

A FALLACY OF THE COMMONS IN BIOTECH PATENT POLICY

By David E. Adelman[†]

TABLE OF CONTENTS

I.	PATENT POLICY AND ECONOMICS	989
A.	The Legal Debate over Patent Scope.....	990
B.	Biotech Patent Data and Qualitative Surveys.....	997
C.	The Divergence of Legal Theory and Biotech Patenting	1001
II.	HUMAN GENETICS AND BIOTECH INNOVATION	1004
A.	Complexity in the Biomedical Sciences.....	1006
B.	Implications for Innovation in the Biomedical Sciences	1015
III.	THE INTERPLAY BETWEEN BIOMEDICAL SCIENCE AND BIOTECH PATENTING	1018
A.	The Open Frontier of Biomedical Science and the Public Commons	1020
B.	Scientific Factors Mitigating the Detrimental Limits on Access to Patented Upstream Biotechnologies.....	1023
1.	<i>The NF-κB Patent</i>	1024
2.	<i>The CD34 Antigen Patent</i>	1026
IV.	CONCLUSION	1029

Fears that the recent proliferation of biotech patents is undermining scientific norms and threatening innovation dominate the debate over biotech patent policy. Chief among these issues are protection of the public information commons and concerns about emerging “patent anticommons.”¹ Yet, legal commentators have been surprisingly indifferent to whether the traditional model of the public commons accurately reflects the conditions of innovation in the biomedical sciences. This omission proves to be a critical one, for it obscures a central fallacy—that the com-

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[†] Associate Professor, Rogers College of Law, University of Arizona. For their helpful suggestions and advice, I would like to thank Graeme Austin, John Barton, Mark Lemley, Greg Mandel, Toni Massaro, Carol Rose, and Ted Schneyer; any errors are of course my own.

1. The standard model for the public commons is an area that is vulnerable to over-exploitation by multiple actors because none of them bears the full impact of poor management. Examples include public lands and bodies of water. By contrast, a patent anticommons impedes development because narrow patent rights are dispersed among different entities too broadly, creating conditions under which no single entity has access to the technology needed to conduct research and development. See Rebecca S. Eisenberg, *A Technology Policy Perspective on the NIH Gene Patenting Controversy*, 55 U. PITT. L. REV. 633, 640 (1994); Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698 (1998).

mons for biomedical science is finite and congested. This often implicit presumption is contradicted by the overabundance of research opportunities created by recent advances in genomics (and other biotech fields), which have transformed biomedical science into an unbounded resource. The uniquely open-ended nature of biomedical science requires a reassessment of how patenting affects biotech research and innovation. Contrary to most legal scholarship, this reappraisal leads to the conclusion that the threats to biomedical innovation posed by biotech patenting are generally modest.

The principal gap in the literature on biotech patent policy centers on legal scholars' failure to examine the interplay between the underlying science and patent policy. Indeed, the science at the heart of the biotech revolution is conspicuously absent from the current debate over biotech patent policy. To the extent that science is considered, it is either filtered through an economic lens or treated generically.² Typically, unique features of biotech science are important only insofar as they affect the dynamics of innovation, such as whether biotechnology evolves discretely or cumulatively.³ More often, legal commentators have focused their attention, often quite understandably, on the protection of scientific norms, such as communalism and free access to data, which are even further removed from the science itself.⁴ Little, if any, of this discourse considers how the practical limits, specific research tools, and technical details of biomedical science shape patent strategy and incentives.⁵

The hyperbole surrounding advances in biotechnology, particularly in genomics and other "omic" sciences, contributes to the superficial treatment of biotech science in the legal policy debate. Overly optimistic claims obscure the technical barriers and experimental uncertainties that

2. See, e.g., Robert P. Merges & Richard L. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 880 (1990).

3. *Id.* at 880-84. In particular, while Merges and Nelson argue that issues of patent policy, such as patent scope, "depend on the nature of the technology," they limit their consideration to "the relationship between technical advances in the industry, and the extent to which firms license technologies to each other." *Id.* at 843.

4. Arti K. Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77, 90-92 (1999); Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 289, 289 (2003).

5. Economic data are similarly missing from the debate, although recent studies are beginning to have an impact. See, e.g., John P. Walsh et al., *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, in PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285 (Wesley M. Cohen & Stephen A. Merrell eds., 2003).

continue to plague biotech research and development.⁶ Most importantly, this rosy vision hides the disparity that exists between the power of biotech methods to generate data, such as genome sequences, and to produce effective medical procedures and drugs. Research employing biotech methods has produced vast quantities of genetic data, which are often useful research tools (for example, drug targets and genetic probes), but the translation of this knowledge into new products has been far less impressive.⁷ This dichotomy, when layered onto the complexity of biological processes themselves, has created an environment in which research opportunities far exceed the capacities of the scientific community. It is this basic dynamic that makes biotech science, in important respects, an effectively unbounded, uncongested common resource.⁸

The debate over biotech patent policy has favored economic theorizing that overlooks the defining characteristics of biomedical science that influence biotech patenting. Legal commentators have proposed numerous theories on patent scope and strategies for mitigating the negative impacts of patenting on biomedical innovation.⁹ Contrasting proposals range from

6. The significance of the scientific barriers should not be underestimated, and is best illustrated by the declining rate of new drug development over the past decade, despite increased spending (and patenting) by the public and private sectors. See FOOD & DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 2 (2004), available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>; Richard S. Cooper & Bruce M. Psaty, *Genomics and Medicine: Distraction, Incremental Progress, or the Dawn of a New Age?*, 138 ANNALS INTERNAL MED. 576, 577 (2003); Robert F. Service, *Surviving the Blockbuster Syndrome*, 303 SCIENCE 1796, 1799 (2004) (“The plain truth is that many of the most dramatic scientific advances that have recently been made in the lab have not transformed medical care.” (quoting FDA Commissioner Mark McClellan)).

7. Jenifer Couzin, *NIH Dives into Drug Discovery*, 302 SCIENCE 218, 219 (2003) (describing how drug companies are “barely dipping their toes into the ‘data dump’ that is the human genome sequence”); Service, *supra* note 6, at 1799.

8. In other contexts, particularly environmental regulation, property theorists have recognized that commons problems do not emerge until a commons becomes “congested,” that is, the number of users rises beyond the point of sustainable exploitation of the resource. See Carol Rose, *Rethinking Environmental Controls: Management Strategies for Common Resources*, 1991 DUKE L.J. 1, 5-7. The distinction I make here is a simple variation on this basic insight, with the proliferation of patents restricting access to intellectual resources taking the place of the mounting numbers of resource extractors in the typical tragedy of the commons scenario.

9. See, e.g., John H. Barton, *Non-Obviousness*, 43 IDEA 475 (2003); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1040-41 (1989); Maureen A. O'Rourke, *Toward A Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177 (2000); Arti K. Rai, *Engaging the Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM.

arguments that biotech patents should have narrow scope¹⁰ to claims that federal agencies, such as the National Institutes of Health (NIH), should be empowered to protect biotech innovation from incipient patent anti-commons.¹¹ One of the more provocative proposals has argued for an eclectic approach premised on a technology-specific synthesis of patent policy, which maintains that biotech patents should be both broader and fewer in number.¹²

The simple economic narratives of the legal theories on biotech patenting starkly contrast with the conflicting messages of empirical studies. For example, contrary to the fears of many legal commentators, there are few signs that biotech patenting has impeded biomedical innovation.¹³ Other studies have found that the relationship between patent policy and innovation is more nuanced and less predictable than anticipated.¹⁴ On the other hand, some evidence suggests that broad patents on upstream discoveries have the potential to impede research.¹⁵ In short, few of the predictions made or the solutions advocated by legal scholars are borne out consistently by empirical studies of biotech patenting. I argue that the dynamics created by the uncongested, open-ended status of biomedical science account for much of this divergence.

This Article proceeds in three parts. Part I provides a brief overview of the current debate over patent scope and evaluates the available data on biotech patenting. Part II explains the central features of biomedical science that are relevant to patent policy, paying particular attention to the roles of important research tools. I identify two classes of research tools,

L. REV. 1035 (2003); Lawrence M. Sung, *On Treating Past as Prologue*, 2001 U. ILL. J.L. TECH. & POL'Y 75.

10. Merges & Nelson, *supra* note 2, at 915.

11. Heller & Eisenberg, *supra* note 1, at 698.

12. Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1202-03 (2002) [hereinafter Burk & Lemley, *Technology-Specific*]; Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575 (2003) [hereinafter Burk & Lemley, *Policy Levers*].

13. Walsh et al., *supra* note 5, at 289, 331.

14. BRONWYN H. HALL, BUSINESS METHOD PATENTS, INNOVATION, AND POLICY (Dep't of Econ., Univ. of Cal., Berkeley, Working Paper No. E03-331, 2003), available at <http://repositories.cdlib.org/iber/econ/E03-331>. Professor R. Polk Wagner has also noted how the complex relationships between, and among, patent law doctrines creates indeterminacies in how they affect patent scope and incentives. R. Polk Wagner, *Of Patents and Path Dependency: A Comment on Burk and Lemley*, 18 BERKELEY TECH. L.J. 1341, 1342-43 (2003).

15. Walsh et al., *supra* note 5, at 331.

common-method and problem-specific,¹⁶ and conclude that only the patents on common-method tools pose potential risks to biomedical innovation. Part III reexamines the competing legal proposals and argues that scholars misapply the standard finite-commons model because they fail to recognize how the complexity of biological processes and the power of existing biotech methods to produce genetic data make biomedical science, in crucial respects, an unbounded and uncongested common resource. Taken together, these findings imply that the potential adverse effects of biotech patenting are both qualitatively different from and often less significant than the effects many legal commentators have predicted.

I. PATENT POLICY AND ECONOMICS

Two central factors have combined to put biotech patents in the spotlight. First, the Bayh-Dole Act of 1980¹⁷ arguably constitutes the single most important event, as it expanded both the range of entities patenting inventions and the types of inventions being patented.¹⁸ Following passage of the Bayh-Dole Act, universities and research institutes increased their patent filings dramatically, further blurring the line between commercial and basic-science research.¹⁹ This increase in university patenting has been accompanied by a steep rise in the patenting of basic-science research tools (“upstream technologies”) that are integral to a broad cross-section of biotech research.²⁰ Second, rapid scientific developments during the 1980s and 1990s led to large influxes of private funding for biomedical research, outpacing government funding for the first time in 1992, and

16. Common-method research tools involve uniquely powerful methods of broad applicability (for example, the polymerase chain reaction (PCR), which is used to replicate DNA), whereas problem-specific research tools involve data or information that are of narrow applicability and available in many forms (for example, drug targets and gene probes).

17. 35 U.S.C. §§ 200-212 (2000).

18. Rebecca S. Eisenberg, *Bargaining over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?*, in EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY 226-27 (Rochelle Cooper Dreyfuss et al. eds., 2001) [hereinafter EXPANDING THE BOUNDARIES].

19. Walsh et al., *supra* note 5, at 295 (noting that the trend is viewed as a major change by both universities and the private sector).

20. NAT. ACADS. OF SCI., A PATENT SYSTEM FOR THE 21ST CENTURY 17, 20 (Stephen A. Merrill et al. eds., 2004) [hereinafter NAS REPORT]; Walsh et al., *supra* note 5, at 295. Archetype examples of upstream technologies are the famous Cohen-Boyer patent, which covered the canonical methods for replicating and expressing foreign genes in microorganisms, and the PCR for copying DNA. Eisenberg, *supra* note 18, at 229-30.

continuing to do so today.²¹ These trends have transformed the biomedical sciences, and have brought private and public sector research closer together and occasionally into conflict.²²

Legal commentators have responded to these developments with a panoply of proposals and concerns.²³ They have paid particular attention to the increased patenting of research tools and the rapid growth in the number of biotech patents, both of which have the potential to impede innovation and research.²⁴ Broadly speaking, legal commentators are separable into two camps, one optimistic and the other pessimistic, about whether licensing and other market agreements can resolve these tensions. The optimists appeal to experience in well-established industries (for example, electronics and automobiles) to argue that the market will work out any tensions between patents and scientific progress.²⁵ The pessimists typically focus on anecdotal evidence and other incipient signs that aggressive patenting is threatening biomedical research and development.²⁶

This Part discusses the legal and economic elements of the debate over biotech patenting. Section A provides an overview of the competing legal proposals and perspectives. Section B discusses the available economic information and recent survey data on biotech patenting. The first two sections expose the many differences between the legal perspectives and empirical observations. The sources of this divergence are discussed in Section C.

A. The Legal Debate over Patent Scope

Legal commentators tend to advocate one of three approaches to patent policy: (1) a traditional law-and-economics approach, emphasizing bright-line rules and market roles; (2) an agency-based approach, relying on experts to intervene when necessary to overcome market failures or to protect scientific norms; or (3) a judicial activist model, relying on so-called

21. Eisenberg, *supra* note 18, at 227 n.15.

22. NAS REPORT, *supra* note 20, at 20-21; Eisenberg, *supra* note 18, at 225-28; Walsh et al., *supra* note 5, at 29.

23. See Burk & Lemley, *Policy Levers*, *supra* note 12, at 1596-614.

24. Eisenberg, *supra* note 18, at 230-31 (suggesting that transaction costs of negotiating technology licenses are a significant problem in biomedical sciences); Robert P. Merges, *Institutions for Intellectual Property Transactions: The Case of Patent Pools*, in EXPANDING THE BOUNDARIES, *supra* note 18, at 129 (“[T]he key issue is the cost of integrating disparate rights.”).

