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How Does the Republic of Science Shape the Patent System? Broadening the Institutional Analysis of Innovation Beyond Patents

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How Does the Republic of Science Shape the Patent System? Broadening the Institutional Analysis of Innovation Beyond Patents

Fiona E. Murray,* Joshua S. Gans,** and Mackey L. Craven***

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In their recent volume *The Patent Crisis*, Dan Burk and Mark Lemley argue that the patent system, as an undifferentiated catchall set of institutional rules shaping all innovating sectors of our economy equally, fails to account for significant variations in the nature of innovation and the needs of innovators from one sector to another.¹ Their remedy is *not* to propose an industry-specific patent doctrine in response to the challenge of heterogeneity.² In their own words, the

* MIT Sloan School of Management. Thanks to Dan Burk, Mark Lemley, and participants at the 2010 University of California, Irvine symposium “Bend or Break: Tailoring the Patent System to Promote Innovation.” Other aspects of this paper have benefited from valuable feedback from the Organisational Economics Workshop (Sydney), 2009 International Industrial Organization Society Conference (Boston), and seminars at MIT, Northwestern, Stanford, Melbourne, and the Australian National University. J.G. acknowledges an ARC Discovery Grant for financial assistance. F.M. acknowledges a National Science Foundation Science of Science Policy Grant. Responsibility for all errors lies with us.

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1. DAN L. BURK & MARK A. LEMLEY, *THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT* (2009).

2. Some commentators have advocated legislative patent reform aimed at making technology-

authors argue that “[p]atent law gives the courts substantial freedom to do this by means of flexible legal standards we call ‘policy levers.’”³ They illustrate how, in practice, patent doctrine inherently provides for a series of policy levers that enable courts to produce significant variation in the precise ways in which patents influence innovators across technical arenas and over time.⁴

This paper extends the Burk-Lemley perspective in two ways. First, it illustrates how another institutional setting—the Republic of Science—also provides overarching rules to reward knowledge production by a wide variety of innovators by drawing out the parallels between the patent system and the publication system at the level of an idealized doctrine.⁵ Through a detailed example from protein crystallography, we then highlight how the publication system has also been highly flexible in practice, illustrating the ways in which the Republic (and more specifically the publication system) adapted to dynamic scientific and technical changes. This allows us to understand the nature of various “levers” that have enabled editors, reviewers, funders, and others to respond to the dynamic and heterogeneous nature of innovation and, in doing so, to enhance incentives, knowledge disclosure, and knowledge accumulation. By drawing parallels between the levers in the patent and publication system, we support the general approach proposed by Burk and Lemley and generate a set of implications for how such flexibility might effectively be implemented.

Second, and more importantly, this paper illustrates how the two institutional arrangements supporting incentives for innovation—patents and publications—not only have significant parallels but also are intertwined in the ways in which they shape the incentives for innovation, enable knowledge disclosure, and promote knowledge accumulation. We illustrate this interaction and the complementarities that arise using a simple economic model grounded in the

specific rules. See, e.g., S. Benjamin Pleune, *Trouble with the Guidelines: On Urging the PTO to Properly Evolve with Novel Technologies*, 2001 U. Ill. J.L. TECH & POL’Y 365 (2001). Others have promoted other forms of systematic change. See, e.g., Stuart Minor Benjamin & Arti K. Rai, *Who’s Afraid of the APA? What the Patent System Can Learn from Administrative Law*, 95 GEO. L.J. 269 (2006–07) (advocating the application of administrative law principles to the patent system as a means to bring attractive change to the system). Additionally, some commentators have advocated individual changes to patent law doctrine. See, e.g., Stephen M. Maurer & Suzanne Scotchmer, *The Independent Invention Defense in Intellectual Property*, 69 ECONOMICA 535 (2002) (advocating that independent invention should be a defense to infringement); John S. Leibovitz, Note, *Inventing a Nonexclusive Patent System*, 111 YALE L.J. 2251 (2002) (advocating a patent system where multiple nonexclusive patents may be granted); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989) (arguing that basic scientific research can be protected by adding an experimental use exemption to patent infringement liability).

3. Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent*, 89 VA. L. REV. 1575, 1579 (2003).

4. *Id.*

5. For the origin and meaning of the term “Republic of Science” see Michael Polanyi, *The Republic of Science: Its Political and Economic Theory*, 1 MINERVA 54, 72 (1962). The term has been used more recently in the new economics of science literature as illustrated by Partha Dasgupta & Paul A. David, *Toward a New Economics of Science*, 23 RESEARCH POL’Y 487 (1994).

negotiation between a scientist and a funder taking into account both the potential competitive implications of disclosure through patenting but also the reputational benefits for publishing as faced by the scientist. This model illustrates the key levers from the Republic of Science that influence the level of patent disclosure and the overall incentives available to innovators. The notion that these two institutional arrangements are intertwined is then illustrated through two carefully developed examples—HIV (human immunodeficiency virus) and human embryonic stem cells. In each case, reconsideration of key levers in the Republic of Science—attribution of the inventive step, the nature of an inventive step, and the required level of disclosure—by the scientific community not only shaped the behavior and practices of scientists operating with the community, but also influenced the ownership, validity, and strength of patents. Taken together, the model and examples highlight the importance of broadening the context in which we consider patent policy levers in such a way as to include those levers provided for in the Republic of Science.

From a policy perspective it is possible that, by taking advantage of the pace of change in the scientific community, we can more rapidly and profoundly shape patenting and incentives for innovators via the Republic of Science than through the courts. Alternatively, publication levers may serve to undermine patent levers being enacted in the courts in ways that stifle the agenda set by those engaged in shaping the patent system to reward and enable innovation. At the very least, key patent levers designed to influence innovation in particular technical fields must be considered in the broader context of the intertwined institutions of the Republic of Science and the Patent System.

I. THE REPUBLIC OF SCIENCE AS DOCTRINE AND PRACTICE

A. The Doctrinal View

In his pioneering work on the sociology of science, Robert Merton provides an overarching, doctrinal perspective on the scientific community when he posits that the behavior of scientists is controlled by adherence to a set of norms: universalism, communism, disinterestedness, organized skepticism, originality, and autonomy.⁶ This work has subsequently been extended including the classic labelling of the scientific community as a “Republic of Science” by Michael Polanyi who intended the expression to mean that the “community of scientists is organized in a way which resembles certain features of a body politic and works according to economic principles similar to those by which the production of material goods is regulated.”⁷ While not as strictly observed or codified as the legal

6. ROBERT K. MERTON, SOCIAL THEORY AND SOCIAL STRUCTURE 550–61 (Free Press rev. ed. 1957) (1949).

7. Polanyi, *supra* note 5.

doctrines shaping intellectual property, and strongly criticized by later generations of sociologists, Merton's view provides a useful doctrinal foil in science to intellectual property doctrine.⁸ Much like the doctrines of patent law, the Republic of Science rewards the disclosure of new knowledge in publications and enables subsequent credit allocation (the version of the disclosure that mirrors patent disclosure and the rewards enabled through exclusionary property rights), and could be explained by reference to these internalized values. While not the core focus of Merton's work, subsequent scholars, most notably Warren Hagström, observed that publication with its exchange of knowledge in return for credit reinforced the core institutional logic of science: the published paper is a gift of information made in exchange for the hope of social recognition.⁹ Published papers also are the mechanism through which social recognition is bestowed. The contributor cites work that he found useful, thereby signalling the value of the work of previous contributors.

In its idealized doctrinal formulation, the publication process has striking parallels to the patent system: most papers receive reviews prior to publication designed to adjudicate the basis of the claims, their link to prior knowledge, and the extent to which they are indeed novel and considered a contribution. In contrast to the patent system in which review is not blinded (and while the scientific peer review process cannot be described as truly blind—most knowledgeable reviewers in a given field know the work being done in the labs of their peers), most academic science is subject to so-called “double-blind” review and the very energy that goes into making the process appear disinterested serves to reinforce this principle. The system has a variety of flaws (some of which are well documented, including the extent to which ascriptive characteristics such as gendered names seem to influence single-blind review outcomes); nonetheless, at least in the natural sciences, it is an extensive element of the system with clear editorial guidelines and apparently widespread agreement on what constitutes a contribution, i.e. an inventive step.¹⁰ Rules governing falsification of findings also exist through the system of scientific retractions and associated mechanisms such as the Office for Scientific Integrity at the National Institutes of Health; however, jurisdiction over such false claims remains complex, with a scientist's employer, the journal, and the funding agency all potentially participating in the adjudication process.

After publication, the value of any particular discovery is determined, at least

8. Rebecca S. Eisenberg, *Propriety Rights and the Norms of Science in Biotechnology Research*, YALE L.J. 97 (1987).

9. See WARREN O. HAGSTRÖM, *THE SCIENTIFIC COMMUNITY* (1965).

10. In the social sciences, the clarity of guidelines and what constitutes a contribution is more controversial. See Joshua S. Gans & George B. Shepherd, *How Are the Mighty Fallen: Rejected Classic Articles by Leading Economists*, 8 J. OF ECON. PERSPECTIVES 165 (1994) for an analysis of the case in economics.

in part, by the number of scientists citing the work in their own publications, again reinforcing the autonomy of academic science. Indeed, in a striking parallel to the patent system, for individual scientists, the incentive to publish comes from the importance the Republic of Science places on originality and priority. Merton can be credited with delineating how the fight for priority is the engine that energizes the widespread disclosure of scientific results. Merton observes that the history of science has been frequently punctuated by acrimonious and hard-fought battles between scientists over who should be credited with a discovery. Considerable institutional energy is put forth in determining the outcome of such priority fights, signalling the importance of these claims not just to individual egos, but to the functioning of the institution. Successful claims make scientists “owners” of discoveries, receive credit and rewards for their findings—but at the same time make this new information available to other scientists. Institutional insistence that such claims be adjudicated fairly underlines the importance of originality. It also motivates scientists to publish their results quickly to preempt the claims of others.

Employers in academic science reinforce the importance of disclosure through publication. Publication and its attendant status may be directly valued by those who engage in academic science, but it is also translated by universities and research labs into promotion and future resources to continue scientific pursuits. Universities closely monitor the publication records and citation patterns of scientists in their employ and base important career decisions on these records. By premising career rewards (such as tenure) on disclosure through publication, universities become virtual “outposts of disciplines” that give up many of their organizational prerogatives in employment to the collective judgment of the scientific community.¹¹

By reviewing publication through a doctrinal lens on the Republic of Science, we do not mean to suggest a Panglossian view of science and publication in particular. Rather, the aim is to lay out the doctrines that shape the Republic of Science in such a way as to clearly illustrate the parallels with the patent system. Nonetheless, much like the patent system, the way in which novel scientific knowledge is adjudicated, published, and rewarded is grounded not simply in broad norms and rules but instead in the daily practices of academic scientists. On a daily basis, scientists deal with a variety of sources of indeterminacy in the rules of publishing and rewards, including the fact that the institutional logic of Science

11. See JOSEPH BEN-DAVID, *THE SCIENTIST'S ROLE IN SOCIETY* (1971). While closely associated with university research, Open Science is also feasible (and profitably adopted) by private firms, including many within industries dependent on the life sciences. See Iain M. Cockburn & Rebecca M. Henderson, *Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery*, 46 J. INDUS. ECON. 157 (1998); Fiona Murray, *Innovation as Co-evolution of Scientific and Technological Networks: Exploring Tissue Engineering*, 31 RES. POL'Y 1389 (2002); Scott Stern, *Do Scientists Pay to Be Scientists?*, 50 MGMT. SCI. 835 (2004); Lynne G. Zucker et al., *Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises*, 88 AM. ECON. REV. 290 (1998).

may be internally inconsistent (as Merton noted about priority fights, the norm of originality conflicts with disinterestedness), and perhaps more importantly for our purposes, that the terms of the exchange of knowledge for recognition are underspecified (how much information in a given publication, what forms of recognition, etc.). This lack of specificity on the one hand allows for the flexibility and robustness of the system, enabling as it does high levels of variation from one discipline to another in terms of what constitutes enough novelty for a publication and variation over time as the tools and techniques of science render once intractable problems that might have been the subject of an entire Ph.D. thesis now solvable in an afternoon.

B. *The Dynamic Challenge*

The need for such flexibility is best illustrated by example. In the field of protein chemistry, technical advances have changed the nature of a publishable contribution. In 1964, Dr. Dorothy Hodgkin received the Nobel Prize for Chemistry for her “determinations by X-ray techniques of the structures of important biochemical substances” based on her work solving the structures of penicillin and vitamin B-12.¹² Max Perutz during the same period discovered the structure of hemoglobin and together with John Kendrew (who worked on myoglobin) received the Nobel Prize for Chemistry in 1962.¹³ In order to complete their work, Hodgkins, Perutz, and colleagues all used Kendrew-style “brass models at a scale of 5 cm/Ångstrom . . . built and supported within 2,500 vertical rods arranged to fill a cube six feet (2 meters) Colored clips were attached to the rods to signify electron density, and guide the building of the model.”¹⁴

In her Nobel Prize Lecture, Hodgkin provided more insight into the challenges of crystal structure determination from the vantage point of 1964. She noted:

12. *The Nobel Prize in Chemistry 1964*, Nobelprize.org, http://nobelprize.org/nobel_prizes/chemistry/laureates/1964/ (last accessed Mar. 11, 2011); see also Dorothy Crowfoot Hodgkin et al., *X-ray Crystallographic Investigation of the Structure of Penicillin*, in CHEMISTRY OF PENICILLIN (1949); Dorothy Crowfoot Hodgkin et al., *The Crystal Structure of the Hexacarboxylic Acid Derived from B₁₂ and the Molecular Structure of the Vitamin*, 176 NATURE 325 (1955); Dorothy Crowfoot Hodgkin et al., *Structure of Vitamin B₁₂*, 173 NATURE 64 (1956).

