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KNOWLEDGE AND TECHNOLOGY MOBILIZATION TO ADVANCE PUBLIC HEALTH: AN NIH PERSPECTIVE

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PLAN

I. INTRODUCTION

The National Institutes of Health (NIH) is an agency of the Department of Health and Human Services (HHS). Its mission is to discover new knowledge that will lead to improved public health. NIH advances that mission by conducting and supporting research and fostering the communication of biomedical information. There are both intramural and extramural

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components to conducting and supporting this research. The extramural aspects include Federal funding for the conduct of basic biomedical research, pre-clinical (animal studies) and early stage clinical trials, training, grants, contracts, and co-operative agreements. This extramural component consumes approximately 85% of NIH's annual Congressional appropriation, which in fiscal year 2005 totaled 27.8 billion U.S. dollars. This extramural funding provides for more than 50,000 annual awards supporting over 212,000 researchers at over 2,800 mostly academic institutions. Approximately 10% of the total budget supports more than 2,000 projects by over 6,000 intramural researchers at the twenty seven Institutes and Centers that make up the NIH. The focus of the basic research, whether intramural or extramural, is to elucidate fundamental underlying causes, mechanisms and pathways of human disease. The magnitude of this ongoing public investment makes NIH the premier institution in the United States for basic biomedical research.

Approximately three-quarters of the extramural funding is directed to investigator-initiated basic research, while the remainder targets basic or applied research projects envisioned by NIH as needing new funding. All these extramural projects are awarded through a peer-reviewed process organized by NIH. Establishing priorities for such public funding of biomedical research involves a complex interplay between Government health administrators, Congress, and various stakeholder constituencies in the scientific, health, patient advocacy, and business communities. Often, this research is directed toward filling gaps in basic research that are too high-risk and early stage to attract investment from private industry. Success in such publicly-funded research is designed to complement and induce later product development by industry.

Historically, medical information and outcomes arising from this enterprise are communicated via traditional academic modes of information transfer. Such collegial avenues typically take the form of peer-reviewed publications, symposia, workshops, scientific conferences, and other mechanisms of collaboration directed toward the open sharing and free exchange of ideas, results, and research materials. These open forms of communication are consistent with the goals of a government research operation, as well as the traditions of academic recipients of NIH funding. As a result, open communication was the norm, and conflict seldom arose regarding sharing results from Federally-funded NIH research.

However, issues of concern began to develop in certain research areas, and the need arose for policy and guidelines regarding public health and Federally-supported research. In response to these issues, NIH issued policy and guidelines establishing standards in NIH-funded research involving human subjects, humane treatment of laboratory animals, and early recombinant DNA protocols. Such policy and guidance communications were produced after iterative consultation between the relevant stakeholders. This paper discusses another set of communications, policies, and guidelines NIH has developed in the area of data sharing and technology transfer.

II. THE BAYH-DOLE AND STEVENSON-WYDLER ACTS

A little more than a quarter century ago, the U.S. Congress enacted economic development legislation (The Bayh-Dole and Stevenson-Wydler Acts) that added dramatic new perspectives to managing research outcomes from NIH scientists and its funding recipients. Toward the end of the 1970s, the U.S. Government was concerned with a perceived decline in U.S. competitiveness in numerous commercial markets. Congressional inquiries identified disconnects between Government funding of research and effective patent protection providing incentives for commercial product development. One important disconnect related to a lack of ownership of patent rights for inventions made by recipients of Federal funding under grants and contracts. In the rare occasions when the Government pursued intellectual property protection, the patent rights had to be non-exclusively licensed in accord with traditional Government open-access policies in Federal acquisitions. There was no centralized organization managing such patenting and licensing activities. The effort and cost of obtaining patent protection was borne by the originating agency or laboratory. However, any royalty income arising from licensing the patent went directly to the U.S. Treasury. Consequently, there was little incentive for intramural scientists, extramural recipients, or private industry to use the patent system to develop products arising from federally-funded research programs. Proposed legislative remedies spanned the spectrum of divergent political philosophies toward patents. These ranged from vesting ownership and patenting rights to the funding recipients, at one end, to a centralized Government control that still disavowed exclusive licensure of Federally-funded inventions, particularly to large businesses, at the other end. When introducing his proposed bill, Senator Birch Bayh of Indiana stated:

