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Technology Transfer

The author outlines the key ingredients for effective material transfer agreements and provides tips on how to avoid conflicts between the receivers and providers of research materials.

Material Transfer Agreements: Avoiding Collisions With Technology Managers

By VICTOR RODRIGUEZ

Material transfer agreements may be used in connection with the transfer of materials for research purposes [1]. While providing access to materials not available within an organization, MTAs might threaten control over research material, erode scientific or technological leads, accelerate the dissemination of undesired results, exhaust time for patent negotiation, or cause disputes over intellectual property rights relating to the exchanged material.

The experience of Yihai Cao, Judah Folkman, and Michael S. O'Reilly illustrates the risks that may accompany the exchange of materials under MTAs. Cao, Folkman, and O'Reilly have been conducting cancer research at the Children's Medical Center Corp., a hospital in Boston. Folkman, director of the Surgical Research Laboratory at CMCC, theorized that tumors produce anti-angiogenic and angiogenic substances that stimulate their growth. If identified, these anti-angiogenic substances might suppress tumor growth.

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In April 1994, O'Reilly and Folkman filed a patent application disclosing and claiming the protein Angiostatin, which inhibits the proliferation of blood vessels. The patent issued in June 1997.

Angiostatin, presently in phase I clinical trials, is part of a larger protein commonly known as plasminogen, which contains five distinct regions known as *Kringles*, and one non-Kringle region known as the protease domain. Angiostatin consists of Kringles 1 through 4 of plasminogen and does not include Kringle 5.

Thereafter, O'Reilly concentrated his research in the area of in vitro testing of Kringles 1 through 4 on mice tumors. Meanwhile, Cao proceeded to investigate the anti-angiogenic effects of plasminogen fragments including Kringle 5. In order to do so, however, Cao needed plasminogen fragments in addition to those he prepared himself. Accordingly, in April 1994, Cao asked Davidson, a research biochemist at Abbott Laboratories, if he could provide fragments of human plasminogen for Cao's research at CMCC.

In late May 1994, Davidson supplied Cao with human plasminogen. At the time, Davidson did not request a confidentiality agreement or otherwise indicate that the fragments were proprietary to Abbott. In March 1995, again without a confidentiality agreement, Davidson furnished Cao with recombinant Kringle 1.

In early June 1995, Davidson sent Folkman a confidential disclosure agreement signed by Abbott. When Folkman received the CDA, he signed it without reviewing it in any detail and forwarded it to the technology transfer office at CMCC.

Dippel, a technology transfer officer in CMCC, reviewed the agreement, determined it was unacceptable to CMCC and, as a result, never signed the CDA or returned it in an executed form to Abbott. Rather, he made various revisions, underlinings and markings on the CDA that strongly favored Abbott and disfavored CMCC.

By letter dated July 5, 1995, Dippel sent Davidson an alternate proposal, an MTA. The cover letter advised Abbott that the MTA would be CMCC's "version of an agreement for" the transfer of the material from Abbott. In sharp contrast to the CDA, the MTA proposed that CMCC would be "free to file patent applications" and claim inventions through the use of the material supplied by Abbott [2].

The crisis at CMCC offers a time-lapse example of a problem more and more technology managers are confronting: "How can we reach outside our own walls for the research materials we need?" Requests for material transfers between industry laboratories are widespread, although not of high frequency. About 60 percent of industry respondents initiated at least one request in the last two years. And approximately 40 percent of them have received such a request in the same period [3].

Why Receivers May Clash With Providers.

In order to avoid disputes over control of the provided material, MTAs may contain a broad definition of the material, including not only the original material but also the progeny, the unmodified derivatives, and even confidential information related to the material. The progeny is the unmodified descendant from the original materials, such as virus from virus, cell from cell, or organism from organism. The unmodified derivatives are substances created by the recipient which constitute an unmodified functional subunit or product expressed by the original material, such as subclones of unmodified cell lines, monoclonal antibodies secreted by a hybridoma cell line, or purified or fractionated subsets of the original material.

