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Distribution and licensing of drug discovery tools – NIH perspectives

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Now, more than ever, drug discovery conducted at industrial or academic facilities requires rapid access to state-of-the-art research tools. Unreasonable restrictions or delays in the distribution or use of such tools can stifle new discoveries, thus limiting the development of future biomedical products. In grants and its own research programs the National Institutes of Health (NIH) is implementing its new policy to facilitate the exchanges of these tools for research discoveries and product development.

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▼ In 1997, Harold Varmus, then Director of the National Institutes of Health (NIH), established a Working Group to look into increasing apprehension that intellectual property restrictions might be stifling the broad dissemination of new scientific discoveries and thus limiting future avenues of basic research, drug discovery and product development. Specific areas of concern were raised in the scientific community regarding:

- Problems or delays encountered in the distribution, licensing and use of unique research tools.
- Competing interests of intellectual property owners and research tool users.
- The need for guidance to NIH-funded scientists and their collaborators on tool sharing and distribution issues.

In trying to develop new programs to deal with these concerns, the NIH was cognizant, as a public sponsor of biomedical research, of its need to balance its interest in accelerating scientific discovery with that also of facilitating product development for health and patient care.

As a result, on 23 December 1999, NIH announced its new *Research Tools Policy* for the sharing of research resources developed with NIH funding [1]. The policy is a two-part document, consisting of: (1) *Principles*, setting forth the fundamental concepts; and (2) *Guidelines*, providing specific information to scientists, patent and license professionals, and sponsored research administrators for implementation of this policy. It was developed in response to the research community's voiced need for the dissemination and use of unique research resources and the competing interests of intellectual property owners and research tool users. This policy is an amplification of the NIH's longstanding policy on the sharing of unique research resources, and further promotes the goals of the Bayh–Dole Act **(Title 35 US Code 200 *et seq.*),** which ensure that inventions made with public funding are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery. It is the intent of the *Principles* and *Guidelines* that scientists and institutional administrators funded by the NIH (as well as others) will acquaint themselves with and fully implement the NIH *Research Tools Policy* to further research, enhance discovery, support a robust research enterprise, and improve public health.

What are research tools?

Basically, 'research tools' are defined in their broadest sense to embrace the full range of tools that scientists use in the laboratory, such as targets and tools for scientific discovery. There is a wide variety of research resource types, including certain applications of monoclonal antibodies, receptors, animal models, libraries, computer software, and databases. Such resources tend to be readily useable and distributable as a tool, and, as a tool, broad access and availability are needed. Generally speaking, a research tool can be patented or unpatented, and the useful lifecycle of a research tool generally tends to be short, being quickly replaced by other more current technologies. Some examples of research tools

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and their research uses include: D2 dopamine receptor, which can be used in screening; immortalized liver cells, which can be used as a disease model; estrogen receptor knockout (ERKO) mice, which can also be used in screening; basement membrane, which is used as a reagent for growing cells; and anti-G-protein antibodies used in a variety of laboratory applications.

What roles do the NIH and researchers play?

The NIH has a mission to uncover knowledge to benefit the public health, and it plays an important role in the overall research enterprise. It is one of the world's largest users of biomedical reagents and tools through its procurement channels. In addition, the NIH is a leading provider of many difficult-to-find items through repositories and contractor agents. Furthermore, the NIH supports basic science for the public health with nearly 90% of its annual budget through grants for tool users and providers.

As both a sponsor of research and a member of the research community, the NIH recognizes along with others that research tools have value as a commodity and that there is a need to recognize the financial and intellectual contribution of inventors. Furthermore, good science happens in both academia and industry, so there is a need for the two-way exchange of materials. Yet, in each case, benefiting the public health remains of paramount importance.

The evolution of the NIH *Research Tools Policy*

In the early days of research, there was a practice of unrestricted flow of materials and there was little in the way of associated documentation. Materials would be sent out freely from researcher to researcher in an academic atmosphere of camaraderie. But then, the landscape changed. Commercial uses of molecular biology arose, and universities and federal laboratories obtained ownership and financial rights to inventions. Recognizing the potential financial value in these materials, material transfer agreement (MTA) or licensing practices of pharmaceutical companies were adopted by researchers' organizations.

Unfortunately, problems started to arise in the flow of research materials. As agreements had to be in place before materials were transferred, negotiation of these agreements became lengthy and could include undue restrictions. The result was a decrease in the availability of research resources and a stifling of the research enterprise.