> A wealth of scientific talent at American colleges and universities–talent responsible for the development of numerous innovative scientific breakthroughs each year–is going to waste as a result of bureaucratic red tape and illogical government regulation…
>
> The problem very simply, is the present policy followed by most government agencies of retaining patent rights to inventions.
>
> Government sponsored research is often basic rather than applied research. Therefore many of the resulting inventions are at a very embryonic stage of development and require substantial expenditures before they actually become a product or applied system of benefit to the public.
>
> It is not government's responsibility–or indeed, the right of government–to assume the commercialization function. Unless private industry has the protection of some exclusive use under patent or license agreements, they cannot afford the risk of commercialization expenditures. As a result, many new developments resulting from government research are left idle. [1]

The resulting Bayh-Dole Act of 1980 created a sea change in technology transfer by vesting ownership of extramural inventions to Federal-funding recipients. The Stevenson-Wydler Act was passed in the same lame-duck session of Congress following the November 1980 elections. It, and subsequent amendments in 1986 and 1995, vested technology transfer responsibility for Government-owned inventions in each Federal laboratory, thereby retaining all royalty income within the laboratory and establishing royalty sharing incentives for Government inventors. The bureaucracy created by the original Stevenson-Wydler Act assured that NIH intellectual property management was not substantially consolidated until the rnid-1990s.

Although signed into law in 1980, it was not until 1984 that the Bayh-Dole Act and its implementing regulations were compiled in Sections 200-212 of Title 35 of the United States Code and Title 37 of the Code of Federal Regulations. This major shift in patent policy contained checks and balances to assuage the divergent patent philosophies of the times.

Funding recipients must comply with a number of reporting requirements before electing to receive title to an invention, as well as after the patent application is filed. Certain exceptions were identified whereby election of title to the recipient could be denied or limited by the funding agency. These included foreign recipients, inventions to conduct foreign intelligence or counter-intelligence activities, inventions related to Department of Energy naval nuclear propulsion and weapons-related programs, and what is referred to as "exceptional circumstances" to better promote the goals of the Act. When a Federal agency invokes a "Declaration of Exceptional Circumstances" (DEC) to restrict or deny title to inventions arising from proposed funding, it must complete a complex administrative process including concurrence through the Department of Commerce, which has responsibility for administering the Bayh-Dole Act. DECs ate most often invoked in large contracts where the Government is particularly interested in ongoing control of the deliverable and associated intellectual property. DECs are rarely applied to basic research grants.

The funding agency receives a nonexclusive, nontransferable, irrevocable, royalty-free license to practice or have practiced for or on behalf of the United States any subject invention throughout the world. This royalty-free Government-use license, of course, extends only to infringement of patent rights. It neither provides the Government with free products or services, nor allows the Government to sell such products or services. While the law initially applied only to nonprofit and small business funding recipients, large businesses were subsequently added via a pair of Presidential Executive Orders. All products arising from Federally-funded inventions used or sold in the United States must be manufactured in the United States. Only the funding agency can waive the U.S. manufacturing requirement.

The "march-in" provision of the law permits a federal agency to compel additional licensing of the invention if an exclusive licensee is not taking steps to achieve practical application of the invention, and such licensing is necessary to alleviate a public health or public safety need. Again, "march-in" requires the agency to undergo an elaborate administrative proceeding that is subject to court appeal before the compulsory licensing takes effect. NIH has never exercised its march-in rights.

Interestingly, there are no provisions or implementing regulations for the licensing of Government-owned inventions under the Stevenson-Wydler Act. Rather, the Bayh-Dole Act additionally includes important provisions directed to licensing of Government-owned inventions. It provides Federal agencies the right to seek patents in foreign countries. For the first time, Federal agencies are permitted to exclusively and partially exclusively license its patent rights. The law places two requirements upon the licensing of all Government-owned patents and a number of restrictions specifically upon exclusive licenses. The U.S. manufacturing requirement, indicated above, is also extended to all Government-owned patent licenses. The law further requires all applicants for licenses to Government-owned patents to submit a development or marketing plan for the invention.