13. *The Nobel Prize in Chemistry 1962*, Nobelprize.org, http://nobelprize.org/nobel_prizes/chemistry/laureates/1962/index.html (last accessed Mar. 11, 2011); see also Hilary Muirhead & Max Ferdinand Perutz, *Structure of Haemoglobin: A Three-Dimensional Fourier Synthesis of Reduced Human Haemoglobin at 5.5 Å Resolution*, 199 NATURE 633 (1963); Max Ferdinand Perutz et al., *Three-Dimensional Fourier Synthesis of Horse Oxyhaemoglobin at 2.8 Å Resolution: (I) X-ray Analysis*, 219 NATURE 29 (1968); Max Ferdinand Perutz et al., *Three-Dimensional Fourier Synthesis of Horse Oxyhaemoglobin at 2.8 Å Resolution: the Atomic Model*, 219 NATURE 131 (1968); John Cowdery Kendrew et al., *A Three-dimensional Model of the Myoglobin Molecule Obtained by X-ray Analysis*, 181 NATURE 662 (1958).

14. Eric Martz & Eric Francoeur, *History of Visualization of Biological Macromolecules, Physical Representations*, <http://www.umass.edu/microbio/rasmol/history.htm#physical> (last revised Aug. 2004).

The experimental data we have to employ are the X-ray diffraction spectra from the crystal to be studied, usually recorded photographically and their intensities estimated by eye. These spectra correspond with a series of harmonic terms which can be recombined to give us a representation of the X-ray scattering material in the crystal, the electron density One is then in the position that, from a sufficient number of measurements, one can calculate directly the electron density and see the whole structure spread out before one's eyes. However, the feat involved in the calculations described two years ago was prodigious—tens of thousands of reflections for five or six crystals were measured to provide the electron-density distribution in myoglobin and haemoglobin. More often, and with most crystals, the conditions for direct electron-density calculation are not initially met and one's progress towards the final answer is stepwise Our early attempts at structure analysis now seem to be very primitive.¹⁵

Similarly, Kendrew in his Nobel Prize Lecture (in 1962) described how

Even at the first stage of the analysis we made use of an electronic computer, EDSAC I, which though small and slow by modern standards was at the time one of the very few such instruments in operation in the world; it is significant that these early Fourier syntheses of the myoglobin data were, to the best of my belief, the first crystallographic computations ever carried out on an electronic computer and initiated a practice which later (and incidentally after a time lag of several years) became universal among crystallographers.¹⁶

It was not until the mid-1970s that researchers were able to solve a protein crystal structure and visualize it computationally without using a rather cumbersome “Kendrew”-style model—instead using a computer system developed at the University of North Carolina.¹⁷ By the mid-1990s, both commercial and freeware software became available to researchers for the visualization of biological molecules on the basis of their underlying amino acid structure combined with crystallographic data as well as the emerging use of magnetic resonance imaging techniques. Over the past fifty years, “[t]he rate of structure determination has accelerated mainly due to the introduction of new algorithms and computer programs for diffraction data collection, structure solution, refinement, and presentation.”¹⁸ Accordingly,

15. Dorothy Crowfoot Hodgkin, *The X-ray Analysis of Complicated Molecules*, in NOBEL LECTURES, CHEMISTRY 1942–1962, 71, 71–72 (1964).

16. John C. Kendrew, *Myoglobin and the Structure of Proteins*, in NOBEL LECTURES, CHEMISTRY 1942–1962, 676, 680 (1964).

17. See Karl M. Beem *et al.*, *Metal Sites of Copper-Zinc Superoxide Dismutase*, 16 BIOCHEMISTRY 1930 (1977); John A. Tainer *et al.*, *Determination and Analysis of the 2 Å Structure of Copper, Zinc Superoxide Dismutase*, 160 J. MOL. BIOL. 181 (1982).

18. Pavlína Řezáčová, *Advances and Problems in Protein Crystallography*, 16 MATERIALS STRUCTURE k7, k7 (2009).

[t]he data collection process with current X-ray sources, detectors and computer software is one of the easiest and most automated steps in protein crystallography The availability of many different protein fold models allows use of molecular replacement for about half of all structures currently deposited in the Protein Data Bank (PDB). Advances in computer software for model building and refinement as well as computer graphics allow for user-friendly and even automatic model building and refinement.¹⁹

The shifting technology of structure determination is reflected both in the daily practices of scientists and also in their publications of this period. Take the example of insulin: the first publications of the full structure came in 1971 after several decades of work and a series of publications describing fragments of the structure.²⁰ By the 1990s, leading journals had shifted from publishing the low-resolution protein structures to, for example, a comparison of three different types of insulin.²¹ Moving beyond insulin, it is instructive to examine the effect of this shifting technology on the scope of answerable research questions and by extension the nature of publications in the field protein structure determination. In 1972, the advent of molecular cloning allowed for mass production of proteins for structural studies²² and, in 1978, nuclear magnetic resonance (NMR) was first used as an alternative to X-ray crystallography.²³ The combined ability to produce large quantities of a desired protein and then determine the structure in solution instead of in crystal form allowed for comparative structural studies as well as investigations of more complex properties such as solvent interactions.²⁴ Better conceptual models of proteins, such as the development of the ribbon model in 1981, and continued refinement of then existing imaging techniques²⁵ allowed for the determination of complex structures such as those of integral membrane proteins for which the 1988 Nobel Prize in chemistry was awarded.²⁶ In fact, the

19. *Id.*

20. See, e.g., Margaret J. Adams et al., *Structure of Rhombohedral 2-Zinc Insulin Crystals*, 224 NATURE 491 (1969); Tom Blundell et al., *Atomic Positions in Rhombohedral 2-Zinc Insulin Crystals*, 231 NATURE 506 (1971).

21. See, e.g., Qing Xin Hua et al., *Paradoxical Structure and Function in a Mutant Human Insulin Associated with Diabetes Mellitus*, 90 PROC. NAT. ACAD. SCI. 582 (1993).

22. See David A. Jackson et al., *Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia coli*, 69 PROC. NAT. ACAD. SCI. 2904 (1972).

23. See Gerhardt Wagner & Kurt Wuthrich, *Dynamic Model of Globular Protein Conformations Based on NMR Studies in Solution*, 275 NATURE 247 (1978).

24. See Stephen Sprang et al., *Solvent Accessibility Properties of Complex Proteins*, 280 NATURE 333 (1979).

25. See Jane S. Richardson, *Early Ribbon Drawings of Proteins*, 7 NATURE STRUCT. & MOL. BIOL. 624 (2000); Johann Deisenhofer et al., *X-ray Structure Analysis of a Membrane Protein Complex. Electron Density Map at a 3 Å Resolution and a Model of Chromophores of the Photosynthetic Reaction Center from Rhodospseudomonas viridis*, 180 J. MOL. BIOL. 385 (1984).

26. The Royal Swedish Academy of Sciences, *The Nobel Prize in Chemistry 1988*, Press Release, Oct. 19, 1988, http://nobelprize.org/nobel_prizes/chemistry/laureates/1988/press.html.

level of detail achieved in the 1980s allowed protein structure determination to be accepted as a drug design tool to combat diseases such as HIV.²⁷ With the realization in 1990 that protein structures could be determined using a synthetic amino acid, selenomethionine, through multi-wavelength anomalous diffraction (MAD), the number of crystal structures determined in a given year increased four-fold by 1996.²⁸ This increase in quantity was complemented by an increase in quality as more complex structures such as ion channels²⁹ and the ribosome were first determined in 1998 and 1999 respectively.³⁰ In fact, both discoveries garnered the Nobel Prize in Chemistry, with the potassium channel being recognized in 2003³¹ and the ribosome in 2009.³² At the turn of the millennium, advances in genome-scale studies in genetics led to the study of “structural genomics”; with the goal of determining the three-dimensional structure of every protein in entire genomes.³³ In addition, continual refinements of existing techniques allowed for more complex protein structures to be determined including that of RNA polymerase in 2001,³⁴ which was recognized by the 2006 Nobel Prize in chemistry.³⁵ The shifting technology of protein structure determination redefined what constituted a publication in the field, both in terms of quantity and quality of structures determined.

These changes are not, obviously, confined to chemistry. More salient to those considering the parallels between the scientific system of publication and the patent system are the changes in the nature of a contribution in human genetics—a topic that has animated legal scholars and others concerned with the potential

27. See Manuel A. Navia et al., *Three-Dimensional Structure of Aspartyl Protease from Human Immunodeficiency Virus HIV-1*, 337 NATURE 615 (1989); Michael Miller et al., *Structure of Complex of Synthetic HIV-1 Protease with a Substrate-Based Inhibitor at 2.3 Å Resolution*, 246 SCIENCE 1149 (1989).

28. See Wei Yang et al., *Structure of Ribonuclease H Phased at 2 Å Resolution by MAD Analysis of the Selenomethionyl Protein*, 249 SCIENCE 1398 (1990); *Structural Biology and Synchrotron Radiation: Evaluation of Resources and Needs*, BIOSYNC (1997) http://www.ornl.gov/sci/techresources/Human_Genome/biosync/intro.shtml (last accessed May 21, 2011).

29. See Declan A. Doyle et al., *The Structure of the Potassium Channel: Molecular Basis of K⁺ Conduction and Selectivity*, 280 SCIENCE 69 (1998).

30. See Ante Tocilij et al., *The Small Ribosomal Subunit from Thermus thermophilus at 4.5 Å Resolution: Pattern Fittings and the Identification of a Functional Site*, 96 PROC. NAT. ACAD. SCI. 14252 (1999); Nenad Ban et al., *Placement of Protein and RNA Structures into a 5 Å Resolution Map of the 50S Ribosomal Subunit*, 400 NATURE 841 (1999); William M. Clemens et al., *Structure of a Bacterial 30S Ribosomal Subunit at 5.5 Å Resolution*, 400 NATURE 833 (1999).

31. Press Release, The Royal Swedish Academy of Sciences, *The Nobel Prize in Chemistry 2003* (Oct. 8, 2003) http://nobelprize.org/nobel_prizes/chemistry/laureates/2003/press.html.

32. Press Release, The Royal Swedish Academy of Sciences, *The Nobel Prize in Chemistry 2009* (Oct. 7, 2009) http://nobelprize.org/nobel_prizes/chemistry/laureates/2009/press.html.

33. See Stephen K. Burley et al., *Structural Genomics: Beyond the Human Genome Project*, 23 NATURE GENETICS 151 (1999).

34. See Patrick Cramer et al., *Structural Basis of Transcription: RNA Polymerase II at 2.8 Å Resolution*, 292 SCIENCE 1863 (2001).

35. Press Release, The Royal Swedish Academy of Sciences, *The Nobel Prize in Chemistry 2006* (Oct. 4, 2006) http://nobelprize.org/nobel_prizes/chemistry/laureates/2006/press.html.

ramifications associated with gene patenting.³⁶ The need for dynamic considerations is vividly illustrated by considering the scientific work that goes into gene sequencing.³⁷ In the 1980s, a graduate student might consider the similarities and differences between two homologous genes in yeast.³⁸ Fast forward to 1986, when the first Applied Biosystems sequencer replaced simple chain termination methods and could analyze up to 4,800 base pairs each day. This and subsequent advances allowed theses of the early 1990s to encompass complete genetic maps of organisms as complex as mice.³⁹ By 2010, the most recently launched machines sequence between 25 billion and 100 billion base pairs each day.⁴⁰ This is not to say that Ph.D. candidates in biology no longer have research projects to accomplish, but rather that what once constituted a significant and novel step towards scientific progress has now become highly automated, with the novelty requiring the combination of significant amounts of data to provide insights into the workings of individual as well as collections of genes.

Research in crystallography has come a long way from the era when the painstaking work of understanding a single protein in a particular crystal form took the course of a career. Today's leading crystallographers, enabled by technological advances, can "solve multiple structures of a single enzyme with bound substrates, analogs, and products, to acquire a series of 'snapshots' of a single enzyme."⁴¹ Likewise in genetics, researchers who once published the sequence of a single gene now must assemble complete genomes. Thus, we see that just as the uneven nature of technical change across time and across disciplines renders the doctrinal approach to the patent system challenging,⁴² so it challenges the scientific community. Even when the core intellectual question animating the field is stable, as in protein chemistry, the combination of cumulative progress, together with technical advances requires that the definition of a significant building block of new knowledge be a dynamic one. Less a question of what is obvious or not, instead what is at issue is the depth of insight and newly acquired information that constitutes a leading publication, the amount

36. See, e.g., LEGAL RIGHTS AND HUMAN GENETIC MATERIAL (B.M. Knoppers, T.A. Caulfield & T.D. Kinsella eds., 1996); Rebecca S. Eisenberg, *Patenting the Human Genome*, 39 EMORY L. J. 721 (1990); John Murray, *Owning Genes: Disputes Involving DNA Sequence Patents*, 75 CHICAGO-KENT L. REV. 231 (1999); Matthew Rimmer, *Myriad Genetics: Patent Law and Genetic Testing*, 25 EUR. INTELL. PROP. REV. 1 (2003).

37. See Heidi Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome*, (Nat'l Bureau of Econ. Research, Working Paper No. 1213, 2010).

