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Juggling Between Open Science and the Market: Public Science Responses to the Patentability of Biomedical Research Tools

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Abbreviations:

EPO	European Patent Office
ESTs	Expressed Sequence Tags
IP	Intellectual Property
NIH	National Institutes of Health
PROs	Public research organizations
R&D	Research and development
USPTO	United States Patent and Trademark Office
WARF	Wisconsin Alumni Research Foundation

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Abstract

The aim of this study is to give an overview of the institutional realignments in the biomedical research sector brought about by changes in the intellectual property (IP) regime that enabled the expansion of patent protection to new areas, such as living organisms and basic biological information, and new actors, such as universities and public research institutes. These changes created two risks: a weaker dissemination of knowledge due to high access costs to research tools and findings, and the disruption of the norms of openness, traditionally associated with scientific progress. The present study elaborates a typology of public scientists' IP responses with respect to research tools and traces the main factors behind them on the basis of personal interviews and documentary analysis. The co-existence of different and often conflicting IP responses shows that public researchers operate in a hybrid institutional system, which forces them to juggle constantly between the rules of the market and the conventions of »open science«. Although they are often able to do so relatively smoothly, some responses clearly point at problems in the patent regime. Moreover, they are indicative of some major changes in the research system, where new IP practices and growing science and technology interaction profoundly affect science funding policies, firm creation propensity and the organization of R&D across the public and the private sphere.

INTRODUCTION

This paper sets out to understand the responses of the academic community to changes in the intellectual property regime that enabled the expansion of patent protection to new areas, such as living organisms and basic biological information, and to new actors, such as universities and public research institutes. I focus mostly on organizations in the US for a pragmatic reason: this country was at the forefront of scientific and technological advances in biomedicine and biotechnology, as well as the forerunner of changes in regulations that are relevant for the problem that I am analyzing. The paper is based on primary sources such as personal interviews with the representatives of the public research sector and written accounts of major developments in biotechnology, as well as on a variety of secondary sources.

The IP changes analyzed in this paper spurred a massive increase in patents on research results that are considerably distant from downstream products. This has especially been the case in biomedicine, which has witnessed a proliferation of patents on inventions that could

be defined as »research tools«. According to the main powerhouse of biomedical research in the US, the National Institutes of Health (NIH), research tools include inputs such as cell lines, monoclonal antibodies, reagents, animal models, growth factors, clones and cloning tools, methods, laboratory equipment and machines, databases and computer software *(1)*. They are therefore tangible or informational inputs whose primary usefulness is as tools for research and for the discovery of drugs, diagnostics and other medical applications, rather than as products themselves. Research tools became the flashpoint of heated and still largely unresolved IP debates. The reactions of the biomedical research community to the patentability of research tools have been varied. The diversity of IP responses reflects the different incentives, pressures and events to which biomedical research actors have been exposed.

THE CHANGING IP REGIME AND ITS IMPLICATIONS

Legal changes that enabled an upsurge of patents on biomedical research tools can be traced to a combination of factors, ranging from the dynamics of science and technology co-evolution in the field of molecular biology to a general ideological change – first occurring in the US – in attitudes towards patents and towards the idea of commercialization of public research *(2, 3)*.

The phenomenon of growing convergence and interdependence between science and technology in molecular biology started in the late 1970s, after Stanley Cohen's and Herbert Boyer's discovery of a method for manipulating the genetic characteristics of a cell in order to induce it to produce a specific protein such as a human hormone. This discovery marked the beginning of a widespread use of the techniques of genetic engineering, which enabled the rise of the biotechnology industry and caused profound changes in the way in which pharmaceutical R&D was organized. A shift occurred from an internalized and relatively self-sufficient model of research organization within large pharmaceutical firms towards a more networked model of innovation, marked by a stronger interaction between established firms, small biotechnology firms close to public science and public research organizations (PROs).

The new opportunities and organizational arrangements brought about by biotechnology led to a growing tension between two contrasting ambitions of the major knowledge-producing actors: the rapid disclosure and sharing of research results, typical of public science norms, and the appropriation of knowledge by commercial firms. The drive toward appropriation has especially been strong for biotech firms, whose business models depended heavily on IP. Most biotech firms are in fact essentially research entities with few products on the market. They have therefore relied on venture capital as a source of funding, and patents are major assets to attract venture capital *(4, 5)*.

With rapid advancements in genomic technologies, a fierce competition between two opposing views on the desirability of patenting DNA and genetic data and techniques began. This clash occurred in the context of a pro-patenting trend in US research policy, which started in the late 1970s and which facilitated the passage of the Bayh-Dole Act in 1980. The Act enabled universities to apply for patents on the results of federally funded research and to grant exclusive and non-exclusive licenses to other parties. A related law passed in the same year was the Stevenson Wydler Act, which charged government owned research laboratories, like those of the NIH, with the responsibility of using the patent system to promote the commercialization of inventions. The rationale behind these two acts was that IP protection would facilitate the commercialization of the results of federally financed research.