The restrictions upon exclusive licensing of Government-owned patents are particularly significant. Consistent with its open-access tradition, a Federal agency must provide public notice and opportunity to file written objections to the intent to exclusively license the patent to an identified party. Before opening the proposed license to public notice and comment, the Federal agency must make the following determinations:

1. the interest of the Federal Government and the public will best be served by the proposed license, in view of the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public;

2. it is unlikely that expeditious practical application can be achieved under a nonexclusive license;

3. exclusive licensing is a reasonable and necessary incentive to call forth the investment of risk capital and expenditures to bring the invention to practical application or otherwise promote the inventions utilization by the public;

4. the proposed terms and scope of exclusivity are not greater than reasonably necessary to provide the incentive for bringing the invention to practical application or otherwise promote the invention's utilization by the public; and

5. exclusive licensing will not tend substantially to lessen competition or result in undue concentration in any section of the country in any line of commerce to which the technology relates.

If the business/development plan submitted by a small business is equally likely to bring the invention to practical application compared to a plan submitted by a large business, the law requires a first preference be afforded to the small business entity. Even if the subject of the exclusive license is foreign patent rights, the above determination regarding lessening competition and undue concentration in the United States must be considered.

The Bayh-Dole and Stevenson-Wydler Acts recognize that effective transfer of patent rights is critical for private industry to commercially develop products from Federally-funded research. This adds an important new element to the NIH mission of discovering new knowledge that will lead to improved public health by conducting and supporting research and fostering the communication of medical information; i.e., the transfer of patent rights to private industry to promote commercial development of products. Integration of concepts associated with patent protection and commercial development into the psyche and collegial communication traditions of NIH and academic communities is a challenging task. This integration process, however, was not facilitated by legislation that placed NIH and its funding recipients on different playing fields relative to technology transfer. While the law was very clear on how the exclusionary rights of patents must be transferred (i.e., licensed) for Government-owned inventions, it gave no guidance on how patent rights, technology transfer, and commercialization should be exercised for the public good for inventions discovered by Federally-funded recipients. This lack of technology transfer policy for inventions funded by an agency such as NIH to advance a common public health mission has led to tensions between NIH and elements of the academic community.

To better understand the technology transfer policy interplay between NIH and its funding recipients in academia, we need to examine how NIH translates its technology transfer responsibilities to the research outcomes that typically come from our laboratories. An important realization is that our involvement in the patent process is divorced from the traditional rationale of why patents are important to society. NIH and our academic grant recipients do not seek patents as an alternative to maintaining trade secrets. There is no quid pro quo involving the exchange of an enabling disclosure of our inventions in return for a time-limited right to exclude others from practicing the inventions. NIH scientists willingly disclose inventions through publication without the need of patent disclosures. They do not rely on patents to learn about new enabling science, and typically disseminate their findings to others through peer-reviewed publication, NIH websites, public meetings, and other forms of open communication. In general, NIH scientists are not supportive of the concept of excluding anyone from practicing the successful outcomes of their research as they view those results as a public benefit.

Consequently, the fundamental concept of seeking patent protection is contrary to the traditional activities of our intramural and extramural scientists.

The reason NIH embraces patent protection is reflected in the quote reproduced earlier by Senator Bayh when introducing his legislation. For the most part, the basic research at NIH represent early stage inventions and proof of concept studies that would lay idle without private industry providing the resources, know-how, and later-stage development needed for FDA approval/clearance, scale-up manufacturing, and launch as commercial products. Private industry will not invest the resources needed to take products along what FDA terms "the Critical Path to Medical Product Development" without the security of exclusive patent protection to assure they can recoup their development costs and make a profit in a competitive marketplace. The development of a drug along this "Critical Path" is estimated to cost between 800 million and a billion U.S. dollars, and can take between 10-12 years to complete. [2] Therefore, patents are sought because private industry partners require them to turn NIH-funded research into commercially viable products for patient benefit. Inventions funded by NIH that satisfy this scenario tend to be pharmaceutical drug candidates, vaccines, some devices, and some diagnostics. NIH and its funding recipients under Bayh-Dole understand these commercial realities associated with inventions requiring further research and development (R&D). Patent protection and transfer of those patent rights to private industry through exclusive licensing are appropriate means to advance product development for this type of invention. When patents on such inventions are exclusively transferred to the private sector for diligent product development, the mission of NIH and the mandates of Bayh-Dole and Stevenson-Wydler are in concert.