38. See, e.g., Peter Joseph Schatz, *Analysis of α -tubulin in Yeast* (1982) (Unpublished Ph.D. Thesis, MIT Department of Biology) (on file with MIT Library).

39. See, e.g., William Frank Dietrich, *A Complete Genetic Map of the Mouse and its Application to the Study of Mouse Models of Human Disease* (1993) (Unpublished Ph.D. Thesis, MIT Department of Biology) (on file with MIT Library).

40. J. Craig Venter, *Multiple Personal Genomes Await*, 464 NATURE 676, 677 (2010).

41. Catherine Drennan, *The Crystallographic Approach*, MIT DRENNAN LAB, <http://web.mit.edu/cld/research/crystallography/crystallography.html> (last visited Mar. 14, 2011).

42. See BURK & LEMLEY, *supra* note 1.

of information that must be disclosed and the form that will render it enabling to those seeking to build cumulatively, and the appropriate rewards for that knowledge. Consequently, the nature of disclosure and rewards in the Republic of Science is dynamic. The mechanisms that allow the community to provide such dynamic adaptation in light of these challenges and opportunities and the levers that could ensure its responsiveness are of potential interest to those exploring effective policy levers for the patent system.

C. The Practice View—Dynamic Adaptation

As a result of the ongoing desire to make their claim for and to maintain professional autonomy, scientists have engaged in social action and boundary work to define the distinctiveness of “science” and avoided the imposition of constraints or practices from outside of science.⁴³ Nonetheless, a variety of scholars have argued that the “strong norms” (or doctrinal) perspective on the Republic of Science is, in fact, more realistically understood as arising through overlapping networks of epistemic communities whose own norms and practices reflect the realities of laboratory life in all its rich complexity.⁴⁴ Just as patent law “gives the courts substantial freedom . . . by means of flexible legal standards” operating at some remove from overarching patent doctrine,⁴⁵ so the publication system on the ground as enacted by scientists enables much greater discretion and allows for dynamic adaptation to changing needs across disciplines and over time. Serving as editors and reviewers, colleagues and advisors, scientists shape the requirements and meaning of disclosure.

The successful flexibility of the Republic of Science, therefore, provides compelling evidence to reinforce the view “that we should not jettison our nominally uniform patent system in favor of specific statutes that protect particular industries.”⁴⁶ Instead “there are other ways the law can take account of the needs and characteristics of different industries” in applying general patent rules to specific cases.⁴⁷

Returning to our discussion of the dynamics of human gene sequencing provides just one example of a community-wide but expert-based approach to the dynamics of disclosure and enablement. Prior to the formalization of the Human

43. See STEVEN SHAPIN, *A SOCIAL HISTORY OF TRUTH: CIVILITY AND SCIENCE IN SEVENTEENTH-CENTURY ENGLAND* (1994); Thomas F. Gieryn, *Boundary-Work and the Demarcation of Science from Non-science: Strains and Interests in Professional Ideologies of Scientists*, 48 *AM. SOC. REV.* 781 (1983).

44. See, e.g., BRUNO LATOUR & STEVE WOOLGAR, *LABORATORY LIFE: THE SOCIAL CONSTRUCTION OF SCIENTIFIC FACTS* 129 (1979) (quoting Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent*, 89 *VA. L. REV.* 1575, 1579 (2003)); see also KARIN KNORR-CETINA, *EPISTEMIC CULTURES: HOW SCIENCES MAKE KNOWLEDGE* (1999).

45. Burk & Lemley, *supra* note 3 at 1579.

46. *Id.*

47. *Id.* at 1641.

Genome Project by the Department of Energy and later the National Institutes of Health in 1986, most human gene sequencing took place on an ad hoc basis with only limited disclosure of precise sequence data even when sequences were described in publications. However, as the project became more formal and the need for full sequence information became more salient for rapid and effective follow-on research, the community took steps to shape disclosure rules thus facilitating enablement. In 1996, participants in the Human Genome Project met in Bermuda for a large-scale sequencing strategy meeting for international coordination of human genome sequencing, sponsored by the Wellcome Trust, U.K. Medical Research Council. About fifty scientists from countries publicly supporting large-scale human genome sequencing attended the conference. Among other decisions it was agreed that:

- ❖ All human genomic sequence information, generated by centres funded for large-scale human sequencing should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society.
- ❖ Sequence assemblies should be released as soon as possible; in some centres, assemblies of greater than 1 Kb would be released automatically on a daily basis.
- ❖ Finished annotated sequence should be submitted immediately to the public databases.⁴⁸

At the Second International Strategy Meeting on Human Genome Sequencing in 1997,⁴⁹ participants (participating organizations and funding agencies) reconfirmed their sequencing data release policy and a set of norms of “etiquette” regarding sequence claims:

- ❖ Mapping investment does not automatically entitle sequencing claims over the same region until a sequence ready map has been generated.
- ❖ Potential conflicts with other sequencers to be resolved by early communication.
- ❖ Collaborations with groups with a biological interest in a region should be subject to the same principles of data release and communication.⁵⁰

While less formally organized, the crystallographic community has also dynamically updated its norms around data disclosure and sharing. In the 1960s, “coordinates for individual entries had only been exchanged among a few research laboratories using punched cards. Since each atom was represented by a single

48. “Policies on Release of Human Genomic Sequence Data: Bermuda-Quality Sequence,” *Summary of Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing*, HUMAN GENOME PROJECT INFORMATION (1996), http://www.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml (last visited May 21, 2011) [hereinafter HUMAN GENOME PROJECT].

49. Held in Bermuda from Feb. 27, 1997 to Mar. 2, 1997.

50. HUMAN GENOME PROJECT, *supra* note 48.

card, an exchange of a structure the size of myoglobin required more than 1000 cards.”⁵¹ The idea of streamlining data sharing by developing a central repository for protein structure data was first discussed at an American Crystallographic Association meeting in Ottawa, Canada in 1970.⁵² Discussions among crystallographers continued throughout the year and in 1971 after the Cold Spring Harbor symposium on “Structure and Function of Proteins at the Three Dimensional Level,” Walter Hamilton and Olga Kennard established the PDB archive.⁵³ Although there were only twenty-three entries in 1976, the aforementioned advances in structure determination technology have allowed this number to increase to over 66,000 in 2010.

As these examples highlight, the scientific community takes a broad set of rules and expectations and tailors them to differences across fields and over time. It does so using levers such as the publishing system but with adaptation relying on a rich set of bottom-up interventions made by innovators—scientists—themselves. These individuals not only work at the forefront of knowledge but also take steps to shape the disclosure and reward system that lies at the core of the scientific enterprise in such a way as to be responsive to changes at the frontier. Rather than a single senior scientist judging the legitimacy of a claim for credit, the level of disclosure, or the appropriate scope of an inventive step worthy of journal publication, instead distributed groups of editors and reviewers, faculty tenure committees, and granting agencies work to pull the levers of adaptation in science. It is in the collective but distributed nature of these decisions that the Republic of Science diverges from the patent system. Through careful application of these mechanisms, flexibility is maintained so as to promote, rather than limit, scientific progress and knowledge accumulation. The community has taken an overarching view of the rules of scientific disclosure, a “contribution” and enablement, and tailored them to specific conditions.

What might the parallels be for the patent system? While beyond the scope of this paper, one might consider the role of scientific expertise in shaping administrative review processes at the Patent Office.⁵⁴ Recent steps in this direction include the “peer-to-patent” process that opens the patent examination process to the public for the first time. Started in June 2007, it is conceptualized as using the wisdom of crowds to improve the patent review process, and as of May 2008, over 2,040 registered users had participated in the review of fifty-six patents with 183 people submitting prior art references.⁵⁵ With the permission of the

51. Helen M. Berman, *The Protein Data Bank: A Historical Perspective*, 64 ACTA CRYSTALLOGRAPHICA 88 (2008).

52. *Id.*

53. *Id.*

54. See, e.g., the recent work by Burnstein on the potential for administrative intervention and review at the patent office as an alternative policy lever outside the remit of judges.

55. Community Patent Review, *Site Statistics as of May 11, 2008*, THE PEER TO PATENT PROJECT, <http://dotank.nyls.edu/communitypatent/reviewerdemographics.html> (last visited on July

inventor, the program enables the public to submit prior art and commentary relevant to the claims of pending patent applications specifically in the area of Computer Architecture, Software, and Information Security (TC2100). In July 2008, the scope was extended to include Technology Center 3600 (Class 705). Accordingly,

[a]nyone in the public can participate as a reviewer, a patent application facilitator, and by sharing information about the pilot with others. Inventors can submit a qualified patent application for open review. Public participation is crucial to demonstrating the value of openness and making the case for greater USPTO accountability to the technical community. A successful pilot will also make a case for expanding to other subject matter.⁵⁶

While quite distinct from the peer-review process or the editorial process found in the Republic of Science, this particular initiative is suggestive of the role of expert peers in enabling adaptation and tailoring of the patent system in such a way as to meet the needs of different innovators.

II. INTERTWINED RELATIONSHIP BETWEEN THE PATENT SYSTEM & THE REPUBLIC OF SCIENCE

At its most simplistic, the Republic of Science provides a parallel institutional system for the disclosure of knowledge from which we might learn lessons or draw parallels to guide our understanding of the ways in which the patent system can adapt to the dynamics of innovation. However, this is based on the assumption that these two systems are parallel but separate. As an alternative, we posit that the two systems are intertwined in such a way that the levers shaping disclosure in the Republic of Science also in fact influence the patent system.

To put it another way, by grounding our analysis of knowledge disclosure only in the context provided by patent law, we fail to recognize another critical influence on knowledge disclosure—namely the system of scientific publication.⁵⁷

20, 2010).

56. Community Patent Review, *About Community Patent*, THE PEER TO PATENT PROJECT, <http://dotank.nyls.edu/communitypatent/about.html> (last visited on July 20, 2010).

57. In contrast, a much more extensive literature has examined the possible extent to which the patent system influences the scientific community. Some scholars have focused on the negative implications of the patent system on the scientific community. See, e.g., Yochai Benkler, *Intellectual Property: Commons-Based Strategies and the Problems of Patents*, 305 SCIENCE 1110 (2004); Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 ARIZ. L. REV. 457 (2004); Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77 (1999); Michael A. Heller and Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989); Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge?: An Empirical Test of the Anti-Commons Hypothesis*, J. ECON. BEHAV. & ORG. 648 (2007); Murray et al. (2009) and Murray (forthcoming) for an empirical analysis that suggests that the

In this section, we argue that the precise levers and adaptive processes of the publication system outlined above not only shape knowledge disclosure in publications; in areas where knowledge can be disclosed in publications and patents, they also have a strong and significant impact on patenting. Therefore, by placing the patent system into the broader institutional context of knowledge disclosure that includes the Republic of Science, we provide a more complete institutional picture and a more comprehensive set of practices that enable adaptation to the demands of different innovators, solve some of the apparent crises of the patent system, and enable some key facets of “industry tailoring” that are less plausibly accomplished through patent reform. Indeed, the changing rules and norms of the Republic of Science directly shape policy levers in the patent system, including the degree and nature of patent disclosure—a point often ignored by legal scholars and economists who more typically examine the incentives for invention within the narrowly constructed boundaries of the patent system.⁵⁸ Instead we assume that disclosure decisions by innovators take place within the intertwined institutional systems of patent law and publication norms. This section illustrates these interrelationships with a simple model and two empirical examples.

A. A Simple Model—Disclosure in Publications & Patents

At the core of the system of knowledge disclosure in patents is the recognition that the cumulative acquisition of knowledge lies at the heart of persistent economic growth. The fundamental spillover identified by Romer, amongst others, was the fact that knowledge produced today increases the productivity of the R&D sector in producing knowledge tomorrow.⁵⁹ However, in evaluating the incentives for innovation and disclosure, it is critical to examine not only the patent system as the institutional setting shaping disclosure but also the variety of alternatives available to a given innovator. Specifically, we lay out the range of disclosure choices available to scientists (we use this term broadly to include engineers and others engaged in technical work that might be potentially disclosed in a variety of different mechanisms including the patent system). Our

influence of the patent system is negative in the short run but that the scientific community rapidly adapts the nature and use of patents to enable continued scientific openness. *But see* David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 985 (2005) (contending that the patent system has not hindered biomedical research and other commentators have not focused on the inherent technical barriers in the biomedical sciences).

58. Focusing on the historic literature, Petra Moser examines differences in patent systems around the world and their influence on inventions in the Great Exhibition. Petra Moser, *How Do Patent Laws Influence Innovation? Evidence from Nineteenth-Century World's Fairs*, 95 AM. ECON. REV. 1216 (2005). The empirical economics literature is focused on the relationship between the patent system and innovation. *See, e.g.*, Richard C. Levin, *A New Look at the Patent System*, 76 AM. ECON. REV. 199 (1986). Similarly, the theoretical perspective is laid out by Scotchmer (2006) and prior papers.

59. Paul M. Romer, *Endogenous Technological Change*, 98 J. POL. ECON. S71 (1990).

approach is then to examine those factors (or levers, to use the language outlined above) that shape the disclosure decision. To illustrate the subtleties of this choice, we focus on the disclosure of scientific or technical knowledge generated as a result of for-profit funding (though our approach can be extended to university funding).⁶⁰ The specific disclosure choices, as we will outline, are grounded both in the range of institutional arrangements that influence disclosure and in the negotiations that arise between scientists and those who fund them when their disclosure preferences diverge.

