Distribution of data and unique material resources made with NIH funding

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Abstract

The research community, particularly in academic and public sector institutions, recognises that scientists have an obligation to publish the results of their research and otherwise make available data or unique materials that are necessary for others to replicate or advance their research. Over the past 15 years, the US National Institutes of Health (NIH) has developed policies to make such obligations a requirement for recipients of NIH funding. The view of the NIH and a number of other institutions is that the public is best served as the ultimate beneficiary of public research funding when barriers are reduced for sharing unique research resources. At the same time, recipients of funding have an obligation to facilitate the commercialisation of new technologies by transferring such technologies to the private sector, sometimes on an exclusive commercial basis. These various policies are meant to provide a framework in which publicly funded research institutions may strike an appropriate balance between these goals and obligations. In practice, this balance most often is realised. However, when that is not possible, the public sector has an obligation to place public benefit above its own or its corporate partners' financial gain.

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INTRODUCTION

A key ingredient in ensuring a robust research enterprise is the public dissemination of scientific results in a manner that allows others to analyse, replicate and build upon the work.[1] The research community recognises this principle in accepting an obligation to release final experimental results along with a clear description of materials and methods. When unique sources of materials are involved, scientists are responsible for making such unique materials available to others within a reasonable timeframe and under reasonable terms. Scientific progress is thwarted when key data are withheld and unique materials are not made available expeditiously. As a governmental institution funding a large portion of biomedical research in the USA, the National Institutes of Health (NIH), a component agency of the Department of Health and Human Services, plays an important role in providing guidance to recipients of NIH funding with regard to their obligation to disseminate the results of their research. In the end, when these principles are upheld, the public serves as the ultimate beneficiary through improved public health.[2]

There have always been at least a few scientists and institutions that have lacked a cooperative philosophy in sharing unique materials. One common reason has been a desire to stay ahead of 'the competition'. With the passage of the Bayh–Dole Act and Stevenson–Wydler Act in 1980, recipients of US Government research funds could take title to and license new inventions arising from their research.[3] In concert with the tremendous growth of such technology transfer activities in the public sector, the rise of the biotechnology industry has added new potential licensees, collaborators and subsequent commercial value to biomedical materials and associated data. These commercial prospects may serve as another impetus for some researchers to delay or avoid

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sharing the fruits of their publicly funded research.

Yet, institutions can and do fulfil their legal obligations to engage in technology transfer activities leading to the ultimate commercialisation of new inventions while fulfilling their obligations as recipients of taxpayer funds to make the fruits of their research available to the greater research community. Each of these efforts benefits the public – through the commercial introduction of new therapies, products and services and by supporting a research system where all researchers have the opportunity to build upon the work of their peers. The policies discussed here were developed to provide clarification and uniformity to recipients of NIH funding in striking this balance between public research obligations and private commercial interests.

In analysing these issues, one must distinguish intangible intellectual property rights, such as patents and copyrights, from rights to tangible materials, such as cell lines. Patent rights allow the patent owner to exclude anyone from making, using, selling or importing the invention[4] but do not give the patent holder ownership in the actual tangible embodiment of the invention that someone else produced. Owners of tangible materials protect their interest using contractual agreements governing the transfer and use of the materials, usually in the form of a Material Transfer Agreement (MTA). Thus, if a material and the patent governing it are owned by different parties, one may need rights to use the material from one party and a licence to the patent rights from another. It also means that the party who supplies the material, whether patented or not, can attempt to capture or enforce greater rights in the MTA than one might have in enforcing patent rights. For example, the terms of the MTA may provide the supplier of a material with certain rights in new, patentable technologies that are made using the material.

The NIH first developed a model MTA in 1988 to standardise and facilitate the exchange of research materials

MODEL MATERIAL TRANSFER AGREEMENTS

The NIH, as part of the US Public Health Service (PHS), has always supported the principles of public availability of research data and unique materials. Yet it was not until 1988 that the NIH developed an explicit policy statement regarding the need to share unique research resources.[5] This policy applied, and those that followed likewise apply, to scientists and institutions receiving research grant and contract funding from the NIH, the extramural community, as well as scientists working at the NIH, the intramural research programme.[6] With respect to research grants, the PHS Grants Policy Statement is incorporated as a condition of award of each grant. In the past ten years, the NIH has issued various policies to expound upon, clarify and enhance these basic requirements as a *quid pro quo* for receiving public research funds.[7]

The agreement governing the transfer of materials, the MTA, can itself be an administrative barrier to the transfer of materials. The NIH has worked over the past 15 years with the extramural community to establish acceptable standard terms and to reduce the administrative burden in negotiating many different versions of MTAs. In 1989, PHS adopted a standard MTA for use by PHS scientists and encouraged others to adopt similar agreements that were not unduly restrictive. Among other things, the standard MTA required the recipient to exercise care in working with the materials, to control the further distribution of the materials and to acknowledge the provider in any relevant publications. The MTA also limited the liability of the provider to its own negligence and, when PHS was the provider, it sought indemnification to the extent the recipient could legally provide it.[8]

This MTA was used for essentially all transfers of materials from the intramural programme to non-profit institutions, except for clinical purposes, in which case

More than 250 institutions worldwide are parties to the UBMTA

additional terms pertaining to human subjects were added. Some materials were and continue to be transferred to for-profits under MTAs, for example materials used in NIH-funded research including Small Business Innovative Research (SBIR) grants. However, it has been more common for the NIH to transfer patented and unpatented materials from its intramural laboratories to for-profit institutions for a fee under internal use licences to biological materials and patents, where applicable.[9] However, in neither case has the NIH ever placed constraints on the recipient's distribution or ownership of new inventions or materials, claimed rights to income generated from the licensing of new inventions, or required pre-publication review of articles.