III. RESEARCH TOOL INVENTIONS

The vast majority of research outcomes flowing from NIH and academic laboratories seldom fit the mold of inventions needing significant private investment in further R&D to launch commercial products. Generally, our research outcomes are incremental advancements in knowledge about basic biological or disease processes. Whether purely knowledge-based or material in nature, these outcomes can be categorized as research tools in the scientific enterprise. They are used by colleagues in advancing or refining their research activities. Occasionally, these tools are substantial, and they have the potential to make significant enabling contributions to future research. A common characteristic of such tools is that they seldom require significant further research and development to make them available and useful. Their applicability is generally evident upon disclosure and introduction into the research community. The overriding interest to scientists is freedom to apply these tools quickly in their research. When the tool is a material, it is often desirable to gain rapid access to it, rather than have to make it. [3]

Identification of technologies as research tools neither diminishes their value to the scientific community nor their potential commercial value. Research tools are made available to

others in the research and commercial communities in various ways. Knowledge-based tools traditionally are made available via publication or public databases. Tangible materials traditionally were made freely available to colleagues upon request, usually through Material Transfer Agreements (MTAs). Biological materials capable of replication often are made available through repositories such the American Type Culture Collection (ATCC). Research materials and reagents are occasionally distributed by commercial distributors. When distributed commercially, the greatest value to the scientific community comes when tools are sold as commodities.

Identification of these technologies as research tools also does not diminish their potential to be legitimate subject matter for patents. Indeed, commercial research tool companies have all the same incentives to establish patent-based market exclusivity for their products. Owners of patent rights to upstream research tools sometimes realize their maximum value by seeking royalties on the sale of downstream end products developed using the tool rather than on sale of the tool itself or the number of times the tool is used. This is referred to as a reach-through royalty.

It is not unusual for product development in therapeutic, vaccine, and diagnostic fields to utilize numerous research tools. If such tools have patent protection, they may individually or collectively create a barrier to the R&D process. A patent holder, for example, can create a barrier by refusing to license patent rights on the tool to competitors. Alternatively, this can happen when the financial licensing terms sought exceed commercial feasibility to the customer. Patent thicket or anticommons situations may develop when multiple licenses to patented tools must be negotiated, and the aggregate transactional cost in money and or time chills or precludes progress of a project. [4] The more marginal the market for a potential product, the more sensitive is the R&D process to patent thickets.

IV. NIH POLICY ON RESEARCH TOOLS

Research tool technologies and inventions requiring significant further R&D, therefore, are categories of invention that lend themselves well to analysis of the technology transfer mandates for Govemment-owned inventions under the Bayh-Dole and Stevenson-Wydler Acts. NIH analyzed an array of early stage inventions coming from its laboratories and developed a patent policy consistent with the Bayh-Dole exclusive licensing criteria. This policy allows NIH to keep to its tradition of rapid and open transfer of scientific outcomes to the research community, and our mission to advance public health.

The NIH patent policy encourages seeking patent protection to facilitate availability of an invention for commercial use when needed to advance public health. Consequently, patents should be limited to those inventions requiring exclusivity as an incentive to industry to further develop commercially viable products. The corollary of this policy is that patent protection

should not be pursued if further R&D is unnecessary to realize the benefits of the technology. The policy cautions against delays in public disclosure of research outcomes due to filing of patent applications. While recognizing research tools as patentable subject matter with potential commercial value, this policy recommends against seeking patent protection on such inventions. As a matter of policy, NIH feels it is not desirable to seek a tool, such as patents, designed to exclude others from making and using the common currency of the research realm. This is particularly relevant for publicly-funded discoveries that are broadly enabling, and that should be shared for maximum benefit. NIH believes such enabling early stage discoveries should not be sequestered in the hands of individual companies for exclusive commercial advantage. In establishing its policy, however, NIH realized that certain research tools are difficult to make and distribute. Under such circumstances, patent protection and exclusive licensing to manufacturers and distributors for the express purpose of making the tool widely available may be appropriate. [5]

Many early-stage inventions at NIH unfortunately do not always sort neatly into one of these distinct technology transfer modes. Many NIH inventions have multifaceted components and potentials embracing research tool utilities, as well as those that would benefit from patent protection. In other cases, the inventions are so early stage that their ultimate utilities are not always evident. Compounding this uncertainty is pressure from the patent laws to file for patent protection as quickly as possible. Our general policy is to err on the side of caution, and file for patents in these gray areas.

