. We then follow up with commercial licensees. Six license agreements have been signed with companies for this mouse. The fee charged for the p53 mouse is on the low end of the range because a different p53 knock-out mouse is available from another supplier. In 1998, Jackson Labs sent M.I.T.'s p53 mouse to over 1,000 academic researchers.

2. Single-tiered licensing.

“Single-tiered licensing” refers to sending the mice to anyone who asks for them (commercial or nonprofit) with minimal fees and minimal restrictions (i.e., they can breed, but not distribute, the mice beyond their own lab). As in two-tiered licensing, the mice can be maintained and distributed either from the investigator’s lab or through a distributor.

3. Exclusive licensing.

In exclusive licensing, the mice are sent to a single company. We rarely license transgenic mice on an exclusive basis at M.I.T. However, this may be an appropriate scheme if the mouse is being licensed as a part of a larger patent portfolio or if the mouse would be used to produce antibodies and not as a research tool. Keep in mind that distribution to researchers at academic institutions would still be necessary if the work was done under NIH sponsorship or published in a peer-reviewed journal; however, this distribution could be accomplished with an MTA with strong restrictions on further distribution, cross-breeding, etc. At M.I.T. it is our policy to make research materials available to academic institutions for noncommercial research, even if the research materials are exclusively licensed to a company.

C. Using a Distributor

A mouse distributor is a company that will breed and maintain transgenic mouse strains and send them to researchers and companies upon request. Several companies do this work, a few of which we will discuss below.

There are benefits to using a distributor. Distributors breed and maintain the stocks so that the investigator

does not have to keep the strain going in his or her lab, taking up space and resources. Distributors will handle the shipping and paperwork involved in distributing the mice, which again takes pressure off the researcher. Also, the distributor takes care of marketing the mice.

However, there are also disadvantages to using a distributor. The licensing office loses much of the control it would otherwise have if the mice were held locally. Most distributors will send the mice to any company that requests them and is willing to pay for the mice. If the mouse is very valuable and distribution to companies should be governed by individually negotiated license agreements, or if the investigator wants to maintain strict control over distribution, using a distributor may not be advantageous.

License agreements with distributors may be exclusive or nonexclusive. In an exclusive arrangement, it is important for the university licensing office to retain certain rights—namely, to retain the right for the university to use the mouse for its own internal use; the right to distribute the mouse to other academic institutions from the university lab, or the agreement should ensure that the distributor will maintain an adequate supply of the mice so that they will be available to academics; and, under certain circumstances, the right for academic recipients to breed and cross-breed the mice.

1. Not-for-profit distributors.

Jackson Labs is a non-profit entity in Bar Harbor, Maine, and is the leading repository for transgenic mice, with thousands of mice in their inventory. Jackson Labs will accept and keep stocks of many mouse strains, including those that have limited market value. Jackson Labs, however, does not accept all mice. It will evaluate each strain. Jackson Labs charges relatively low prices for the mice and

generally imposes few restrictions on the use of the mice.

2. For-profit distributors.

There are many for-profit companies that will breed and distribute mice. Some examples are Taconic Farms and Charles River Laboratories. Because these companies are for-profit organizations, we usually enter into a basic license agreement with them with a royalty on all sales. The distributors sometimes use a differential pricing strategy, charging a modest fee for each mouse while restricting breeding, but granting breeding and/or cross-breeding rights for a significantly higher fee.

IV. CONCLUSIONS

Transgenic mice have revolutionized research and drug discovery and have proven to be of great value to both academic and industrial researchers. In spite of their great potential, however, transgenic mice have not generated large amounts of income for universities. Nonetheless, with a thoughtful licensing strategy, it is possible to bring in a reasonable amount of income for the investigator and the institution, and to provide a valuable service to the research community through dissemination of research materials.

The methods we have discussed for licensing transgenic mice have evolved over years of trying different licensing strategies. We expect that the scientific tools and business models will continue to evolve and that licensing models will continue to change to meet these needs.

Appendix A

**Tangible Property License Agreement for
For-Profit Companies**

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
and
<<COMPANY>>
TANGIBLE PROPERTY LICENSE AGREEMENT

This Agreement is made and entered into this ____ day of _____, 200__, (the "EFFECTIVE DATE") by and between the MASSACHUSETTS INSTITUTE OF TECHNOLOGY, a corporation duly organized and existing under the laws of the Commonwealth of Massachusetts and having its principal office at 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, U.S.A. (hereinafter referred to as "M.I.T."), and _____ a corporation duly organized under the laws of _____ and having its principal office at _____ (hereinafter referred to as "LICENSEE").

WITNESSETH

WHEREAS, M.I.T. is the owner of certain TANGIBLE PROPERTY (as later defined herein) relating to M.I.T. Case No. _____, "_____" by _____, and has the right to grant licenses under said TANGIBLE PROPERTY;

WHEREAS, LICENSEE desires to obtain a license under the TANGIBLE PROPERTY upon the terms and conditions hereinafter set forth.