While this model MTA was a move in the right direction, it became clear in a few years that the disparity in terms of agreements, requiring extensive negotiation and amendment prior to execution, was an impediment to the exchange of materials among researchers. In an attempt to overcome some of these problems, the NIH began working with the extramural community to craft a new model MTA that was released in 1995. The goal in developing this agreement, the 'Universal Biological Material Transfer Agreement' (UBMTA), was to reduce this administrative impediment and to establish standard reasonable terms.[10]

The UBMTA is a master agreement and model MTA for the exchange of materials

To further simplify the transfer process, the UBMTA is structured as a master agreement signed by an institution with the actual agreement used to transfer specific materials limited to a one-page form, the Implementing Letter, which references the terms of the master agreement. It was anticipated that this agreement would be appropriate for use with the majority of materials to be transferred. The Association of University Technology Managers (AUTM) administers the UBMTA and its signatories. As of December 2004 they report 256 institutional signatories, representing government laboratories, universities, medical centres and foundations worldwide.[11] A Simple Letter Agreement was developed for the transfer of non-proprietary materials or for use by institutions that are not signatories to the UBMTA.

With biological and biochemical materials, particularly those that can replicate, challenges arise with regard to the precise meaning and application of the terms Materials, Unmodified Derivatives and Modifications to materials that are progeny or have been modified in minor ways. For the first time in a model agreement, the drafters of the UBMTA attempted to distinguish between the Original Material, as opposed to Progeny, Unmodified Derivatives, Modifications and anything else newly isolated, with subsequent clarification of rights of the Provider and the Recipient in these various types of materials. For example, one could receive a nucleic acid (Original Material), replicate it (Progeny) and develop a diagnostic involving the use of that nucleic acid (Modification), or one could use it as a probe to identify and clone a new, homologous gene (a new material owned by the recipient).

SPONSORED RESEARCH AGREEMENTS AND RESEARCH TOOLS GUIDELINES

As universities' ties with industry grew stronger and more complex in the early 1990s, the NIH became concerned about some terms in agreements governing for-profit funding of research at non-profit institutions, termed 'Sponsored Research'. The non-profit recipient of research funding could give the funding entity an inappropriate level of control over the output of NIH-funded research such that the interest of the research community and the public at large could be compromised. For example, a for-profit might influence the direction of research to avoid potentially important findings that would not be of interest, or actually could be contrary, to the interest

of the corporate funder. As a result, the NIH issued a policy in 1994 entitled 'Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts'.[12] In this guidance, one of the Universal Points for Consideration for institutions entering into sponsored research agreements is to ensure that the terms do not unduly restrict the dissemination of research results generated using NIH funds. In particular, it points to the Grants Policy Statement requiring publication of research results and responsibilities to disseminate information of unique research resources.

Research Tools may be patented and licensed to a company for sale to the research community

In the mid-1990s, the NIH also heard from scientists concerned about long delays in obtaining unique research materials, onerous terms in MTAs or, worst of all, the inability to obtain materials that were described in publications of NIH-funded research. In 1997, Dr Harold Varmus, NIH Director at that time, established a committee to investigate these problems and provide recommendations. The committee, consisting of representatives of the NIH, academic researchers, legal experts and biotechnology industry, listened to the views of individuals and groups representing a similar full range of academic and commercial interests. The final report made several recommendations to the NIH[13] that were incorporated, after public comment, in 1999 into a policy document entitled 'Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts' (also known as the 'Research Tools Guidelines').[14] These Guidelines were incorporated into the NIH Grants Policy Statement and represent terms of award of NIH grants and contracts. Shortly following the release of these Guidelines, Congress passed the Technology Transfer Commercialization Act of 2000 amending one of the purposes of the Bayh–Dole Act 'to 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*.'[15] With this small statutory change, Congress expressed its support for the greater goals of the NIH Research Tools Guidelines.

The Research Tools Guidelines aim to promote widespread distribution of research tools

This policy established a broad definition of 'unique research resources' to ensure that the full range of laboratory research tools was captured: 'Cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines.' The document notes that databases and software may also be research tools and thus encompassed by this definition, while also recognising that they raise additional issues, such as copyright, that not fully explored by this document.

The Principles of this document set forth the fundamental concepts and the Guidelines provide specific information for implementation. The Principles are to (1) ensure academic freedom and publication, (2) ensure appropriate implementation of the Bayh–Dole Act, (3) minimise administrative impediments to academic research and (4) ensure the dissemination of research resources developed with NIH funds. The Guidelines then provide specific information, strategies and model language for implementation of the Principles. Most importantly, the policy considers that the same material might be used both as a research tool and a commercial product. In such a case, the types of agreements used for each purpose differ not only in scope but in content. One can grant an exclusive licence for use of a material and associated intellectual property as a commercial product while reserving the right to grant non-exclusive licences for both commercial and non-profit research. Alternatively, the exclusive licensee might be required to make the material available for research purposes through sublicensing or commercial sale of the material itself. Operating within the scope of these policies for many years, the NIH Office

of Technology Transfer (OTT) has established a large, effective programme resulting in approximately 200 products that have been introduced into the market, including 20 FDA-approved and marketed drugs and vaccines, that utilise some intellectual property licensed from the NIH.[16]