V. NIH LICENSING POLICY

Patents are a stark exclusionary right. However, significant flexibility exists in exercising patent rights within the terms of patent licenses. NIH has developed an official licensing policy that exploits the flexibilities of the licensing process, and adapts the patent portfolio to complement NIH’s institutional philosophy and goals. This licensing policy reconciles NIH's patent policy with the need to file for patent protection before appropriate markets mature for the inventions. This licensing policy transforms a one-dimensional right to exclude into a multidimensional tool to advance our public health mission.

The NIH licensing policy instructs to license nonexclusively where possible and exclusively when necessary. When exclusive licensing is necessary, provisions are included to ensure the license is limited to the fields of use and territories that actually will be developed and worked by the licensee. Additionally, NIH exclusive licenses ensure expeditious development of the invention by including appropriate performance benchmarks. This licensing policy takes special notice of NIH’s responsibility not to encumber the research process, and to ensure the continuing nonexclusive availability of our research tools and materials. When research materials are licensed, the NIH licensing policy seeks to treat them as commodities without reach-through royalty provisions. [6]

Attention to the NIH patent and licensing policies permits the agency to be faithful to its tradition of supporting biomedical research through open sharing of knowledge and material exchange, and also to its mandate to transfer Federally-funded inventions to the private sector for commercial product development. These policies effectively advance NIH's public health mission. The extramural research funded by NIH, of course, goes to advancing that same public health mission. Successful applicants for NIH funding have clearly aligned their research interests and approaches with that mission. Responsibility for the patent and licensing policies associated with the research outcomes of that funding, however, inure to the funding recipients along with ownership under Bayh-Dole. As discussed previously, patenting and licensing by funding recipients are not subject to the exclusive licensing restrictions required of Government-owned patents under Bayh-Dole. The technology transfer offices at academic institutions are under different pressures relative to the commercialization process compared to NIH. Those pressures are often focused on returning a financial profit for the institution. [7]

VI. ACADEMIC TECHNOLOGY TRANSFER

While the academic technology transfer community understands and appreciates the NIH philosophy of patenting and licensing, there is a wide spectrum of practices and levels of sophistication among these offices. This is evident from the outcomes across the academic community. Notable examples inconsistent with the NIH philosophy include exclusive licensing of the "Oncomouse" patents by Harvard University and embryonic stem cell patents by the University of Wisconsin's commercialization wing, Wisconsin Alumni Research Foundation (WARF)/WiCell. Although these inventions may be classified as research tools encompassing a wide variety of research approaches, very broad patents were obtained for these inventions. More importantly, the exclusive licensees of these patents are not in the business of making research tools widely available. The commercial value to these licensees resides in excluding competitors, or exploiting the technology to the research community in non-traditional ways. Consequently, licensing terms sought unacceptable grant-backs on inventions made using the patented invention, including reach-through royalties. In both cases, NIH was obliged to negotiate Memoranda of Understanding with the involved parties to ensure open assess to the technology for research purposes. This open assess was negotiated on behalf of funding recipients of NIH grants and contracts, as well as for Government scientists.

Another example of inappropriate exclusive licensing is the commercialization of the patents for diagnostic testing for breast cancer susceptibility using the BRCA genes. The exclusive licensee of these University of Utah patents, Myriad Genetics, requires all tests be performed through their facilities despite the capacity for numerous laboratories to provide the test, including research and teaching labs associated with academic cancer treatment centers. Beyond the additional time and expense this may engender, this exclusivity precludes independent verification and validation of the test results performed by Myriad.

These examples are notable because they involve sequestering broadly enabling tools desired by many diverse research programs and restrictive use of a diagnostic that attained important clinical interest. While these examples maybe considered worse-case scenarios, they are discussed here to demonstrate that a spectrum of behaviors exist in the technology transfer community. The efficient transfer of research tools and materials, however, is important to researchers and product developers. Indeed, considerations regarding availability of necessary tools are important decision-making criteria in corporate board rooms when determining which projects or lead compounds to pursue. Individual events hindering, slowing, or preventing transfer of research tools usually do not register in the media or in attempts to survey and quantify this issue. [8, 9] Furthermore, stakeholders in technology transfer offices and corporate board rooms may view the potential cures as worse than the current state of the disease. Such potential means of dealing with this issue might involve invoking Bayh-Dole Declarations of Exceptional Circumstances by Federal funding agencies such as NIH, or new legislation exempting research from infringement or exempting research tools as patentable subject matter. Such solutions may be analogized to using a sledge hammer to resolve an ant infestation in the kitchen. Consequently, players in this game muddle along, and occasionally take interesting steps to retain special types of research tools in the public domain.