25. F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697, 719-22 (2001); see, e.g., Merges, *supra* note 24, at 130.

26. Kieff, *supra* note 25, at 719-22; see, e.g., Merges, *supra* note 24, at 130.

patent “policy levers” latent in existing legal doctrines.²⁷ Notably absent is a legislative approach, which commentators widely agree would fall prey to undue public choice pressures from specific industry interests.²⁸ Each of the three competing views is discussed below.

Market-oriented commentators are unmoved by concerns about patent scope. They start from the premise that “there is no easily-defined ‘ideal’ menu of property rights for a given economy at a given moment in time.”²⁹ They argue that determining an optimal level of patent protection is precluded by our lack of reliable metrics for analysis.³⁰ This belief leads them to reject legislative reform and judicial intervention as potential solutions and to embrace a market solution.³¹ Their logic runs as follows: “Complex questions lack right answers. When there is no right answer—and when people bear the costs of their actions—we rely on those affected to make their own decisions.”³² Therefore, market-oriented commentators prefer clear rules, strong property rights, and institutions that promote negotiations (by reducing transaction costs) to solve property rights problems.³³ Moreover, they claim that recent technical advances reduce trans-

27. The Federal Circuit, for its part, has increasingly opted for bright-line rules and legal formalism over discretionary standards to promote clarity and predictability. See Burk & Lemley, *Policy Levers*, *supra* note 12, at 1672-73.

28. *Id.* at 1578, 1631-38; Rai, *supra* note 9, at 1128-30.

29. Robert P. Merges, *As Many as Six Impossible Patents Before Breakfast: Property Rights Business Concepts and Patent System Reform*, 14 BERKELEY TECH. L.J. 577, 588 (1999). Strong market skeptics, like Judge Frank Easterbrook, contend that refining existing patent laws creates more risks than potential benefits because (1) we know too little about the effect of the existing patent regime on innovation and (2) solutions developed in the dark are much more likely to be harmful than helpful. Frank H. Easterbrook, *Who Decides the Extent of Rights in Intellectual Property*, in EXPANDING THE BOUNDARIES, *supra* note 18, at 405-06.

30. See, e.g., Easterbrook, *supra* note 29, at 406. As Judge Easterbrook has put it, “If firms that put millions of dollars on the line cannot make reliable decisions about technology, what would make us think that scholars [or policy makers] with no money on the line do well at devising legal rules to govern technology?” *Id.* at 408.

31. See, e.g., *id.* at 408-11 (arguing that legislators fail for public choice reasons; that judges are unreliable because they are not accountable for their decisions and lack the necessary technical training and knowledge; and that courts create incoherent strategy because of limited time, differing perspectives, and uneven knowledge).

32. *Id.* at 411. This is just a restatement of the Coase Theorem: “[T]he more complex the problem, the more the ‘right’ answer varies over time and the affected population; and the easier it is to address the problem by private contract, the less we should attempt to resolve it by law.” *Id.*

33. See, e.g., *id.* at 411-13.

action costs already, making their standard Coasian approach all the more relevant.³⁴

Modified market-oriented approaches also exist that endorse a competitive model for maximizing innovation. Robert P. Merges and Richard L. Nelson have led the move to reject prospect theory, which maintains that the central role of patenting is to allow for coordinated, rational development of a patent prospect (that is, field or area of invention), as opposed to providing *ex ante* incentives to invent.³⁵ Merges and Nelson instead assert that competition should be favored over prospect theory's reliance on broad pioneer patents in most technological areas.³⁶ They argue that prospect theory runs awry because it misstates the problem:

But with the technological 'prospects' . . . no one knows for sure what possible inventions are in the technological pool. . . . Because of this uncertainty, development of technology is critically different from other common pool problems. The real problem is not controlling overfishing, but preventing underfishing after exclusive rights have been granted. The only way to find out what works and what does not is to let a variety of minds try.³⁷

Accordingly, competition spurs innovation much more effectively than monopolies because it allows multiple inventors to work simultaneously and because use of an idea, unlike a traditional resource prospect, is not mutually exclusive.³⁸

This modified market-oriented theory, unlike its counterpart, anticipates an active role for judges and, arguably, the Patent and Trademark Office (PTO). Judges should be guided by the modified theory's narrow-patent principle when applying patent doctrines, such as nonobviousness

34. *See, e.g., id.*

35. Merges & Nelson, *supra* note 2, at 843 (arguing that patent scope policy is highly dependent on the nature of the technology with "[1] the relationship between technical advances in the industry, and [2] the extent to which firms license technologies to each other").

36. *Id.* at 843-44; *see* Walsh et al., *supra* note 5, at 291 n.11 ("[It is] well recognized in the economics of innovation [] that, given a technological objective (*e.g.*, curing a disease) and uncertainty about the best way to attain it, that objective will be most effectively achieved to the extent that a greater number of approaches to it are pursued.").

37. Merges & Nelson, *supra* note 2, at 873.

38. Merges and Nelson single out "science-based" technologies, such as biotech, in this regard, arguing that "the patent system should be particularly careful in awarding patents of broad scope" in such areas. *Id.* at 884. Their fear is that "a real danger [exists] that allowing patent scope to be overbroad may enable the individual or firm who first came up with a particular practical application to control a broad array of improvements and applications." *Id.*

and patent disclosure requirements. Merges and Nelson refine their theory further by establishing categories of inventive activity, which are governed by distinct rules for applying patent doctrines and optimizing patent scope.³⁹ They argue, for example, that judges should limit patent scope and apply the doctrine of equivalents narrowly for cumulative and science-based technologies.⁴⁰ Consistent with their basic insight, the greater the scientific uncertainty and complexity, the more innovation will benefit from a diversity of approaches and the competition engendered by numerous narrow patents.⁴¹

The anticommons theory of Michael A. Heller and Rebecca S. Eisenberg challenges these competitive market models.⁴² A patent anticommons threatens to emerge when patent rights become so fragmented that no single scientist or company can access the technology necessary to conduct research in their field.⁴³ Heller and Eisenberg expose a major defect in the view that narrow patents necessarily promote competition and a broad range of inventive activity. The two demonstrate that, while this may be true, it is valid only up to the point at which fragmentation of patent rights causes the transaction costs associated with obtaining multiple technology licenses (for example, search costs and negotiations) to limit access to needed technologies.⁴⁴ Heller and Eisenberg argue that the risk of a patent anticommons emerging is exacerbated by individual cognitive biases and cultural differences between private and public sector researchers that impede negotiations.⁴⁵ They conclude that these tendencies are most acute in biotech patenting because the inventions at issue, particularly research tools such as drug targets, are both costly to identify and initially very difficult to value.⁴⁶

39. Their approach also maintains that several different models of technological invention exist: (1) discrete invention for inventions like the safety razor, some pharmaceuticals, and toys, which are relatively insensitive to patent scope; (2) cumulative technologies, such as those associated with aircraft, automobiles, lights, semiconductors, and computers, which are highly sensitive to patent scope; (3) chemical technologies, particularly manufacturing processes, which are similar to cumulative technologies; and (4) science-based technologies, such as biotechnology, which tend to be a blend of the other categories and reliant on unpredictable factors. *Id.* at 880-83.

40. *Id.* at 906-11, 915.

41. *Id.* at 915.

42. Heller & Eisenberg, *supra* note 1, at 698.

43. *Id.*

44. *Id.* at 698-99.

45. *Id.* at 700.

46. *Id.* at 698. Eisenberg also raises important issues that seem to derive from the high uncertainty of the science and the huge windfalls that can accrue from the research. Eisenberg, *supra* note 18, at 225, 229, 248-49; *see also* REPORT OF THE NATIONAL

The threat of a patent anticommons has inspired numerous proposals. Arti K. Rai and Rebecca S. Eisenberg argue that federal grant-making agencies, such as the NIH, should be empowered to abrogate patent rights when an anticommons threatens innovation and research.⁴⁷ The technical complexities and scientific uncertainties of biotechnology lead Eisenberg to conclude that it is better to “leave[] more discretion for agencies to determine on a case-by-case basis whether the public interest would be better served by obtaining patent protection or by leaving certain basic research discoveries in the public domain.”⁴⁸ In effect, they opt for a quasi-Kitchian prospect theory approach that replaces private entities with a federal agency to coordinate research and development. Complementing this agency-based model, Eisenberg, Rai, and others have argued for an expanded research exemption to patent infringement to mitigate further the adverse effects of patent anticommons.⁴⁹

In contrast, Dan L. Burk and Mark A. Lemley propose a broad policy synthesis that is as expansive as it is provocative. Their proposal stands out because, among other elements, it relies on judges actively calibrating patent doctrines, which they refer to as “policy levers,” on a technology-specific basis.⁵⁰ Drawing on the earlier work of Merges and Nelson, they make the case that patent policy ought to be technology specific—after all,

INSTITUTES OF HEALTH (NIH) WORKING GROUP ON RESEARCH TOOLS (1998), *available at* <http://www.nih.gov/news/researchtools>.

47. Rai & Eisenberg, *supra* note 4, at 310-13 (suggesting recommendations for NIH action and modifications to the Bayh-Dole Act to avoid problems of overly aggressive patenting of research tools). Rai has also argued that greater deference to the PTO would improve biotech jurisprudence. See Arti K. Rai, *Genetic Technology: Social Values and Personal Autonomy in the 21st Century*, 34 WAKE FOREST L. REV. 827, 828 (1999). More generally, Rai has proposed a number of broad institutional and procedural changes within the PTO and the courts. Rai, *supra* note 9, at 1041, 1075-78, 1091, 1097-101, 1124-25.

48. Eisenberg, *supra* note 1, at 640.

49. Rai, *supra* note 9, at 1041. Taking a slightly different tactic, Rochelle Dreyfuss has suggested an elegant refinement to the research exemption by tying it to a commitment that any inventions generated by the research will not be patented. Rochelle C. Dreyfuss, *Varying the Course in Patenting Genetic Material: A Counter-Proposal to Richard Epstein's Steady Course* 8-11 (Apr. 2003), *available at* <http://ssrn.com/abstract=394000>. More specifically, Dreyfuss provides that a university or nonprofit research institute would be immune from prosecution for using patented materials in research if (1) “those materials were not available on reasonable terms” (Nelson amendment), and (2) “the university or other research organization agrees not to patent anything that came out of the research.” Richard R. Nelson, *The Market Economy and the Scientific Commons* 27-28 (Nov. 2003) (restating and adding to Dreyfuss's plan), *available at* <http://ideas.repec.org/p/ssa/lemwps/2003-24.html>.

50. Burk & Lemley, *Policy Levers*, *supra* note 12, at 1578-79.

research and development costs, patent incentives, and rates of technological progress vary greatly across industries.⁵¹ Therefore, making the natural inference from these observations, they conclude that legal incentives must be optimized to promote innovation on an industry-by-industry basis.⁵² Burk and Lemley marshal further support by pointing out that the Federal Circuit already applies legal doctrines in a technology-specific manner.⁵³

Having made a case for technology-specific patent law, Burk and Lemley develop a systematic program for calibrating various patent doctrines, or policy levers, for specific technologies.⁵⁴ Incorporating prospect theory, Merges and Nelson's competition-based model, and the Heller and Eisenberg anticommons theory, Burk and Lemley describe several policy lever regimes and link them to specific technologies.⁵⁵ Thus, for example, biotechnology raises issues that span prospect theory (broad patents) and anticommons problems (too many patents), resulting in a policy favoring a relatively small number of broad patents. To achieve this, Burk and Lemley propose that the patentability standard of "nonobviousness" be raised and the written description required of an invention be reduced for patentability purposes.⁵⁶

The evolution of more than a decade of patent policy debate is brought almost full circle in a short article by R. Polk Wagner.⁵⁷ Wagner accepts that differences exist in the application of patent law to distinct areas of

51. *Id.* at 1581-86, 1588-89.

52. *Id.* at 1588-89.

53. *Id.* Again biotech patents are showcased: in this case, for the notably weak obviousness standard and exceptionally stringent written description requirements the Federal Circuit has applied to biotech patents. Burk and Lemley also argue that such judge-based policies are unavoidable, as failure to articulate a clear policy is a policy decision itself. *Id.* at 1669, 1678.

54. Policy levers are context-specific standards, and include the rule against patenting abstract ideas, utility, experimental use, level of skill in the art, secondary considerations for obviousness, written description, reasonable interchangeability, pioneer patents, reverse doctrine of equivalents, presumption of validity, new secondary considerations, patent misuse, and injunctions. *Id.* at 1641-68.

55. In an earlier article, Burk and Lemley also argue that the person having ordinary skill in the art (PHOSITA) for obviousness and disclosure requirements should be "decoupled" because of the reciprocal relationship between obviousness and enablement. Burk & Lemley, *Technology-Specific*, *supra* note 12, at 1202-03.

56. This approach follows directly from their inferences that patent scope is directly proportional to the standard for obviousness, but indirectly proportional to the enablement and written description requirements. Burk & Lemley, *Policy Levers*, *supra* note 12, at 1593-94.