To understand the range of disclosure choices available to innovators whose knowledge is of potential scientific value but also a useful inventive step, consider the following: disclosure of knowledge cannot be necessarily taken as a given (although it might be a direct consequence of reverse-engineering when knowledge is placed in the marketplace in the form of physical products). Instead, disclosure is a choice made by scientists and their funders (call them firms). One form of disclosure is, of course, the quid pro quo of obtaining patent protection. However, we must recognize that obtaining a patent is a choice, especially when such disclosures may be more harmful to a firm in the marketplace than would be compensated by the protection a patent afforded. The other form of disclosure is, of course, through publications. By publications, we do not just mean journal publication but also presentation at seminars and conferences and through all of the potential mechanisms afforded by the institutions of science. As noted above, the incentive for such disclosure in this case is driven not just by norms requiring this to be part of a scientific community,⁶¹ but also by the benefits of recognition and prestige associated with being the first to discover a new piece of knowledge—loosely called kudos. Yet a third alternative—at times posited as the alternative to patenting—is of course secrecy, which could be an explicit choice made by innovators in the form of trade secrets.⁶²

As outlined in Section I, many discussions of disclosure and patenting allow for a treatment of patenting and publishing as two entirely separate mechanisms. Indeed, it is at times posited that patenting (or the alternative of secrecy) pertains to useful knowledge while publishing (and the less frequently discussed alternative

60. What follows is an informal exposition of the formal analysis contained in Joshua S. Gans, Fiona E. Murray & Scott Stern, *Contracting over the Disclosure of Scientific Knowledge: Intellectual Property Protection and Academic Publication*, (Aug. 22, 2010) available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1559871.

61. ROBERT K. MERTON, *THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS* (Norman W. Storer ed., 1973).

62. See Richard Levin, *Appropriability, R&D Spending and Technological Performance*, 78(2) AM. ECON. REV. 424 (1988) (Papers and Proceedings of the One-Hundredth Annual Meeting of the American Economic Association); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783 (1987) (Special Issue on Microeconomics); Edwin Mansfield, Mark Schwartz & Samuel Wagner, *Imitation Costs and Patents: An Empirical Study*, 91 ECON. J. 907 (1981).

of scientific secrecy) pertains to fundamental knowledge.⁶³ Superficially, the choice of publishing or patenting or secrecy arises as a conflict between scientists and firms over disclosure. For the scientist, the kudos that arise from publication and the citations that arise from knowledge accumulation direct them towards wanting that knowledge to be published with whatever levels of disclosure are required for the most prestigious journal in their field. But for the firm, use of knowledge can imply imitative competition or a speeding up of entry that itself reduces the commercializable length of their current technological lead. Thus, scientists prefer more disclosure and ease of knowledge use while the firms would prefer the opposite. Recall that patent disclosures are a cost of being able to enjoy the other monopoly property rights of a patent and so are a contractual rather than a voluntary act.

But, as is often the case, conflict of interest does not necessarily translate into realized conflict of action when two parties are forced to cooperate: a firm cannot easily compel scientists to secrecy (except under narrow conditions of trade secrecy) anymore than scientists can assert their rights to free publication if this would eviscerate any commercial return. Some negotiation must take place that balances these competing interests. It is in the context of this negotiation that the interaction between patenting and publishing is revealed. First, for knowledge that arises in Pasteur's Quadrant,⁶⁴ in fact four rather than three disclosure mechanisms are possible: patenting, publishing, secrecy, or (with the appropriate timing of disclosure) patenting and publishing, sometimes referred to as patent-paper pairs.⁶⁵ Such pairs are two documents—a patent and an academic publication—that both disclose knowledge generated in the course of the same project. Thus, whether or not patent-paper pairs are selected as the disclosure mechanism, the patent system is intertwined with the system of scientific publishing.

The interaction among the different choices and therefore the different institutions can be strong and, in that respect, highly relevant for the design of patent policy. The key issue is the extent to which the patent shapes the costs the firm faces from publication of the same project and vice versa.⁶⁶ To the extent that a patent can perfectly block any entrant from building on the research with a

63. See Partha Dasgupta & Paul A. David, *Toward a New Economics of Science*, 23 RES. POLY 487 (1994).

64. See DONALD E. STOKES, *PASTEUR'S QUADRANT: BASIC SCIENCE AND TECHNOLOGICAL INNOVATION* (Brookings Institution 1997) for a definition. The explanation of Pasteur's Quadrant given here is taken from Murray & Stern, *supra* note 57.

65. Murray, *supra* note 11.

66. See, for example, Murray & Stern, *supra* note 57, and Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape the Long-Run Supply of Public Knowledge? Evidence from Human Genetics*, 52 ACAD. MGMT. J. 1193 (2009) for analyses on publishing and patenting. See Pierre Azoulay et al., *The Determinants of Faculty Patenting Behavior: Demographics or Opportunities?*, 63 J. ECON. BEHAV. & ORG. 599 (2007) for the determinants of patenting and publishing at the individual level.

competing product, then disclosures (in publications) which otherwise might assist such entry are not a cost to the firm at all. In this respect, perfect patent protection eliminates the firm's costs from publication (in competitive terms without considering any time involved in preparing an additional manuscript) and with it any conflict. Similarly, any moves to improve the ability of patents to block such entry will have a positive impact on the expected degree of publication rights afforded to scientists. Abstracting away from the case where patent protection is "complete," we can then understand the interaction among patenting and publishing as arising through two levers: the difference in the disclosure level between patents and publications and the difference in the type of disclosures required for publications and patents.

To the extent that the level of disclosure required by an academic publication is higher than that required in a patent, additional publishing by scientists will provide a level of knowledge that could encourage or facilitate entry by others. Therefore, we are likely to see fewer patent-paper pairs and a decline in academic publishing relative to a period of lower disclosure requirements. Patents, of course, have their own disclosure requirements. A first-order impact of requiring patent disclosures to be greater and to be more like the disclosures found in publications would be to reduce the additional costs associated with publication itself. Having given much of the game away in a patent application, the firm's costs of letting scientists publish are consequently reduced.

Similarly, what arises if the disclosure overlaps between patents and papers differ not so much in the level of disclosure but in the type of knowledge that is required in one forum versus another? Overall, to the extent that the additional disclosure requirements required by scientific institutions such as journals or research centers are distinct from those required in the patent system, we would expect to see less publishing and may see less patenting because the scope of the publication may impact commercial returns. For instance, publication scope and the provision of key scientific materials not required in the patent can influence the ability of entrants to easily find work-arounds to the patent. Conversely, any shift in patent disclosures more akin to those required in publications may enable higher levels of publication. While not a direct interaction, indirectly the system of scientific publishing can serve to shift firms and scientists into modes permissive of patenting.

All this suggests that strong publications and a shift towards greater openness in science, accompanied by a range of additional types of disclosure including materials and methods, may be associated with a lower degree of patenting and publishing despite the inherent conflict of interest between scientists and firms on this issue. Extending beyond the narrow confines of the model that focuses on the overlap in disclosure and the levels of disclosure, the general point must be made that the adjudication of knowledge within the Republic of Science itself intimately shapes the level, nature, and validity of

knowledge disclosed within the patent system. Changes in the system of publishing point towards changing norms in the scientific or technical communities of innovators with which firms often engage and, thus, signal norms of enablement that could be incorporated into considerations regarding patent litigation. Likewise, adjudications of obviousness considered narrowly within the scope of a given patent in a particular technical field may ignore norms of obviousness emerging within the technical community where engineers are educated, may collaborate, and certainly publish. Thus, again within a legal setting, such levers of the patent system become strongly informed by norms emerging from the Republic of Science. Two cases clearly illustrate this intimate interconnection between the two systems—the disclosure and adjudication of the claims of validity of the human immunodeficiency virus (HIV) and the claims of inventiveness of the discovery of human embryonic stem cells (hESCs).

B. Patent & Publication Disputes over Human Embryonic Stem Cells

The case of human embryonic stem cells (hESCs) illustrates the degree to which one key lever of the patent system—obviousness—that might traditionally be thought to have rested on narrow patent-based interpretation can also be intimately linked to the adjudication of this issue by the scientific community. The case begins as far back as July 9, 1981, when Sir Martin Evans and Professor Matthew Kaufman published their discovery of “pluripotential cells” in mouse embryos, a discovery that would earn Evans one third of the 2007 Nobel Prize in Physiology or Medicine.⁶⁷ That December, Professor Gail Martin of the University of California, San Francisco, published her independent discovery of these cells and described them as “embryonic stem cells,” the name by which we know them today.⁶⁸ These discoveries were critical because embryonic stem cells (ESCs) are pluripotent; they have the ability to self-replicate and differentiate into any cell type.⁶⁹ The scientific community quickly recognized this value, and by 1989, several research teams had used ESCs to create knockout mice, a technology that proved to be essential for the biotechnology industry.⁷⁰ Within a year, techniques for isolating ovine (sheep) and porcine (pig) ESC lines were widely

67. Martin J. Evans & Matthew H. Kaufman, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, 292 NATURE 154 (1981).

68. Gail R. Martin, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Culture in Medium Conditioned by Teratocarcinoma Stem Cells*, 78 PROC. NAT. ACAD. SCI. 7634 (1981).

69. Evans & Kaufman, *supra* note 67; Martin, *supra* note 68.

70. See, e.g., Beverley H. Koller et al., *Germ-Line Transmission of a Planned Alteration Made in a Hypoxanthine Phosphoribosyltransferase Gene by Homologous Recombination in Embryonic Stem Cells*, 86 PROC. NAT. ACAD. SCI. 8927 (1989); Simon Thompson, *Germ Line Transmission and Expression of a Corrected HPRT Gene Produced by Gene Targeting in Embryonic Stem Cells*, 56 CELL 313 (1989); Maarten Zijlstra, *Germ-Line Transmission of a Disrupted β_2 -microglobulin Gene Produced by Homologous Recombination in Embryonic Stem Cells*, 342 NATURE 435 (1989).

known.⁷¹ However, it was not until 1994 that the *Milwaukee Journal* announced that Professor James Thomson at the University of Wisconsin-Madison's primate center had successfully isolated an ESC line in primates.⁷² Thomson understood that his success with primates (rhesus monkeys) meant that isolating a human ESC line was not far off. Indeed, after the *Milwaukee Journal* story, he had a year (until November 4, 1995) to file for a patent or let his discovery pass into the public domain.⁷³ The Wisconsin Alumni Research Foundation (WARF)⁷⁴ submitted a patent application in January⁷⁵ and, three days later, Thomson submitted his findings for scientific publication.⁷⁶

The patent filed on January 20, 1995, by WARF (U.S. Patent Application 08/376,327) made "composition of matter" and "method" claims for primate ESC lines and included three independent claims: Claims 1 and 3 were composition of matter claims while Claim 9 described a method for isolating primate ESC lines.⁷⁷ The composition of matter claims were submitted as follows:

1. A purified preparation of primate embryonic stem cells which (i) is capable of proliferation in vitro culture for over one year, (ii) maintains a normal karyotype . . . through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) will not differentiate when cultured on a fibroblast feeder layer. . . .
3. A purified preparation of primate embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-3 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have [normal] karyotypes.⁷⁸

It is important to note that these claims cover ESC lines from all primates, including humans. This makes Claim 1 very broad given that Thomson's results

71. See, e.g., Jorge A. Piedrahita et al., *On the Isolation Embryonic Stem Cells: Comparative Behavior of Murine, Porcine and Ovine Embryos*, 34 THERIOGENOLOGY 879 (1990).

72. Paul Raeburn, *Embryonic Monkey Cells Isolated*, MILWAUKEE J., Nov. 4, 1994.

73. 35 U.S.C. § 102(b) (2009).

74. It should be noted that the WARF, founded in 1925, serves the same function within the University of Wisconsin system as a traditional Technology Licensing Office within other American universities. Specifically, "The official mission of this private, nonprofit organization is to support scientific research at the UW-Madison. WARF accomplishes this by patenting inventions arising from university research, licensing the technologies to companies for commercialization, and returning the licensing income to the UW-Madison to support further scientific endeavor." *Our History*, WISCONSIN ALUMNI RESEARCH FOUNDATION, <http://www.warf.org/about/index.jsp?cid=26> (last visited Mar. 6, 2011).

75. U.S. Patent Application No. 08/376,327 (submitted Jan. 20, 1995) [hereinafter U.S. Patent Application '327].

76. James A. Thomson et al., *Isolation of a Primate Embryonic Stem Cell Line*, 92 PROC. NAT. ACAD. SCI. 7844 (1995).

77. U.S. Patent Application '327, *supra* note 75.

78. *Id.*

consisted primarily of rhesus monkey ESCs in 1995.⁷⁹ Claim 9 details the method for purifying ESCs and is as follows:⁸⁰

9. A method of isolating a primate embryonic stem cell line, comprising the steps of:
 - (a) isolating a primate blastocyst;
 - (b) isolating cells from the inner cell mass of the blastocyst of (a);
 - (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;
 - (d) dissociating the mass into dissociated cells;
 - (e) replating the dissociated cells on embryonic feeder cells;
 - (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and
 - (g) culturing the cells of the selected colonies.⁸¹

On January 17, 1996, the application was initially rejected.⁸² Susan Dadio, the patent examiner assigned to the Application (08/376,327), initially objected to the independent claims for “reasons of indefiniteness, and all the pending claims were rejected for obviousness on the prior art.”⁸³ Specifically, Dadio claimed that since “there are some traits in common between the cells of Bongso et al.⁸⁴ and those of the applicant here, that the burden is placed on the applicant to demonstrate that there is a nonobvious difference between the cells” and in turn justify the composition of matter claims.⁸⁵ Dadio also argued that “the functioning of the applicant’s method in primates was predictable with reasonable certainty” because of the success with similar methods in a wide range of mammals.⁸⁶ While WARF submitted a response to these critiques, amended the claims, and requested reconsideration, the application was given a final rejection on October 29, 1996.⁸⁷ However, WARF had anticipated this decision and already submitted a continuation-in-part (CIP) application on January 18, 1996, the day after U.S.