VII. ESTs AND SNPs

Rapid advances in genomic technology provided circumstances where certain participants became unlikely partners and engaged in uncharacteristic behaviors. The ability to create and identify large numbers of expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs) created gold-rushes to file patents on enormous numbers of these research tools. NIH, the Wellcome Trust, and a number of large pharmaceutical companies saw this as creating potential patent thickets that could chill research and product development relying on these tools.

In February 1997, the United States Patent and Trademark Office (USPTO) indicated that it was prepared to issue patents on ESTs based on their utility as probes. For several years, the USPI'O withheld issuance of patents on millions of EST sequences pending resolution of patentability issues. Following concerns communicated by NIH, the National Academy of Science, research associations, and some larger biotechnology/pharmaceutical companies, the USPTO reversed their position, and in January 2001 issued new guidelines regarding utility requirements for patentability. [10]

As the Human Genome Project was progressing, interest increased in defining variations in the sequence. There was concern that the patentability issues that effectively blocked issuance of large numbers of ESTs could not be relied upon to prevent millions of SNP sequences from being patented. The pharmaceutical industry was sufficiently concerned about the potential of SNP patent thickets threatening future product development that a number of their members

formed a consortium with the nonprofit Wellcome Trust to address the problem. The SNP Consortium financed the discovery and defensive patent filings (Statutory Invention Registrations) on millions of SNPs. This defensive filing maneuver was part of an overall strategy to place the SNPs ultimately into the public domain. [11] While not able to be an official member of the SNP Consortium, NIH financed SNP discovery in concert with Consortium activities.

VIII. THE UBMTA AND RESEARCH TOOLS GUIDELINES

For its part, NIH has engaged in several activities to guide and aid funding recipients relative to research tools arising from it research funding, NIH responded to perceived problems in the research community associated with sharing research materials with both nonprofits and industry. Through the early 1990s, NIH worked with various academic institutions to develop new material transfer agreements and policies. This culminated in 1995 with the release of the "Universal Biological Material Transfer Agreement" (UBMTA). [12] The UBMTA was structured as a treaty-like document setting out a fair set of rules governing the sharing of research materials. Over 250 Government, academic, and nonprofit organization became signatories to this master agreement administered by the Association of University Technology Managers (AUTM). Transfer of materials between UBMTA signatories was carried out via an Implementing Letter identifying the parties and the material. For transfer of materials between parties who are not signatories to the UBMTA, a separate Simple Letter Agreement was developed, and its use was advocated.

Despite widespread endorsement of the UBMTA and its principles, few signatories actually use the agreement when transferring their materials. Instead, they returned to using their own individually negotiated agreements. Many of these agreements moved to more restrictive terms than the open-access principles of the UBMTA. Once again, NIH began hearing complaints from the academic and private communities about the inability to obtain research materials quickly and without onerous financial or publication demands. Consequently, NIH established a Research Tools Working Group in 1997 to investigate this issue. By 1999, the findings and recommendations of that working group were fashioned into a NIH policy statement known as "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts." [13] This policy statement broadly defines biomedical research materials as including monoclonal antibodies, cell lines, animal models, clones and cloning tools, combinatorial chemistry libraries, research reagents, databases, and some forms of software.

This policy statement, generally referred to as the "Research Tool Guidelines," set out four basic principles. The first of these principles instructed recipients of NIH funding to ensure academic freedom and publication. This principle is satisfied by avoiding agreements that

unduly limit the ability to publish, freely collaborate or automatically grant co-authorship or intellectual property rights to providers of materials.

The second principle ensured appropriate implementation of Bayh-Dole, and reiterated recipients' ownership rights to inventions arising from NIH funding. However, it reminded recipients that ownership begets responsibilities to promote public availability and use of these inventions. It established the fundamental principle that exclusive licensing of patent rights is not the only way to advance recipients' goals and obligations under Bayh-Dole. The policy indicated that for research tools not needing further R&D to realize the utility of the tool, that alternative means of technology transfer should be considered. These alternatives include dedication to the public through publication, deposit in repositories, and non-exclusive licensing strategies.