A *grant-back* clause aims at protecting the provider's competitive position in the event that the recipient of the material obtains a patent or makes a related invention. Although the obligation to negotiate royalties thus applies only to inventions derived directly from the transferred material, some agreements attempt to *reach-through* and secure royalties on a broader category of products. These provisions have given rise to concerns under competition law, arising from fears that they may be used to extend a provider's dominant market position.

Controlling material distribution, limiting its use in a laboratory, and ensuring return of unused materials are critical to maintaining the provider's competitive edge. The materials should only be used at the recipient's organization and under direct supervision of the scientist's laboratory. The materials should not be transferred to anyone else within the recipient's organization.

MTAs frequently include provisions designed to prevent access to the material by third parties, so as to make sure that the material does not reach parties not

bound by the confidentiality commitments. Such provisions may, for instance, require the recipient to separate research activities on the transferred material from other research, and to introduce control procedures to restrict the number of staff that will have access to it.

If patents are expected to result from research on the transferred material, MTAs may stipulate that the receiver's publication of research based on the material be deferred for a stated period of time so that patent rights can be obtained in the interim. The agreement may also require parties to report to each other any actions they may take with respect to patents so as to protect their mutual rights to royalties, and to facilitate patent applications in case the nonpatenting party has information needed in the application.

Difficulties may arise when an investigator uses two materials from two different providers. In such a situation, it is quite likely that the terms of the agreement covering the two materials will be incompatible. This type of conflict should be avoided. Thus, providers often require investigators and their organizations to state in their agreements that no such conflicts currently exist, and that none will be allowed to develop.

Since the provider of the material does not usually fund the research project of the receiver, the receiver needs to ensure that its intellectual property obligations to those sponsors who do fund the work do not conflict with the proposed obligations to the provider of the material. Because so much research is externally funded, it may be important to clearly acknowledge in the MTA the rights of the financial supplier regarding inventions that may be made with the material.

An agreement may require that the recipient indemnify the provider against any damage that occurs through use of the material, implying that the provider is not responsible even if the material is provided without proper warnings as to associated hazards or needed precautions. Some materials are in fact hazardous to the user, and recipients tend to require that such hazards be disclosed and that the provider takes responsibility for negligence in disclosure of known hazards. Such requirements are aimed at maintaining safety of employees, not all of whom may be equally knowledgeable about hazards.

To avoid the dissemination of undesired results, limitations may be imposed on recipients' publication of their research result without the provider's approval. The purpose of such a restriction is to allow the provider to determine whether its own confidential information has been improperly disclosed in the manuscript or presentation, and whether new intellectual property may have arisen from use of the material that the provider wants to protect. Even if such a provision is framed in equitable language, the recipient investigators will need to decide whether they can comply with such a restriction, and if not, the agreement should not be signed.

Considering the Risk of Material Request Denial.

Representatives from several private companies have said that they would only use MTAs if the firm has little or no interest in the research of the receiver scientist to whom it is lending a research material. If an organization anticipates that the receiver's research will yield valuable results, that organization is likely to propose a more substantial relationship, perhaps involving research sponsorship or collaboration [4].

The situation is different in large research consortia that include a significant portion of firms in a field. Although governments often encourage such consortia, many firms are hesitant to share technology under these circumstances. Being competitors rather than collaborators, the firms will typically share only less valuable material.

The nature of a consortium almost dictates that each member of the consortium receive a non-exclusive license to any invention emerging from the effort. However, the commercial value of such a license is often small; hence, firms may not attempt to obtain patents on such material. Such consortia tend to focus on relatively basic research, or on research that can benefit all members and for which costs can therefore be shared.

Restrictions and reach-through provisions of MTAs can be so onerous, and yet dispersed throughout a population of claimants, that negotiations over research materials may become prohibitive, with the research held hostage to a phalanx of technology managers [5]. Repeated granting of reach-through provisions can be chaotic; a receiver cannot promise an exclusive license to future discoveries more than once in the course of a research project before creating conflicting obligations [4].

Between 22 percent (receiver's estimate) and 26 percent (provider's estimate) of industry-to-industry laboratories' requests for research materials are denied. The consequence of being denied tangible research input can be more severe than the inability to license another's intellectual property, because in the latter case work may proceed, albeit at some liability risk. The most common reason given for denying or ignoring a material request is the need to protect commercial value and the receiver's unwillingness to accept restrictive MTA terms.