NOW, THEREFORE, in consideration of the premises and the mutual covenants contained herein, the parties hereto agree as follows:

1 - DEFINITIONS

For the purposes of this Agreement, the following words and phrases shall have the following meanings:

1.1 "TANGIBLE PROPERTY" shall mean the [mouse strain name] mice and any additional progeny or unmodified derivatives thereof.

1.2 "FIELD OF USE" shall mean for research purposes only. [Expand as necessary]

2 - GRANT

2.1 M.I.T. hereby grants to LICENSEE the nonexclusive right and license for the FIELD OF USE to use the TANGIBLE PROPERTY, for ten (10) years, unless this Agreement shall be sooner terminated according to the terms hereof.

2.2 M.I.T. retains ownership of any TANGIBLE PROPERTY included or incorporated within modifications.

2.3 LICENSEE shall not have the right to enter into sublicensing agreements.

2.4 LICENSEE agrees not to transfer the TANGIBLE PROPERTY to third parties.

2.5 Nothing in this Agreement shall be construed to confer any rights upon LICENSEE by implication, estoppel or otherwise as to any technology or patent rights of M.I.T. or any other entity other than the TANGIBLE PROPERTY.

3 - ROYALTIES

3.1 For the rights, privileges and license granted hereunder, LICENSEE shall pay M.I.T. a License Fee of _____ Dollars (\$_____), due immediately upon the EFFECTIVE DATE.

3.2 All payments due hereunder shall be paid in full, without deduction of taxes or other fees that may be imposed by any government.

4 - PRODUCT LIABILITY

4.1 LICENSEE shall at all times during the term of this Agreement and thereafter, indemnify, defend and hold M.I.T., its trustees, directors, officers, employees and affiliates, harmless against all claims, proceedings, demands and liabilities of any kind whatsoever, including legal expenses and reasonable attorneys' fees, arising out of the death of or injury to any person or persons or out of any damage to property, resulting from the production, manufacture or consumption of the TANGIBLE PROPERTY or arising from any obligation of LICENSEE hereunder.

4.2 M.I.T., ITS TRUSTEES, DIRECTORS, OFFICERS, EMPLOYEES, AND AFFILIATES MAKE NO REPRESENTATIONS AND EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, AND THE ABSENCE OF LATENT OR OTHER DEFECTS, WHETHER OR NOT DISCOVERABLE. NOTHING IN THIS AGREEMENT SHALL BE CONSTRUED AS A REPRESENTATION MADE OR WARRANTY GIVEN BY M.I.T. THAT THE PRACTICE BY LICENSEE OF THE LICENSE GRANTED HEREUNDER SHALL NOT INFRINGE THE PATENT RIGHTS OF ANY THIRD PARTY.

IN NO EVENT SHALL M.I.T., ITS TRUSTEES, DIRECTORS, OFFICERS, EMPLOYEES AND AFFILIATES BE LIABLE FOR INCIDENTAL OR CONSEQUENTIAL DAMAGES OF ANY KIND, INCLUDING ECONOMIC DAMAGE OR INJURY TO PROPERTY AND LOST PROFITS, REGARDLESS OF WHETHER M.I.T. SHALL BE ADVISED, SHALL HAVE OTHER REASON TO KNOW, OR IN FACT SHALL KNOW OF THE POSSIBILITY OF THE FOREGOING.

5 - EXPORT CONTROLS

LICENSEE shall comply with all United States laws and regulations controlling the export of certain commodities and technical data, including without limitation all Export Administration Regulations of the United States Department of Commerce. Among other things, these laws and regulations prohibit or require a license for the export of certain types of commodities and technical data to specified countries. LICENSEE hereby gives written assurance that it will comply with all United States export control laws and regulations, that it bears sole responsibility for any violation of such laws and regulations by itself, and that it will indemnify, defend, and hold M.I.T. harmless (in accordance with Section 4.1) for the consequences of any such violation.

6 - NON-USE OF NAMES

LICENSEE shall not use the names or trademarks of the Massachusetts Institute of Technology, nor any adaptation thereof, nor the names of any of its employees, in any advertising, promotional or sales literature without prior written consent obtained from M.I.T., or said employee, in each case, except that LICENSEE may state that the TANGIBLE PROPERTY is licensed from M.I.T.

7 - ASSIGNMENT

This Agreement is not assignable and any attempt to do so shall be void.

8 - TERMINATION

8.1 If LICENSEE shall cease to carry on its business, this Agreement shall terminate upon notice by M.I.T.

8.2 Upon any material breach or default of this Agreement by LICENSEE, M.I.T. shall have the right to terminate this Agreement and the rights, privileges and license granted hereunder effective on sixty (60) days' prior written notice to LICENSEE. Such termination shall become automatically effective unless LICENSEE shall have cured any such material breach or default prior to the expiration of the sixty (60) day period.