As the NIH is a leader and major sponsor of scientific biomedical research, the research community came to the NIH and raised its concerns about the increased unavailability of research resources. In response to the research community, the NIH Director, Harold Varmus, formed an NIH Research Tools Working Group to review, evaluate, and make recommendations with respect to research tools.

To ensure that the widest perspectives of research interests were represented, the NIH Research Tools Working Group was made up of representatives from industry, academia, and government organizations. The Working Group reviewed and discussed many issues. Some of the resources taken into account were the NIH's longstanding policy on the sharing of unique research resources and NIH's *Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts* document. The Working Group came up with five recommendations:

- Promote free dissemination of research tools without legal entanglements;
- Further use of Uniform Biological Material Transfer Agreement (UBMTA);
- Develop guidelines for extramural MTA and licensing;
- Review and strengthen current policies; and
- Establish 'research tools forum'.

Along these lines, the Working Group developed a draft two-part document consisting of: (1) *Principles*, setting forth the fundamental concepts; and (2) *Guidelines*, providing specific information to scientists, patent and license professionals, and sponsored research administrators for implementation of this policy (http://www.nih.gov/news/researchtools/index.htm). After requesting, receiving, and reviewing further input and comments from the public and private sectors including industry and academia, the final version of the document was published in the Federal Register on 23 December 1999.

The NIH *Research Tools Policy*

Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts was adopted by the NIH for application to all recipients of NIH funding. As noted earlier, this NIH policy consists of two parts, the *Principles* and the *Guidelines*. Basically, there are four principles that need to be adhered to in furthering the research enterprise. These are: (1) ensuring academic freedom and publication; (2) minimizing administrative impediments; (3) implementing the Bayh–Dole Act; and (4) disseminating research resources. As a complement to this, the *Guidelines* provide specific information, strategies, and model language for recipient institutions in obtaining and disseminating biomedical resources. The *Principles* (Box 1) are as follows:

Principle 1: Ensure academic freedom and publication

Academic research freedom based upon collaboration, and the scrutiny of research findings within the scientific community, are at the heart of the scientific enterprise.

Box 1. Four key principles of NIH Research Tool Policy

- Ensure academic freedom and publication
- Appropriate implementation of the Bayh–Dole Act
- Minimize administrative impediments to research
- Ensure dissemination research resources developed with NIH funds

Institutions that receive NIH research funding through grants, cooperative agreements or contracts (recipients) have an obligation to preserve research freedom, safeguard appropriate authorship, and ensure timely disclosure of their scientists' research findings through, for example, publications and presentations at scientific meetings. Recipients of NIH funding are expected to avoid signing agreements that unduly limit the freedom of investigators to collaborate and publish, or that automatically grant co-authorship or copyright to the provider of a material.

Reasonable restrictions on collaboration by academic researchers involved in sponsored research agreements with an industrial partner that avoid conflicting obligations to other industrial partners, are understood and accepted. Similarly, brief delays in publication might be appropriate to permit the filing of patent applications and to ensure that confidential information obtained from a sponsor or the provider of a research tool is not inadvertently disclosed. However, excessive publication delays or requirements for editorial control, approval of publications, or withholding of data all undermine the credibility of research results and are unacceptable.

Principle 2: Ensure appropriate implementation of Bayh–Dole act

When the NIH funds an institution's research, the activity is subject to various laws and regulations, including the Bayh–Dole Act. Generally, funding recipients are expected to maximize the use of their research findings by making them available to the research community and the public, and through their timely transfer to industry for commercialization through licensing or other means.

The right of funding recipients to retain title to inventions made with NIH funds comes with the corresponding obligations to promote use, commercialization, and public availability of these inventions. The Bayh–Dole Act encourages funding recipients to patent and license subject inventions as one means of fulfilling these obligations. However, the use of patents and exclusive licenses is not the only, nor in some cases the most appropriate, means of implementing the Act. Where the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote use, commercialization and public availability of the invention.

In determining an intellectual property strategy for an NIH-funded invention that is useful primarily as a research tool, organizations should analyze whether further research, development and private investment are needed to realize this primary usefulness. If it is not, the goals of the Bayh–Dole Act can be met through publication, deposit in an appropriate databank or repository, widespread non-exclusive licensing, or any other number of dissemination techniques. Restrictive licensing of such an invention, such as to a for-profit sponsor for exclusive internal use, is antithetical to the goals of the Bayh–Dole Act. Where private sector involvement is desirable to assist with maintenance, reproduction, and/or distribution of the tool, or because further research and development are needed to realize the invention's usefulness as a research tool, licenses should be crafted to fit the circumstances, with the goal of ensuring widespread and appropriate distribution of the final tool product. Exclusive licensing of such an invention, such as to a distributor that will sell the tool or to a company that will invest in the development of a tool from the nascent invention, can be consistent with the goals of the Bayh–Dole Act.