79. See Jeanne F. Loring & Cathryn Campbell, *Science and Law: Intellectual Property and Human Embryonic Stem Cell Research*, 311 SCIENCE 1716 (2006).

80. It should be noted that composition of matter claims are generally stronger than method claims because composition of matter claims cover the material itself irrespective of how it has been created or how it is intended to be used. In addition, methods of production or isolation can easily change over time in ways that make existing method patents obsolete. However, Claim 1 of this application was so broad that even if a new isolation method were discovered, anyone who used it would be infringing on this patent as soon as he or she possessed the resulting primate ESC line.

81. U.S. Patent Application ‘327, *supra* note 75.

82. *Applicant Arguments/Remarks Made in an Amendment*, U.S. Patent Application 08/376,327, July 23, 1996, Nicholas Seay.

83. *Id.* at 3.

84. Ariff Bongso, *Fertilization and Early Embryology: Isolation and Culture of Inner Cell Mass Cells from Human Blastocysts*, 9 HUM. REPROD. 2110 (1994);

85. Seay, *supra* note 82 at 4.

86. *Id.* at 6; see also Piedrahita et al., *supra* note 71.

87. *Final Rejection*, U.S. Patent Application 08/376,327, Oct. 29, 1996, Jean Witz.

Patent Application 08/376,327's initial rejection, with identical claims.⁸⁸

WARF's CIP, U.S. Patent Application 08/591,246, was eventually approved and published as U.S. Patent 5,843,780 despite being nearly identical to the previous application.⁸⁹ The only difference was that the first claim no longer contained the assertion that a purified preparation of human embryonic stem cells would "differentiate in the presence of human leukemia inhibitory factor alone," which was by no means the criterion for rejection of the previous application.⁹⁰ While Examiner Brumbak initially rejected the patent on the grounds that the application neglected to specify "the best mode"⁹¹ of the invention through a "representative cell line," WARF successfully argued that because the "procedure taught in the specification [had] repeatedly yielded cell lines with the characteristics cited in the claims"⁹² the "additional information about the testing which had been conducted"⁹³ should be used as an alternative to the specification of a single cell line. Despite the examiner's approval, the director of the patent examining group sent a memorandum attempting "to re-open prosecution" before the patent was granted.⁹⁴ And yet, for reasons that seem more likely to be attributed to bureaucracy than conspiracy, the memo failed to reach the issue control officer before the patent was granted on December 1, 1998.⁹⁵

Earlier that year, Thomson succeeded in purifying human ESCs for the first time. Consequently, WARF filed for a divisional patent application specifying human ESCs within the claims of U.S. Patent Application 08/591,246 just before Thomson submitted his manuscript to *Science* for review, again making the disclosure a patent-paper pair.⁹⁶ WARF's divisional application, U.S. Patent Application 09/106,390, was initially and finally rejected because the examiner believed the evidence provided did not meet the standard of "germ line potency" for a cell line to be designated an ESC.⁹⁷ However, WARF successfully appealed the final rejection by arguing that the art accepted a definition of human ESCs that did not include "germ line potency" because the ESCs described in *Embryonic Stem*

88. In general, CIPs allow inventors to incorporate improvements to their design during the patent application process by refiling and associating the new filing date with all changes to the previous application. However, WARF was able to use this mechanism to essentially refile the original patent and see if a different examiner would be willing to approve it.

89. U.S. Patent No. 5,843,780 (filed Jan. 18, 1996) (issued Dec. 1, 1998).

90. U.S. Patent Application No. 08/591,246 (submitted Jan. 18, 1996).

91. 35 U.S.C. § 112 (2009).

92. *Examiner Interview Summary Record*, U.S. Patent Application No. 08/591,246, Jan. 22, 1998, Brenda Brumbak.

93. Seay, *supra* note 82.

94. *Memorandum*, U.S. Patent Application No. 08/591,246, Nov. 19, 1998, John Doll.

95. *Decision on Petition*, U.S. Patent Application No. 08/591,246, Dec. 1, 1998, Karna Cooper.

96. James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998); U.S. Patent No. 6,200,806 (issued Mar. 13, 2001).

97. *Non-Final Rejection*, U.S. Patent Application No. 09/106,390, Sept. 24, 1999; *Final Rejection*, U.S. Patent Application No. 09/106,390, Jan. 14, 2000, Deborah Clark.

Cell Lines Derived from Human Blastocysts, the article resulting from Professor Thomson's aforementioned manuscript, were considered to be human ESCs by the peer reviewers and editors of *Science* without demonstrating "germ line potency."⁹⁸ WARF was subsequently granted U.S. Patent 6,200,806 on March 13, 2001, and, in turn, commercial rights to all purified human ESCs until 2015.⁹⁹ However, several important events in the history of hESCs began during this appeals process.

Shortly after the 5,843,780 patent was issued in December 1998, WARF licensed exclusive commercialization rights for cardiomyocytes, neural cells, pancreatic islet cells, hematopoietic cells, osteoblasts, and chondrocytes to Geron Corporation.¹⁰⁰ WARF also created a nonprofit, the WiCell Research Institute, to distribute human ESC lines according to the aforementioned licensing agreement as well as future agreements.¹⁰¹ When Geron then attempted to exercise its option to license up to twelve additional cell lines, WARF sued them, challenging Geron's right to exercise the option and implicitly deprive other researchers of access to the additional stem cell types in light of President George W. Bush's restrictions on stem cell research.¹⁰² Before the trial, an agreement was reached in which Geron relinquished its licensing option as well as its exclusivity on the commercial use of hematopoietic cells, osteoblasts, and chondrocytes.¹⁰³ In addition, WiCell and the NIH signed a Memorandum of Understanding that gave the NIH and NIH funded researchers at other noncommercial institutions access to WiCell's human ESC lines as long as they paid a "fee to cover [WiCell's] handling and distribution expenses in supplying these cell lines."¹⁰⁴

98. Thomson et al., *supra* note 96; *Appeal Brief*, U.S. Patent Application No. 09/106,390, Sept. 15, 2000, Carl Schwartz.

99. See Fiona Murray, *The Stem Cell Market: Patents & the Pursuit of Scientific Progress*, 356 NEW ENG. J. MED. 2341 (2007); U.S. Patent No. 6,200,806 (issued Mar. 13, 2001).

100. Geron Corp. had funded much of the research carried out in the Thomson laboratory under a sponsored research agreement with the University of Wisconsin; Brian Vastag, *Suddenly, 64 Stem Cell Lines*, 286 J. AM. MED. ASS'N 1163 (2001); *Stem Cell Lines*, GERON CORPORATION (2006), <http://www.geron.com/technology/stemcell/stemcellines.aspx> (last visited Sept. 24, 2011).

101. Sander Rabin, *The Gatekeepers of hES Cell Products*, 23 NAT. BIOTECH. 817 (2005); Meredith Wadman, *Licensing Fees Slow Advance of Stem Cells*, 435 NATURE 272 (2005).

102. *NIH's Role in Federal Policy: Stem Cell Research*, NAT'L INST. HEALTH, (2006), <http://stemcells.nih.gov/policy/NIHFedPolicy.asp> (last visited Apr. 29, 2010); Antonio Regalo & David P. Hamilton, *How a University's Patents May Limit Stem-Cell Research*, WALL STREET J., July 18, 2006; Vastag, *supra* note 100.

103. Rabin, *supra* note 101.

104. News Release, National Institutes of Health and WiCell Research Institute, Inc., Sign Stem Cell Research Agreement (Sept. 5, 2001). By 2002, the IP and research development landscape around hESCs began to stabilize with the result that it was impossible to perform research on hESCs without NIH funding or a commercial licensing agreement from either WARF or Geron. See Rabin, *supra* note 101. In fact as late as 2005, the "handling and distribution" fee for an NIH-funded academic researcher to use one of WARF's hESC lines was \$5000 and came with a non-distribution clause, making it very hard for some junior faculty to acquire the cells. In addition, commercial licenses ranged from \$75,000 to beyond \$250,000 in addition to annual fees and royalty payments and

Throughout this period, WARF was pursuing another patent, specifically a CIP of U.S. Patent 6,200,806, stemming from Thomson's work on hESC cells.¹⁰⁵ Although the claims in U.S. Patent Application 09/982,637 evolved significantly throughout the review process, including the cancellation of all methods claims due to "double patenting" concerns with U.S. Patent 5,843,780, the resulting claims as approved in U.S. Patent 7,029,913 on April 18, 2006, are noteworthy:

1. A replicating in vitro cell culture of human embryonic stem cells comprising cells which (i) are capable of proliferation in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor, (ii) maintain a karyotype in which the chromosomes are euploid through prolonged culture, (iii) maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) are inhibited from differentiation when cultured on a fibroblast feeder-layer.
2. The preparation of claim 1, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.
3. The preparation of claim 1 wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, and express alkaline phosphatase.¹⁰⁶

These claims furthered WARF's reach by explicitly claiming ownership over a sustainable "in vitro cell culture of human embryonic stem cells"—a fundamental prerequisite for many tissue engineering and regenerative medicine applications.¹⁰⁷ By July 2006, over 300 academic labs and twelve private companies had licensed hESC lines from WARF; but many in academia and industry believed that WARF's functional monopoly on human ESC lines was unhealthy for the advancement of science and for the development of innovative therapeutic companies.¹⁰⁸ As a result, the Public Patent Foundation (PUBPAT) on behalf of the Foundation for Taxpayer and Consumer Rights (FTCP), now called Consumer Watchdog, requested an ex parte reexamination of every claim in U.S. Patents 5,843,780 and 6,200,806 as well as an inter partes reexamination of every claim in U.S. Patent 7,029,913 on the grounds that the aforementioned claims were obvious and therefore should be not be patentable under 35 U.S.C. § 103.¹⁰⁹

potential equity agreements. *See* Wadman, *supra* note 101; Regalo & Hamilton, *supra* note 102.

105. U.S. Patent No. 7,029,913 (issued Apr. 18, 2006).

106. *Id.*

107. *Id.*

108. *See, e.g.*, Loring & Campbell, *supra* note 79; Regalo & Hamilton, *supra* note 102.

109. *Request for Ex Parte Reexamination of U.S. Patent No. 5,843,780*, July 18, 2006, Daniel B. Ravicher, <http://www.pubpat.org/assets/files/warfstemcell/780Request.pdf>; *Request for Ex Parte Reexamination of U.S. Patent No. 6,200,806*, July 18, 2006, Daniel B. Ravicher, <http://www.pubpat.org/assets/files/warfstemcell/806Request.pdf>; *Request for Ex Parte Reexamination of U.S. Patent No. 7,029,913*, July 18, 2006, Daniel B. Ravicher, <http://www.pubpat.org/assets/files/warfstemcell/913Request.pdf>.

While not unusual as a patent litigation strategy among corporations, it was rare to find a consumer group litigating a patent on the basis of its obviousness. The idea for the reexamination came from Dr. Jeanne Loring, Director of the Center for Regenerative Medicine at The Scripps Research Institute, when she learned that WARF expected the California Institute for Regenerative Medicine (CIRM)¹¹⁰ to pay licensing and royalty fees.¹¹¹ She recounted:

I was already working on deriving human ES cell lines, as were several of my colleagues in the field, when I learned about the patents, and I began to worry about what impact this monopoly would have. My concern about the patents grew as it became clear that the patent holder intended to exploit its monopoly, charging for licences to use human ES cells. I started seriously researching patents and came across an article about Dan Ravicher, an attorney who had founded the Public Patent Foundation in New York to challenge patents that threatened the public interest. I called him for advice, and within a month he had become my teacher and partner in the challenge to the patents that we brought in the summer of 2006.¹¹²

Ravicher, an experienced attorney, had a track record of corporate concessions and favorable initial rulings from the U.S.P.T.O. against major patents including Pfizer's Lipitor patent and Microsoft's FAT file system patent.¹¹³ Their case was supplemented by an expert scientific declaration of support stating:

Dr. Thomson deserved the recognition he received for his work relating to human embryonic stem cells because he was able to get the human embryos and financial support needed for such work. He did not, however, make a scientific advance that was surprising to those of us with skill in the art. It was his ability to secure those extremely limited resources that provided him the ability to achieve his accomplishment. Had I or any other stem cell scientist been given human embryos and sufficient funding, we could have made the same accomplishment, because the science required to isolate and maintain human embryonic

110. CIRM is a nonprofit designed to give \$3 billion of California tax revenues in the form of grants for California-based stem cell research established as a result of a statewide vote on Proposition 71, the California Stem Cell Research and Cures Initiative. The CIRM has awarded over \$1 billion in grants since 2006, more than half of which focus on hESCs.

111. Erika Check, *Patenting the Obvious?*, 447 NATURE 16 (2007); Cal. Health & Safety Code § 125291.30 (West 2004).

112. Jeanne F. Loring, *A Patent Challenge for Human Embryonic Stem Cell Research*, NATURE REPORTS STEM CELLS, Nov. 8, 2007, <http://www.nature.com/stemcells/2007/0711/071108/full/stemcells.2007.113.html>.

