

Licensing and Distribution of Research Tools: National Institutes of Health Perspective

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HISTORICAL PERSPECTIVE

Targets and tools for scientific discovery in the biomedical sciences are represented by a wide variety of resources, including monoclonal antibodies, receptors, animal models, tracer libraries, and others. For basic research to fully benefit public health, broad access and availability for these research tools are needed. These tools should be readily useable and distributable, in part because their useful life cycles are generally short.

These research tools may be patented or not, but they generally exclude diagnostic and therapeutic products and exclude commercial-scale production and products sold as a result of the use of the tool.

Historically, the practice had been to allow unrestricted flow of materials. However, recently there have arisen commercial uses for the results of molecular biology research, with universities and federal laboratories able to claim ownership and receive financial benefits from licensing their inventions. In the subsequent negotiation of material transfer agreements (MTAs) or licensing agreements, however, problems have arisen due to lengthy negotiations regarding terms and conditions.

ROLE OF THE PUBLIC HEALTH SERVICE IN RESEARCH TOOLS

The strong interest of the Public Health Service (PHS) in research tool matters results from several perspectives. First, as one of the world's largest users of biomedical reagents and research tools, PHS has a major interest in purchasing or obtaining research tools for its own use. Second, in addition to its role in funding basic science, the PHS is also a repository for and leading provider of many difficult-to-find items. Therefore, it is important to recognize that research tools do have value as commodity products stemming from the financial and intellectual contribution of universities, federal laboratories, or others who develop them. In-

deed, National Institutes of Health (NIH) scientists are encouraged to take credit for new research tools as inventions. The NIH recognizes that good science happens in both academia and industry and that a two-way exchange is needed to serve the paramount interest of public health.

For many years, the NIH's own Intramural Research Tool Distribution Policy has required NIH scientists to make available to the public the results of its research. Further studies cannot be limited due to restrictions on the prompt availability of research materials to qualified individuals or reach-through obligations placed on future inventions. The tools are typically distributed directly by the original researcher, or they may be made available via a licensee or a centralized repository. License fees may be charged to commercial users or the payment of distribution costs sought. It is anticipated that the success of this internal program can be extended to all federally funded research.

RECENT ACTIONS OF NIH REGARDING RESEARCH TOOLS

The NIH has taken a number of actions regarding research tools and research tool distribution issues during the past decade (see Table 1).

DEVELOPMENT OF THE NIH RESEARCH TOOL GUIDELINE PRINCIPLES

The recommendations of the NIH Director's Working Group (www.nih.gov/news/researchtools/index.htm) focused on disseminating research tools without legal entanglements, further using the Universal Biological Material Transfer Agreement (UMBTA), developing guidelines for extramural MTAs and licensing, reviewing and strengthening current policies, and establishing a research tools forum.

The new "Guidelines for Recipients of NIH Grants and Contracts" was published in the *Federal Register*

Table I NIH Actions Regarding Research Tools

1994	EST (expressed sequence tag) patent applications were withdrawn by the National Institutes of Health (NIH) because of their tool nature.
1995	A new patent policy in limited filing of patents on research tools and a new licensing policy provided for nonexclusive licensing of research tools without reach-through restrictions. UBMTA (Universal Biological Material Transfer Agreement) was established to allow for material exchanges among nonprofits. Industry working group was convened to facilitate the exchange of research tools to study HIV. NIH declined to sign an agreement with Human Genome Sciences. The Institute for Genomic Research database was later made public. Materials Cooperative Research and Development Agreement (M-CRADA) was created to allow the provider of unique materials to maintain rights when working with the NIH. Grantees gain authority to license unpatented research tools. New genomic sequencing grantees were required to release data rapidly.
1996	New NIH intramural policy was established for transgenic/gene-deleted mice.
1997	NIH/DuPont cre-lox Memorandum of Understanding (MOU) expanded access for NIH and grantees. A report was issued by the NIH Director's Working Group on Research Tools.
1998	Draft NIH Research Tool Guidelines were issued for review. Final NIH Research Tool Guidelines were issued.
1999	Access to the DuPont OncoMouse™ was expanded consistent with the new NIH Research Tool Guidelines.

(www.ott.od.nih.gov/NewPages/RTguide_final.html), and included four basic principles: ensuring academic freedom and publication, implementing the Bayh-Dole Act, minimizing administrative impediments, and disseminating research resources.