A few comments received by the NIH referred to the document as 'anti-patent'. This may be a harsh label as the policy does not instruct an institution not to patent. The focus of the policy is to encourage the use of the patent system when intellectual property protection serves as an incentive for commercial development and public use as well as to point out potential disadvantages of patents when such an incentive is not needed. In particular, the document encourages owners of materials that serve solely as research tools to consider that it might not be in their interest and that of the greater public to patent a particular material. In such cases, patenting the material may add expense and administrative burdens to its distribution, perhaps without concomitant benefits. The policy does note, however, that there are times where patenting a research tool would serve as an incentive to develop the tool. A strategy to license such a patented tool to a research tool distribution company, for example, would fulfil the NIH policy goals.

On the other hand, the NIH would generally deem it inappropriate to grant an unlimited exclusive licence to a company for an unpatented research tool, such as a unique mouse model of Parkinson's disease. The NIH, along with a number of other institutions, believes the public is best served when many researchers utilise such an animal model in cutting-edge research to advance this field of research. In the case of the Cohen–Boyer patent for recombinant DNA technology, the NIH gave its approval to Stanford University and the University of California, San Francisco, to patent this invention.[17] Thus, patenting per se is not antithetical to the NIH mission as much as a licensing strategy supports the mission when it ultimately provides broad access to the fruits of research involving unique research methods and materials.

The terms of MTAs should not encumber newly discovered research tools

The Guidelines address the importation of research materials into NIH-funded research programmes as well as materials generated *de novo* with NIH funding. Agreements governing the transfer of materials into NIH-funded research should respect any proprietary aspects of the provider's materials but should not encumber new research tools in a manner that does not permit full compliance with this policy. For example, an NIH-funded researcher should not enter into an MTA for a research material that restricts the research institution's ability to transfer newly created research tools to any researcher who wants to use the tools once they have be appropriately characterised. MTA terms that are restrictive in this manner include the use of an overly broad definition of the material owned and provided such as, for example, 'material provided, and all progeny and modifications thereof ('Material').' When a commercial provider has a concern about potentially being blocked by inventions involving new uses of its proprietary material, the NIH does not object to a recipient granting rights in new inventions back to the provider, particularly an internal use licence or a royalty-bearing commercialisation licence to new inventions made in the course of the research.[18] The Guidelines take into account the difficulty a recipient may have in ensuring the dissemination of new research tools made with NIH funding to the extent they embody the provider's proprietary material.

For research tools generated *de novo* by the researcher, the institution should find a means of making them available to the research community. The document recognises the importance of the for-profit research community by also including these researchers in the overall definition of research community but allows institutions to devise the general

structure of the transfer, for example at no cost under an MTA or for a royalty fee under a licence. While fees are permissible, providers of materials funded by the NIH should not use 'reach through' terms. These would include an overly broad definition of materials, that give the provider ownership rights in new inventions made using the provider's materials, far beyond the commonly agreed-upon right to use the new inventions in internal research. Similarly, the provider should not request royalties on future products that do not embody, or services that do not directly utilise, the research tool. The concern is that such terms discourage the use of tools and thus diminish their value and potential contribution to science.

In order to minimise the administrative burden of negotiating many different MTAs, the policy includes a model Simple Letter Agreement (SLA) for the transfer of materials, which is meant to include only those legally essential terms needed to protect the provider and the recipient institutions. Unlike the NIH model MTA from 1989, for example, it does not include an indemnification clause. The NIH adopted this SLA for use by its intramural researchers and has encouraged the use of this agreement or the UBMTA for as many transfers of materials as possible. Finally, strategic licensing is needed to strike a balance between reserving rights to permit research uses of research tools while carefully defining the scope of commercial licence rights in granting only those exclusive rights necessary to provide an incentive to develop materials into commercial products or for use in commercial services.

Institutions funding research in the US and UK have adopted policies similar to the Research Tools Guidelines

Overall, the Research Tools Guidelines have been well received. The working group that made the recommendations to the NIH included representation from the academic, governmental and the commercial sectors. When the policy was first open for public comment in May 1999,[19] NIH received general support from organisations such as the US Pharmaceutical Research and Manufacturers of America (PhRMA), the Council on Governmental Relations (an organisation of research universities) and the American Association of Medical Colleges. These groups also offered useful suggestions, many of which were incorporated into the final policy statement.

Other funding agencies and organisations have endorsed the NIH Guidelines or provide similar guidelines to their own recipients of funding. The US National Science Foundation (NSF)[20] and the Howard Hughes Medical Institute (HHMI)[21] have adopted similar policies. The UK Royal Society has noted the importance of making data and unique research materials developed with public funding broadly available to the research community.[22] Governmental and university officials visiting the NIH from other countries have expressed interest in adopting similar policies. Industry has funded research in some basic research areas, such as the SNP (Single Nucleotide Polymorphism) Consortium, where they find greater good in collaborating with non-profit organisations to make the results of the research freely available.[23] A study conducted by the US National Academy of Sciences notes that there has not been 'as much breakdown or even restricted access to research tools as one might expect because firms and universities have been able to develop ''working solutions'' ', noting in part the role of the NIH.[24]

Not all comments on the proposed NIH Research Tools Guidelines were positive. In particular, objections were raised primarily by some biotechnology companies that rely on exclusive control of research tools to underpin and promote their business interests. While these represented a minority of the opinions, NIH took the concerns into serious consideration. In weighing the potential benefit to the public in providing one corporate entity an incentive to exploit a particular research tool solely for its own use, the NIH found its mission and the

public interest was best served by making government-funded research tools broadly available through distribution or manufacture and sale. Similarly, the NIH considered a comment concerning what one entity found to be potentially conflicting obligations under the Research Tools Guidelines and the obligation of recipients of SBIR grants to focus on the commercialisation of their technology, which would not permit them to disseminate research tools with minimal intellectual property encumbrances. NIH noted that SBIR grantees, like all grantees, are subject to the dual obligations of disseminating research tools while promoting utilisation, commercialisation and public availability of their inventions. In fact, a number of SBIR grantees are in the business of selling research tools.