57. Wagner, *supra* note 14, at 1341.

technological development, but he questions whether these differences align with the technologies (“macro-specificity”) as opposed to the substantive differences (“micro-specificity”) within each technology.⁵⁸ Wagner asserts that the inter-technology differences that Burk and Lemley identify can be explained by micro-specificity.⁵⁹ Of equal importance, Wagner uses several elegant logical arguments to demonstrate that the Burk and Lemley synthesis fails because the application of their policy levers is hopelessly indeterminate.⁶⁰ He then returns to traditional economic theory, arguing for clearer, more stable patent doctrine and less, not more, judicial discretion.⁶¹

It is worth briefly stepping back to take stock of the legal policy arguments. Prospect theory argues for broad patents because, by granting control of a technology, they ensure efficient coordination of innovation. Standard economic theory maintains that patent scope is secondary to clear rules, strong property rights, and low transaction costs. However, Merges and Nelson’s modified market approach is premised on innovation being proportional to the number of independent inventors, which entails narrow patents. Qualifying this theory, Heller and Eisenberg argue that patent rights can become too fragmented, creating an anticommons to which no one has ready access; consequently, they call for intervention by experts in federal agencies. Finally, the Burk and Lemley synthesis maintains that “everyone is right,” though only for specific technologies, and relies on judges to manage patent policy on a technology-specific basis. Stated succinctly, these proposals reduce to: (1) more is more (broad patents preferred); (2) less is more (narrow patents preferred); (3) more is sometimes more and sometimes less; and (4) neither (patent scope is irrelevant). Although none of these proposals has prevailed, their logical completeness is gratifying.

58. *Id.* at 1343-44.

59. *Id.* at 1347.

60. *Id.* at 1348-49. This indeterminacy arises because disclosure requirements and the obviousness standard each affect the scope of a patent and, at the same time, are linked through the legal construct of the PHOSITA. Further, both are indirectly proportional to the scope of a patent, but patent disclosure is directly proportional to the skill level of the PHOSITA, whereas obviousness is indirectly proportional. *Id.* at 1348. These relationships create tradeoffs that nullify the simple relationships Burk and Lemley describe. In an earlier article, however, Burk and Lemley do advocate decoupling the PHOSITA standard in the disclosure and obviousness regimes. Burk & Lemley, *Technology-Specific*, *supra* note 12, at 1202-05.

61. Wagner, *supra* note 14, at 1358-60. Indeed, Wagner persuasively argues that Burk and Lemley’s many criticisms of Federal Circuit doctrine demonstrate that there is little reason to have confidence that judges will make the right judgments about aligning legal doctrine with good policy. *Id.* at 1359.

B. Biotech Patent Data and Qualitative Surveys

Studies of patenting in the biomedical sciences remain very limited. Nonetheless, we do know that there has been both a striking increase in the number of patents on research tools and a significant rise in defensive patenting, particularly in the genomic sciences.⁶² However, recent data suggest that the surge has slowed and that biotech patent applications may be declining.⁶³ In addition, we know that university patenting accounts for a significant fraction of this increase in patenting. For example, universities' share of the patents issued in three key biomedical utility classes increased from eight to twenty-five percent between the early 1970s and the mid-1990s.⁶⁴ Thus, the limited data available on patenting in the biotech sector lend support to concerns about emerging patent anticommons.

Anecdotal evidence lends support to the existence of an anticommons in biotech patenting as well. One of the most publicized and debated cases from the biotech sector has involved efforts to reduce the incidence of blindness due to vitamin A deficiency by genetically modifying rice to produce vitamin A.⁶⁵ In order to undertake this research, researchers had to negotiate licenses to seventy patents and obtain access to fifteen pieces of technical property spread over thirty-one institutions.⁶⁶ Although ultimately resolved through a collective set of agreements for royalty-free licenses, this case has become the poster child for critics who have been critical of expansive biotech patenting and its potential to impede research.⁶⁷

Similar examples have been identified in more traditional areas of the biomedical sciences. Two legal commentators identified one hundred patents related to the andrenergic receptor, which is important in metabolic

62. NAS REPORT, *supra* note 20, at 10; Walsh et al., *supra* note 5, at 295. Consistent with Walsh et al., "research tools" will be defined broadly to include "any tangible or informational input into the process of discovering a drug or any other medical therapy or method of diagnosing disease." Walsh et al., *supra* note 5, at 287.

63. See, e.g., FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, BIOTECHNOLOGY INNOVATION REPORT 2004, at 8-9 (Arie M. Michelsohn ed., 2004), available at http://www7.nationalacademies.org/step/STEP_Projects_Proteomics.html.

64. Walsh et al., *supra* note 5, at 295.

65. See, e.g., Richard C. Atkinson et al., *Public Sector Collaboration for Agricultural IP Management; Intellectual Property Rights*, 299 SCIENCE 174, 174 (2003); Roger N. Beachy, *IP Policies and Serving the Public*, 299 SCIENCE 473, 473 (2003); Ronald L. Phillips, *Intellectual Property Rights for the Public Good: Obligations of U.S. Universities to Developing Countries*, 6 MINN. J.L. SCI. & TECH. 177, 181 (2004).

66. Walsh et al., *supra* note 5, at 288 n.6.

67. *Id.* at 298.

pathways.⁶⁸ Fourteen patents controlled by several organizations cover the hepatitis-B vaccine; thus, stacking royalties totaling \$1.47 per dose, or thirteen to fifteen percent of sales, add to the cost of the vaccine's production.⁶⁹ Concern also persists about patents that restrict access to critical drug targets (for example, receptors and mutated genes) or biotech techniques (for example, genechips and diagnostic tests).⁷⁰

Prompted by concerns about patent anticommons and anecdotal experiences about biotech patenting, the research arm of the NAS commissioned a study on the effects of patenting in the biomedical sciences ("Walsh Study").⁷¹ Surprisingly, the authors of the Walsh Study found "little evidence of routine breakdowns in negotiations over rights, although research tool patents are observed to impose a range of social costs and there is some restriction of access."⁷² They also concluded that although "access . . . to foundational upstream discoveries has not yet impeded biomedical innovation significantly, . . . interviews [by the authors] and prior cases suggest that the prospect exists and ongoing scrutiny is warranted."⁷³ The authors opined that, in addition to several "working solutions" that had evolved over time, the large number of opportunities in

68. Heller & Eisenberg, *supra* note 1, at 699. However, a subsequent review identified 135 patents using the search term "adrenergic receptor," but concluded that, at most, a handful of patents needed to be licensed for typical research on the receptor. Walsh et al., *supra* note 5, at 294-95 (discussing research done by R.K. Seide and J.M. MacCloud in response to Heller and Eisenberg).

69. Walsh, *supra* note 5, at 298 n.18. Other upstream patents that have garnered attention include those on DNA probes based on expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs), although recent tightening of the PTO's written description and utility requirements have defused some of these concerns. *Id.* at 287, 299.

70. NAS REPORT, *supra* note 20, at 62; Rai & Eisenberg, *supra* note 4, at 302.

71. According to the NAS committee, "there was only one area—biotechnology research and development, primarily where applied to humans' health—where it was repeatedly suggested that there might be a significant problem of access to patented technology." NAS REPORT, *supra* note 20, at 59.

72. Walsh et al., *supra* note 5, at 289, 331. This includes the risks from patent anticommons that were paramount in many people's minds. *Id.* at 317. The NAS committee also "found little evidence, one way or the other, of the economic effects of the many steps taken during the 1980s and 1990s to extend and strengthen intellectual property rights." NAS REPORT, *supra* note 20, at 9. For example, a patent term may be extended to account for the time consumed to obtain FDA approval to market and sell a drug in the United States. NAS REPORT, *supra* note 20, at 10, 24.

73. Walsh et al., *supra* note 5, at 331. The study further noted that it is important to distinguish between research tools with only rival uses (such as Geron's stem cells and diagnostic tests) and those that have nonrival uses as well, since the latter are much less likely to be used exclusively by the patentee. *Id.* at 332-33.

biotech research had neutralized much of the potential for patents to impede innovation.⁷⁴

The more detailed findings of the Walsh Study provide insight into these broader conclusions about the rise in biotech patenting. In a series of interviews, the Walsh Study found near unanimity among those interviewed that addressed the issue that the patent landscape has become more complex and requires more extensive due diligence.⁷⁵ Yet, while some respondents acknowledged that a large number (sometimes hundreds) of patents may need to be considered initially, “in [general] practice there may be, in a complicated case, about 6-12 that they have to seriously address, but that more typically the number was zero.”⁷⁶ In sum, the number of patents one must evaluate is generally manageable. Consistent with this general result, the Walsh Study found that, although time consuming, negotiations over licensing agreements rarely halted projects⁷⁷ and that royalty payments rarely threatened the commercial viability of downstream products and virtually never halted research projects.⁷⁸

The Walsh Study is equivocal about patents on research tools. The primary issue it identified in this context is ensuring access to important research tools, such as unique drug targets and stem cells that are covered by one or a few patents.⁷⁹ Half of the Walsh Study’s respondents complained of licensing fees on research tools, but nevertheless conceded that

74. *Id.* at 331-32.

75. *Id.* at 294.

76. *Id.* at 294-95.

77. *Id.* at 315-16. In fact, fifty-four of fifty-five respondents could not even identify a specific incident. *Id.* Further, although only indirectly related to patenting, material transfers were found to be “a source of some concern and vexation,” as the process is very bureaucratic and time intensive. *Id.* at 319-21. Even when parties are willing to share, the process is complicated by agreements, with time often increasing from days to months. *Id.*

78. *Id.* at 299. The norm for royalty payments on drug development programs, for instance, is one to five percent of sales, with exclusive royalties being higher, and royalties of ten percent being viewed as “high” or “ridiculous.” *Id.* at 300. Royalty stacking could affect a decision made at the margins (where there were two equally viable candidates); probability of success and the size of the market are more central concerns. *Id.* at 304.

79. *Id.* at 305-06 (“[T]his is not a problem of accessing multiple rights but one of accessing relatively few—perhaps even one—patent on a key tool or discovery.”). Particular concern has been expressed about exclusivity arrangements for drug targets (that is, “any cell receptor, enzyme, or other protein implicated in a disease, thus representing a promising locus for drug intervention”). *Id.* at 310. Indeed, one of the genes with a strong association with breast cancer, BRCA1, has been the subject of substantial controversy because of the limited access the patent owner for the gene is permitting. *Id.* at 312.

the costs did not preclude projects.⁸⁰ Further, while royalties are often high, respondents acknowledged that fees on research tools were within reason given productivity gains.⁸¹ Redirecting research projects around research tool patents was also found to be common, but in most cases did not entail shifting to an entirely new research area (for example, new disease or technical approach).⁸² The complexity of most diseases apparently permits a range of different research strategies.

The Walsh Study concluded by describing a number of working solutions that have mitigated the potential impact of strategic patenting in the biomedical sciences. Most of them are obvious, such as licensing, inventing around, and court challenges, but a few are more unexpected. Two significant working solutions are the use of technology without a license and the resurgence of support for public databases in the public and private sectors.⁸³ Norms of the research community, as Arti Rai has argued, play an important role in these developments.⁸⁴ In particular, researchers, whether public or private, are less likely to enforce their patents when it will erode the personal relationships and the information exchange integral to the scientific community.⁸⁵ As a consequence, university researchers, and to a lesser extent even those in the private sector, routinely use patented inventions without obtaining a license under the guise of a “research exception” to patent liability.⁸⁶ The viability of this working solution is aided by the difficulty of enforcing patent rights against research in-

80. *Id.* at 300.

81. *Id.* at 301, 335. Exceptions to this general finding do of course exist. DNA chips were singled out as particularly expensive and beyond the reach of most small labs, forcing—for better or worse—collaborations between companies. *Id.* at 302. There also have been some efforts by companies to allow access to research tools at reduced costs to academic researchers. *Id.*

82. *Id.* at 303. Moreover, redirection was generally associated with patents on specific compounds, not on processes or techniques. *Id.*

83. *Id.* at 331.

84. Rai, *supra* note 4, at 90-92.

85. Walsh et al., *supra* note 5, at 331 (stating that companies, in particular, rarely sue universities for fear of the bad press that would ensue). The importance of scientific norms is also reflected in the reluctance of early university inventors to patent landmark biotech methods (for example, the Cohen-Boyer process). Rai, *supra* note 4, at 93-94.

86. Walsh et al., *supra* note 5, at 324-28, 334. The recent Federal Circuit opinion in *Madey v. Duke University*, 307 F.3d 1351, 1361-62 (Fed. Cir. 2002), may foreclose this working solution. The court held that the research exception does not apply to basic science research at universities because research is, in effect, the business of universities. *Madey*, 307 F.3d at 1362. The court further held that only acts “solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, . . . qualify for the very narrow and strictly limited experimental use defense.” *Madey*, 307 F.3d at 1362.

fringement because it is difficult to detect given its small scale and the absence of an open sale or manufacture of an infringing product.

The recent growth of public databases and efforts to promote public access to information and techniques play an important role as well. Major databases exist for genes (such as GenBank), proteins (such as Blueprint Worldwide and Protein Data Bank), and genetic probes (such as the quasi-public Merck Gene Index and SNPs Consortium).⁸⁷ Similarly, Merck has initiated a program to provide to the research community, at cost, 150 patent-free transgenic mice without use restrictions.⁸⁸ The scientific community has also been instrumental in preserving and enhancing openness and access to technologies. Biology journals, for example, often require authors to deposit gene and protein sequences in public databases.⁸⁹ More recently, the NIH has negotiated generic license agreements for academic researchers to ensure that they obtain access to important privately-owned research tools, has provided funding for development of new research tools (for example, transgenic lab animals), and has conditioned receipt of grants on commitments not to patent inventions that derive from NIH-supported research.⁹⁰ These developments, coupled with the results of the Walsh Study, suggest that forces beyond those identified by legal scholars are having a major effect on biotech patenting.