Another legal landmark in the biomedical IP arena in 1980 was the US Supreme Court *Diamond vs. Chakabarty* decision on the patentability of a genetically modified bacterium. After this ruling, inventions involving life forms were considered patentable in the US. In the following years, many European countries modified their IP legislations in order to emulate the US approach. Other important changes in IP policy in the last few decades include the expansion of the scope of patent protection to areas such as software, algorithms and information on biological materials; a relaxation of the patentability criteria of novelty, utility and non-obviousness; and a broader protection conferred by patents, including protection for a wide range of applications unknown at the time of patenting, such as still unidentified functions of genes and DNA sequences *(6, 7)*.

It also became more difficult for scientists, especially in the US, to rely on exemption for research use of patented inventions. Thus, in the 2002 Madey v. Duke case, the Court of Appeal of the Federal Circuit in the US held that research exemptions should be granted only when research is for amusement, to satisfy idle curiosity, or for strict philosophical inquiry. According to the Court's ruling, doing basic or applied research was part of the central business of a university and could not qualify for research exemption *(3)*.

Two interrelated theoretical concerns have been raised in the innovation literature with respect to these IP changes. The first one is that increasing patenting could negatively affect research and innovation by limiting the accessibility of knowledge and by creating high transaction costs *(8)*. The second major concern, which can be traced to Robert Merton's *(9)* analysis of the science system as an institution, is that the private appropriation of scientific knowledge could erode the norms of »open science«, thus threatening the very prerequisites of effective knowledge production *(10)*.

According to some analysts, the public and the private research communities, although complementary, are very different and should be kept separated *(11)*. The private sector is geared toward maximizing rents from knowl-

edge and is governed by economic institutions like IP rights, while the public research community is aimed at maximizing the total stock of available knowledge by rapidly disclosing and sharing new knowledge, and is regulated by »open science« norms. The institutional marriage between the two communities and the escalation of academic patenting creates risks such as publication delays, secrecy and withholding of data and materials *(12)*; the shifting of the orientation of university research away from basic towards applied research *(13)*; and the »locking up« of a substantial amount of biomedical knowledge in patents *(4)*. This is particularly problematic when this knowledge represents the necessary building blocks or research tools for other inventions. The goal of this study is to examine how pressures related to patents on research tools are being resolved by different actors in the public research system.

OVERVIEW OF PUBLIC RESEARCH RESPONSES WITH RESPECT TO RESEARCH TOOLS

The responses of the public research community to the newly arisen IP situation in biotechnology have been very heterogeneous. Depending on how close they are to »open science« or to market institutions, they can be grouped into four categories. The first one comprises a set of »roll-back« IP responses that oppose or challenge the patent system. The second category of responses could be called »informal adaptation« and primarily it implies a disregard of patents and IP incentives in general. The third category comprises several »hybrid responses« that attempt to find a compromise, or even a win-win solution, between IP and »open science« institutions. Finally, the last category of IP strategies used by public researchers could be called »market acceptance«. It involves the support of the patent system and the pursuit of an aggressive patenting and licensing policy.

Roll-back responses

Categorical opposition to patents is nowadays a rare IP response in the public biomedical sector, especially in the US. The public and the private sector have become so intertwined that categorically contesting patents on research tools and other upstream inventions would be contrary to the policy and funding models of universities and other PROs. An area where some organized attempts to mobilize opposition to patents appeared was genetic testing, although this opposition came primarily from the medical profession rather than the scientific community. There are more than 1,000 genetic diseases that can be diagnosed through available tests and most of the genes associated with these diseases are not free of patents *(14)*. In the late 1990s a number of professional societies of doctors and clinical geneticists were outspoken critics of these disease gene patents, especially if subjected to exclusive licensing to perform diagnostic tests. They claimed that patent-based restrictions on who may perform genetic tests increase the cost of genetic tests and prevent the identification and validation of new mutations by other laboratories, thus interfering with the practice of medicine.

Most actors nowadays think that correcting the patent system in some domains where it has »gone wrong« is a more feasible option than opposing patents on genes and other naturally occurring substances altogether. One of the ways in which PROs can try to do that is by **challenging patents.** Once a patent is granted, there are two ways to attack it: by asking the court to declare the patent invalid in a lawsuit or by petitioning the USPTO, the EPO or the other relevant patent authority to re-examine the patent. Both lawsuits and patent re-examinations have serious drawbacks as strategies to challenge the patent system.