After a period of implementation, the NIH sought feedback from the biomedical research community concerning its experience with the Research Tools Guidelines. At the 2004 AUTM national meeting, an informal survey by the NIH OTT of attendees suggested that the Guidelines have had a significant impact in facilitating the transfer of materials between non-profit institutions. With respect to materials transferred from for-profit to non-profit institutions, the attendees, mostly from non-profits, reported that the Guidelines have provided a strong justification to resist pressures from some for-profit institutions to accept terms that most non-profits found to be objectionable.[25]

NIH funded researchers are required to provide a specific sharing plan if they anticipate developing model organisms

On the other hand, for-profits have reported informally to the NIH that they believe some universities tend to overvalue their research materials or sometimes require reach-through claims to royalties on the company's sale of products developed using the research tool. The NIH finds it acceptable to charge a company for the value of the research material itself and a licence fee for any associated intellectual property, but believes that attaching rights to downstream inventions can stifle scientific progress, increase costs and potentially limit product development. If multiple providers of research materials each claimed a percentage of sales on products developed using those materials, the combined royalties, known as 'stacking royalties', could also be sufficiently high to hinder commercialisation.[26]

One particular subgroup of research tools that has garnered a greater level of attention is model organisms, such as rodents, zebrafish and fruitfly models critically important to various fields of research study. These models include spontaneous mutant phenotypes that have been inbred, as well as those carrying knock-in and knock-out alleles that have been generated to study the activity of specific genes. It is because these models are so important to researchers that the NIH now requires researchers submitting funding applications (as of 1st October, 2004) to include a specific plan for sharing model organisms when the research plan anticipates the development of such organisms.[27]

The NIH developed a model MTA for the transfer of model organisms (MTA-TO), especially for those organisms that raise particular legal issues associated with animal custody, care and use.[28] The MTA-TO for example, transfers ownership of the organisms to the recipient institution, unlike many other MTAs, while allowing the provider institution to retain certain rights in its 'intellectual property', viz. the allele(s) or genotype that gives the organism its special characteristics. By relinquishing ownership of the organisms themselves, the provider institution reduces its liability associated with the recipient institution's compliance with national and local laws governing animal care and use.

In addition to tangible materials such as organisms, the sharing of research data is critically important to extracting the greatest biomedical benefit from NIH-funded research. To this end, the NIH issued proposed guidance in March 2002 and a Final Statement on Sharing

Research Data in February 2003.[29] The statement reiterates the NIH commitment to the timely release of final research data for all the research it supports. Applicants seeking funds greater than US$500,000 direct costs in a any single year must also address in the application a specific data-sharing plan. Reviewers of grant and contract applications will comment on this plan and the other material-sharing plans that are described in grant applications and contract proposals but will not take the plan into account in arriving at a scientific merit or priority score. However, applicants will have to remedy any deficiencies identified by the reviewers or NIH staff prior to grant or contract award.

BEST PRACTICES FOR LICENSING GENOMIC INVENTIONS

More recently, the NIH has attempted to address concerns about the manner in which genomic inventions are patented, licensed for research and commercialisation, and shared with the greater research community.[30] It has looked to its own technology transfer experience, and that of other like-minded institutions, in striking a reasonable balance between providing appropriate incentives for commercialisation of products and services while ensuring that intellectual property governing genomics technologies and any unique research materials are made available to the research community, both for-profit and non-profit uses, under reasonable terms. Again, the guiding principle is to ensure a robust research enterprise worldwide that ultimately benefits public health.

Genomic technologies have gathered special attention by the NIH and OECD

The Best Practices for the Licensing of Genomic Inventions are being issued as 'Best Practices' to reinforce the fact that there is no general requirement under this guidance for the submission of specific technology transfer plans or additional terms of grant award. These Best Practices flow out of the Research Tools Guidelines and other mainstream principles academia has upheld as ideal.[31] As such, institutions and organisations are encouraged to adopt and promote them. Rather than specifying specific terms and conditions, these Best Practices consist of a licensing strategy with points for consideration. Similar goals are shared by the Organisation for Economic Co-operation and Development (OECD),[32] which is actively pursuing guidelines that ultimately strive to balance the interests of both the public and private sectors.[33]

Genomic inventions are particularly challenging to manage because they often represent early-stage, high-risk technologies but have greater impact potential, and they may be patent protected. Inventors, administrators and company collaborators may exert pressure upon institutions to grant exclusive licences to these technologies and in turn expect significant revenue generation. These inventions can provide challenges in managing the intellectual property in that the same genomic technology may have utility as a research tool, as a component of a diagnostic assay and potentially as a human therapeutic as well. As with many research tools, however, not all innovations require further research and development to meet the needs of the research community or public health. The Best Practices do not require, but ask those managing the technology to consider, that in these cases patenting may not be necessary or beneficial to the biomedical research enterprise or the public health in the long term. Significant resources and funds can be saved by not seeking patent protection when patent rights are not needed as an incentive for companies to invest significant commercial resources to bring the invention to its full potential. When the invention is a biological material, resources can then be devoted to licensing commercially viable unpatented tools,[34] and incremental improvements will still advance the field through publication. These Practices provide a standard but leave final decisions on patenting and licensing to the institutions holding title to the inventions.