C. The Divergence of Legal Theory and Biotech Patenting

None of the previously described legal theories readily captures the dynamics of patenting in the biomedical sciences. First, although the Walsh Study found that the expanding number of patents requires more negotiations for licenses and increases the costs of biomedical research,⁹¹ it has not led to Heller and Eisenberg's dire anticommons predictions. Biomedical research has not been markedly impeded by the growing number of biotech patents.⁹² It appears instead that working solutions aided, as

87. Walsh et al., *supra* note 5, at 329. Celera Genomics, founded to complete the task of sequencing and assembling the human genome, has recently decided to make all of its genomics information publicly available after acknowledging that its business model for selling genomics information was failing. *See, e.g.*, Andrew Pollack, *Celera to Quit Selling Genome Information*, N.Y. TIMES, Apr. 27, 2005, at C2. Some have argued that this openness benefits the large pharmaceutical companies at the expense of the biotech sector, as it is in the interest of the pharmaceutical companies to undercut business opportunities of biotech firms and then to "compet[e] on the exploitation of this shared information." Walsh et al., *supra* note 5, at 329.

88. Walsh et al., *supra* note 5, at 329.

89. *Id.*

90. *Id.*

91. *See* discussion *supra* Part I.B.

92. *Id.*

I will argue below, by the characteristics of the science itself have mitigated many of the negative effects of this trend.

Second, the most serious threats the Walsh Study identified were from discrete patents on key research tools.⁹³ This finding undercuts Merges and Nelson's narrow-patents theory because, even where narrowly drawn, patents on key research tools can be used to limit a diverse range of work by competitors. For example, even a narrow patent on the foundational technology for all recombinant DNA processes discovered by Stanley Cohen and Herbert Boyer, or other irreplaceable research tools, would have a broadly preclusive effect if access to the technology were denied. Conversely, where numerous alternative research tools are available, promotion of narrow patents is unnecessary, as alternative avenues for conducting research already exist. For similar reasons, the prescriptions that Burk and Lemley advocate are inappropriate.⁹⁴ Raising the obviousness standard, as Burk and Lemley advise, will have little or no effect, because key research tools by their very nature represent major advances beyond the prior art. Worse still, the loosening of disclosure requirements urged by Burk and Lemley stands to aggravate technology-access problems by allowing patents on research tools to claim a broader constellation of uses.⁹⁵

The failings of the other legal theories might incite market enthusiasts to claim victory for traditional economic theory. According to this line of argument, the defects of these other theories demonstrate that patent scope is secondary to maintaining clear rules, strong property rights, and low transaction costs for technology licensing. The problem with this view is that transaction costs for licensing biotech patents are in fact significant and are not diminishing.⁹⁶ More importantly, the two working solutions identified by the Walsh Study—reliance on the now defunct research exemption and dedication of research tools to the public domain—do not center on reducing transaction costs or clarifying the law, but instead in-

93. Walsh et al., *supra* note 5, at 305-06.

94. Burk and Lemley conclude that “[b]iotechnology is in part about pharmaceuticals—and therefore prospect theory—and in part about DNA research—and therefore anticommons theory.” Burk & Lemley, *Policy Levers*, *supra* note 12, at 1676.

95. *Id.* These problems also lend credence to Wagner's micro-specificity argument, for it appears that different biotech inventions pose different sets of problems for patent policy. *See supra* Part I.A. If this is the case, it makes no sense to treat biotech patents on a technology-specific basis.

96. Walsh et al., *supra* note 5, at 314-15 (noting that more than a third of the respondents in the study commented that transaction costs and delays associated with licensing technology were significant).

volve abrogating property rights and abandoning private ownership altogether.⁹⁷

Biotech patenting dynamics are not solely attributable to legal or economic factors, though both are important.⁹⁸ Making sense of the interplay between law, economics, and science in the biomedical sciences requires that the third prong of this trio be more fully understood and taken into account. The Walsh Study includes two revealing observations in this regard. First, one of the respondents remarked that “[w]e have more targets than we have chemists to work on them” and noted later that the value for targets has decreased over time due to their abundance.⁹⁹ Second, another respondent commented:

I have never worked with a disease where one particular protein makes the only difference. A patent gets you exclusive rights to a class of drugs, but there may be other classes. . . . I could imagine a genetic disease where a single target was involved, but I don't think that the big medical problems fall into this case.¹⁰⁰

Both observations highlight the diverse set of research options that have emerged in the biomedical sciences.¹⁰¹ This diversity helps explain the

97. *Id.* at 324-27, 329. In a recent article that challenges the “Conventional Critique in the intellectual property (IP) world,” Merges refers to strategies that involve dedicating technology and data to the public domain as “property-preempting investments,” which he argues are motivated by the desire of firms and individuals to “preempt[] or undermin[e] the potential property rights of economic adversaries.” See Robert P. Merges, *A New Dynamism in the Public Domain*, 71 U. CHI. L. REV. 183, 183 (2004). This Article ascribes these strategies to factors that go beyond broad economic theorizing, which does not necessarily imply that the scientific factors discussed here have a significant impact on individual economic calculations.

98. For example, recent cases that have invalidated or narrowed the scope of important patents have eased some concerns about patenting. Walsh et al., *supra* note 5, at 330. The recent case of *Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004), *cert denied*, 125 S. Ct. 629 (2004), is a case in point. The Federal Circuit invalidated the broadly claimed patent based on a stringent application of the written description requirement. *Rochester*, 358 F.3d at 928-29.

99. Walsh et al., *supra* note 5, at 304-05; see also Allison Abbott, *Geneticists Prepare for Deluge of Mutant Mice*, 432 NATURE 541, 541 (2004) (forecasting a “glut of new mouse strains” for use as experimental models of human disease).

100. Walsh et al., *supra* note 5, at 324.

101. These statements are borne out by estimates that the total number of “druggable” targets is about 5,000 to 10,000—notably, the number of targets for safe and effective existing drugs is a mere 483. Jurgen Drews, *Drug Discovery: A Historical Perspective*, 287 SCIENCE 1960, 1961-62 (2000); cf. Andrew L. Hopkins & Colin R. Groom, *The Druggable Genome*, 1 NATURE REV. DRUG DISCOVERY 727, 729 (2002) (estimating that the number of small molecule targets is likely between 600 and 1500 whereas the likely druggable targets number approximately 3000). However, regardless of what the exact

(apparently) lowered protectionist tendencies of inventors in the private and public sectors. Just as importantly, these observations point to the numerous opportunities for developing new research tools.¹⁰² As argued more fully below, the nature of biomedical science itself has played a critical role in reducing potential friction between biotech innovation and the patent system.

II. HUMAN GENETICS AND BIOTECH INNOVATION

The systemic technical barriers inherent in the biomedical sciences that are responsible for the diversity of research opportunities and the uncertainty of success rarely are factored into patent policy.¹⁰³ This Part aims to redress this oversight.¹⁰⁴ The Part begins by highlighting the gulf that exists between the popularized version of biotech science and the more complex, less deterministic factors that shape biomedical science. This Part also challenges the common portrayal of genes as rigid blueprints that fully determine an individual's susceptibility to disease. These distinctions are critical to appreciating the relationship between biomedical science and biotech patenting.

The public and scientific images of human genetics are chronically estranged. In its most simplistic form, public perception is that genes determine and control an individual's susceptibilities to disease. This view is analogous to the claim that the food one eats fully determines who one is and what one does. Literally speaking, we certainly are constructed out of what we eat, but it is equally true that we are much more than these constituent parts—traits and characteristics emerge at the level of a whole or-

number of druggable targets is, a great deal of sifting of genetic data will be required given that scientists estimate there are 20,000 to 25,000 genes in the human genome and that the number of proteins is possibly about 1 million. Christopher P. Austin et al., *NIH Molecular Libraries Initiative*, 306 *SCIENCE* 1138, 1138 (2004).

102. See Walsh et al., *supra* note 5, at 304-05.

103. I do not mean to suggest that the interplay between science and patenting is absent from the legal literature as a whole, only that it has not been adequately considered in the biotech context. See, e.g., Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 *TEX. L. REV.* 989, 1035-37 (1997) (describing how "subsequent developers . . . must work within the parameters of the physical laws, and hence may be forced to build on the original inventor's work").

104. For a more detailed discussion of factors inhibiting genomics research, see David E. Adelman, *The False Promise of the Genomics Revolution for Environmental Law*, 29 *HARV. ENVTL. L. REV.* 117, 151-67 (2005).

ganism that cannot be reduced to the elements that make them up.¹⁰⁵ What we eat or do not eat may influence our behavior or fate, but it would be absurd to infer that humans are fully determined by what they eat. The relationship between an individual's genetic makeup and disease susceptibilities is no different; a few susceptibilities have strong genetic influences, while the majority are affected by genetic factors only weakly.¹⁰⁶

This less deterministic understanding is illustrated by the story of the BRCA1 and BRCA2 genes, which are strongly associated with breast and ovarian cancers. The BRCA genes represent a best-case scenario for biotech methods because they involve single genes that have a large impact on risk.¹⁰⁷ However, while these mutations are strongly correlated with cancer, only about ten percent of women with breast cancer develop the disease because they have a mutation in either of these genes.¹⁰⁸ Moreover, the estimates of the genetic link (eighty-five percent for breast cancer; forty-five percent for ovarian cancer) are in doubt, as other genetic and environmental factors play a role in disease etiology.¹⁰⁹ As a result,

105. See Kenneth M. Weiss & Anne Buchanan, *Evolution by Phenotype: A Biomedical Perspective*, 46 PERSP. BIOL. MED. 159, 178 (2003).

106. A number of diseases such as cancer have been associated with genetic variations in tens of genes. *Id.* at 172. Further, the relationship between genetics and disease can be complicated by much more mundane factors, such as physiological differences that may aggravate or neutralize the effect of a genetic mutation. See, e.g., Samuel M. Cohen, *Risk Assessment in the Genomics Era*, 32 TOXICOLOGIC PATHOLOGY, at 5-6 (Supp. 1 2004) (describing how basic physiological differences between animal models and humans are determinative of whether certain chemicals heighten this risk of bladder cancer and concluding that “[g]enomics will contribute little to this risks assessment”).

107. Weiss & Buchanan, *supra* note 105, at 167, 175.

108. Ruth Hubbard & Richard C. Lewontin, *Pitfalls of Genetic Testing*, 334 NEW ENG. J. MED. 1192, 1192 (1996). Over one hundred variants of the two genes have been identified, but only a few have been linked to tumor growth, and predominantly in women whose family histories provide independent grounds for finding a high familial risk of breast cancer. *Id.*

109. *Id.* Recent work, for example, has shown that lifetime risks vary significantly (for example, depending on the decade when the woman was born), suggesting that the cancer risks associated with these mutations may be overstated. Weiss & Buchanan, *supra* note 105, at 175. An important potential source of error is confounding factors in multiply-affected families. Weiss & Buchanan, *supra* note 105, at 175. In other words, scientists have not yet demonstrated that mutations BRCA1 and BRCA2 result in the increased susceptibility, as other genes or factors in these families could be the putative “cause.” Hubbard & Lewontin, *supra* note 108, at 1192. This ambiguity arises because one cannot know *a priori* whether a trait is common because of an inherited characteristic or because of a functional genetic reason. Weiss & Buchanan, *supra* note 105, at 174. A disease may be common because an environmental factor affects a particular genetic or molecular-level pathway shared by everyone or because a specific underlying genetic variant is common. Weiss & Buchanan, *supra* note 105, at 174.

even a positive test provides a highly ambiguous guide for a doctor in counseling her female patient given the underlying uncertainties of the causal link.¹¹⁰

These qualifications have led patients and doctors alike to view genetic testing and genomic methods skeptically.¹¹¹ They also highlight the many complexities and uncertainties that underlie biomedical research—even after specific genetic anomalies have been identified. Legal commentators often fail to appreciate fully the seriousness of these obstacles, or the open-ended nature of the biomedical sciences, at this point in their development.¹¹² The following discussion explains the scientific origins of these uncertainties and barriers to development in order to examine how they impact biotech patenting.

A. Complexity in the Biomedical Sciences

The human genome and the translation of genes into biologically active molecules (usually proteins) are far more complex than popularized versions of genetics would lead one to believe. First, less than two percent of the human genome codes for proteins, and more than fifty percent consists of repeat sequences with currently undefined functions.¹¹³ Second, genes themselves are oddly constructed—most are interspersed with long

110. See Weiss & Buchanan, *supra* note 105, at 175. Furthermore, in the case of relatively rare genetic disorders, such as BRCA1 and BRCA2, broad public genetic testing may not even be cost effective, particularly given the risk of false positives. Neil A. Holtzman & Theresa M. Marteau, *Will Genetics Revolutionize Medicine?*, 343 *NEW ENG. J. MED.* 141, 142-44 (2000); Hubbard & Lewontin, *supra* note 108, at 1193-94; see Paolo Vineis et al., *Misconceptions About the Use of Genetic Tests in Populations*, 357 *LANCET* 709, 710-11 (2001).

111. Richard S. Cooper & Bruce M. Psaty, *Genomics and Medicine: Distraction, Incremental Progress, or the Dawn of a New Age?*, 138 *ANN. INTERNAL MED.* 576, 577-78 (2003) (“[T]he available empirical data support the argument against a clinical role for susceptibility testing for chronic disease.”); Hubbard & Lewontin, *supra* note 108, at 1192-93.

112. See, e.g., Burk & Lemley, *Policy Levers*, *supra* note 12, at 1677-78 (“The availability of research tools has made the isolation and characterization of biological macromolecules routine.”); Eisenberg, *supra* note 9, at 1070 (“[D]educing a gene sequence from its amino acid sequence [is] not . . . a particularly risky or uncertain step.”); Rai & Eisenberg, *supra* note 4, at 289 (“Once largely a matter of serendipity or trial-and-error, drug discovery is now critically dependent on basic knowledge of genes, proteins, and associated biochemical pathways.”).