8.3 LICENSEE shall have the right to terminate this Agreement at any time on six (6) months' prior written notice to M.I.T., and upon payment of all amounts due M.I.T. through the effective date of the termination.

8.4 Upon termination of this Agreement for any reason, nothing herein shall be construed to release either party from any obligation that matured prior to the effective date of such termination; and Articles 1, 4, 5, 6, 8.4, 8.5, and 10 shall survive any such termination.

8.5 Upon termination, LICENSEE shall return or destroy the TANGIBLE PROPERTY, and such destruction shall be confirmed in writing.

9- PAYMENTS, NOTICES AND OTHER COMMUNICATIONS

Any notices required or permitted under this Agreement shall be in writing, shall specifically refer to this Agreement, and shall be sent by hand, recognized national overnight courier, confirmed facsimile transmission,

confirmed electronic mail, or registered or certified mail, postage prepaid, return receipt requested, to the following addresses or facsimile numbers of the parties:

If to M.I.T.: Technology Licensing Office, Room NE25-230
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, MA 02139-4307
Attention: Director
Tel: 617-253-6966
Fax: 617-258-6790

If to LICENSEE: _____

Attention: _____
Tel: _____
Fax: _____

All notices under this Agreement shall be deemed effective upon receipt. A party may change its contact information immediately upon written notice to the other party in the manner provided in this Section.

10 - MISCELLANEOUS PROVISIONS

10.1 All disputes arising out of or related to this Agreement, or the performance, enforcement, breach or termination hereof, and any remedies relating thereto, shall be construed, governed, interpreted and applied in accordance with the laws of the Commonwealth of Massachusetts, U.S.A.

10.2 The parties hereto acknowledge that this Agreement sets forth the entire Agreement and understanding of the parties hereto as to the subject matter hereof, and shall not be subject to any change or modification except by the execution of a written instrument signed by the parties.

10.3 The provisions of this Agreement are severable, and in the event that any provisions of this Agreement shall be determined to be invalid or unenforceable under any controlling body of the law, such invalidity or unenforceability shall not in any way affect the validity or enforceability of the remaining provisions hereof.

10.5 The failure of either party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement shall not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition by the other party.

IN WITNESS WHEREOF, the parties have duly executed this Agreement the day and year set forth below.

MASSACHUSETTS INSTITUTE
OF TECHNOLOGY

By _____

Name _____

Title _____

Date _____

<<COMPANY>>

By _____

Name _____

Title _____

Date _____

NOTES

- ¹ USPN 4,736,866, "Transgenic non-human mammals," by Philip Leder and Timothy Stewart, issued April 12, 1988.
- ² 35 U.S.C. § 200.
- ³ Tennant, R.W., J.E. French, and J.W. Spalding, "Identifying chemical carcinogens and assessing potential risk in short-term bioassays using transgenic mouse models," *Environmental Health Perspective*, 103(10), October 1995: 942-950.
- ⁴ P. Martin Simpson, Jr., "Use of Bailment in Transferring Technology from a University," *Journal of the Association of University Technology Managers*, Vol. 10 (1998): 85-100.
- ⁵ USPN 4,959,317, "Site-specific recombination of DNA in eukaryotic cells," by Brian Sauer, issued September 25, 1990.
- ⁶ <http://www.nih.gov/od/ott/cre-lox.htm>.
- ⁷ Jackson Laboratories is a non-profit entity located in Bar Harbor, Maine. It is the leading repository for transgenic mice.
- ⁸ USPN 4,736,866, "Transgenic non-human mammals," by Philip Leder and Timothy Stewart, issued April 12, 1988.
- ⁹ USPN 5,087,571, "Method for providing a cell culture from a transgenic non-human mammal," by Philip Leder and Timothy Stewart, issued February 11, 1992. USPN 5,925,803, "Testing method using transgenic mice expressing an oncogene," by Philip Leder and Timothy Stewart, issued July 20, 1999.
- ¹⁰ <http://www.nih.gov/od/ott/oncomous.htm>.
- ¹¹ AUTM Web site (<http://www.autm.net>). See Agreements/UBMTA/Federal Register for UBMTA as published in Federal Register, March 8, 1995. See also NIH Biomedical Research Resources at AUTM Web site for related discussions in regard to sharing biomedical research resources.
- ¹² <http://www.autm.net>; Agreements; UBMTA; Signatories.
- ¹³ <http://www.autm.net>; Agreements; UBMTA; Implementing Letter.
- ¹⁴ <http://www.autm.net>; Agreements; UBMTA; New Simple Agreement.