Licensing on an exclusive basis may be necessary and appropriate when industry must invest significant funds in research and development, including clinical trials, to bring the product or service to market. However, the scope of the exclusive licence should be limited to that needed to develop the technology. The terms should require expeditious development of the technology through milestone and diligence provisions, and the license should be tailored to address relevant public health benefits as appropriate. For example, it would not be in the public interest to license a broad platform technology, such as recombinant DNA, exclusively to one company, especially without significant requirements to sublicense and permit the full exploitation of the technology. Similarly, if a technology has multiple therapeutic uses, no exclusive licensee should be permitted to 'cherry pick' the most lucrative market while blocking the development of other less lucrative, but potentially important clinical uses. The NIH OTT and other university technology transfer offices operate under these principles and facilitate the transfer of many technologies for commercialisation while generating a royalty income stream, a portion of which serves as a reward to the inventors, and pays technology transfer expenses. Remaining royalty funds are funnelled back to support research that otherwise would not have been performed.

EXPERIMENTAL RESEARCH EXEMPTION

Most US patent owners refrain from enforcing their intellectual property rights against non-profit researchers

The *Madey v Duke*[35] infringement case last year awakened those who were not aware, and reminded those who were, that the USA has long had a common law research exemption but one that is quite limited in scope. As Federal courts have affirmed, the exemption applies to the use of a patented technology 'solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.'[36] The *Madey* court noted that the exemption does not divide researchers into for-profit and non-profit camps. Researchers may not legally avail themselves of the invention if they are outside the realm of the exemption and particularly if the infringing acts are 'in furtherance of [their] legitimate business', even if that business is non-profit research.[37]

A more recent Federal case affirmed the value of patents on research tools in ruling that preclinical use of a drug screening technology was not protected by the statutory safe harbour of the Hatch–Waxman Act, which excludes from infringement the use of an invention reasonably related to requirements for submission of information to the Food and Drug Administration (FDA).[38] The court ruled that Merck's preclinical research to identify a candidate drug was too early in the drug development chain to fall within the exemption. Despite these rulings, there are few cases of infringement brought against non-profit researchers, particularly those who are not partnering with a commercial institution. For years, investigators in the non-profit sector have relied on the lack of incentives, in many cases, a wariness to elicit bad public relations by suing a researcher and a non-profit institution, as well as the understanding by patent owners that most research using a patented technology can add value to the invention by reinforcing or broadening its potential usefulness.[39]

While the *Madey* decision may not have unleashed a Pandora's Box, a number of universities have noted to the NIH their receipt of a greater number of infringement letters requesting that the university enter into a royalty-bearing licence to patented technology for internal non-profit research purposes, some specifically citing the *Madey* decision as justification.[40] The concern of the NIH and universities relates to the prospect of non-profit research institutions having to pay licence fees to every patent owner whose technology they utilised in research. In such case, the administrative costs in monitoring such use, negotiating such agreements and paying licence fees could certainly stifle

Government funded research tools need not be free but should be freely available

the non-profit research enterprise. In an attempt to avoid this prospect, the NIH has worked with various patent owners who sought licences from the NIH and its non-profit grantees to draft model, non-royalty bearing licences with terms that otherwise comply with NIH policies.[41] Thus, NIH policies and negotiation of model agreements with patent and materials owners play an important role in sustaining a research environment in which research tools are more widely available and non-profit research is not excessively burdened with royalty fees when materials or software are not transferred.

SPECIAL TERMS AND CONDITIONS

In addition to these general policy guidelines and terms of grant award, the NIH may apply more specific special terms of awards to particular grants, usually grants submitted under special initiatives and announced as Requests for Applications (RFAs) or special Program Announcements (PAs), and contracts submitted in response to Requests for Proposals (RFPs).[42] For example, an RFA for Mutagenesis Screens/Phenotyping Tools for Zebrafish[43] funds research under a grant mechanism seeking to exploit zebrafish as a model for development and disease research. It contains a Special Requirement that applicants provide plans for managing any resulting intellectual property and rights regarding patentable research resources. It particularly notes that timely sharing of these resources to the broader research community is critical to the success of the programme. The announcement also notes the NIH's concerns with respect to this particular initiative that patents on mutant fish, their gametes, phenotypic screens and other research resources might have a chilling effect on the long-term development of products and information that may improve public health. While the NIH acknowledges the institution's right to patent inventions, it asks for plans that avoid unnecessary patenting and manage intellectual property and materials in a manner that does not inhibit further research. The research community receiving these funds has supported this strategy of open access.

NIH uses special terms and conditions of grant award for initiatives where the goal is to develop research tools for widespread use

The Bayh–Dole Act is well known as the statutory authority permitting recipients of US federal research and development funding to elect title to any inventions made during the course of the funded research. However, the Act itself permits a federal agency to retain rights in inventions made under a funding agreement 'in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objects of [the Act].'[44] When the agency makes this determination for a particular funding agreement, usually under a Request for [contract] Proposals (RFP), it is termed a 'Declaration of Exceptional Circumstances' (DEC).