113. Alan E. Guttmacher & Francis S. Collins, *Genomic Medicine—A Primer*, 347 *NEW ENG. J. MED.* 1512, 1514 (2002).

segments of non-coding DNA.¹¹⁴ Third, many critical processes that alter the activity of a gene or its protein product are not controlled by DNA sequences.¹¹⁵ Cellular processes may include complex feedback mechanisms that act directly on the protein or influence gene activity levels, for example.¹¹⁶ These complex “epigenetic” dynamics are a distinguishing feature

114. *Id.* In fact, different coding sequences of a gene may be linked together in a variety of ways, such that the 30,000 to 35,000 genes in the human genome code for more than 100,000 proteins. *Id.*

115. *Id.* (citing examples such as the signals that turn genes on and off and molecules that activate and deactivate critical proteins). These alternate control mechanisms have emerged because “[t]he evolution of additional complex attributes is essentially an organizational one,” not a product of major genetic modifications. Gerald M. Rubin et al., *Comparative Genomics of the Eukaryotes*, 287 *SCIENCE* 2204, 2214 (2000). Current evidence suggests that “the majority of phenotypic variation between individuals (and species) results from differences in the control architecture, not the proteins themselves.” John S. Mattick & Michael J. Gagen, *The Evolution of Controlled Multitasked Gene Networks: The Role of Introns and Other Noncoding RNAs in the Development of Complex Organisms*, 18 *MOLECULAR BIOL. EVOLUTION* 1611, 1622-23 (2001); *see also* David K. Gifford, *Blazing Pathways Through Genetic Mountains*, 293 *SCIENCE* 2049, 2049 (2001).

116. A recent issue of *Science* contained a special section on “Mathematics in Biology,” and other recent articles have also highlighted the rising importance of mathematical modeling and the study of complexity in biological systems. *See* Gilbert Chen et al., *Biology by the Numbers*, 303 *SCIENCE* 781, 781 (2004); Ronald N. Germain, *The Art of the Probable: System Control in the Adaptive Immune System*, 293 *SCIENCE* 240, 244 (2001) (“[I]t is now time to add the power of mathematics, systems analysis, and quantitative cell-based modeling [to the study of complex biological systems (e.g., the immune system)].”); Hiroaki Kitano, *Systems Biology: A Brief Overview*, 295 *SCIENCE* 1662, 1662 (2002); Robert F. Service, *Exploring the Systems of Life*, 284 *SCIENCE* 80, 82 (1999) (arguing that scientists will need to develop complex models for biological systems). This focus on modeling is motivated both by the needs of genomics research and the realization that biological systems often operate more as networks, with different pathways interacting, than as systems driven from the smallest level up by the same fundamental forces.

of biological systems.¹¹⁷ They also cannot be ignored because epigenetic processes play an important role in certain diseases.¹¹⁸

These features of human biology make the process of identifying genes far from trivial, and the task of linking genes to specific diseases extraordinarily challenging.¹¹⁹ Finding the genetic origin of a disease is further complicated by the fact that genetic mutations, if present, are not necessarily determinative of disease onset.¹²⁰ Environmental factors, such as nutrition, exercise, and chemical exposures, are believed to be more important for common diseases.¹²¹ This multifactor etiology follows from

117. Epigenetics is the study of heritable changes in gene expression that occur other than those resulting from a change in DNA sequence. Rebecca E. Watson & Jay I. Goodman, *Epigenetics and DNA Methylation Come of Age in Toxicology*, 67 TOXICOLOGICAL SCI. 11, 11 (2002) (stating that “adaptive epigenetic inheritance challenges the ‘central dogma’ that information is unidirectional from DNA to protein” and that epigenetic processes are unimportant in assessing potential chemical toxicity). Examples of epigenetic phenomena include silencing of tumor genes through chemical modifications, short double-stranded RNA (RNAi) segments that mediate gene expression, and DNA-DNA, DNA-RNA, and RNA-RNA interactions that trigger gene silencing. Alan P. Wolffe & Marjori A. Matzke, *Epigenetics: Regulation Through Repression*, 286 SCIENCE 481, 483 (1999).

118. Frederica P. Perera & I. Bernard Weinstein, *Molecular Epidemiology: Recent Advances and Future Directions*, 21 CARCINOGENESIS 517, 521 (2000) (stating that many carcinogenic chemicals act “through indirect genotoxic or epigenetic mechanisms”).

119. A test of gene detection methods on the *Drosophila* genome, for instance, was mixed. The accuracy of the methods used to find genes varied between five to ninety-five percent, and they incorrectly identified up to fifty-five percent of the genes studied. Teresa K. Attwood, *The Babel of Bioinformatics*, 290 SCIENCE 471, 471 (2000) (citing M.G. Reese et al., *Genome Annotation Assessment in Drosophila melanogaster*, 10 GENOME RES. 483 (2000)).

120. Weiss & Buchanan, *supra* note 105, 172-73; Walter C. Willett, *Balancing Life-Style and Genomics Research for Disease Prevention*, 296 SCIENCE 695, 696 (2002) (“[T]he majority—probably the large majority—of important cancers in Western populations are due to environmental rather than genetic factors.”). Indeed, critics of genomics methods reject the view “that the genetic determinants of complex traits are tractable, and that knowledge of genetic variation will materially improve the diagnosis, treatment or prevention of a substantial fraction of cases of the diseases that constitute the major public health burden of industrialized nations.” Kenneth M. Weiss & Joseph D. Terwilliger, *How Many Diseases Does It Take to Map a Gene With SNPs?*, 26 NATURE GENETICS 151, 151 (2000).

121. Cooper & Psaty, *supra* note 6, at 578-79 (“The primary disease-producing forces are rooted in our technology based lifestyle and the resulting patterns of consumption, behaviors, and environmental exposures.”); Weiss & Buchanan, *supra* note 105, at 174 (“[E]nvironmental factors play a major—probably the major—role in risk for common diseases.”); Willett, *supra* note 120, at 695-96 (arguing that “most diseases contributing to mortality in Western populations” are dominated by nongenetic factors).

genes being a necessary but only very rarely a sufficient contributor to disease.¹²²

Two central barriers to biomedical innovation emerge from this understanding: (1) genes do not have a fixed negative or positive impact on human health, and (2) a weak causal association exists between a person's genetic makeup and her susceptibility to disease.¹²³ These barriers place the most significant limits on the commercialization of biotechnology. They are also responsible for the disparity that exists between the power of biotech methods to generate data, such as genome sequences and probes, and their ability to promote the discovery of new medical procedures and drugs. Biotechnology is in the somewhat paradoxical position that it can produce vast quantities of genetic data, much of which are useful as research tools, but has so far had great difficulty overcoming these two fundamental barriers to innovation.¹²⁴ The following discussion describes each of these barriers to innovation in greater detail.

A canonical principle in biology is the dependence of a gene's function on other genes and environmental factors. According to this principle, known as the "Genetic Theory of Relativity," a gene may be highly beneficial in a person with one set of genetic attributes or genetic background, and extremely harmful to another person having a different genetic background.¹²⁵ As a consequence, genes typically have multiple effects depending on one's genetic background and the environment in which one lives.¹²⁶ This variation creates two central challenges: first, it negates the

122. Jonathan Rees, *Complex Disease and the New Clinical Sciences*, 296 *SCIENCE* 698, 699 (2002); Richard Strohmman, *Maneuvering in the Complex Path from Genotype to Phenotype*, 296 *SCIENCE* 701, 701 (2002).

123. Weiss & Terwilliger, *supra* note 120, at 152 (stating that the central inferential problem is that a specific genotype does not imply a specific phenotype nor does a specific phenotype imply a specific genotype; they are not necessarily correlated).

124. *Id.*

125. Anne Glazier et al., *Finding Genes That Underlie Complex Traits*, 298 *SCIENCE* 2345, 2345 (2002) ("The propensity of genetic background to modify the phenotypic expression of most if not all Mendelian traits suggests that few if any traits are truly monogenic and that instead most are genetically complex."); Elliot Sober & Richard C. Lewontin, *Artifact, Cause, and Genic Selection*, 49 *PHIL. SCI.* 157, 159 (1982) ("[N]o gene has a fixed selective value, the same gene may confer high fitness on one genetic background and be virtually lethal on another.").

126. Mark S. Boguski, *Biosequence Exegesis*, 286 *SCIENCE* 453 (1999). Some scientists have argued that,

If only 1 in 10,000 of the [mutations] present in the human population has some quantifiable [tangible] effect, then there would be more than enough unique combinations of these [mutations] to assure that every

central genomic mission of ascribing fixed disease susceptibilities to genes; second, it introduces variability that undermines biotech methods designed to link disease states using gene sequence or expression levels.

Even in single-gene diseases, the disease phenotype depends on an individual's genetic background and environmental conditions.¹²⁷ The effect of the genetic mutation that causes sickle cell anemia provides a simple example of this variability. The mutation involved in sickle cell anemia has counterbalancing effects—when present in two copies, it degrades the functioning of red blood cells and when present in only one copy, it provides resistance to malaria.¹²⁸ Symptoms consequently range from severe anemia for individuals with two copies of the mutation, to resistance to malaria for individuals who have one mutated and one normal copy, to no effects for individuals with two normal copies of the gene who are not exposed to malaria.¹²⁹ For complex diseases, the variation will be more intricate because a number of interacting genes will be involved.¹³⁰ The end result is the same. Genes rarely exert fixed effects in individuals with different genetic backgrounds or across different environments.

Thus, the causal relationship between genetic makeup (“genotype”) and disease susceptibility (“phenotype”) is not a simple one.¹³¹ First, natural selection acts primarily on phenotype, and only indirectly on genotype.¹³² This indirect relation decouples genotype from phenotype, such

human being (with the exception of identical twins) should have a unique [set of tangible effects]

John L. Hartman IV et al., *Principles for the Buffering of Genetic Variation*, 291 SCIENCE 1001, 1001 (2001).

127. Hartman et al., *supra* note 126, at 1001 (stating that there is no “wild-type” in nature; all disease and chemical toxin susceptibilities are “arbitrarily defined [at a] point along a spectrum”); Julian Little et al., *The Human Genome Project Is Complete. How Do We Develop a Handle for the Pump?*, 157 AM. J. EPIDEMIOLOGY 667, 669 (2003); Weiss & Buchanan, *supra* note 105, at 167.

128. Sober & Lewontin, *supra* note 125, at 163-64.

129. *Id.* at 163-67.

130. Ernst Mayr, *The Objects of Selection*, 94 PROC. NAT'L ACADS. SCI. USA 2091, 2092 (1997).

131. Robert Milliken, *The Changing Face of Epidemiology in the Genomics Era*, 13 EPIDEMIOLOGY 472, 474 (2002) (arguing that a huge gap exists in understanding the relationship between genotype and phenotype because unmeasured genetic and environmental factors can influence expression); Strohmman, *supra* note 122, at 701 (stating that the progression from genotype to phenotype extends over four basic levels of control, “[e]ach control level [of which] is defined by a dynamic system of self-organizing proteins, the output of which is governed by laws that are still poorly understood”).

132. Mayr, *supra* note 130, at 2093; Weiss & Buchanan, *supra* note 105, at 160. This distinction is important because the indirect relationship between natural selection and genotype allows genetic drift (that is, selectively neutral genetic variation) to propagate

that a phenotype may remain fixed under the pressures of natural selection, while the underlying genotype varies significantly.¹³³ As a consequence, it generally is not possible to infer genotype from an observed phenotype because the same phenotype can arise from multiple genotypes.¹³⁴ The absence of a unique, or even well-defined, genotype-phenotype relationship complicates the process of identifying meaningful genetic signatures of disease, and may erode the association between genetics and disease altogether.

Second, biological processes actively buffer phenotype from variations in genotype.¹³⁵ A genetic mutation that, for example, inhibits the activity of an important metabolic enzyme may be neutralized by processes that counteract the impact of the mutation on the enzyme's function or by redundancies built into the specific metabolic process.¹³⁶ Buffering mechanisms may also cause specific genotypes to be associated with diverse

over time. Weiss & Buchanan, *supra* note 105, at 159 (“[G]enetic variation is abundant in all natural species, and most is expected to be neutral or nearly neutral with respect to fitness.”). The term “natural selection” is used in its traditional sense to mean the process in which environmental factors impose pressures on species that create differential levels of survival and reproduction, such that, in the long run, the best adapted (“fittest”) members of the species are selected for survival.

133. Hubbard & Lewontin, *supra* note 108, at 1192 (stating that appearance of the same trait in different people need not be associated with the same genetic polymorphism; for example, 200 different nucleotide variations appear to produce hemophilia B); Weiss & Buchanan, *supra* note 105, at 164. In fact, “even strong [natural] selection favoring a specific phenotype closely tied to specific genes does not usually purify [genetic] variation.” Weiss & Buchanan, *supra* note 105, at 170-71.

134. Weiss & Buchanan, *supra* note 105, at 165. Moreover, once the classical two-allele (abnormal, wild-type) classification scheme is abandoned, substantial phenotypic equivalence and a broad genotype-phenotype distribution results from numerous alleles. *Id.* at 167-68.