The first principle, academic freedom and publication, is intended to preserve academic research freedom, safeguard appropriate authorship, and ensure timely disclosure of results. This applies to all funding recipients. The second principle, to implement the Bayh-Dole Act, is intended to maximize utilization of new tools by the research community, allow for timely transfer to industry for commercialization of the tool,

and allow widespread distribution of the final tool for use by the public without unnecessarily restrictive licensing practices and perhaps even without patents.

The third principle, to minimize administrative impediments to academic research, is intended to avoid encumbrances to new discoveries, such as reach-through rights controls on academic freedom and publications, or improper valuations that might restrict access to the tool. These can be achieved by the implementation of clear tool acquisition policies and the streamlining of academic transfers via simple letters of agreement or no agreement at all.

Finally, the fourth principle is to ensure dissemination of NIH-funded tools. For most tools, this can be easily achieved since they are typically readily useable and distributable either directly or through a research products licensee, unlike products that are subject to expense and risk of approval by the Food and Drug Administration (FDA). Institutions receiving private financial support for use in NIH-funded projects should make such private sponsors aware of the NIH's expectations for research tool distribution. Rights to the future use and distribution of the tool for research uses should always be retained, but exclusive licenses may be negotiated under certain circumstances when extensive development is required to make the tool available for actual use.

In general, restrictions on the distribution of new tools are to be avoided, and delays in publication of more than 60 days at the request of sponsors are unacceptable. However, for-profits may obtain limited grant-backs or option rights for proprietary materials provided to academic institutions (balancing value and the Bayh-Dole Act), if there is a benefit to public health in the commercialization of the tool and if enforceable plans for development ensure timely and useful development of the tool.

There are a number of other important issues for the NIH, universities, and industry to consider regarding research tools and research tool-related agreements. Overlapping contract obligations may become impossible to satisfy, especially if there are severe restrictions on the use of new materials or other discoveries. The overriding concern is that limitations on future distribution or other legal encumbrances will hinder public health objectives.

RESEARCH TOOL LICENSING PRACTICES OF THE NIH

The NIH itself recognizes a variety of license types for providing research tools and reagents to industry. For sales of reagents, possibilities include nonexclusive

Table II Examples of National Institutes of Health (NIH) Research Tools Useful in Commercial Applications

D2 dopamine receptor	Screening
Muscarinic receptor	Screening
Immortalized liver cells	Disease models
Estrogen receptor knock-out (ER KO) mice	Screening
Basement membrane	Reagent sales
G-protein antibodies	Reagent sales
Human immunodeficiency virus (HIV) protease	Screening

Table III Typical Subjects of Research Product Licenses

Zwitterionic detergent (CHAPS)
Antisera
Monoclonal antibodies

patent commercialization or biological material commercialization agreements. For tools, there are the non-exclusive patent for internal use, the biological material for internal use, and the commercial evaluation license.

Research tool licenses for internal use are typically nonexclusive and prohibit "reach through" to products. They provide materials, such as muscarinic receptors, and allow screening of compounds for subse-

quent development. The agreements reached have been very popular with large companies such as those in the pharmaceutical industry and involve paid-up term licenses or annual fees. A few more examples of such tools and reagents are listed in Table II.

For commercial evaluation, licenses generally are nonexclusive. Materials are provided for feasibility testing only; screening is not permitted. These licenses involve a rather modest paid-up cost for a period of approximately 18 months for evaluation of either patents or products. For research products licenses, smaller firms predominate as licensees, although this industry is also becoming more consolidated. Because of the variety of materials available and their modest prices and sales level, these licenses have low up-front costs but relatively higher earned royalty rates because they are for finished or close-to-finished products. A few examples of the subjects of such agreements are listed in Table III.

CONCLUSION

Access to research tools remains a critical issue in the rapid development of new diagnostic and therapeutic products from basic research, whether conducted at nonprofit or for-profit institutions. The NIH hopes that the recently enacted guidelines will provide sufficient direction for NIH-funded institutions to be able to ensure proper sharing and distribution of these important resources. Although these guidelines are not typically mandatory but only recommended for NIH-funded research projects, it is hoped that they will give sufficient direction to clear up current problems in the sharing of such tools without specific regulatory or statutory intervention.

The Patenting of Tools for Drug Discovery and Development

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In December 1999, the National Institutes of Health (NIH) published its "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Re-

sources." The stated principles were to ensure academic freedom and publication, ensure appropriate implementation of the Bayh-Dole Act, minimize administrative impediments to academic research, and