There are only a few DECs imposed on the many research and development contracts awarded by the NIH. One example, however, is the Osteoarthritis Initiative (OAI) contracts for clinical centres[45] for which a DEC was applied only to data, radiological images, DNA and biological specimens collected under the contract 'to ensure [their] unrestricted availability', a provision supported by the osteoarthritis research community.[46] It does not apply to other potential inventions made under the contract as these were not deemed as vital to the programme goals as to ensure they were free of any encumbrances of institutional ownership in intellectual property. These other inventions are also more likely to require commercial development such that a patent would provide an important incentive for commercialisation. The NIH is committed to using DECs in truly exceptional circumstances when justified. Even then, the scope of the DEC is limited, as in the OAI, to only those inventions where broad unrestricted access is programmatically necessary.

CONCLUSION

The entire biomedical research community – for-profit, non-profit and governmental institutions – has a responsibility to ensure, each in their own way, that the results of research inures ultimately to the benefit of the public health worldwide. Just as a company has a responsibility to act in the best interest of its shareholders, the NIH must support the interests of its 'shareholders', the research community and the public at large. With respect to Government-funded research, the NIH has a special responsibility to develop policies and standards that overcome existing barriers or prevent the construction of future barriers that interfere with the broad distribution of the results of NIH-funded research. These results include not only research tools and model organisms but also data sets that are required by other researchers to evaluate, reproduce and build upon the original research. The NIH recognises the important yet complementary roles played by for-profit and non-profit researchers in requiring that research tools are made available by some reasonable means to the research community.

The research community and the public benefit from a system that utilises exclusive licensing mechanisms appropriately

The NIH has strived to be proactive in developing policies before significant weaknesses develop in the research enterprise. However, there are limits to what the NIH can and should do. The entire community has a role to play in ensuring that as much public good as possible is extracted by the biomedical research enterprise. This means that restraint should be shown by patent owners where non-profit research is carried out that may well add value to the invention, profiting both the owner and the public health. Patent owners are certainly entitled to a financial return from institutions making commercial use of the patented technologies. However, all parties involved in technology transfer should work together where possible to reduce barriers to the transfer of materials between for-profit and non-profit institutions. It also means that research tools should be exchanged without impeding future activities by providers who retain 'reach-through' rights to products developed using these tools. That is not to say that all research tools should be free, but that the means of exchanging them, either by sale or licence, should occur in a manner that does not obstruct future research and product development. It also means that patent owners, particularly in the academic and public sectors, should adopt licence practices that make the improvement of public health for all people the highest objective, while retaining the subordinate goal of a reasonable financial return.[47] In this manner, researchers and the public at large will reap the most benefit from the investment of time, money and creativity as we confront the challenges facing public health.

References and notes

1. See, for example, National Research Council (2003), 'Sharing Publication-Related Data and Materials, Responsibilities of Authorship in the Life Sciences', The National Academies Press, Washington, DC.
2. See Walsh, J. P., Arora, A. and Cohen, W.M. (2003), 'Effects of research tool patents and licensing on biomedical innovation', in 'Patents in the Knowledge-Based Economy', Cohen, W. M. and Merrill, S. A., Eds, National Research Council of the National Academies, noting that 'active intervention' by the NIH is among one of several factors that 'reduce the threat of breakdown and access restriction [to research tools].' The US National Research Council has expressed concern that basic research could be harmed if research tools are not readily available. 'A Patent System for the 21st Century', Merrill, S. A., Levin, R. C. and Myers, M. B., Eds, Board on Science, Technology, and Economic Policy, National Research Council of the National Academies, 2004 (URL: www.nap.edu/books/0309089107/html).
3. The Bayh–Dole Patents and Trademark Amendments Act of 1980, Public Law 96–517, is codified at 35 USC sec. 200 *et seq*. The Stevenson–Wydler Technology Innovation Act of 1980, Public Law 96–480, is codified at 15 USC sec 3710 *et seq*. By law, title to inventions made with US Government funding is held by the recipient institution, not by the Principal Investigator. *Ibid*.