135. See Suzanne L. Rutherford, *Between Genotype and Phenotype: Protein Chaperones and Evolvability*, 4 NATURE REV. GENETICS 263, 263-64 (2003) (stating that specific biological molecules exist that buffer the “expression of genetic variation as phenotypic variation”). The prevalence of genetic buffering is driven by the important role it plays in natural selection. Genetic buffering allows a reserve of neutral genetic variation to build up in a population under stable conditions. *Id.* at 271. This reserve is critical to a species' resiliency to environmental change and alters natural selection pressures because it provides a genetic reservoir upon which a species can draw in response to changed circumstances. *Id.* at 263, 271.

136. Suzanne L. Rutherford, *From Genotype to Phenotype: Buffering Mechanisms and the Storage Genetic Information*, 22 BIOESSAYS 1095, 1095 (2000) (stating that many ways exist in which phenotypes are buffered from perturbation by genomic and environmental variation).

phenotypes.¹³⁷ Buffering of the genetic trait therefore weakens the association between gene activity levels, which are central to genomic studies, and disease susceptibility.¹³⁸

Third, a simple one-to-one relationship does not exist between genotype and phenotype because they are separated by intervening epigenetic and apparently random processes.¹³⁹ For example, epigenetic processes may determine whether or not a gene is activated and may play a significant role in the toxicity of certain compounds.¹⁴⁰ Similarly, growing evidence indicates that stochastic processes are integral to disease-response mechanisms.¹⁴¹ This innate uncertainty adds to the complexity of the genotype-phenotype relation because, owing to variations in environmental conditions, a given genotype will have multiple corresponding phenotypes.¹⁴²

All three of these factors—natural selection acting on phenotype, active buffering processes, and stochastic biological processes—stand in the way of discovering effective medical procedures and drugs. Each of these

137. Hubbard & Lewontin, *supra* note 108, at 1192 (explaining that having the same DNA sequence in a gene does not guarantee that different people will display the same phenotype; for example, autosomal dominant retinitis pigmentosa display a range of effects from complete blindness to completely functional vision); Rutherford, *supra* note 136, at 1095 (noting that the genotype of essential biochemical pathways, for instance, can be disrupted in some strain backgrounds with minimal phenotypic effect, while in other genetic backgrounds the organism is severely affected).

138. Rutherford, *supra* note 136, at 1097. An important problem for genomics methods is that they cannot distinguish between cases in which a phenotype arises because of limited genetic variation due to a high degree of buffering or because the trait is constrained in some other way (for example, biochemical constraints). *Id.* at 1102.

139. Michael B. Elowitz et al., *Stochastic Gene Expression in a Single Cell*, 297 *SCIENCE* 1183, 1183, 1186 (2002) (explaining that random epigenetic signaling can generate long-term heterogeneity among animals with identical genetic backgrounds); Germain, *supra* note 116, at 241 (“[T]he difference between health and disease could be the ‘stochastic’ activation of a single cell, followed by positive feedback in the form of a gain in [] sensitivity and multiplication of the responding cells to high numbers.”); Simon A. Levin et al., *Mathematical and Computational Challenges in Population Biology and Ecosystems Science*, 275 *SCIENCE* 334, 337 (1997) (“[S]tochastic effects become paramount [in biological systems].”); Mayr, *supra* note 130, at 2092.

140. Elizabeth Pennisi, *Behind the Scenes of Gene Expression*, 293 *SCIENCE* 1064, 1065 (2001) (describing how epigenetic deactivation of tumor-suppressor genes can cause cancer); Watson & Goodman, *supra* note 117, at 12-13 (describing how chemical modifications to DNA that affect gene activity have been connected to chemical toxicity).

141. Germain, *supra* note 116, at 240-41; Hartman et al., *supra* note 126, 1001 (noting that diseases or toxic susceptibilities can be influenced differentially by environment factors, stochastic events, or interactions with other genes); Rutherford, *supra* note 136, at 1100.

142. Rutherford, *supra* note 136, at 1100.

processes complicates the interpretation of genetic studies by attenuating and, in some cases, completely obscuring the connection between gene-expression levels and the biological processes relevant to the disease responses and susceptibilities that scientists are attempting to monitor and understand. This decoupling makes the process of identifying useful drug targets and understanding the biology of diseases very challenging and uncertain, often necessitating extensive trial-and-error research.¹⁴³

These three factors are compounded by the fact that most human health conditions are complex and multigenic.¹⁴⁴ The simple cases in which biotech methods have been applied successfully are the relatively rare exceptions.¹⁴⁵ Further, the most important, typically chronic, diseases in the United States have late onsets (that is, after an individual's reproductive years) which are even less likely to be determined by genetic traits alone.¹⁴⁶ This additional barrier arises because the late onset of these diseases makes them selectively neutral.¹⁴⁷ The end result is that biotech methods will have great difficulty overcoming the complex etiologies of

143. See Austin et al., *supra* note 101, at 1138-39 (describing the importance of small molecules in the trial-and-error research that will be necessary to exploit the Human Genome Project).

144. See Vineis et al., *supra* note 110, at 710-11 (stating that mutations in genes coding for proteins that metabolize environmental toxins are prototypical of common, but weakly associated, genetic defects that affect individual susceptibility to toxins); Weiss & Buchanan, *supra* note 105, at 174 (stating that evidence to date indicates that simple genetic variants with major effects on risk are the exception, not the rule).

145. Even simple organisms, such as yeast, display a high degree of complexity in their gene-gene interactions. In one recent study, scientists found an average of 34 gene-gene interactions per gene based on an analysis of 143 genes in yeast mutants. Lee Hartwell, *Robust Interactions*, 303 *SCIENCE* 774, 775 (2004). As the study's author acknowledges, "[f]or those interested in uncovering the genetic basis of disease susceptibility in the human population, this result is daunting." *Id.*

146. Julian Peto, *Cancer Epidemiology in the Last Century and the Next Decade*, 411 *NATURE GENETICS* 390, 390 (2002) (citing studies that suggest, for example, that cancer risks in old age may depend on diet in early life as much as a person's habits when she tract the cancer); Weiss & Buchanan, *supra* note 105, at 156 ("Late-onset chronic diseases—whose elimination through genetics is currently the supreme object of our affections—are much more complex by comparison.").

147. See Weiss & Buchanan, *supra* note 105, at 153. Type 2 diabetes, for example, has become much more severe in recent times, implying that environmental factors dominate. *Id.* at 154. Further, even the pandemic among certain Native American tribes, which has been shown to have a genetic component, is still aggravated by environmental factors because it was rare in the same populations sixty years ago. *Id.* at 175.

many important diseases (such as cancer, heart disease, and diabetes) found in the United States and elsewhere.¹⁴⁸

The complexity of biological systems has important implications for patent policy. Above all, it means that multiple approaches will exist for understanding and treating most diseases, as multiple genes, biochemical pathways, and epigenetic factors are likely to be involved. However, it also has an obvious downside. Because human biology does not fit into a simple Newtonian model of science in which genes are the elementary objects that define biological systems as a whole, gene discovery does not lead inexorably towards an understanding of disease processes and viable treatment options.¹⁴⁹ Biotech methods are uncertain in large part because individual genes have a highly variable and typically very limited effect on disease processes.¹⁵⁰ Because of this, developing effective methods for monitoring and understanding common diseases will ultimately require scientists to address these more complex dynamics.¹⁵¹ Until then, and likely beyond, biomedical science will be subject to large, unavoidable uncertainties that will require a great deal of trial-and-error research, creat-

148. See Nelson Freimer & Chiara Sabatti, *The Human Phenome Project*, 34 NATURE GENETICS 15, 16 (2003) (“[T]here is still relatively little known about how to integrate this effort with investigation of environmental influence on phenotype.”); Strohman, *supra* note 122, at 701, 703 (noting that scientists are particularly ignorant of the interplay between disease and environmental factors); Weiss & Buchanan, *supra* note 105, at 153 (“[G]enetic factors are not likely to explain [common, chronic] diseases in the usual causal sense.”).

149. See RICHARD C. LEWONTIN, *THE TRIPLE HELIX* 113-14 (2000). Lewontin writes: It is not new principles that we need but a willingness to accept the consequences of the fact that biological systems occupy a different region of the space of physical relations than do simpler physico-chemical systems, a region in which the objects are characterized, first, by very great internal physical and chemical heterogeneity and, second, by a dynamic exchange between processes internal to the objects and the world outside of them. That is, organisms are internally heterogeneous open systems.

Id.

150. Biological signaling processes that control cellular responses to environmental exposures, for example, involve networks with “complex properties that are independent of genetic factors.” Upinder S. Bhalla & Ravi Iyengar, *Emergent Properties of Networks of Biological Signaling Pathways*, 283 SCIENCE 381, 386 (1999).

151. Strohman, *supra* note 122, at 703 (objecting to policies that “continue to see complex phenotypes as primarily derivable from genomic and proteomic databases”). Biomedical scientists also acknowledge the need to come to terms with complex biological processes. Geoffrey Duyk, *Attrition and Translation*, 302 SCIENCE 603, 603-04 (2003) (arguing that the shrinking number of drugs being discovered is attributable to the failure of scientists to address biological complexity in a systematic manner).

ing a few islands of significant advances and insights in an ocean of rapidly proliferating genetic data.

B. Implications for Innovation in the Biomedical Sciences

The deficiencies of a heavily genetics-oriented approach to understanding human disease are evident in the limited successes of genomics thus far. The ideals of rational drug design and personalized medicine hyped by scientists are currently more aspiration than reality. The decline in new drug therapies, despite large infusions of public and private support, exposes the seriousness of these technical barriers,¹⁵² as does the recent stream of published reports for which experimental results could not be reproduced.¹⁵³ Ironically, the power of biotech methods—particularly their ability to monitor thousands of genes simultaneously—comes at a significant price. The vast quantities of data generated raise extremely challenging problems for its analysis.¹⁵⁴ Indeed, discerning meaningful results from the masses of background noise requires novel methods that are computationally intensive and highly complex.¹⁵⁵ Predictably, the few

152. Rees, *supra* note 122, at 698; Strohman, *supra* note 122, at 702.

153. Habibul Ahsan & Andrew G. Rundle, *Measures of Genotype Versus Gene Products: Promise and Pitfalls in Cancer Prevention*, 24 *CARCINOGENESIS* 1429, 1429 (2003); Kirk E. Lohmueller et al., *Meta-Analysis of Genetic Association Studies Supports a Contribution of Common Variants to Susceptibility to Common Disease*, 33 *NATURE GENETICS* 177, 177 (2003) (finding that, in a meta-analysis of 301 published studies covering twenty-five different disease associations, “less than half of [the] genetic association studies [were] statistically significant”); Weiss & Buchanan, *supra* note 105, at 171-72; Kenneth M. Weiss & Andrew G. Clark, *Linkage Disequilibrium and the Mapping of Complex Human Traits*, 18 *TRENDS GENETICS* 19, 22 (2002).

154. PIERRE BALDI & WESLEY HATFIELD, *DNA MICROARRAYS AND GENE EXPRESSION: FROM EXPERIMENTS TO DATA ANALYSIS AND MODELING*, at viii (2002) (“The bioinformatics solutions to problems associated with the analysis of data on this scale are a major current challenge.”); Hopkins & Groom, *supra* note 101, at 729 (finding that the viability of “targets identified by proteomic or transcriptional-profiling studies is likely to be low”); Richard D. Irwin et al., *Application of Toxicogenomics to Toxicology: Basic Concepts in the Analysis of Microarray Data*, 32 *TOXICOLOGIC PATHOLOGY* 72, 72 (2004) (“The amount and complexity of the data means that confounding factors can be easily missed and potential[ly] important changes may be overlooked.”).

155. BALDI & HATFIELD, *supra* note 154, at 55-56 (discussing the multidimensional nature of biological systems and the sophisticated probabilistic methods that are being used to analyze them); Christopher P. Austin, *The Completed Human Genome: Implications for Chemical Biology*, 7 *CURRENT OPIN. CHEM. BIO.* 511, 512 (2003) (describing the huge number of genetic targets to be evaluated and the diverse range of experimental methods needed to validate them).

successful treatments that have emerged from biotechnology involve relatively simple cases.¹⁵⁶

The difficulty of these challenges is perhaps best illustrated by the genetic variation found in DNA repair genes, which play an essential role in correcting mutations. Scientists have identified over 450 variants of DNA repair genes using genetic screens of a representative sample of the U.S. population.¹⁵⁷ The large number of genetic variants, each of which may have multiple phenotypes or no phenotype at all, creates a near-intractable problem for biotech methods:

The complexity of . . . associating genetic variation with risk becomes apparent when it is realized that these repair pathways require activity of 20-40 different proteins to complete the repair process. Thus, given the large number of different variant[s], the typical individuals will be variant for 10-15 proteins required for repair of a specific class of damage. But, these typical individuals will not have similar pathway genotypes as these 10-15 variants will be drawn from a pool of 100-200 different [genetic variants].¹⁵⁸

The numerous combinations possible imply that few people will have the same genetic variants, making genetic associations much harder to detect. Further, because the pathway as a whole determines disease risk, causal links between individual genetic variants in the pathway and disease susceptibility will be obscured. Moreover, the process is confounded by the underlying biological mechanisms discussed in the preceding Section. In essence, identifying gene-disease associations is analogous “to search[ing] for a needle in a needle stack,” where the challenge is to identify the subset of genes that is causally related to the disease in question from a far greater number that are not.¹⁵⁹

Three central areas pose particularly difficult problems for biotech researchers: (1) identifying genes and linking proteins to genes, or vice

156. Service, *supra* note 6, at 1799; *see also* Cooper & Psaty, *supra* note 6, at 577 (“To date, both [gene expression] studies and genome-wide scans have identified only weak and inconsistent genetic signals [for common diseases in the United States such as cardiovascular disease and cancer].”).