113. Daniel Ravicher founded PUBPAT in 2003 to challenge patents that he deemed to be restrictive of public freedom. On April 15, 2004, PUBPAT filed a formal request to revoke the patent on Microsoft's FAT File System. (U.S. Patent 5,579,517). On September 30, 2004, the USPTO rejected Microsoft's patent as written, requiring Microsoft to narrow its claims. Similarly, on September 14, 2004, PUBPAT filed a formal request to revoke Pfizer's patent on Lipitor (U.S. Patent 5,969,156). The patent was rejected as written on June 29, 2005, causing Pfizer to relinquish much of its broad claim language.

stem cells was obvious at the time.¹¹⁴

The argument that all three patents should be re-examined and rejected was based on the notion that “each of the claims of [the relevant patents] are invalid for being anticipated by Williams and for being obvious in light of Robertson 1983,¹¹⁵ Robertson 1987,¹¹⁶ and Piedrahita¹¹⁷.”¹¹⁸ Essentially, prior art had already described the cell lines and methods claimed in the WARF patents. It is important to note that while Piedrahita was used in the prosecution of U.S. Patent Application 08/376,327 and was therefore prior art with respect to its CIP (5,843,780), Piedrahita could be used in a reexamination of U.S. Patent 5,843,780 because it “was not applied directly to the rejection of the present claims.”¹¹⁹ On September 29, 2006, the USPTO agreed to re-examine all three patents.¹²⁰

Taking action not in the courts, not even in a legal setting, WARF reacted to the U.S.P.T.O. decision by shaping their behavior towards the scientific community: they voluntarily implemented several new, more generous licensing policies on January 23, 2007.¹²¹ For the first time, WARF allowed firms “to sponsor research at an academic or nonprofit institution without a license, regardless of the location and regardless of the IP rights passing from the research institutions the company.”¹²² This gave firms their first opportunity to perform research on hESCs without making a significant investment. In addition, WARF reduced the fee for obtaining a human ESC line from \$5,000 to \$500, mitigating the financial barrier to researching human ESCs.¹²³ WARF also clarified that the CIRM did “not require a license agreement from WARF” nor did WARF expect any remittance for payments made to the CIRM by grantees.¹²⁴

On March 30, 2007, the U.S.P.T.O. preliminarily rejected 5,843,780,

114. Jeanne F. Loring, *Declaration of Dr. Jeanne F. Loring, Ph.D. in Support of FTCR and PUBPAT Requests*, July 18, 2006, <http://www.pubpat.org/assets/files/warfstemcell/LoringDeclarations.pdf>.

115. TERATOCARCINOMA STEM CELLS 647–83 (Lee M. Silver et al. eds., 1983).

116. TERATOCARCINOMAS AND EMBRYONIC STEM CELLS, A PRACTICAL APPROACH 71–112 (Elizabeth J. Robertson ed., 1987).

117. Piedrahita et al., *supra* note 71.

118. *Request for Ex Parte Reexamination of U.S. Patent No. 5,843,780*, July 18, 2006, Daniel B. Ravicher, <http://www.pubpat.org/assets/files/warfstemcell/780Request.pdf>; *see also* U.S. Patent No. 5,166,065 (issued Nov. 24, 1992).

119. *Ex Parte Reexamination Communication Transmittal Form*, U.S. Patent Application No. 90/008,102, Mar. 30, 2007, Padmashri Ponnaluri.

120. *Reexamination: Granting of Request*, U.S. Patent Application No. 90/008,139, Sept. 29, 2006, Bennett M. Celsa; *Reexamination: Granting of Request*, U.S. Patent Application No. 95/000,154, Sept. 29, 2006, Gary L. Kunz; Ponnaluri, *supra* note 119.

121. Press Release, *Wisconsin Alumni Research Foundation Changes Stem Cell Policies to Encourage Greater Academic, Industry Collaboration*, Wisconsin Alumni Research Foundation (Jan. 23, 2007), http://www.warf.org/news/news.jsp?news_id=209.

122. *Id.*

123. Alisa Opar, *U.S. Tosses Out Patents on Three Wisconsin Stem Cell Lines*, 13 NAT. MED. 519 (2007); Wisconsin Alumni Research Foundation, *supra* note 121.

124. WISCONSIN ALUMNI RESEARCH FOUNDATION, *supra* note 121.

6,200,806, and 7,029,913.¹²⁵ Although these rejections seem to represent three distinct reexamination rulings, the patents were reexamined by a single team of four examiners and each case was assigned to three out of the four. The examiners found that “the method of isolating ES cells in the present claim method is the exact same process taught by [the] Robertson references and [the] Piedrahita reference.”¹²⁶ They also found that “Williams et al. [taught] that the embryos used may be isolated from animals including humans (primate).”¹²⁷ Therefore, the examiners concluded that “one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of [the] Robertson references, [and the] Piedrahita reference with the teachings of Williams et al such that pluripotent ES cells from humans (primate) [could have been] isolated.”¹²⁸ The examiners even went beyond the references supplied by Ravicher and cited U.S. Patent 5,690,926 which claimed “pluripotential stem cells which can . . . be maintained on feeder layers for at least 20 passages or indefinitely,” seemingly making the duration clause in Claim 1 of with U.S. Patent 7,029,913 obvious.¹²⁹ After developing the above conclusions, the examiners preliminarily rejected U.S. Patents 5,843,780, 6,200,806, and 7,029,913 as obvious to someone with “ordinary skill in the art.”¹³⁰

WARF amended each of these patents on May 30, 2007, and continued the reexamination process.¹³¹ It amended U.S. Patents 5,843,780 and 6,200,806 by modifying claim 1 “to recite that the cells are derived from a pre-implantation embryo,” adding the qualifier “capable of proliferation for over one year” to ESCs in Claims 9 and 11, and introducing a new independent Claim 12 along with its dependent Claims 13 and 14 to further specify differences between isolating mouse and human ESCs.¹³² WARF also made the same modification to Claim 1 in U.S. patent 7,029,913 as it did in the previous two patents.¹³³ Beyond straightforward claim recommendations, WARF engaged the examiner’s rejection

125. *Ex Parte Reexamination Communication Transmittal Form*, U.S. Patent Application No. 90/008,139, Mar. 30, 2007, Bennett M. Celsa et al.; *Inter Partes Reexamination Communication Transmittal Form*, U.S. Patent Application No. 95/000,154, Mar. 30, 2007, Gary L. Kunz et al.; *Ex Parte Reexamination Communication Transmittal Form*, U.S. Patent Application No. 90/008,102, Mar. 30, 2007, Padmashri Ponnaluri et al.

126. Ponnaluri et al., *supra* note 119.

127. *Id.*

128. *Id.*

129. Kunz et al., *supra* note 125; U.S. Patent No. 5,690,926 (filed Nov. 25, 1997).

130. 35 U.S.C. § 103(a) (2009).

131. *Applicant Arguments/Remarks Made in an Amendment*, U.S. Patent Application No. 90/008,102, May 30, 2007, Katherine R. Doyle et al., [hereinafter Doyle, ‘102]; *Applicant Arguments/Remarks Made in an Amendment*, U.S. Patent Application No. 90/008,139, May 30, 2007, Katherine R. Doyle et al., [hereinafter Doyle, ‘139]; *Applicant Arguments/Remarks Made in an Amendment*, U.S. Patent Application No. 95/000,154, May 30, 2007, Kathryn R. Doyle et al. [hereinafter Doyle, ‘154].

132. Doyle, ‘102, *supra* note 131; Doyle, ‘139, *supra* note 131.

133. Doyle, ‘154, *supra* note 131.

arguments through claim interpretation and relevant literature as well as turning to the scientific literature to provide strong support for the novel and nonobvious nature of the hESC isolation.¹³⁴ Indeed, they pointed out and supported using written statements from other scientists that “for nearly two decades from the discovery of mouse ES cells, others repeatedly tried and failed to isolate non-murine ES cells, particularly primate/human ES cell lines.”¹³⁵ WARF also argued that the purification methods cited in Robertson’s¹³⁶ and Piedrahita’s¹³⁷ work had only been applied to a handful of mammals and the techniques varied unpredictably across species.¹³⁸ In fact, they argued that, even though Williams proposed the isolation of human ESCs in his scientific paper, neither he nor others were able to extend his technique beyond mice for a period of time.¹³⁹ Turning again to the system of scientific review and publication to support their arguments, the lawyers note that “[t]he level of acclaim in the art for Dr. Thomson’s invention bears witness to the fact that the isolation of primate/human ES cells represented true innovation that was not simply a small step in embryonic stem cell research.”¹⁴⁰ As the response to the office action outlines, Thomson had been the recipient of a number of awards by the scientific community establishing the importance and transformational nature of his scientific work including:

- ❖ The 2005 American Association for the Advancement of Science (AAAS) “Milestones of Science” recognition.
- ❖ The 2006 American Association for Laboratory Animal Science Nathan R. Brewer Scientific Achievement Award for discoveries in the field of embryonic stem cells.
- ❖ The 1999 Golden Plate Award by the American Academy of Achievement in 1999 “recent breakthrough in culturing human embryonic stem cells outside the body.”
- ❖ The 2004 American College of Veterinary Pathologists Outstanding Achievement Award, for his work with embryonic stem cells.¹⁴¹

Based on these repeated forms of validation for nonobvious and groundbreaking work from the scientific community, the examiner found that the “the prior art of record fails to disclose [a] replicating in vitro cell culture of human embryonic stem cells derived from a pre-implantation embryo” and that

134. Doyle, ‘102, *supra* note 131; Doyle, ‘139, *supra* note 131; Doyle, ‘154, *supra* note 131.

135. Doyle, ‘139, *supra* note 131.

136. Robertson (1983), *supra* note 115; Robertson (1987), *supra* note 116.

137. Piedrahita et al., *supra* note 71.

138. Doyle, *supra* note 131.

139. See Robert A. Cherny et al., *Strategies for the Isolation and Characterization of Bovine Embryonic Stem Cells*, 6 REPROD. FERTIL. DEV. 569 (1994); U.S. Patent No. 5,166,065 (issued Nov. 24, 1992).

140. Doyle, ‘102, *supra* note 131, at 5.

141. *Id.* at 6–7.

the preponderance of the evidence of record is quite clear that the instantly claimed replicating in vitro culture of human embryonic stem cells are not obvious because of the highly complex and unpredictable nature of the art of isolating and maintaining embryonic stem cells leading to lack of a reasonable expectation of success. Without a reasonable expectation of success, there can be no *prima facie* case for obviousness.¹⁴²

In this regard the scientific literature and the fanfare that greeted Thomson's research when it was published in *Science* in 1998 provided strong evidence to counter the claim of obviousness, certainly within the scientific community.¹⁴³ As a result of evidence disclosed and adjudicated in the scientific literature rather than the patent system, the examiner withdrew his rejections on the claims of U.S. Patent 7,029,913 and used similar reasoning to restore the other two patents.¹⁴⁴

The consumer group had a right to appeal the reexamination of U.S. Patent 7,029,913 to the Board of Patent Appeals and Interferences (BPAI) through their *inter partes* status, a right they exercised on June 20, 2008.¹⁴⁵ A decision was reached by the BPAI on April 28, 2010, that reversed the examiner in full, potentially invalidating U.S. Patent 7,029,913.¹⁴⁶ The BPAI first tackled the question of "whether Williams described and enabled human embryonic stem cells derived from a pre-implantation embryo."¹⁴⁷ Based on the fact that Williams proposed both the existence of human ESCs and provided two methods for their purification—in essence an experimental path that someone who is of "ordinary skill in the art" could follow to attempt to isolate human ESCs—the BPAI concluded that "Williams described and enabled human embryonic stem cells derived from a pre-implantation embryo, anticipating the subject matter of claim 1."¹⁴⁸ A very distinct conclusion from the one made by the scientific community who first rewarded Thomson's team with his *Science* publication, this anticipation

142. *Inter Partes Reexamination: Detailed Action: Action Closing Prosecution*, U.S. Patent Application No. 95/000,154, Feb. 25, 2008, Bennett M. Celsa et al.

143. Doyle, '102, *supra* note 131; Doyle, '139, *supra* note 131; Doyle, '154, *supra* note 131.

144. *Inter Partes Reexamination: Detailed Action: Action Closing Prosecution*, U.S. Patent Application No. 95/000,154, Feb. 25, 2008, Bennett M. Celsa et al.; *Reexamination: Reasons for Patentability/Confirmation*, U.S. Patent Application No. 90/008,139, Mar. 5, 2008, Bennett M. Celsa et al.; *Reexamination: Reasons for Patentability/Confirmation*, U.S. Patent Application No. 90/008,102, Mar. 5, 2008, Padmashri Ponnaluri et al. It is important to recognize that the reexaminations of U.S. Patents 5,843,780 and 6200806 were ex parte whereas the reexamination of U.S. Patent 7,029,913 was inter partes. Once the examiners ruled on the ex parte cases, the FTCP had no recourse until "a substantial new question of patentability" arose either through discovery of new prior art or a change in the relevant case law. *See* 35 U.S.C. § 302; 35 U.S.C. § 303.

145. *The Foundation for Taxpayer & Consumer Rights v. Wisconsin Alumni Research Foundation*, U.S. Patent Application No. 95/000,154, Apr. 28, 2010, Richard M. Lebovitz et al.; 35 U.S.C. § 315 (2009).