One of the most discussed recent challenges of research tools patents was the challenge of the University of Wisconsin Research Foundation (WARF)'s embryonic stem cell patents led by the California-based Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation. This case illustrated well the problems associated with challenging patents, such as the limited maneuvering space that challengers have when attacking a patent, as well as the fact that the final decision in a re-examination proceeding is made by the patent office, which tends to favor patent holders. Thus, despite a preliminary denial of claims contained in the human embryonic stem cell patents, after an appeal from WARF the USPTO upheld the patents. Another problem of patent re-examination proceedings is that they can, paradoxically, reinforce the positions of patent holders. If a patent stands the re-examination, it is also much more likely to be successfully defended in a potential lawsuit *(15)*.

The academic community has so far been rarely involved in patent challenges. The interviews on which this study is based suggest that the main reasons for this are the legal, administrative and financial difficulties involved in challenging patents, as well as the fact that patents are still seldom enforced on academics. However, there are examples of patents on research tools that have been successfully challenged by the public research community, such as the BRCA1 and BRCA2 genes patents in Europe in 2001 and 2002. The challenges were led by the French cancer research center Institut Curie and some other French and Italian research institutes *(14)*.

A similar challenge has since May 2009 been underway in the US. The Association for Molecular Pathology and other plaintiffs, which among others comprise scientific associations representing approximately 150,000 researchers, filed a lawsuit against the USPTO, Myriad Genetics and the University of Utah Research Foundation, which holds the patents on the BRCA1 and BRCA2 genes. They asked the court to rule that patents on these two human genes associated with breast and ovarian cancer are unconstitutional and invalid, and that those patents stifle diagnostic testing and research that could lead to cures by placing restrictions on competition and blocking alternatives to the patented tests and the practice of interpreting or comparing gene sequences that involved those genes. The plaintiffs also challenged the

idea that isolated nucleic acid molecules are patentable because they are »products of nature«. Surprisingly, this is the first case in the US that directly considers whether DNA sequences are patentable subject matter *(16, 17)*.

A more frequent roll-back response of PROs is **pre-emptive publication**. This is the strategy that was used by the leadership of the Human Genome Project, which had the policy of releasing genomic information on publicly available databases within 24 hours of their discovery, since the patent law stipulates that an invention cannot be patented if it has already been disclosed. Large collaborative projects aimed at identifying genomic data and immediately placing them on publicly available databases, in order to prevent their patenting by other actors, are institutional innovations that not only survived in the world of academia, but that were also supported and adopted by several large pharmaceutical companies. They were the model for projects such as the EST Consortium, the SNP Consortium, the International HapMap project, the Mouse Sequencing Consortium, the ENCODE project, the International Diabetes Initiative and the Cancer Genome Atlas project.

A project that perhaps deserves special attention is the ENCODE project (Encyclopedia of DNA Elements), because it was at the inception of this project in 2003 that the NIH and some other major genome research financing bodies defined more precisely their IP policies towards large-scale genomic projects. ENCODE was envisaged by the NIH as »*a community resource project*« that required participants, as resource producers, to release data as soon as they are verified *(18)*. At a Wellcome Trust sponsored meeting of large-scale DNA sequence producers and users, community resource projects were defined as projects »*specifically devised and implemented to create a set of data, reagents or other material whose primary utility will be as a resource for the broad scientific community*« *(19)*.

However, the ENCODE project was also somewhat different from prior large-scale genome sequencing projects, since its goal was to identify the functional elements of a defined portion of the human genome, such as transcription factors binding sites, which is information that could certainly have »utility« in the patent law sense of the term. This was explicitly recognized in the main ENCODE policy document, but so was the need to refrain from patenting even in the case of data that satisfy the patent utility criteria but are still very upstream in the research process. These data are considered pre-competitive, in the sense that a considerable amount of work would need to be done beyond the initial data production to demonstrate utility *(18)*.

The pre-competitiveness argument has also been endorsed by many pharmaceutical firms, which not only verbally supported, but also financed the production and the placing in the public domain of sequencing and other genomic data. The first company to do that was Merck, which in 1995 began to fund gene sequencing at the Washington University in St. Luis. The project was initiated in a period when biotech companies such as Incyte and Human Genome Sciences were already intensively patenting ESTs. More than ten years after this move of Merck, the idea of keeping pre-competitive genomic data in the public domain is still popular among pharmaceutical companies. For instance, in 2006 Novartis released online all its sequencing data on Type 2 Diabetes produced in collaboration with three PROs. In the same year, another pharmaceutical giant, Pfizer, in cooperation with the NIH, launched the Genetic Association Information Network, a project aimed at unraveling the genetic causes of several common diseases and making the information publicly available.