The third principle minimized administrative impediments to research. This section requested recipients to use the UBMTA and the Simple Letter Agreement when transferring research materials in order to avoid unnecessary delays associated with negotiating each material transfer agreement *de novo*. This principle appealed to non-recipient for-profits to minimize encumbrances when transferring research materials to NIH funding recipients. Such encumbrances included unreasonable publication delays, exclusive grant backs on all improvements, and reach-through royalty requirements. When such unreasonable encumbrances are sought, the Research Tool Guidelines instruct recipients to refrain from yielding to such demands.

The fourth principle was a general call to ensure dissemination of research resources developed with NIH funds. This principle outlined the importance of open access to research tools and materials for the progress of science. It placed responsibility on recipients of NIH funding to ensure open access for unique research resources arising from that funding. It also placed responsibility upon recipients to manage their relations and interactions with private parties so as not to diminish this principle of open access.

The Research Tool Guidelines have been adopted by our extramural grant administrators and incorporated into the official NIH Grants Policy Statement. Congress recognized the significance of these research tool principles in an amendment to the Bayh-Dole Act. The Technology Transfer Commercialization Act of 2000 amended the Bayh-Dole directive "to ensure that inventions made with public funding are used in a manner to promote free competition and enterprise" by adding to the end of that statement the phrase, "without unduly encumbering future research and discovery."

IX. DATA SHARING AND COMMUNITY RESOURCE PROJECTS

Data release of genomic sequence information into the public domain represents a notable expression of the NIH policy toward research tools. By the time the Human Genome Project began sequencing activity, it was important to establish a unified policy to disseminate the sequencing data quickly and openly to the research community. This ambitious project included multinational government participation, as well as non-profit organizations such as the Wellcome Trust. Centers working on the sequencing project included academic laboratories funded by NIH and the U.S. Department of Energy, who had Bayh-Dole rights to their inventions. Therefore, it was important also to establish a set of rules governing how generators of the sequence data would handle issues related to intellectual property rights. The funding participants in the Human Genome Project (i.e., the International Sequencing Consortium) met in February 1996 in Bermuda and unanimously agreed upon a data sharing and patenting policy. [14] The Bermuda Rules established that all human genomic DNA sequence information generated by the centers would be deposited in publicly available databases within twenty four hours. To prevent a privileged control or exploitation of the sequence information, no patents would be sought on the raw sequence data. The rationale proffered by Consortium members was that the sequence data were pre-competitive, and would require further functional association in order to have patentable utility. Even though the arbiter of patentability in the United States is the U.S. Patent and Trademark Office, the NIH, through the Bermuda Rules, counseled its funded academic sequencing centers not to consider the sequence data patentable subject matter under the Bayh-Dole mandate. Without the necessity of a Declaration of Exceptional Circumstance (DEC), the academic sequencing centers adopted the open access norm prescribed by the Bermuda Rules. As indicated previously, NIH funded and supported identification of SNPs independently of the SNPs Consortium. Again, centers participating in this NIH funded project agreed to principles of open access to the SNP data without the necessity of imposing a formal DEC.

The principles set forth in the Bermuda Rules of 1996 were extended at a 2003 meeting of the International Sequencing Consortium in Fort Lauderdale. [15] The Fort Lauderdale meeting expanded the concept of a "Community Resource Project" beyond genomic sequence data to include protein structure information, gene expression analysis, and microarray data. In concert with these international data sharing principles and our existing Research Tool Guidelines, NIH moved forward with additional policy guidance. [16, 17]

In 2003, NIH published a policy statement on Sharing Research Data. [18] This policy requires applicants for grant funding in excess of $500,000 per year to submit a data-sharing plan. These plans must address issues of how materials and data will be made widely available to the research community, the institutional patenting and licensing policy on research tools, and how any pre-existing third party agreements will be managed to avoid conflict with these open

access principles. While not part of the merit priority score, reviewers comment on such plans. Any deficiencies identified by reviewers must be remedied before award.

Most observers agree that NIH, the Wellcome Trust, and like-minded partners in the pharmaceutical industry have succeeded in placing into the public domain significant amounts of data pertaining to bulk genomic sequence and genomic variation from humans and numerous research organisms. While the jury is still out, and room still exists for caution, the opportunity for patent thickets and anticommons conditions in this critical area of genomics appears to have been avoided or at least delayed. From a policy perspective, these may have been the easy battles in the ongoing war to make research tools and materials widely available. Participants in publicly-funded bulk sequencing projects readily accepted the norm of Community Resource Projects and the wisdom of placing this information into the public domain." Increasingly greater challenges arise as large-scale genomic association studies, such as the HapMap [19] and Encode [20] projects, move into outcomes with clearer patentable utilities.