Principle 3: Minimize administrative impediments to research

Each iteration in a negotiation over the terms of a license agreement or materials transfer agreement delays the moment when a research tool can be put to use in the laboratory. Funding recipients should take every reasonable step to streamline the process of transferring their own research tools freely to other academic research institutions using either no formal agreement, a cover letter, the *Simple Letter Agreement* of the UBMTA, or the UBMTA itself (http://ott.od.nih.gov/NewPages/UBMTA.pdf). The NIH has published an updated free-standing version of the *Simple Letter Agreement* (available online at: http://ott.od.nih.gov/NewPages/SimplLtrAgr.pdf), which is strongly encouraged for transfers of unpatented research materials.

Where they have not already done so, institutions receiving NIH funds should develop and implement clear policies that articulate acceptable conditions for acquiring resources, and refuse to yield on unacceptable conditions. NIH acknowledges the concern of some for-profit organizations that the concept of purely academic research might be diluted by the close ties of some not-for-profit organizations with for-profit entities, such as research sponsors and spin-off companies in which such organizations take equity. Of concern to would-be providers of a proprietary research tool is the loss of control over the tool that, once shared

with a not-for-profit institution for academic research, results in commercialization gains to the providers' for-profit competitors. Funded institutions must be sensitive to this legitimate concern if for-profit organizations are expected to share tools freely.

For-profit organizations, in turn, must minimize the encumbrances they seek to impose upon not-for-profit organizations for the academic use of their tools. 'Reach-through' royalty or product rights, unreasonable restraints on publication and academic freedom, and improper valuation of tools impede the scientific process whether imposed by a not-for-profit or for-profit provider of research tools. In fact, 'reach-through' royalties in research tool licenses have started to attract the attention of the courts as possible examples of patent misuse and antitrust violations [2]. Although these *Principles* are directly applicable only to recipients of NIH funding, it is hoped that other not-for-profit and for-profit organizations will adopt similar policies and refrain from seeking unreasonable restrictions or conditions when sharing materials.

Principle 4: Ensure dissemination of research resources developed with NIH funds

Progress in science depends upon prompt access to the unique research resources that arise from biomedical research laboratories throughout government, academia, and industry. Ideally, these new resources flow to others who advance science by conducting further research. Prompt access can be accomplished in several ways, depending on the type of resource that has been developed, whether it has broad or specific uses, and whether it is immediately useful or needs private sector investment to realize its usefulness. The goal is widespread, timely distribution of tools for further discovery. When research tools are used only within one or a small number of institutions, there is a great risk that fruitful avenues of research will be neglected.

Unique research resources such as tools arising from NIH-funded research are to be made available to the scientific research community. Recipients are expected to manage interactions with third parties that have the potential to restrict the recipients' ability to disseminate research tools developed with NIH funds. For example, a funding recipient might use NIH funds with funds from one or more third-party sponsors, or acquire a research tool from a third-party provider for use in an NIH-funded research project. Either situation could result in a funding Recipient incurring obligations to a third party that conflict with the funding recipient's obligations to the NIH. To avoid inconsistent obligations, funding recipients are encouraged to share these *Principles* with potential co-sponsors of research projects and third-party providers of materials.

Institutions should also examine and, where appropriate, simplify the transfer of materials developed with NIH funds to for-profit institutions for internal use by those institutions. The NIH endorses making the distinction between internal use by for-profit institutions and the right to commercial development and sale or provision of services. In instances where the for-profit institution is seeking access for internal use purposes, funding recipients are encouraged to transfer research tools developed with NIH funding to such institutions without seeking option rights or royalties on the final product.

The NIH *Research Tools Policy* today

This policy highlights the concerns that the free flow and access of research resources needs to be maintained for research to effectively and efficiently move forward to benefit public health. Yet, certain legal encumbrances could hinder such public health objectives. Therefore, it is important for the researcher to be cognizant of severe restrictions on the use of materials and distribution limitations for new tools and derivatives that might have a negative impact on the research enterprise. Furthermore, care needs to be exercised to retain appropriate ownership of inventions, as well as to avoid liability for overlapping agreement obligations in which a technology might be inadvertently promised exclusively to multiple parties.