146. Lebovitz et al., *supra* note 145.

147. *Id.*

148. *Id.*

invalidates the claim by making it obvious. The BPAI then examined “whether Hogan’s description of the ES cells derived from germ cells anticipated and claimed the ES cells derived from a pre-implantation embryo.”¹⁴⁹ The Board upheld the examiners withdrawal in this case because they found structural differences between ESCs and ESGs and since ESGs cannot transform into ESCs, there was “no evidence that Hogan’s embryonic stem cells could be converted into ES cells derived from a pre-implantation embryo.”¹⁵⁰

In their final statement, the BPAI then criticized the examiners’ threshold for “obviousness,” stating that having a “reasonable expectation of success” is far more stringent than the “obvious to try” threshold set by the Supreme Court.¹⁵¹ In 1995, the effective filing date of U.S. Patent 7,029,913, isolating human ESCs would certainly have been “obvious to try.”

The decision, as it stood in 2010, countered the received wisdom of the scientific community which has made no attempt to regard the Thomson publication as anything other than a scientific landmark, even while disagreeing with and protesting the execution of the licensing rights by WARF.¹⁵² Indeed, this view in the scientific community was captured as early as 1999 with the announcement in *Science* that hESCs were the “Breakthrough of the Year,” commenting that

in a technological breakthrough that triggered a burst of research and a whirlwind of ethical debate, two teams of researchers announced that they had managed to prolong the moment of cellular youth. They kept embryonic and fetal human cells at their maximum potential, ready to be steered into becoming any cell in the body.¹⁵³

It is important to note that the patent decision is not final; WARF can either amend its claims, gather new evidence to reopen patent prosecution, or request a rehearing with the BPAI to address its new rejection claims.¹⁵⁴ In light of the disagreement between the scientific community and the patent system, it would not be surprising if the decision remained controversial.

149. *Id.*

150. *Id.*

151. *KSR v. Teleflex*, 550 U.S. 398 (2007); Lebovitz et al., *supra* note 145.

152. Thomson also received numerous awards from outside the scientific community including in 2001, a profile in *TIME* magazine as one of the doctors “who [is] changing our world.” *America’s Best Science & Medicine*, *TIME*, August 20, 2001, at cover. Calling him “The man who brought you stem cells,” *TIME* recognized Thomson as the scientist who had first isolated human embryonic stem cells. Thomson was also inducted into the Biotech Hall of Fame in 2001 for work that had “set the stage for a revolution in medicine and science.” *Biotech Recognizes the Year’s Best*, BURRILL & COMPANY (Oct. 11, 2001) http://www.burrillandco.com/news-263-Biotech_Recognizes_the_Year’s_Best.html.

153. Gretchen Vogel, *Breakthrough of the Year: Capturing the Promise of Youth*, 286 *SCIENCE* 2238 (1999).

154. Lebovitz et al., *supra* note 145.

C. Publications & Patents in HIV-AIDS

The discovery of the HIV-AIDS virus provides a canonical example of the tight coupling between the patent system and the scientific community with its complexity of norms, practices, and modes of self-governance and one in which the coupling is more synchronous than the stem cell case. The interaction was initiated by the scientific discoveries made and patents filed by Dr. Robert Gallo of the United States and Dr. Luc Montagnier of France from 1983 to 1984. Prior to that time on June 5, 1981, the U.S. Centers for Disease Control and Prevention (CDC) published an article in its *Morbidity and Mortality Weekly Report* concerning the deaths of five previously healthy men to *Pneumocystis carinii* pneumonia (PCP).¹⁵⁵ While, at the time, this was regarded as an epidemiological curiosity, as PCP had historically affected only the most immunocompromised individuals, we now know this marked the beginning of the AIDS epidemic. By August 1982, just 15 months later, there had been 470 documented cases and 184 AIDS-related deaths.¹⁵⁶ This statistic presented a clear and growing need for the biomedical research community to identify the cause of AIDS.¹⁵⁷ While HIV was discovered to be the cause of AIDS less than a year later, an international debate over the discovery lay unresolved for nearly a decade and in its resolution not only the matter of scientific priority was adjudicated, but also patent ownership and validity.¹⁵⁸

Dr. Robert Gallo, then chief of the Laboratory of Tumor Cell Biology at the National Cancer Institute, was an expert in retrovirology. In the early 1980s, his group had isolated the first two human retroviruses, human T-cell leukemia virus-1 (HTLV-1) and human T-cell leukemia virus-2 (HTLV-2).¹⁵⁹ It was no surprise then that Dr. Gallo was the first to notice similarities between the transmission, cellular pathology, and epidemiological origins of AIDS and HTLV-1, observations that led him to hypothesize that AIDS was caused by a retrovirus thought to be a lymphotropic retrovirus found in human T-cell cultures.¹⁶⁰ While his initial experiments linking HTLV-1 to AIDS were unsuccessful, and therefore unpublished, his retrovirus theory spread quickly throughout the research community.¹⁶¹ By the end of 1982, Dr. Luc Montagnier, then head of the Viral

155. Michael S. Gottlieb et al., *Pneumocystis Pneumonia—Los Angeles*, 30 MORBIDITY & MORTALITY WKLY. REP. 250 (1981).

156. Jean L. Marx, *New Disease Baffles Medical Community*, 217 SCIENCE 618 (1982).

157. *Id.* at 621.

158. Daniel S. Greenberg, *Resounding Echoes of Gallo Case*, 345 LANCET 639 (1995).

159. Vaniambadi S. Kalyanaraman et al., *A New Subtype of Human T-cell Leukemia Virus (HTLV-II) Associated with a T-cell Variant of Hairy Cell Leukemia*, 218 SCIENCE 571 (1982); Bernard J. Poiesz et al., *Detection and Isolation of Type C Retrovirus Particles from Fresh and Cultured Lymphocytes of a Patient with Cutaneous T-cell Lymphoma*, 77 PROC. NAT. ACAD. SCIENCE 7415 (1980).

160. Robert C. Gallo, *Historical Essay: The Early Years of HIV/AIDS*, 298 SCIENCE 1728 (2002).

161. *Id.*; Luc Montagnier, *Historical Essay: A History of HIV Discovery*, 298 SCIENCE 1727 (2002).

Oncology group at the Pasteur Institute, had decided to test Dr. Gallo's hypothesis.¹⁶²

Dr. Montagnier was advantageously positioned to test Dr. Gallo's hypothesis because his Viral Oncology group had been using Interleukin-2 (also discovered by Gallo) to culture T lymphocytes from cancer patients for years.¹⁶³ This allowed Dr. Montagnier and his colleagues to seek out lymphotropic retroviruses in human T-cell cultures which they began doing on January 3, 1983.¹⁶⁴ By February 1983, the French group had isolated a novel T-lymphotropic retrovirus, which they later named Lymphadenopathy Associated Virus (LAV).¹⁶⁵ This discovery was published alongside similar, but less successful, efforts from Dr. Gallo's group¹⁶⁶ and Dr. Myron Essex's group¹⁶⁷ at Harvard University in May of the same year.¹⁶⁸ Further research by Montagnier's group elucidated a second, more aggressive class of retroviruses, Immune Deficiency Associated Viruses (IDAVs).¹⁶⁹ During the summer and fall of 1983, acting in response to a request of Gallo's from April 25, 1983, Montagnier sent what he thought were LAV samples under the condition that the samples would not be used for commercial or industrial purposes.¹⁷⁰ However, it was later discovered that these samples were actually heavily contaminated—a fact that would add significant confusion to the ensuing legal and political turmoil.¹⁷¹

By August 1983, Montagnier's group had developed a diagnostic test against retroviral antibodies in the bloodstream using a LAV sample similarly and unknowingly contaminated with LAI.¹⁷² Subsequently, the group filed a patent application for this test in the United Kingdom on September 15, 1983, under Patent Application Number No. 8,324,800 and in the United States on December

162. *Id.*

163. *Id.*; Doris Anne Morgan et al., *Selective in Vitro Growth of T Lymphocytes from Normal Human Bone Marrows*, 193 SCIENCE 1007 (1976).

164. Montagnier, *supra* note 161.

165. Françoise Barré-Sinoussi et al., *Isolation of a T-lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)*, 220 SCIENCE 868 (1983).

166. Edward P. Gelmann et al., *Proviral DNA of a Retrovirus, Human T-cell Leukemia Virus, in Two Patients with AIDS*, 220 SCIENCE 862 (1983).

167. Myron Essex et al., *Antibodies to Cell Membrane Antigens Associated with Human T-cell Leukemia Virus in Patients with AIDS*, 220 SCIENCE 859 (1983).

168. See Stanley B. Prusiner, *Historical Essay: Discovering the Cause of AIDS*, 298 SCIENCE 1726 (2002).

169. Gallo, *supra* note 160; Montagnier, *supra* note 161.

170. Institut Pasteur v. U.S., 10 Cl. Ct. 304 (1986), *rev'd*, 814 F.2d 624 (Fed. Cir. 1987), *appeal dismissed per stipulation*, No. 730-85C (Cl. Ct. Dec. 4, 1987); Howard L. Singer, Institut Pasteur v. U.S.: *The AIDS Patent Dispute, the Contract Disputes Act and the International Exchange of Scientific Data*, 15 AM. J.L. & MED. 439 (1989).

171. Simon Wain-Hobson, *LAV Revisited: Origins of the Early HIV-1 Isolates from Institut Pasteur*, 252 SCIENCE 961 (1991).

172. Catalina Norman, *Patent Dispute Divides AIDS Researchers*, 230 SCIENCE 640 (1985); Wain-Hobson, *supra* note 171.

5, 1983, under Application No. 558,109.¹⁷³ In March 1984, Gallo's group definitively showed that AIDS was caused by a retrovirus using the same LAV/LAI contaminated strain as Montagnier's group, although under the impression they were using their own previously isolated HTLV-III strain.¹⁷⁴ Like Montagnier's group, they filed a patent application for an AIDS diagnostic kit using HTLV-III (unknowingly contaminated with LAI) on April 23, 1984, before publishing their work in *Science* (in other words their disclosure strategy was a patent-paper pair).¹⁷⁵ Unlike Montagnier's group whose application was delayed during review, Gallo's patent application was approved and the Secretary of Health and Human Services (HHS) was issued U.S. Patent No. 4,520,113 on May 28, 1985.¹⁷⁶ Gallo's patent had four independent claims: Claim 1 described a method for detecting AIDS-specific antibodies while Claims 7, 9, and 10 described specific implementations of a diagnostic test kit for AIDS based on these antibodies.¹⁷⁷ Specifically,

1. A method for the detection of antibodies which specifically bind to antigenic sites of the Human T-cell Leukemia Virus-III (HTLV-III) virion in samples of the body fluids of patients with Acquired Immune Deficiency Syndrome (AIDS) or risk of AIDS (pre-AIDS) which comprises contacting HTLV-III or fractions thereof said sample with antibodies from human sera taken from AIDS patients and measuring the formation of antigen-antibody complexes by strip radioimmunoassay based on Western Blot technique or ELISA (an enzyme-linked immunosorbent assay) or indirect immunofluorescent assay.

7. A diagnostic test kit for detection of AIDS specific antibodies comprising a compartmented enclosure containing multiwell plates which are coated with HTLV-III and ELISA materials for enzyme detection consisting of normal goat serum and peroxidase, labeled goat antihuman IgG and a color change indicator consisting of orthophenylene diamine and hydrogen peroxide in phosphate citrate buffer.

9. A diagnostic AIDS specific test kit for detecting AIDS specific antibodies using the Western Blot technique comprising a container, a cover, and therein containing a nitrocellulose sheet and a polyacrylamide slab gel and sodium dodecylsulfate, and additionally surfactants as well as pH modifiers and bovine serum albumin and the Fab fragment of normal human IgG, and Western Blot analysis container which contains a supply of dilute normal

173. *Institut Pasteur*, 10 Cl. Ct. at 306.

174. Robert C. Gallo et al., *Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS*, 224 *SCIENCE* 500 (1984); Norman, *supra* note 172; Mikulas Popovic et al., *Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS*, 224 *SCIENCE* 497 (1984); Mangalasseril Sarnagadharan et al., *Antibodies Reactive with Human T-lymphotropic Retroviruses (HTLV-III) in the Serum of Patients with AIDS*, 224 *SCIENCE* 506 (1984); Jorg Schupbach, *Serological Analysis of a Subgroup of Human T-lymphotropic Retroviruses (HTLV-III) Associated with AIDS*, 224 *SCIENCE* 503 (1984).

175. Wain-Hobson, *supra* note 171.

176. U.S. Patent No. 4,520,113 (filed April 23, 1984) [hereinafter referred to as the '113 Patent]; *Institut Pasteur*, 10 Cl. Ct. at 306.

177. *Id.*

goat serum and I.sup.125 labeled goat antihuman immunoglobulin and a source of HTLV-III.