Informal adaptation

Regardless the above examples of active resistance to patents, public scientists have mostly been reactive in relation to the developments in the IP regime that allowed patents on upstream research inputs such as genes. »**Business as usual**« is therefore a common IP response that actually implies the disregard of the patents system. For instance, in a survey conducted in the US on a sample of 1688 biomedical researchers, Walsh, Cho and Cohen *(20)* found that only 5 percent of researchers check regularly for patents on research inputs. Factors that facilitate the disregard of patents include the difficulty in perceiving infringement and the low likelihood that firms will sue PROs, especially if products are still far away from the market. Infringement suits against universities are bad publicity for firms. They are usually also bad business decisions, since by tolerating infringement firms get free research on their technology, and if the researcher comes up with something valuable that uses their patented technology, whoever wants to commercialize it will have to go back to the original patent holder *(21)*.

How sustainable is this disregard of patents? As PROs – under a growing pressure to find additional funding sources – become increasingly aggressive patent holders, public scientists also become more vulnerable to patent infringement claims, as the 2001 Madey v. Duke University case showed (3). In academia, in fact, ignoring patents held by others sometimes goes hand in hand with the patenting of one's own research results or at least with a strategy that could be called »patenting by default«, which consists of the submission on the part of principal investigators of short invention disclosure forms to the technology transfer officers, which then make patenting decisions *(22)*.

Hybrid responses

When the rapid advances in biotechnology and the related developments in patent law and practice gave way to an upsurge of patents on inventions that were considered basic scientific discoveries by some, and appropriable technological inventions by others, the need to **set a new boundary** between the scientific commons and proprietary technology appeared. Research policy organizations such as the NIH played a leading role in such an endeavor and introduced the concept of »research tools«. As part of this strategy, since 1998 the NIH has been

warning its researchers and grantees that in cases where the patented invention is primarily a research tool, exclusive licensing practices are likely to thwart rather than promote the utilization, commercialization and public availability of inventions *(1, 23)*.

In advocating its IP policies towards research tools, the NIH took a pragmatic stance. The criteria chosen for drawing a line between common and appropriable inventions in the NIH policies had not so much to do with the science-technology divide or with ethical considerations. Instead, they were based on the calculations related to the trade-off between the need to have certain classes of genomic technologies widely available and the necessity of granting incentives in the form of exclusive rights for firms to realize the diagnostic and therapeutic uses of genomic advances. Thus, the first key document that was produced by the NIH in this respect, the »NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice« *(23)* states that patenting should be avoided or approached with caution if:

»1) the primary usefulness of the resource is as a tool for discovery rather than an FDA-approved product or integral component of such a product;

2) the resource is a broad, enabling invention that will be useful to many scientists (or multiple companies in developing multiple products), rather than a project or product-specific resource; and

3) the resource is readily useable or distributable as a tool rather than the situation where private sector involvement is necessary or the most expedient means for developing or distributing the resource.«

From this document, as well as from other documents on the same subject produced by the NIH, it appears that some broad criteria discouraging patenting have slowly emerged. They include the generic potential of an invention, i.e. the commonness by which it can be used either as a collection of »pre-competitive information« *(18)* or as a research tool (e.g. a cell line or a mouse model), and little need of further private investment in realizing the primary use of an invention. Of course, applying these criteria is often challenging, especially in cases of novel technologies the uses of which is difficult to anticipate.

Open-source biology could also be considered a hybrid IP response in the sense that it tries to find some balance between the IP law and the scientific and technological commons. Open-source biology takes inspiration from open-source approaches in the software industry and the idea is to implement an open system of licensing that does not require payment, but instead requires that any innovation made by using the open-source invention be placed in the public domain. Agricultural biotechnology contains a couple of examples of projects pushing for open source both as a development methodology and as a licensing scheme. For instance, the PIPRA initiative (Public Intellectual Property for Research in Agriculture) was launched in 2003 by a number of PROs in the US, in order to overcome the fragmentation of IP ownership in agricultural biotechnology. In biomedical biotechnology, synthetic biology is a field that has witnessed initiatives towards open source, such as the Registry of Standard Biological Parts. However, the interviews upon which this paper is based have shown that translating the open source paradigm from software to biology has been problematic for a number of reasons, such as the low level at which biotechnology has been modularized, the higher capital costs and longer development times necessary for developing biotech products, as well as the challenges of translating open source licenses from copyright to patent law.

Publicly-minded patenting and licensing is another strategy pursued by PROs that accepts the permeable boundary between »open science« and the market, but also tries to ensure high knowledge dissemination through selective patenting and licensing and through various safeguards. The emergence of publicly-minded IP strategies was the result of a gradual learning process whereby the academic community slowly learned to take up the best elements of the patent system while minimizing its downsides *(21)*.