A survey by J. Walsh and colleagues [5] asked about four possible adverse impacts of denied a material request: project abandonment, reinvestigation delay, research approach change, or in-house material creation. What stood out was the higher incidence of adverse effects for drug discovery and pathway researchers.

Access to research materials is crucial for biotechnology research and development. In a *quid pro quo* approach, two models may facilitate access to patented materials: patent pools and clearing houses. However, if an organization lacks such opportunities for obtaining research materials, there are three alternatives available: the research or experimental use exemption, conventional one-to-one licensing, and the compulsory license.

Problems may arise if the material transfer occurs before the provider has filed a patent application on the material. However, MTAs with confidentiality provisions or trade secret contracts may provide a solution to those problems.

Managerial Implications.

Proprietary claims have reached further upstream from end products to cover fundamental discoveries that provide the knowledge base for future product development. One important reason for this change is a narrowing of the conceptual gap between fundamental research and commercial application, especially in biotechnology.

Once largely a matter of serendipity or trial-and-error, biotechnology is now critically dependent on ba-

sic knowledge of genes, proteins, and associated biochemical pathways. It has the potential to produce plenty of breakthroughs in existing industries such as agriculture, food-processing, and human health. As one commentator noted, "This is the first time that science is the actual business." [6]

The foreseeable practical payoffs of such fundamental research make it easier to obtain patents for discoveries that, in an earlier era, would have seemed too far removed from useful applications for patent protection. As these advances in human understanding have become patentable, new firms have emerged, raising capital to develop and market proprietary research that lies somewhere between traditional academic research and end product development.

The earliest breakthroughs in biotechnology, such as the Harvard Oncomouse, were not downstream products aiming at a consumer market. However, the U.S. Patent and Trademark Office reinforced the trend toward privatization of upstream research by expanding the jurisdiction of the patent system.

Thus, it became possible for technology managers to capture more of the potential revenue stream by adding reach-through provisions to the patent claim. Because reach-through provisions on patents proved too slow and uncertain for privatizing research, however, the biotechnology sector created MTAs.

Proper management of MTAs is extremely important. Only a technology transfer officer who has binding authority should sign MTAs. Each research organization should establish a protocol ensuring that the officer reviews all MTAs.

Researchers, when approached directly for research materials, should know where to forward such requests. And, importantly, copies of the MTAs should be stored in a central file, not "stuck" in a laboratory notebook or "filed" in a laboratory drawer. These documents are contracts, requiring careful study to determine what limitations are placed on the use of the transferred material [7].

W. Streitz et al. [8] have stressed that the MTA's should address inventorship and ownership of inventions. Inventorship needs to be determined by objective standards, such as the U.S. patent law. Ownership based on contribution of the parties is too subjective because each party always feels its contribution is the biggest.

Research results can be shared under confidentiality agreements without affecting issues of inventorship. However, sharing of results may be problematic if research generated by a for-profit organization incorporates confidential information of a third party, e.g., a corporate alliance partner.

Among profit-oriented firms, MTAs frequently arise in the context of non-cooperative research efforts by a firm to develop a specific product. Such agreements, laying out the structure of the research program, will typically authorize the exchange of biological materials, and prohibit their transfer to third parties or use for purposes other than research.

In such cases, the right to and responsibility for patenting the product will be carefully spelled out, as will be the ownership rights in such a patent. These rights will generally be exclusive, for the whole purpose of the research is to develop a new proprietary product. Often the most difficult problem is the allocation of rights to

unexpected inventions—possibly valuable in new markets—that neither firm had considered.

MTAs that accompany materials transferred from other organizations are legally binding documents that must be carefully reviewed. Inbound agreements are of special concern, because they often include terms that impose undue restrictions on recipient investigators.

Technology managers have an obligation to ensure that these agreements do not infringe upon research freedom, namely freedom to choose research methods or questions, freedom to communicate research results, freedom to interpret research results, or freedom to collaborate in research projects. The terms must also be evaluated for potential conflicts with the specific requirements of any funding agreements.

Technology managers must negotiate any language that may place an unwarranted burden on the recipient. Once an agreement is in place, the investigators and technology managers are responsible for adhering to the provisions.

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