10. An AIDS specific test kit for detecting antibodies using the indirect immunofluorescence assay comprising a compartmental container, human test serum containing HTLV-III, phosphate buffered saline, and fluorescein-conjugated goat antiserum IgG.¹⁷⁸

As one would expect, these claims closely mirrored those established in Gallo's 1984 *Science* papers. Specifically, Gallo describes "an immunological screening of serum samples from patients with AIDS and pre-AIDS and from individuals at increased risk for AIDS" using "autoradiography after incubation of . . . strips" prepared by either ELISA or "by SDS-polyacrylamide gel electrophoresis and transferred to a nitrocellulose sheet by the electrophoretic blotting (Western) technique."¹⁷⁹ While less important than the independent claims, the dependent claims of U.S. Patent No. 4,520,113 also closely matched Gallo's findings. For example, Claim 3 is "the method according to claim 1 wherein a 41,000 m.w. fraction of HTLV-III is utilized."¹⁸⁰

In response to accusations by the Pasteur Institute that the U.S. Patent Office rushed Gallo's patent through the approval process while delaying Montagnier's patent, the U.S. Patent Office claimed that "Pasteur had the misfortune of having their patent application processed by an extremely busy office whereas the U.S. had the good fortune of having its applications assigned to an office with a lighter work load."¹⁸¹ As a result of the dispute, by August 1985, the Pasteur Institute initiated a dialogue with HHS regarding the patent situation. Dr. Raymond Dedonder, then director of the Pasteur Institute, made several demands: that the Pasteur Institute be named a coholder on the patent, acknowledgment that Montagnier's group was the first to discover HIV and apply for the diagnostic patent, and a guarantee that Genetic Systems Corporation (the company that held the Pasteur license to the AIDS diagnostic) be allowed in the U.S. market without infringing on the U.S. government's patent.¹⁸² In other words, in adjudicating the claim over patent priority and ownership, the French scientists invoked a determination of priority generated in the Republic of Science and grounded in disclosure in a scientific publication. HHS replied to Dedonder on August 20, 1985, requesting documentation supporting his demands in the following letter:

This letter is in the spirit of affirming our resolution and our common goal in working together with you and the Pasteur Institut in overcoming AIDS. At our meeting of August 7, and your meeting of August 6, with

178. *Id.*

179. Popovic et al., *supra* note 174.

180. '113 Patent, *supra* note 176.

181. Singer, *supra* note 170 at 445 n.36.

182. *Institut Pasteur*, 10 Cl. Ct. at 306; Norman, *supra* note 176; Catalina Norman, *AIDS Priority Fight Goes to Court*, 231 *SCIENCE* 11 (1986).

members of the department, a number of extremely serious representations were made. We would appreciate your providing us with the representations and supporting documentation in as much detail as you choose, in writing, so that we may consider them on a timely basis with respect to your September 6 time frame. We can assure you that consideration will be thorough and fair to all concerned.¹⁸³

Despite Dedonder's same-day reply, the HHS determined that Dedonder's claims were unjustifiable and that patent remained valid as described in their September 6, 1985, letter:

This letter refers to your discussions with me and staff of the Department on August 6 and 7 and the material you subsequently submitted to me in support of your position on the Institut Pasteur applications for a patent on a diagnostic test for Acquired Immune Deficiency Syndrome (AIDS) antibodies

. . . We have carefully reviewed the written material you furnished and the oral representations made during your visit to the Department. Based on that information and our own review of the laboratory records and other documents relating to this matter, we can find no basis to support your position that U.S. Patent No. 4,520,113 is invalid or that the actions you requested be taken by the Department are warranted

. . . Nevertheless, we are concerned that this issue not stand in the way of further cooperation between this Department and the Institut Pasteur, as well as with research scientists throughout the world, towards the cure and prevention of this dreaded disease. We stand ready to discuss these and related matters with you and to review any other materials you may wish to submit relating to this issue.¹⁸⁴

As a result, the Pasteur Institute filed suit against the United States in the U.S. Claims Court on December 12, 1985 (*Institut Pasteur v. The United States* 1986). The Pasteur Institute's central claim was that Dr. Gallo's group used samples Montagnier's group had sent in the development of the American diagnostic system (*Institut Pasteur v. The United States* 1986). This use breached the contract signed by Dr. Mikulas Popovic, a researcher in Gallo's group, on September 23, 1983, expressly forbidding the use of Montagnier's samples for commercial or industrial purposes.¹⁸⁵ As relief, the Pasteur Institute sought acknowledgment that

183. Letter from C. McClain Haddow to Dr. Raymond Dedonder (Aug. 20, 1985) (noted in *Institut Pasteur*, 10 Cl. Ct. at 307).

184. *Id.*

185. Part of this agreement is reproduced below:

Virus LAV1 produced by human T-lymphocytes n degrees I-232 deposited on July 15th, 1983 at the C.N.C.M. The virus LAV1 will be available subject to acceptance of the three following conditions:

- 1) The virus will be used by the recipient himself, exclusively, and only for the following research purposes (fill in): a) *biological*; b) *immunological* and c) *nucleic acid studies*.
- 2) It will not be used for any industrial purpose without the prior written consent of the Director of the Pasteur Institute.

Montagnier's group was the first to discover the retroviral cause of AIDS, records of HHS's profits and royalties from the AIDS diagnostic, all future royalties from the AIDS diagnostic, and over one million dollars in damages beyond interest and legal fees.¹⁸⁶ The court found that the case fell under the Contract Disputes Act (CDA) and since the Pasteur Institute failed to submit a certified damaged claim "to an HHS contracting officer and therefore did not obtain a decision or failure to decide" from the HHS regarding that claim, a prerequisite to claims court jurisdiction, as required by the CDA, the case was dismissed on May 22, 1986.¹⁸⁷ The Pasteur Institute appealed the case to the United States Court of Appeals for the Federal Circuit who reversed and remanded the claims court decision, holding that the breach of contract claim should not have been dismissed solely due to failure to comply with the procedures outlined in the CDA.¹⁸⁸

In a decision that was to reaffirm the intertwined systems of publication and patenting, three weeks after the Appeals decision in March 1987, President Reagan of the United States and President Chirac of France announced a settlement in the case. It allocated each side forty percent of the future royalties, and gave twenty percent to the World AIDS Foundation. However, this was not simply a patent settlement; the decision also recognized Montagnier and Gallo as codiscoverers of the retrovirus that causes AIDS, and renamed the retrovirus in question HIV.¹⁸⁹ By linking the ownership of the patent (more specifically claims on returns from the patent) to claims on scientific priority, the two leaders recognized the importance of the scientific community in adjudicating the production of new knowledge. The creation of this settlement was due in large part to Dr. Jonas Salk,¹⁹⁰ who not only created and funded the World AIDS Foundation through the agreement but also facilitated correspondence between Gallo and Montagnier in the months leading up to the settlement.¹⁹¹ This correspondence allowed the

3) The recipient agrees not to disseminate the virus in any form (to companies or other scientists) without the prior written authorization of the Director of the Pasteur Institute.

The recipient is also informed that the virus LAV1 may constitute a potential biohazard.
I AGREE TO ACCEPT *two samples of virus LAV1 (Mkt-1B and JBB LAV) and anti-interferon sheep serum (2ml)* UNDER THE CONDITIONS LISTED ABOVE.

DATE September 23, 1983

NAME Dr. Mikulas Popovic

Institut Pasteur, 10 Cl. Ct. at 306.

186. *Id.* at 308.

187. Contract Disputes Act, 41 U.S.C. §§ 601–605 (1982); *Institut Pasteur*, 10 Cl. Ct. at 311.

188. *Pasteur v. U.S.*, 814 F. 2d 624, 628 (Fed. Cir. 1987).

189. Colin Macilwain, *France Wins Larger Share of Patent Royalties After AIDS Test Dispute*, 370 NATURE 85 (1994); Singer, *supra* note 170.

190. Salk was the discoverer of the polio vaccine and then Director of the Salk Institute for Biological Studies. He believed "it was not in the best interest of either science or the public to have [the dispute] linger" as it was "an unhealthy state for all concerned." *Medicine: Yalta of AIDS*, TIME, Apr. 13, 1987.

191. Charles Marwick, *Cooler Heads (of State) Prevail. . . Voila, French-American HIV Test Accord*, 258 J. AM. MED. ASS'N. 3482 (1987).

three scientists to develop a chronology of AIDS research and reach the agreement that the two research groups codiscovered HIV, a scientific dispute whose resolution was prerequisite to the broader legal agreement that underscores the intertwined institutions of publishing and patenting particularly for research whose intellectual foundations also has strong commercial consequences.¹⁹²

Salk's efforts seemingly put an end to a transatlantic feud; the two men eventually coauthored the aforementioned chronology of AIDS research.¹⁹³ However, in 1990, controversy returned to Dr. Gallo when an investigative reporter named John Crewdson wrote a scathing piece in the *Chicago Tribune* alleging that Gallo's group had intentionally stolen Dr. Montagnier's retroviral strains for commercial purposes.¹⁹⁴ What followed was a complex series of investigations by the NIH's Office of Scientific Integrity (OSI) into Gallo's research during the critical years of 1983 and 1984 as ordered by Representative John Dingell, a Democrat from Michigan.¹⁹⁵ In addition, the National Academy of Sciences and the Institute of Medicine nominated a panel of "expert but disinterested parties" at the NIH's request, led by Yale University biochemist Professor Frederic Richards, to serve as an advisory body to the OSI investigation.¹⁹⁶ In late 1993, with considerable dissention among the various involved parties, the Office of Research Integrity (ORI) dropped Gallo's case because it felt it could not meet the burden of proof.¹⁹⁷ Although the four-year investigation into Dr. Gallo failed to find him responsible for misconduct, it did unequivocally bring out the fact that he used Montagnier's retroviral strains to perform many of his seminal experiments.¹⁹⁸

As much of the American claim to the diagnostic patent rested on the notion that Gallo had developed the American diagnostic test without the use of French retroviral strains, those interested in property rights defined within the patent system once again looked to the scientific community for guidance. The Pasteur Institute was on the verge of reopening litigation with the United States government if the royalties were not adjusted accordingly.¹⁹⁹ In July 1994, the NIH settled before a suit was even filed and the Pasteur Institute secured sixty percent of future AIDS diagnostic royalties, leaving twenty percent each for the HHS and World AIDS Foundation.²⁰⁰ The method of resolution in this case is

192. *Id.*

193. Robert C. Gallo & Luc Montagnier, *The Chronology of AIDS Research*, 326 NATURE 435 (1987).

194. Jon Cohen & Martin Enserink, *Nobel Prize in Physiology or Medicine: HIV, HPV Researchers Honored, but One Scientist Is Left Out*, 322 SCIENCE 174 (2008).

195. Barbara J. Culliton, *Inside the Gallo Probe*, 248 SCIENCE 1494 (1990).

196. *Id.*

197. Christopher Anderson, *ORI Drops Gallo Case in Legal Dispute*, 262 SCIENCE 981 (1993).

198. *Id.*; Jon Cohen, *Stormy Weather Ahead for OSI's Gallo Report*, 255 SCIENCE 914 (1992); Jon Cohen, *HHS: Gallo Guilty of Misconduct*, 259 SCIENCE 168 (1993).

199. Macilwain, *supra* note 189.

200. *Id.*

remarkable as it was initiated by, and reflected, a change in the (never formalized) view of the scientific community regarding publication (rather than patent) priority and claims of legitimacy. Beyond that, this change was negotiated by leaders of national scientific institutions—by scientists, not lawyers.²⁰¹ Together, these resolution mechanisms demonstrate that the underlying science is central to the political and economic levers that traditionally control patent litigation.²⁰²

III. CONCLUSIONS

In common discourse regarding the role of commercial pressures and, in particular, intellectual property protection on scientific research, it is commonplace to assume that scientific practices are impacted by commercial ones rather than the other way around. But, in fact, the two are interrelated. They share common features and also interact with one another, shaping the practice of law as well as the practice of science.

This paper has outlined the common features between the legal institution of patent protection and also the institution often referred to as the Republic of Science. Both are institutions designed to reward the generation of ideas and innovations as well as provide a means to promote disclosure and wider dissemination. Each operates with similar features including excludable rights (prevention of commercialization by patents and security of priority and attribution by science), disclosure requirements (to obtain the rewards from each system requires a form of publication of the ideas), and a minimum inventive step (requiring novelty and significance in order to generate a reward). In addition, each shares various points of discretion that can evolve dynamically as well as be tailored for specific environmental circumstances.

Beyond these common features, and perhaps because of them, the two institutions interact in ways that are complementary. This is especially true with regard to their dual aims of promoting disclosure and assigning priority. Both conceptually and in our specific examples, we demonstrate that the disclosure requirements in one system can enable additional disclosures in the other, but this also carries the consequence that stringent requirements in one system may cause innovators to opt out of both. This also means that reforms to enhance openness

201. *Id.*

202. While the patent dispute between the United States and France was resolved, there continues to be significant uncertainty as to whether Gallo knowingly used Montagnier's retroviral strains. Although the two researchers seem to have buried the hatchet, as demonstrated in their amicable coauthorship in 2002, the Nobel Assembly had the last word on the controversy: fourteen years after the final settlement, Montagnier and his colleague Dr. Barré-Sinoussi were each awarded a quarter of the 2008 Nobel Prize for Physiology or Medicine for their "discovery of the human immunodeficiency virus." See Cohen & Enserink, *supra* note 194. Notably, Gallo was not only absent from the podium, but the press release as well. See The Nobel Assembly, *The Nobel Prize in Physiology or Medicine 2008*, Press Release, Oct. 6, 2008, http://nobelprize.org/nobel_prizes/medicine/laureates/2008/press.html.

and disclosure in one system may well impact the operation of the other. More subtly, we propose and document with two comprehensive examples—the interrelationship of the patent system and the Republic of Science—beyond disclosure. We demonstrate that the adjudication of claims of novelty, analysis of priority, and the evaluation of usefulness within the Republic of Science have a critical impact on decisions made ostensibly within the patent system. Thus, as we consider the patent crisis, and the role of the courts in solving it, we must consider the surprising influence of the scientific community in shaping legal practice.