In 2006 twelve top US research universities gathered to brainstorm about important societal, policy and legal issues in university technology transfer. They produced a White Paper entitled »In the Public Interest: Nine Points to Consider in Licensing University Technology«, which was later endorsed by the Association of University Technology Managers and disseminated to other universities in the US. The so-called »Nine Points Memo« *(24)* recognizes that when crafting agreements with industry, a balance must be struck between the business needs of the private licensing partners and the shared values of universities. The document emphasizes the following nine principles that must be addressed when patenting and licensing university-produced inventions:

1. *Universities should reserve the right to practice licensed inventions, and to allow other non-profit and governmental organizations to do so;*
2. *Exclusive licenses should be structured in a manner that encourages technology development and use;*
3. *Strive to minimize the licensing of »future improvements;«*
4. *Universities should anticipate and help to manage technology transfer related conflicts of interest;*
5. *Ensure broad access to research tools;*
6. *Enforcement action should be carefully considered;*
7. *Be mindful of export regulations;*
8. *Be mindful of the implications of working with patent aggregators; and*
9. *Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics, and agricultural technologies for the developing world.*

According to some of the interviewees in this study, a smart patenting and licensing strategy does not only serve the public interest by stimulating technology trans-

fer, but it can also perform two other functions that are in the interest of the public. Firstly, it can channel private funding into the research activities of increasingly cash-constrained PROs through industrial partnerships and licensing revenues. Secondly, a strong patent on a foundational technology controlled by a PRO can prevent the patenting of some slightly different follow-up invention by a private firm and thus the potential imposition of high access costs of a technology that is still upstream and enabling. The second point, however, necessitates further examination.

The first example of such a patent is the foundational biotechnology patent on the gene splicing technique, the so-called Cohen-Boyer patent. The patent was filed by Stanford University in November 1974 and jointly awarded in 1980 to Stanford and the University of California of San Francisco. The patent covered a common tool – a technique that was critical for the whole of molecular biology – but that was neither expensive nor difficult to disseminate without private involvement. The IP strategy that was chosen by the two universities was to allow the public sector to use the technology for free, while charging some relatively modest royalties to companies. The patent generated millions of revenues for the universities and is considered one of the most successful patents ever. Nevertheless, many people still frown upon this patent, saying that it should have never been awarded because it covers a basic technique developed in the public sector that did not necessitate IP protection in order to be disseminated *(25)*.

The important policy question that the above examples raise is what are the merits of pre-emptively patenting an enabling technology over merely publishing it? Although many research organizations portray patenting for the purpose of non-exclusive licensing as a publicly-minded practice, the equation between the two is problematic. According to Joel Kirschbaum *(26),* co-founder and director of University of California at San Francisco's technology transfer office, licensees derive little benefit from non-exclusive patent licenses. These licenses are a tax the companies must pay to obtain the freedom to operate with a technology that has already been published or presented publicly. Such licenses do not provide any strategic value or competitive edge for a company and thus give them no additional incentive to commercialize the technology for public use and benefit.

Market acceptance

Finally, the last category of IP responses entails a strong acceptance of markets for knowledge and the pursuit of **a broad patenting strategy and a revenue-maximizing licensing policy**. The primary and secondary data collected for the purpose of this study suggest that there are several ways in which a PRO can pursue an aggressive IP policy: (i) by unselectively and broadly patenting upstream inventions; (ii) by enforcing patents on academics; (iii) by aggressively enforcing patents on upstream discoveries against firms that produce downstream products; (iv) by exclusively licensing research tools that are potentially enabling for a large field and that necessitate the involvement of many research actors; (v) by artificially prolonging the life of patents on research tools by means of continuation applications; (vi) by broadly relinquishing IP rights in exchange for private funding.

As far as the first practice is concerned, for some scientists patenting could be considered a »default strategy« that takes place through the submission of short invention disclosure forms to the technology transfer offices, which then make patenting decisions. The technology transfer experts interviewed for this study reported that, if asked, scientists are almost always in favor of filing patent applications.

The second instance of aggressive IP behavior is the enforcement of patents on research tools against academics. One such tool are embryonic stem cell lines owned by WARF. Another example of a very important research tool patent that was aggressively enforced against academics is the Oncomouse patent. The Oncomouse, a mouse genetically engineered to be susceptible to certain types of cancer, was developed by Philip Leder at Harvard University. The work was sponsored by the DuPont Corporation, which provided six million dollars to finance Leder's research. The *quid pro quo* was that DuPont would be entitled to an exclusive license on any patents stemming from this research *(14)*. When DuPont obtained the license in 1988, it decided to charge academics a fee for the mouse, placed limits on informal exchange of mice between scientists and demanded that scientists give DuPont the rights to any future invention made using the Oncomouse *(27)*.

A third instance of aggressive IP behavior with respect to research tools is the enforcement of patents on upstream discoveries against firms that produce downstream products. For instance, the University of Rochester was awarded a patent on the gene for the COX-2 enzyme on the basis of a discovery that stomach irritation associated with nonsteroidal anti-inflammatory drugs is caused by the inhibition of a protective enzyme Cox-1 that is distinct from a similar enzyme Cox-2 that causes inflammation. The Rochester scientists hypothesized that molecules that selectively inhibit only Cox-2 might provide relief from pain and inflammation without provoking gastrointestinal side effects. Although the University of Rochester did not identify nor test any such molecule, eight years after its application it obtained a patent on a method for selectively inhibiting Cox-2 in human hosts. Before the patent was granted, a pharmaceutical company, Pfizer, had already developed independently a selective Cox-2 inhibitor and the University of Rochester sued them for infringement. The suit was, however, unsuccessful *(14)*.