It should be noted that the policy does not discourage patenting nor does it prohibit exclusive licensing, but rather, the policy encourages strategic patenting and strategic licensing. For example, exclusive licensing might be appropriate to tool companies for product development and broad dissemination to the research community. Further, this policy does not support holding a technology for defensive or blocking purposes, but rather, encourages dissemination of the technology.

NIH experience in licensing tools for drug discovery

In its licensing practices for its own internally-generated tools, the NIH has been able, through its Office of Technology Transfer (OTT), to show the practical use of its *Research Tool Policy* in successfully achieving the balance of promoting competition and commercial development without unduly encumbering future research and discovery by distributing tools for sale or commercial sale. Indeed, many of the guidelines themselves evolved from policies originally developed and tested through the NIH Intramural Research Program. For licensing of research tools, three types of agreements are generally used based on published models.

Research Products (Internal Use) Licenses are non-exclusive licenses agreements to allow a licensee to make and use, but not sell, NIH technology in its own internal research

program. Here, materials (patented or unpatented) are typically provided by the NIH laboratory, but screening uses are permitted. There are no 'reach-through' royalties or similar obligations imposed by NIH on the licensee. Companies can choose to structure these licenses as either a paid-up term agreement for a few years or one with annual payments. This type of agreement has historically been popular with biomedical firms who are eager to acquire access to external reagents to accelerate their own internal development programs (see http://ott.od.nih.gov/NewPages/Bmlintrn.pdf and http://ott.od.nih.gov/NewPages/Comm-Use.pdf for model internal use agreements for unpatented or patented materials, respectively).

Research Products (Commercialization) Licenses are non-exclusive agreements that permit a licensee to sell the research tool in the research products market. Here, the NIH again generally provides materials with smaller firms predominating as licensees. 'Substantial' US manufacturing is required for product sales within the USA unless a waiver is granted. Companies usually find that the financial structure of these license agreements involve modest execution royalties but higher earned royalty payments on product sales because the materials included in the license agreement are frequently very similar to the commercial product (see http://ott.od.nih.gov/NewPages/Bml.pdf and http://ott.od.nih.gov/NewPages/Nonexclu.pdf for model commercialization agreements for unpatented and patented materials, respectively). An interesting new distribution model that is emerging in this area is that of the 'commercial reagent repositories', which will license any and all materials available for distribution to the research products marketplace from a given laboratory (for one example, see http://www.sciencereagents.com).

Commercial Evaluation Licenses are short-term non-exclusive license agreements to allow a licensee to conduct feasibility testing but not the sale or screening use of a new NIH technology. These typically have a term of a few months, have a modest cost associated with them and include relevant materials that are supplied by the NIH laboratory. This agreement has proven to be ideal for emerging technologies that have a wide variety of potential but unproven applications that a company might be considering (see http://ott.od.nih.gov/NewPages/Cel.pdf for a model evaluation agreement suitable for research tools).

Conclusion

Since the NIH *Research Tools Policy* was adopted for NIH-funded research on 23 December 1999, it has also been included in the NIH Grants Policy as an amplification of NIH's longstanding policy of sharing of unique research resources. Furthermore, the Bayh–Dole Act was amended on 1 November 2000 to promote its goals 'without unduly encumbering future research and discovery' in the spirit of the NIH *Research Tools Policy*. Further, the extramural technology transfer policy staff of the NIH OTT continue to work with industry, academia, and other offices on resolving issues associated with the appropriate implementation of this policy.

Access to research tools is a prerequisite to continuing scientific advancement whether conducted at non-profit or for-profit institutions. Ensuring broad access to tools for drug discovery and other basic research applications while preserving opportunities for product development requires thoughtful, strategic implementation of the Bayh-Dole Act. The NIH urges all parties, not only Recipients of NIH funding, to develop patent, license, and material sharing policies with this goal in mind, realizing both product development as well as the continuing availability of new research tools to the scientific community. Just as this policy was developed synergistically among industry, academia, and the government, the NIH continues to look to the private sector and academia for further leadership in developing additional creative approaches for achieving both commercialization and dissemination of important new tools. Only by working together can the research community most effectively and most efficiently further research, enhance discovery, support a robust research enterprise, and improve public health.

References

1 NIH Dept of Health and Human Services (1999) Principles and guidelines for recipients of NIH research grants and contracts on obtaining and disseminating biomedical research resources final notice. *Federal Register Notice* 23 December 1999 [64 FR 72090] (see http://ott.od.nih.gov/NewPages/64FR72090.pdf)

2 Bayer AG versus Housey Pharmaceuticals (2001) 169 F. Supp. 2d 328