4. 37 USC sec. 271(a).
5. Policy Relating to Distribution of Unique Research Resources Produced with PHS Funding, *NIH Guide for Grants and Contracts*, Vol. 17(29), 16th September, 1988.
6. More than 9 per cent (US$2.7m) of the total NIH budget for Fiscal Year 2004 was allocated to the intramural research programme (supporting a research infrastructure involving 6,000 to 7,000 MD and/or PhD scientists), and over 80% (US$22.9m) supported extramural grants and contracts (URL: http://www4.od.nih.gov/officeofbudget/FY05pubs/ObligationsHistorybyMech.pdf).
7. For an analysis of the legal authorities available to the NIH in instituting and enforcing these policies, see 'Report of the NIH Working Group on Research Tools', 4th June, 1998, Appendix D Analysis of NIH Options under Current Law (URL: http://www.nih.gov/news/researchtools/index.htm).
8. Adler, R. G. (1990), 'Sharing materials: An analysis of the issues is overdue', *New Biol.*, Vol. 2, pp. 495–497. Also see Uniform Biological Material Transfer Agreement: Discussion of Public Comments Received; Publication of the Final Format of the Agreement, Fed. Reg., Vol. 60, pp. 12771–12773, 8th March, 1995.
9. See Model PHS Biological Materials Agreement for Internal Use (URL: http://ott.od.nih.gov/modelagr.html). Unlike US federal laboratories, universities have more legal flexibility in being able to grant licenses and recoup fees under an MTA.
10. See Uniform Biological Material Transfer Agreement, *Fed. Reg.*, Vol. 60, pp. 12771–12773.
11. URL: http://www.autm.net
12. *Fed. Reg.*, Vol. 59, No. 215, Nov. 8, 1994, pp. 55674–55679 (URL: http://iedison.gov/Edison/sponsored.html).
13. Report of the NIH Working Group on Research Tools, 4th June, 1998 (URL: http://www.nih.gov/news/researchtools/index.htm).
14. URL: http://ott.od.nih.gov/res_tools.html, or *Fed. Reg.*, Vol. 64, pp. 72090–72096, 23rd December, 1999. Intramural scientists are subject to the same guidelines, see, in part, Guidelines for the Conduct of Research (URL: http://www.nih.gov/campus/irnews/guidelines.htm).
15. Italicised words in main text were added by the amendment; Public Law 106–404 enacted 1st November, 2000, codified at 35 USC sec. 200.
16. URL: http://ott.od.nih.gov, more specifically, statistics can be found at http://ott.od.nih.gov/current_tta.html. The NIH OTT manages a portfolio of about 2,500 pending and issued patents, more than 1,500 active licences with annual royalty income exceeding US$56m. Similarly, a number of universities have successful technology transfer programmes working within these policy parameters.
17. The patent, filed prior to the Bayh–Dole Act, 'provides no incentive, just a small tax in the form of royalties on the exploitation of the technology'. It is noted this type of patenting is permitted by Bayh–Dole, but it does not directly further any of the goals of the Bayh–Dole Act because the patent did not provide an incentive for commercialisation of the technology. Intellectual Property Rights and Research Tools in Molecular Biology: Summary of a Workshop Held at the National Academy of Sciences, 15th–16th February, 1996 (1997), National Academy of Sciences, Chapter 5, Case Studies (URL: http://books.nap.edu/books/0309057485/html/41.html). The universities' strategy meets the goals of the NIH policy because the technology was licensed non-exclusively and made broadly available to for-profit institutions under fee-based licences, while non-profit institutions were not asked to execute a licence to utilise the technology for research purposes. Contrast this strategy with that involving PCR and Taq polymerase where some researchers claimed the high licence fees 'slowed the progress of PCR products from the research laboratory to the marketplace'. *Ibid.* p. 45.
18. See for example the NIH model Cooperative Research and Development Agreement (URL: http://ott.od.nih.gov/model_agree.html).
19. 'Principles for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Research Resources: Request for Comments', *Fed. Reg.*, Vol. 64, p. 28,205, 25th May, 1999.
20. See section 734 of the NSF Grant Policy Manual (URL: http://www.nsf.gov/pubs/2002/nsf02151.htm#734).
21. URL: http://www.hhmi.org/pdf/4237105.pdf
22. '[A]lthough IPRs [intellectual property rights] are needed to stimulate innovation and investment, commercial forces are leading in some areas to legislation and case law that unreasonably and unnecessarily restrict freedom to access and use information to carry out research. The restriction of the commons by patents, copyright, and databases is not in the interests of society and unduly hampers scientific endeavor.' The Royal Society, 'Keeping science open: the effects of intellectual property policy on the conduct of science', April 2003 (URL: http://www.royalsoc.ac.uk/document.asp?tip=0&id=1374).
23. SNP Consortium (URL: http://snp.cshl.org).
24. See *supra* note 2. However, others point out that reliance on voluntary restraint and non-binding guidance might not be sufficient to

ensure the long-term availability of research tools. Rai, A. K., and Eisenberg, R. S. (2003), 'Bayh–Dole reform and the progress of biomedicine', *Law & Contemporary Problems*, Vol. 66, p. 289.

25. Similar comments were received in response to NIH's request for comments following the implementation of the Research Tools Guidelines. *Fed. Reg.*, Vol. 65, p. 54,293, 7th September, 2000.

26. Also see Rai and Eisenberg, *supra*, Walsh *et al.*, *supra*, National Academy of Sciences, *supra,* and Heller, M. A., and Eisenberg, R. S. (1998), 'Can patents deter innovation? The anti-commons in biomedical research', *Science,* Vol. 280, p. 698. While many writers on this topic acknowledge particular cases where stacking royalties, high licence fees or 'patent thickets' have deterred access to technologies, there is no agreement as to whether the current system is working well enough or whether more intervention is needed.

27. NIH Guide, 7th May, 2004, notice number NOT-OD-04–042. Also see general guidance on NIH policies for Model Organisms (URL: http://www.nih.gov/science/models/).

28. See Model Organism Resource Sharing FAQs, Question/Answer 20 (URL: http://www.nih.gov/science/models/).

29. Final NIH Statement on Sharing Research Data, NIH Guide, 26th February, 2003, notice number NOT-OD-03–032 (URL: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03–032.html).

30. The Organization for Economic Co-operation and Development (OECD) released a report 'Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies' in 2002 (URL: http://www.oecd.org/dataoecd/42/21/2491084.pdf). One recommendation was to develop good practice licensing guidelines (p. 83).