The exclusive licensing of research tools that are potentially enabling for a large field and that necessitate the involvement of many research actors is another instance of revenue-maximizing IP strategy that pays little heed to social welfare. An example of this are the patents on the BRCA1 and BRCA2 genes, underlying hereditary

breast cancer, awarded to Mark Skolnick and the University of Utah, which licensed it exclusively to Myriad Genetics, a biopharmaceutical company founded by Skolnick and others. The company imposed high access costs on the test and requested that all samples be sent to its own laboratory for analysis, thus building exclusive databases and arguably extending its monopoly beyond what was granted by patent law *(28)*.

Artificially prolonging the life of patents on research tools by means of continuation applications is another strategy that is sometimes pursued by PROs and that is hardly in the public interest. Among the many examples of this strategy are the Axel-Wigler patents on the cotransformation process, owned by Columbia University. They were awarded in 1983 and earned Columbia University hundreds of million of dollars in revenues until their expiry in 2000. Columbia University filed a continuation application basically on the same technique and was awarded another patent in 2002, due to expire only in 2019. However, after a lawsuit with companies that refused to take a license for it and a challenge initiated by the Public Patent Foundation on the basis of the argument that the patent violates the restriction against multiple patenting, Columbia waived any right to assert the patent in December 2004 *(29)*.

Finally, broadly relinquishing IP rights in exchange for private funding is another practice that can endanger the circulation of research tools produced in the public sector. Universities took advantage of the biotechnology boom by signing massive research contracts with companies, in which industry received generous promises of IP that was at least partially funded by federal sponsors (30). An early example occurred in 1992, when the Swiss pharmaceutical company Sandoz offered 300 million dollars to Scripps Research Institute in San Diego in return for 100 percent of the resulting IP rights. Although later on the US Congress and the NIH forced Scripps to scale back both the level of funding and the percentage of IP rights, the Scripps-Sandoz story did not end up with a binding policy by the NIH on this issue nor did it diminish the trend of these deals in general.

MAIN EXPLANATORY FACTORS BEHIND THE CONTRASTING ATTITUDES TOWARDS PATENTING IN ACADEMIA

The present section will review the main drivers behind these conflicting responses of researchers to patents on biomedical research tools. One of the goals of my study was to explore to what extent patents are compatible with the »open science« ethos in the eyes of the protagonists of the public biomedical research enterprise. The gathered evidence in the form of interviews and primary and secondary accounts suggest that the actors behind roll-back responses were rarely categorically opposed to patenting, even in the case of many research tools. Opposition was rather limited to patents on certain categories of research tools, the breadth of some patents and the ways in which the patents' licensing was handled. The research tools that seemed to have raised particular concern were raw genomic and proteomic information whose main value lies in databases and research tools such as cell lines or DNA parts with broad generic potential and with often unknown development trajectories. Concerns were particularly accentuated if negative experiences with access to these or similar research tools had been experienced in the past. The gathered data revealed that the representatives of both the public research sector and of pharmaceutical firms are well aware of the importance of having a large toolkit of research tools promptly available for research and development purposes. However, the incentive to maintain this toolkit as free as possible from transaction costs imposed by patents and licenses is balanced constantly with the incentives provided by patents, especially the incentive to accrue additional research funds through licensing income or private funding.

More common than active resistance is passive resistance to patents. Academics often simply ignore patents and the explanations for that include the limited amount of time that scientists have at their disposal for considering patenting issues, the convenience of sticking to some old habits when it comes to the use and exchange of research materials, the low likelihood that infringement will be noticed at the research stage and the low risk of academics being sued for research use of patented inventions.

The incentives to apply for and grant patents are very strong both at the level of individual scientists and at the level of their organizations. At the individual level, patenting can secure researchers unimpeded access to research tools, prestige and financial gain. It can facilitate their scientific lead and secure private research funds through licensing revenues or industrial cooperation and it can also enable them to establish new firms built around exclusive IP rights. These potential benefits that can arise from patents must also be considered in light of the relatively small effort that scientists themselves have to put into writing and handling patent applications (this is primarily the task of technology transfer specialists at universities and of patent attorneys who are paid by the universities) and the fact that the costs of application and maintenance fees are not covered by individual inventors but by their organizations.