157. Harvey Mohrenweiser, *Genetic Variation and Exposure Related Risk Estimation: Will Toxicology Enter a New Era? DNA Repair and Cancer as a Paradigm*, 32 TOXICOLOGIC PATHOLOGY 136, 139 (2004).

158. *Id.*

159. Weiss & Buchanan, *supra* note 105, at 155 (“[C]urrent genetic approaches . . . have been likened to a search for a needle in a needle stack (a great many individually modest effects).”).

versa; (2) characterizing potential drug targets; and (3) using genomic technologies to understand disease etiology and effects. The scientific uncertainty and complexity feed into the dynamics that make patenting so important. Namely, a large differential exists between the cost of discovery, which requires much trial-and-error research, and the cost of copying and producing an invention, which utilizes standardized processes for reverse engineering the patented product. In other words, because scientists are reliant on the same research tools, they face the same barriers, which, once overcome, open the door to easy reproduction of newly discovered products.

Drug discovery, which is the ultimate objective of most biotechnology, adds several additional challenges and constraints. Viable drugs must do more than effectively modify relevant biological processes. They must remain active long enough to have an effect and be biologically available—that is, be adequately absorbed into a patient’s blood stream, readily enter the cell types to which they are targeted, bind to their intended target for a sufficient period of time, and be metabolized at an appropriate rate.¹⁶⁰ These factors place significant constraints on potential drug targets and drugs themselves, which often require determination of a drug target’s structure before it can be addressed.¹⁶¹ The “vast majority of successful drugs” are directed at modifying the activity of proteins, not DNA.¹⁶² More importantly, they narrow the range of therapeutic options available, thus reducing the number of viable needles in the genomics needle stack.

Biotechnology is still a science dominated by statistics and probabilities, rather than one driven by deterministic models and a rigorous understanding of human biology. Genetic data are therefore the starting point for more arduous and extended research. More importantly for the present discussion, the dichotomy between genetic-data production and invention creates an environment in which research opportunities are, as a practical matter, unbounded because they far exceed the capacities of the scientific community.

160. Austin et al., *supra* note 101, at 1139 (observing that drug candidates typically will have to be modified to ensure that they have the proper pharmacokinetic (that is, absorption and permeation) and metabolic properties); Hopkins & Groom, *supra* note 101, at 727 (describing the attributes of chemicals necessary for them to be good candidates for drugs).

161. Hopkins & Groom, *supra* note 101, at 727-28 (noting, for example, that “many targets have failed to show any evidence of binding compounds that are potent and ‘drug-like’”).

162. *Id.* at 727. However, scientists are working towards expanding what has become known as the “druggable genome.” Austin et al., *supra* note 101, at 1138.

III. THE INTERPLAY BETWEEN BIOMEDICAL SCIENCE AND BIOTECH PATENTING

Biotech patenting has evolved in seemingly unpredictable ways when viewed from a purely legal perspective. As one might anticipate from its importance in the biomedical sector, patents have been pursued aggressively from the start, beginning with the seminal Cohen-Boyer process.¹⁶³ This patent set the stage for the subsequent surge in patenting of research tools, which arguably reached its apex in the mid-1990s with the rush to patent DNA probes. Recently, the number of patent applications on gene sequences has flattened and even begun to decline.¹⁶⁴ Further, while concerns have been raised about patents on important drug targets, significant patent anticommons have not emerged. To the contrary, there has been a rise in the dedication of research tools to the public domain.¹⁶⁵ None of the legal theories anticipated these developments.

Developments in the underlying science, as well as its limitations, provide a number of important insights into the evolution of biotech patenting and licensing. The single most important factor is the most obvious one. Research and development in the biomedical sciences are shaped by the high cost and uncertainty of biotech methods, which derive from the extensive trial-and-error research required to evaluate the large number of potential drug targets available and to navigate the complexity of the biochemical interactions involved.

However, the biological complexity that makes discovery so challenging also mitigates the potential for patents to create broad monopoly power. The diversity of human biology makes the biomedical sciences relatively open-ended and less susceptible to patent anticommons. Many biological systems have built-in redundancies that protect against failures of specific processes, and this redundancy is more prevalent in more important processes. For example, DNA repair includes these types of parallel functions.¹⁶⁶ Further, scientists have found a huge range of genetic variants and a multigenic origin for common diseases. This complexity

163. Rai & Eisenberg, *supra* note 4, at 293-94.

164. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, *supra* note 63, at 6-10. The arguments made here do not presume that this trend in biotech patent filings is attributable solely to factors emanating from the underlying science. Clearly a number of factors, particularly the heightened standard for utility promulgated by the PTO in 2001, affect biotech patent filing and issuance as well. See Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098-99 (Jan. 5, 2001).

165. See discussion *supra* Part I.B.

166. See discussion *supra* Part II.B.

defies an atomistic, gene-by-gene analysis of disease processes.¹⁶⁷ More importantly for patent policy, common diseases will, as a consequence, be associated with multiple pathways or molecules, implying that most important diseases will have numerous potential drug targets.¹⁶⁸ Thus, by both affording numerous opportunities for research and a variety of treatment options, the complexity of biological processes reduces the potential for conflict between patenting and biomedical innovation.

The Walsh Study corroborates the importance of complex biological traits. Respondents acknowledged that few, if any, common diseases will have only a single drug target, and one commented that “we have more [drug] targets than [personnel needed] to work on them.”¹⁶⁹ The increasing dedication of information to the public domain also reflects the fruitlessness of protecting overabundant research tools. As another respondent in the Walsh Study observed, dedicating research tools, including drug targets, to the public domain likely benefits established pharmaceutical companies.¹⁷⁰ By making the information freely available, pharmaceutical companies that are generally better positioned to exploit it are spared the cost of acquiring rights to use research tools from smaller biotech companies.¹⁷¹

Biomedical science therefore plays an important role in shaping patent strategy and business models in the biotech sector. These effects are evident in the evolution of biotech patenting and changing biotech business patterns. This Part returns to the legal debate, recasting it in light of the scientific constraints that have been discussed above. Section A examines the traditional commons metaphor in light of the open-ended nature of biomedical science. Section B draws on this discussion, but focuses on factors that mitigate the threats from patentees limiting access to key common-method research tools.

167. See discussion *supra* note 116.

168. Walsh et al., *supra* note 5, at 323-24; Weiss & Terwilliger, *supra* 120, at 153 (discussing how common disease traits will be associated with many potential candidate genes that scientists will have to investigate). Examples of the richness of potential drug targets include the DNA repair processes discussed in Part II.B. Indeed, even relatively simple diseases like malaria reveal complex underlying genetic susceptibilities that offer several potential targets. See discussion *supra* Part II.B.

169. Walsh et al., *supra* note 5, at 304-05, 324.

170. *Id.* at 329.

171. *Id.* Merges has argued that there is a natural counterbalancing that occurs in markets between those interests that are seeking to privatize certain types of inventions and those whose business interests actually favor dedicating them to the public domain. Merges, *supra* note 97, at 185-86. Merges claims that recent efforts to dedicate biotech data and materials to the public domain fit this model. Merges, *supra* note 97, at 185-86.

A. The Open Frontier of Biomedical Science and the Public Commons

The metaphor of the finite public commons provides the principal conceptual framework for biotech patent policy. Prospect theory employed the commons metaphor to argue for broad patents.¹⁷² Merges and Nelson argued for granting narrow patents on the ground that the knowledge commons, unlike traditional physical commons, cannot be overexploited and the belief that the rate of innovation increases with the number of investigators.¹⁷³ Finally, Heller and Eisenberg used the commons metaphor to expose the risk that highly fragmented and broadly dispersed patent rights can impede innovation.¹⁷⁴

All three theories assume implicitly that the underlying science is strictly finite and congested (or congestible).¹⁷⁵ Biomedical science is distinct in that, although some types of research tools are not plentiful, the many potential avenues for research create conditions in which others are practically unbounded—at least at this time. In this context, two types of research tools exist: (1) the relatively small number of common methods (for example, Cohen-Boyer, Kohler-Milstein, and PCR) that are critical to a broad range of biotech research, and (2) problem-specific tools that are plentiful (for example, ESTs, SNPs, and drug targets).¹⁷⁶ The differences between the two classes of research tools are critical to patent policy. Restricting access to patented common-method tools has the potential to im-

172. See discussion *supra* Part I.A.

173. Merges & Nelson, *supra* note 2, at 843-44, 884. They also singled out biotechnology as a field in which particular care should be taken to constrain the scope of patents because such science-based technologies are particularly vulnerable to the negative effects of broad pioneer patents. *Id.* at 915.

174. Heller & Eisenberg, *supra* note 1, at 698.

175. Prospect theory presumes that biotech science can be bounded and managed. Merges and Nelson's proposal assumes some bounding and congestion; otherwise their advocacy of narrow patents is superfluous. Finally, Heller and Eisenberg's theory is explicitly premised on intellectual resources being "scarce," and in any event, only makes sense if the commons are both finite and seriously congested.

176. Admittedly borderline or variable cases will exist. For example, certain "promoters," which are DNA segments that turn genes on and off, are probably best categorized as common-method research tools because they are so broadly used. Powerful constitutive promoters, that is, those that cause a gene to be continuously expressed in all cell types, would fall into this category because they are so broadly applicable and valuable in genetic engineering. However, other promoters, such as those that are cell-specific or activated only under certain circumstances, may be more accurately categorized as problem-specific because their activation properties are so circumscribed. Judgments about how to categorize research tools will therefore by necessity have to take into account context, which will naturally change over time.

pede scientific research and innovation, whereas limiting access to problem-specific tools, because of their abundance, is unlikely to negatively affect biotech innovation.¹⁷⁷

Two distinct policy regimes emerge from the two categories of research tools. The first regime falls within traditional patent theorizing, where a difficult balance must be struck between open access to key upstream research tools and maintaining the incentives to develop research tools in the first place. However, the risk here is not of an anticommons emerging, but whether access to uniquely powerful technologies will be limited. Because patents on common-method research tools are essential to conducting a wide range of research activities, such tools raise the most difficult challenges for balancing patent incentives and protecting scientific norms.¹⁷⁸ A large body of legal scholarship already exists on these issues, and I will not address them here. Instead, the section that follows discusses several scientific factors that mitigate—but by no means negate—the potential for biotech patents to limit access to key common-method research tools.

The second category deviates significantly from standard public commons-based policy arguments. The unbounded nature of the field—scientists have more drug targets than they know what to do with—neutralizes the central problem created by a finite public commons. In the traditional commons scenario, individual self-interest inexorably leads to overexploitation of the resource. However, the tragedy of the commons disappears when individuals cannot collectively overexploit a common resource.¹⁷⁹ For similar reasons, the threat of an anticommons emerging is also neutralized, as areas of dense patenting can always be avoided for uncongested resources. In fact, one might argue that the broad distribution of research activity caused by extensive patenting is a positive outcome. The abundance of problem-specific research tools also has the salutary effect of diminishing the value of those patents, consistent with recent trends toward dedicating these types of research tools to the public domain.¹⁸⁰

177. Rose, *supra* note 8, at 5-7 (noting that uncongested resources do not suffer from commons problem by virtue of the fact that they cannot be adversely impacted by individual actions—control of the resource is beyond the capacity of either individual or collective action).

178. See, e.g., NAS REPORT, *supra* note 20, at 62; Rai & Eisenberg, *supra* note 4, at 302.

179. Rose, *supra* note 8, at 5-7.

180. See discussion *supra* Part I.B. The reduced value of the patents also has important implications for cases, which apparently occur routinely, where a successful scientist conducts research without obtaining a license. The low value of the patents limits the damages a patentee could extract from an inventor in a patent infringement suit after a

The debate over biotech patent policy and fears about patent anticommons center on speculative biotech patenting of problem-specific research tools. Understanding the unbounded nature of biotech research reveals the irrationality of this form of strategic patenting. Inventors cannot predict *ex ante* which problem-specific research tools will be valuable for drug development. Further, many problem-specific research tools exist for prospective research, but only a tiny subset will be necessary for the development of a viable drug product. In this regard, the current state of biotech research and development represents the worst conditions for strategic patenting. If the number of potentially valuable patents were relatively circumscribed and the potential value of any given research tool still highly uncertain, inventors could hedge their bets through expansive speculative patenting. Here, however, the number of patentable research tools is virtually unlimited, making the expected utility of such a strategy diminishingly small.¹⁸¹ Indeed, the most economically viable option for such research tools is licensing them for use in commercial microarrays used in biological assays, where they may end up being one of many thousands of probes, as opposed to being a high-value application.

The variety of potential approaches to studying or treating a disease creates a further disincentive for speculative patenting. As respondents in the Walsh Study observed,¹⁸² the redundancy and intricacy of biological processes allow for multiple lines of research that enable scientists to circumvent existing problem-specific patents. Thus, although biological complexity offers many opportunities for strategic patenting, potentially enhancing the likelihood that a patent anticommons will emerge, this characteristic is a double-edged sword: it also affords many potential routes for engineering around existing patents.¹⁸³ Patentees, as a result, cannot be sure that their patent rights will be sufficient to exclude competitors because little will be known about the relevant biological processes when a speculative gene patent is first filed.

valuable product is discovered. Other factors also mitigate against such windfalls occurring, most important among these being the extensive research that will be required even after a research tool (such as a drug target) is discovered and the weak connection that will exist between the research tool and the final product, whose discovery will only be nominally attributable to the research itself.

181. See discussion *supra* Part II.A. This is not to suggest that there may be localized areas of scarcity (for example, access to gene therapy patents), but this is not inherently a commons problem, or at least it seems that the commons metaphor is inapt. More importantly, the data that do exist suggest that such problems have yet to emerge. See discussion *supra* Part I.B.