31. The Best Practices for the Licensing of Genomic Inventions has been published for public comment in *Fed. Reg.*, Vol. 69, p. 67,747, 19th November, 2004 (URL: http://ott.od.nih.gov/LicGenInv.html). Nearly all comments received to date, from associations, researchers and industry, strongly support these Best Practices.

32. The OECD is an international organisation of 30 member countries that 'share a commitment to democratic government and a free market economy' (URL: http://www.oecd.org).

33. The OECD has noted that '(i)t is of course in the interest of patent holders to make their products and services available as widely as possible to the research community and to the public health authorities.' However, this may not be actually happening in all cases. The general consensus of the OECD is that enhanced public access is desirable. Organisation for Economic Co-operation and Development (2002), 'Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies', p. 52 (URL: http://www.oecd.org/dataoecd/42/21/2491084.pdf). See 'The OECD Draft Guidelines' (URL: http://www.oecd.org/document/20/0,2340,en_2649_34537_34340820_1_1_1_1,00.html).

34. See for example the model PHS Biological Materials Licensing Agreement (URL: http://ott.od.nih.gov/modelagr.html).

35. *Madey v Duke*, 307 F.3d 1351 (Fed. Cir. 2002).

36. *Madey*, 307 F.3d, 1351, 1362. In the EU, most countries have statutory research exemptions that would not have changed the Madey result. For example, research involving the anticipated use of the inventive technology (for example, a method of drug screening used to screen drug candidates as opposed to using such a method as a point of comparison for devising a better method of drug screening) would not have been exempted. See presentation of Joseph Straus, Max Planck Institute for Intellectual Property, to a meeting of Science and Intellectual Property in the Public Interest, 24th April, 2003 (URL: http://sippi.aaas.org/meetings/04242003/straus.htm).

37. The court does not make a distinction as to whether the potential infringer is making money or has an ultimate commercial goal: 'For example, major research universities, such as Duke, often sanction and fund research projects with no commercial application whatsoever. However, these projects unmistakenly further the institution's legitimate business interests.' *Ibid*.

38. *Integra v Merck*, 331 F.3d 860 (Fed. Cir. 2003) reviewing the limits of the safe harbour provision under 35 USC sec. 271(e)(1). Also see Science and Intellectual Property in the Public Interest, *Integra Life Sciences v Merck* (URL: http://sippi.aaas.org/ipissues/cases). However, the US Supreme Court, which has agreed to hear this case, will provide the final interpretation of this statute (URL: http://sippi.aaas.org/1ipissues/updates/?res_id=505).

39. See Walsh *et al.*, *supra*.

40. Some organisations seek a statutory research exemption in the USA. See 'Science and Intellectual Property in the Public Interest', American Association for the Advancement of Science (URL: http://sippi.aaas.org/rschexemption.shtml), and the American Intellectual Property Law Association, which passed a resolution supporting, ' in principle, legislation to codify an exemption from infringement under which uses of a claimed invention related to scientific, research, or experimental inquiries are exempted as acts of infringement'.

41. For example, see the NIH-DuPont Cre/Lox Memorandum of Understanding (URL: http://ott.od.nih.gov/cre-lox.html), the NIH-DuPont OncoMouse Memorandum of Understanding (URL: http://ott.od.nih.gov/archives_2000.html), and the agreements with various providers of human embryonic stem cells (Memorandum of Understanding between WiCell Research Institute and Public Health Service, URL: http://stemcells.nih.gov/research/registry/MTAs/Wicell_MOU.pdf, and Material Transfer Agreement with MizMedi hospital, Seoul, Korea, URL: http://stemcells.nih.gov/research/registry/MTAs/Mizmedi_MTA.pdf). Note that the only fees associated with any of these agreements are reimbursement for the costs of materials transferred, not royalty fees.
42. For definitions, see URL: http://grants.nih.gov/grants/glossary.htm.
43. NIH Guide, 16th February, 2000, RFA: HD-00–004 (URL: http://grants1.nih.gov/grants/guide/rfa-files/RFA-HD-00–004.html).
44. 35 USC sec. 202(a)(ii) and the corresponding regulation at 37 CFR sec. 401.3(a)(2).
45. Clinical Centers for the Osteoarthritis Initiative (URL: http://www.niams.nih.gov/rtac/funding/grants/rfp/rfp0203/rfp0203.pdf).
46. *Id*. at p. 13.
47. This mission is shared by many non-profit institutions, eg Yale University's 'primary goal of commercializing Yale inventions is to disseminate and develop knowledge for the public good. Subsidiary goals include generating revenue. . .' (URL: http://www.yale.edu/ocr/invent-policies/policy2002.html), and the primary objective of Stanford University's technology transfer 'has been to get an invention into the widest possible use, rather than to seek maximum financial return' (URL: http://otl.standford.edu/about/resources/history.html). The UK Medical Research Council Technology states its objectives 'in order of priority' as first 'to develop technology into products and services useful to society' and lastly 'to maximize income to the MRC in the medium to long-term.' A committee convened by the NIH with representatives from government, academia, patient advocacy groups as well as biotechnology and pharmaceutical companies noted the following hierarchy from most to least important returns on the public investment in NIH research: 'fostering scientific discoveries, rapid transfer of discoveries to the bedside, accessibility of resulting products to patients, and royalties'. Report on the NIH Panels on Cooperative Research and Development Agreements, p. 27, 1994, in NIH Response to the Conference Report Request for a Plan to Ensure Taxpayers' Interests are Protected, July 2001 (URL: http://www.nih.gov/news/070101wyden.htm).