At the organizational level, the support for patenting can primarily be explained as an attempt to bring in additional research funds by means of licensing revenues. For some universities in the US licensing has been an important source of income, although in general revenues from government-sponsored research have outweighed patent revenues by an order of magnitude *(31)*. The defensive motive also plays a role. By securing patents on foundational technologies, universities and other PROs can save themselves a lot of trouble and money that they would potentially have to invest in obtaining licenses from other PROs and firms.

A group that has strong incentives to push for more patents and that is often overlooked when studying aca-

demic patenting are patent attorneys. According to Daniel Ravicher *(32),* the Executive Director of the Public Patent Foundation, patent attorneys have developed strong relationships with technology transfer officers and academics and they exert a significant influence on them. Much of the IP discourse is led by patent attorneys, whose interests may not coincide with the interests of scientists and businesspeople in the biotech industry whom they represent. Patent attorneys, argues Ravicher *(32),* have a personal interest in bloating the patent system up so that there is more demand for their services.

The above factors have created a situation in which the biomedical research sector, both public and private, is geared towards producing more upstream and far-reaching patents *(32)*. This is reinforced by the high degree of unpredictability in the patent system that makes it difficult to estimate which patents can be enforced and which not, and whether the freedom to operate in certain research fields can be effectively defended by means other than patents. Some actors reply to this uncertainty by trying to play safe and apply for the broadest possible protection and for multiple patents covering different aspects of their invention. The patent system becomes thus clogged with overarching patent claims that have potentially stifling effects on innovation.

In 2007 the USPTO attempted to pass new rules limiting the number of claims per patent and the number of continuation applications for single inventions. These rules, however, met with resistance from the biotech and the pharmaceutical industry, as well as from some representatives of the public sector and were withdrawn *(33)*. The same holds true for the Patent Reform Act discussed in Congress in 2007, 2008 and then again, in a somewhat watered down version, in 2009 and 2010. Biotech lobby groups have been strongly opposing the Act. According to the Biotechnology Industry Associations *(34),* the proposed changes were aimed to limit the reach of patents on upstream inventions and undermine the strength, value and predictability of patent protection. The Biotechnology Industry Organization and other biotech lobby associations fiercely opposed the Patent Reform Act by testifying in front of Congress and claiming that these changes would devastate life sciences business models. The university technology transfer community weighted in with similar concerns *(35)*.

Although the view conveyed in the University of California brief entitled »Patent reform legislation – Analysis of S.1145, the žPatent Reform Act of 2007' – Provisions of Concern to UC« *(36)* may not be representative of the whole US public research sector, several things about this document are striking, such as the fact that the positions stated in the document are almost identical to those expressed in the statements of biotech lobby groups *(34, 35, 37)* and seem to be in favor of strong patents on upstream inventions. This suggests that, regardless of some examples of proactive involvement of the academic community in attempts to restrain the encroachment of market institutions on the sphere of science and enabling technologies, for the time being the academic community is likely to stay faithful to its offspring, the biotech industry and favorable of a tight IP regime on which this industry depends.

A SLIGHTLY OR A PROFOUNDLY DIFFERENT INSTITUTION OF SCIENCE?

The above analyzed developments, captured by the different IP responses of public scientists to patents on research tools, make one wonder whether today biomedical researchers operate within an institution of science that is markedly different from the one described by sociologists of science a few decades a go *(9)*. The adoption of market practices in the system of public science has most likely been facilitated by the complementarities between the institution of science and the institution of IP. Both institutions serve the public good by stimulating the production and disclosure of knowledge and by coordinating the interactions between the producers of knowledge, as well as between the producers and the users of knowledge. They are both based on some kind of organized system of certifying knowledge according to impersonal criteria. By rewarding originality, i.e. novelty in research contributions, they also set a race for priority among researchers and inventors.

The above parallels, of course, do not preclude important and potentially pervasive differences. To start with, the reward structures of the two institutions – the mechanisms set up to encourage the advancement of knowledge – differ profoundly. The reward system of science is based on collegiate reputations, established through priority in publication of verifiable research findings. Once researchers make a contribution and receive recognition for it, their research findings become part of the public domain. In science property rights become thus whittled down to »the recognition by others of the scientist's distinctive part in having brought the result into being« *(9)*. Recognition, to be sure, brings along prestige, better career prospects and better chances for receiving research grants and prizes. However, no matter how groundbreaking their contributions are, after publishing them scientists have no further control over how and by whom their results are used.

Conversely, the institution of IP purports to stimulate innovation by allowing inventors to reap monopoly profits from their inventions for a limited period of time. Of course, the inventor can choose to restrain from exercising these monopoly rights or to exercise them in a socially responsible manner. Yet the possibility of monetizing research results remains. When this possibility is transferred to the setting of public science, it can magnify an already present potential dysfunction of the science reward system – its sometimes »pathogenic« emphasis upon originality which leads to secretiveness during the early stages of inquiry, violent conflicts over priority and premature publications designed to establish grounds for later claims of having been first *(9)*. In the context of this tremendous institutional imperative towards originality, the ownership of foundational patents becomes an at-

tractive option not least because it can facilitate the preservation of lead positions in certain research lines by accruing research funds through licensing revenues and industrial funding.