X. BIOMARKER TOOLS

Pharmacogenomic and proteomic initiatives drawn to biomarkers for disease diagnosis, susceptibility, and drug design are particularly challenging. A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention." [21] While subject to similar patent thicket concerns, these biomarker technologies raise more complex issues. Unlike ESTs and SNPs, these biomarker discoveries do not necessarily arise from bulk sequencing and simple association procedures. These biomarkers often require further R&D efforts to clinical1y qualify them for an intended use and, thereby, realize their maximum potentials. Private industry, nonprofits, and Government organizations are joining to form focused Public-Private Partnerships to support discovery, protection, and means to make these tools widely available for maximum public benefit

An early NIH attempt to deal with this biomarker issue was the Osteoarthritis Initiative funded by the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). The Osteoarthritis Initiative applied a limited DEC to the Request for Proposals for contracts under this project [22] The DEC was limited in that it applied only to clinical data, radiological images, DNA samples, and biological specimens collected during the project. The DEC, however, did not extend to any other inventions that could arise from the initiative. The idea was to avoid Bayh-Dole patents on aspects of the initiative deemed critical to the programmatic goals drawn to public access to research materials.

XI. SHARING OF MODEL ORGANISMS

In 2004, NIH established a Policy on the Sharing of Model Organisms for Biomedical Research. [23] Analogous to the Data Sharing Policy, applicants for funding relating to research

on model organisms and unique model organism research resources must submit a sharing plan. Model organisms include, but are not restricted to, mammalian models such as mice and rats, and non-mammalian models such, as round worms, fruit flies, frogs, zebra fish, budding yeast, and social amoebae. Research resources include genetically modified or mutant organisms, sperm, embryos, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains. Unlike the Data Sharing Policy, there is no funding threshold associated with the Model Organism Policy.

XII. BEST PRACTICES IN GENOMIC LICENSING

As described previously, NIH has developed a licensing policy that harmonizes its mission to advance products to benefit the public health with the statutory restrictions regarding exclusive licensing of patent rights. The realization that patent protection may be necessary to protect new generations of NIH-funded inventions in pharmacogenomics, proteomics, [24] and emerging fields of personalized medicine, [25] led NIH in 2004 to proffer recommendations to our grantees in the form of Best Practices for the Licensing of Genomic Inventions. [26] Unlike prior guidance and policies, this best practices document does not specify terms and conditions for grants. Rather it discusses points for consideration in establishing licensing policy and strategy that mirrors the NIH intramural licensing policy. It encourages the extramural community to nonexclusively license its genomic patents whenever possible. This recommendation is particularly directed to diagnostic applications of genomic inventions. When exclusive licensing is necessary to provide private sector incentives to develop genomic products, care should be taken to ensure appropriate scope of exclusivity and diligent development of the technology. Furthermore, freedom for research applications and access to materials for research purposes must always be preserved.

The Best Practices recommendations and other advisory policy statements from NIH have been received favorably by many in the scientific community. Organizations such as the National Research Council of the National Academies, [27] the Nuffield Council on Bioethics, [28] and the Association of American Medical Colleges have endorsed these and similar policies. Additionally, there have been calls by some organizations, and in academic publications, for NIH to assume a more aggressive posture in effecting these policies among its funding recipients. [29, 30] Such endorsements do not minimize undercurrents of trepidation from some in the academic community that NIH is progressively over-extending its prerogatives under the Bayh-Dole Act. [31]

Divergent perspectives on these NIH policies conjure the notion that where one stands depends on where one sits. The underlying premise of this cliche accepts viewing the same issue differently based upon conflicting interests. NIH and our grant recipients must reject this premise relative to transfer of technologies arising from Federally-funded research. The NIH policies highlighted in this presentation address a commonality of interest that is shared within

the research community. This commonality of interest is drawn from a long-standing tradition of academic freedom and wide dissemination of research outcomes. That tradition should rise to the level of mutual responsibility when applied to research of public health significance. That responsibility should be immutable and unaltered by the ownership of the research outcomes. Therefore, an academic community's responsibility to technology transfer is distinct from and supersedes its responsibility for technology transfer.

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