Why have scientists been able to accommodate market elements in their institutional roles and yet remain by and large loyal to the institution of science? A possible explanation to this institutional resilience may be related to the fact that institutions are highly multi-dimensional entities, consisting of formal rules, informal norms and culturally shaped, taken-for-granted assumptions about reality. Each dimension has its own principles and practices and not all dimensions change simultaneously *(38, 39)*.

External institutional elements such as patent regulations and incentives were quickly adopted by the institution of science. So were some political ideas about the efficiency of markets for knowledge and the roles of the public research sector in fostering innovation and national competitiveness. However, this process of translation was only partial because of two factors: the problematic enforceability of patent regulations in the research setting and the considerable discretionary role of scientists and their representatives – due also to the relative autonomy of science – in interpreting what research results should be patented, how patent licensing should be handled and to what extent patents should be heeded when performing research.

Therefore, in the day-by-day operation of the institution of science, where activities and interactions tend to be determined more by informal norms than by spelled-out rules, it could be supposed that the process of change proceeded mainly though a gradual recombination of existing institutional elements – in order to adapt them to the new situation – and only to a minor extent though the adoption of new elements. As a result of this sometimes the openness requirements were made stricter than in the past, as in the case of community resource projects requiring immediate publication of data. In other instances, the norms of openness were bent in the name of technology transfer and competitiveness. Whether this process has gone too far, and the ideas that sustain it – such as the assumptions about the necessity of patenting for technology transfer and about the compatibility of patents and the goals of science –have become too taken-for-granted, is not easy to say. Most of these normative changes have been incremental, which may imply that their effects on the dynamics of knowledge advancement could also be incremental.

Market pressures were not only accommodated by some transformations within the system of science with respect to knowledge disclosure practices. They also had wider repercussions, affecting the larger institutional constellation in which science is embedded. Apart from being used as mechanisms of technology transfer through exclusive licensing to incumbent firms, as envisaged by the Bayh-Dole Act, patents began to be viewed by universities also as instruments of accrual of funds through non-exclusive licensing and industrial partnerships, as well as an instrument for spin-off firm formation. For instance, one in three biotech firms located in California were founded by University of Califrnia scientists *(5)*.

This brought PROs much closer to market organizations than the mere patenting for the purpose of exclusive licensing to domestic firms would have. According to Pisano *(5),* technology transfer in biotechnology has mainly taken place through new firm formation rather than through collaboration between academia and established firms. In his view, this propensity to found spin-off firms, together with a more general focus on monetizing IP in academia, might have impeded flows of information and curtailed the ability of incumbent firms to respond to the requirements of risk management, integration and learning at the organizational level.

CONCLUSION

By and large the interviews and the other primary and secondary data examined in this study indicate that the institutional fusion of science and the market has so far not created insurmountable problems. Currently academics seem to be able, at least to a certain extent, to get the best of the two worlds: they can choose to ignore patents and rely on »open science« norms when they act as users of patented inventions and play according to the rules of the market when producing commercially interesting research results. The general trend, however, seems to be a growing acceptance or at least tolerance of market mechanisms in the public sphere.

The presented overview of PROs' IP responses to the patenting of research tools in biomedicine shows that there are also strategies that are critical towards the appropriateness of market mechanisms for some type of scientific information and enabling technologies. These responses indicate that the juggling between the worlds of »open science« and proprietary technology is not always smooth. The problems that these responses highlight are of two types. Firstly, there are problems related to patents *per se*, for instance problems of access to research tools because of privately held and aggressively enforced patents on genes, cell lines and similar resources. The second type of problem is the lack of integration and learning, presumably because of growing secrecy and fragmentation of both public and private research efforts.

Gauging the effects of IP changes on the academic culture of openness and sharing is methodologically challenging, not least because it involves estimating the counterfactual – working out what would have been the level of sharing and openness without the possibility of patent protection *(10)*. Academic involvement in patenting activities has for sure had some self-reinforcing dynamics, in the sense that it contributed to the institutionalization of technology transfer offices endowed with missions of providing licensing income to PROs, the forging of their collaborations with IP prone patent attorneys, the strengthening of the ties between universities and biotech firms and the growing popularity of practices whereby firms finance public research in exchange for exclusive IP rights.

All this created a series of dependencies between PROs and market institutions and organizations. It is prudent to acknowledge that the increasing returns trait of institutions could create organizations with a stake in existing constraints, which would shape policy in their interests, even if the resulting equilibrium was sub-optimal from the social welfare perspective *(39)*. The resistance of the US biomedical research sector to proposals to introduce changes in the IP system might be an indication that this is already taking place.

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