182. See discussion *supra* Part I.B.

183. See discussion *supra* Part I.C.

Finally, enforcement of problem-specific research tools is challenging. Except where a sequence is used as a probe in a commercial microarray assay, detection of infringing uses of a problem-specific research tool will be costly and onerous. In the absence of an infringing product or sale, infringing uses will occur in specific labs and generally will be undetectable in the publicly available research produced. This situation holds particularly true if the lab is constructing its own microarrays in which the patented research tool is just one of hundreds or thousands of probes. Where the specific sequence is integral to the reported results, the rare case, infringement may be detectable without gaining access to the lab itself.¹⁸⁴ Moreover, the ex ante value of the patented sequence, presumably in microarrays, will be small, making damage claims commensurately modest and reducing the incentive to spend valuable time and money enforcing speculative patents in the first place. None of these factors supports speculative genetic patenting as a viable business model. The Walsh Study's failure to identify significant anticommons problem further confirms that speculative patenting is far less of a threat than legal commentators have presumed.

Biomedical science remains a relatively unexplored territory in which the frontier is nowhere near an obvious geographical boundary. The standard commons arguments therefore simply do not apply. This framework explains why anticommons have not been a major factor in biotech patenting, and why they are unlikely to arise anytime soon. Simply put, the public commons model at the heart of the debate over biotech patent policy must be readjusted to reflect the important respects in which biotech patenting is uncongested and biomedical science is unbounded at this stage of its development. On the other hand, the biotech analog of a railroad or other technology providing access to this emerging territory, serves a unique purpose and is limited in number. Accordingly, just as control of railroads determined who had access to the American West, patents on common-method research tools can be used to restrict access to emerging areas of biomedical research.

B. Scientific Factors Mitigating the Detrimental Limits on Access to Patented Upstream Biotechnologies

The combination of common-method and problem-specific research tools has two practical implications for patent policy. First, fears about the patenting of abundant problem-specific research tools are unwarranted be-

184. Indeed, for problem-specific research tools, it is not even clear whether the patentee could prevent production of a down-stream drug product, which in most cases will be distinct from the research tool itself.

cause the public commons-based arguments that have provoked concern erroneously assume that biomedical science is a bounded and congested resource. This conclusion is borne out not only by the move to dedicate these types of research tools to the public domain, but also by the rapid growth in the number of problem-specific research tools over the past few years.¹⁸⁵ Second, as a number of commentators have recognized, patents on common-method research tools do present potentially significant risks to innovation and warrant continuing scrutiny.¹⁸⁶ Nevertheless, while these risks are substantial, several intrinsic scientific factors mitigate this event. The influence of these factors, as I argue below, turns on the fact that powerful common-method research tools typically have many nonrivalrous uses.¹⁸⁷

This Section draws on two examples to examine the factors that mitigate against patents on common-method research tools being used to exclude access to them altogether. The first example involves a class of proteins, the Nuclear Factor κ B (NF- κ B) family, which aids in the regulation of several important biochemical pathways. The second example is the CD34 antigen, which has significant applications in stem cell research and cancer treatment. Both of these research tools have a broad range of potential applications that make them suitable for treatment as common-methods. They also have been cited repeatedly in the legal literature and have been used as examples of how biotech patents threaten research and development.¹⁸⁸

1. *The NF- κ B Patent*

In 2002, a patent on methods for using the NF- κ B proteins issued and was exclusively licensed to Ariad Pharmaceuticals (“Ariad”), which has granted nonexclusive licenses and sought royalty payments from numer-

185. The human genome contains 3 billion base pairs and an estimated 30,000 to 35,000 genes, and rapidly evolving genomics methods are generating information at a stunning speed. Guttmacher & Collins, *supra* note 113, at 1514.

186. The NAS Report, as well as other commentators, also identifies this second issue as one deserving special attention. NAS REPORT, *supra* note 20, at 59-63. Robert Merges and Richard Nelson also highlighted this as a major issue years ago. Merges & Nelson, *supra* note 2, at 843-44.

187. I am using “rivalrous” in the sense that a rivalrous use would involve applications of patented technology in the same market(s), whereas a nonrivalrous application would arise in a distinct market. Uses of certain proteins, for example, can span completely different disease categories.

188. See, e.g., Avital Bar-Shalom & Robert Cook-Deegan, *Patents and Innovation in Cancer Therapeutics: Lessons from CellPro*, 80 MILBANK Q. 637, 638 (2002) (specifically discussing the CD34 patents); Rai & Eisenberg, *supra* note 4, at 302.

ous companies.¹⁸⁹ NF- κ B proteins are important in the regulation of a broad array of critical processes in mammals, including cell death, cell proliferation, immune responses, and tumor development,¹⁹⁰ and are consequently implicated in a large number of diseases, including cancer and immunological deficiencies.¹⁹¹ For this reason, and because of their regulatory functions (that is, turning important biological processes on and off), the NF- κ B proteins are uniquely powerful research tools.

The NF- κ B patent claims more than a dozen methods of treating and studying diseases using NF- κ B regulatory proteins.¹⁹² The patent claims are very broad, covering essentially all of the potential methods for using the NF- κ B proteins conceived at the time the patent was filed—despite the fact that patents on drugs that operated via some of these same mechanisms preceded the filing date of the NF- κ B patent.¹⁹³ Moreover, the patent is broad, not only because the claims anticipate the many ways in which NF- κ B proteins can be used, but also because the NF- κ B proteins help regulate several critically important biological pathways. Nevertheless, the NF- κ B patent is limited in two key respects: it covers neither the NF- κ B proteins themselves nor the various biological pathways in which they are active.¹⁹⁴ In essence, the NF- κ B patent claims a number of general recipes for using NF- κ B proteins for therapeutic and research purposes.

Two standard objections exist for the NF- κ B patent. First, it marries standard methods with a novel compound of unique biomedical importance. The inventors' primary contribution was in discovering the biological role of the NF- κ B proteins. By contrast, the specific methods claimed by the patent were not novel. Once the function of the NF- κ B proteins was understood, it naturally revealed how the proteins could be used in biomedical research and treatments. Second, the NF- κ B patent is an upstream patent on basic, government-financed research that is far removed from practical applications. Put another way, the patent represents a clever way

189. U.S. Patent No. 6,410,516 (issued Jun. 25, 2002) [hereinafter "'516 patent'"].

190. Diana Bolotin & Elaine Fuchs, *More Than Skin Deep*, 421 NATURE 594, 594 (2003); Michael Karin et al., *NF- κ B in Cancer: From Innocent Bystander to Major Culprit*, 2 NATURE REV. CANCER 301, 301 (2002) ("[NF- κ B] is not a single protein, but a small menagerie of closely related protein dimers that bind a common sequence motif known as the κ B site.").

191. Karin et al., *supra* note 190, at 302.

192. Naomi Aoki, *Patenting Biological Pathways Ariad Suit Raises Questions on Laying Claim to Processes in Treating Disease*, BOSTON GLOBE, July 24, 2002, at C4.

193. '516 patent, *supra* note 189, cols.82-90.

194. *See id.*

of indirectly claiming a conceptual advance that, once made, had readily foreseeable practical implications.¹⁹⁵ As such, the NF- κ B patent is a perfect example of a toll levied on upstream research that would have occurred even if patenting was not possible. These objections raise difficult policy questions, and I have no wish to diminish their significance or merit. My interest here, however, centers on whether access to the NF- κ B proteins in fact will be restricted and, if so, how the restriction will affect biotech research and innovation.

The numerous methods covered by the NF- κ B patent ensure that a wide range of nonrivalrous research is made possible using the patented methods. This finding is consistent with Ariad's efforts to license the methods broadly, which follows naturally from the fact that Ariad could not possibly support (or limit) all of the feasible related research.¹⁹⁶ NF- κ B proteins are exceptional, both with respect to their specific regulatory functions and the diversity of biological pathways they affect. These attributes make them a distinctive research tool, but not because they are likely to be the only drug target available. To the contrary, the complex diseases and number of biological pathways with which NF- κ B proteins are associated imply that multiple targets will exist.¹⁹⁷ Moreover, scientists are discovering that the intricate network of NF- κ B interactions has its downsides, as it can complicate research and diminish the value of the NF- κ B proteins as drug targets.¹⁹⁸ These factors, and the cost and uncertainty of biotech research and development, stand to mitigate the potential negative impacts of the NF- κ B patent. In short, the scope of the patent, which derives from the diverse effects of NF- κ B proteins, has a significant downside—precisely because they interact with multiple processes, using NF- κ B proteins clinically is far more complicated and unpredictable. These realities will limit any tendency that Ariad may have to limit access to or charge exorbitant licensing fees on its patented methods.

2. *The CD34 Antigen Patent*

Researchers at Johns Hopkins University patented and later licensed the CD34 antigen to Baxter Healthcare Corp. ("Baxter").¹⁹⁹ The CD34 an-

195. See Merges & Nelson, *supra* note 2, at 906-07.

196. Aoki, *supra* note 192, at C4.

197. See *supra* Part II.B.

198. Bolotin & Fuchs, *supra* note 190, at 595. Scientists, for example, have found that the many complex interactions associated with NF- κ B "raise caveats about the use of NF- κ B inhibitors to treat cancer." *Id.*

199. U.S. Patent No. 4,965,204 (issued Oct. 23, 1990) [hereinafter "CD34 patent"]; Bar-Shalom & Cook-Deegan, *supra* note 188, at 639-40. Johns Hopkins University actu-

tigen is found on the surface of human stem cells, which are immature cells that can be transformed into a variety of human tissues.²⁰⁰ This plasticity makes stem cells potentially valuable for treatment of individuals with cancer, Alzheimer's disease, and other conditions.²⁰¹ However, one of the major challenges in using stem cells is their scarcity. Analogous to the Cohen-Boyer process, the CD34 antigen overcomes this problem by providing a generic means of purifying stem cells. Because CD34 antigens exist only on stem cells, the antigens provide an ideal molecular target for isolating stem cells from a sample dominated by other cell types. In this process, stem cells are purified from a sample containing many cell types by tagging them with an antibody that selectively binds to CD34 antigen.²⁰²

The principal claim of the CD34 patent covers *all* antibodies that selectively bind to the CD34 antigen.²⁰³ In the patent specification, this genus claim is supported by a single example, the My-10 antibody. The open-ended nature of this genus claim constitutes its most troubling aspect—it implicates both undiscovered binding sites on the CD34 antigen and unknown antibodies, created by scientists, that bind to the CD34 antigen. Tellingly, much of the frustration associated with the litigation over the CD34 patent²⁰⁴ derived from the perception that the patent's coverage is too broad,²⁰⁵ to which the CellPro litigation lent further support because the defendant had independently discovered a distinct antibody that bound

ally obtained four patents on the CD34 antigen. My focus here is on just one of these, the CD34 patent.

200. *Johns Hopkins Univ. v. Baxter Healthcare Corp.*, 152 F.3d 1342, 1346 (Fed. Cir. 1998).

201. Bar-Shalom & Cook-Deegan, *supra* note 188, at 640-41; Jennifer L. Enmon, *Stem Cell Research: Is the Law Preventing Progress?*, 2002 UTAH L. REV. 621, 624.

202. Bar-Shalom & Cook-Deegan, *supra* note 188, at 640-41. The basic process is simple: (1) a sample of cells is treated with an antibody that binds to the CD34 antigen; (2) the stem cells are isolated by selectively binding them to a filter based on the properties of the bound antibody; and (3) the stem cells are released in a purified form from the filter. CD34 patent, *supra* note 199.

203. CD34 patent, *supra* note 199, cols.20-22; Bar-Shalom & Cook-Deegan, *supra* note 188, at 641.

204. *See, e.g.*, *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998); *Johns Hopkins Univ. v. CellPro, Inc.*, 931 F. Supp. 303 (D. Del. 1996).

205. *See CellPro*, 152 F.3d at 1350-51; Bar-Shalom & Cook-Deegan, *supra* note 188, at 643-44. The process the defendant used to purify stem cells also represented an improvement beyond that covered by the Johns Hopkins patents. *CellPro*, 152 F.3d at 1350-51.

to an entirely new (and unanticipated) binding site on the CD34 antigen and had superior binding properties.²⁰⁶

Concerns about the CD34 patent derive from its potential to restrict access to purified stem cells, not because it has particular biological significance in and of itself. The potential for the CD34 patent to impact biotech innovation consequently arises at two levels. First, Baxter will have a strong incentive to restrict development of any other antibodies that could compete with its My-10 antibody. Baxter will therefore use its patent to control the market for CD34 stem cell purification processes. This market was at issue in the protracted CellPro litigation over the CD34 patent.²⁰⁷ Consequently, to the extent that Baxter's strategy retards development of new antibodies and purification methods using the CD34 antigen, biotech research and development will be impacted negatively. However, the CD34 patent is not meaningfully distinct from patents on many patented research instruments, which have not been subject to significant criticism in the legal literature. Moreover, to the extent that there is reason for heightened concern, it does not derive from the CD34 patent being an upstream patent per se, but rather from it being unjustifiably broad on substantive technical grounds.

Second, Baxter will have a strong incentive to make the CD34 stem cell purification process broadly available for a fee. In light of the company's actual business interests, it simply is not plausible that Baxter would limit access to CD34 purification process. The CD34 antigen is found on all stem cells, which have a diverse range of applications that no single entity could possibly fully exploit; similar to the NF- κ B example, there will be many nonrivalrous uses of the technology. Further, the large number of applications for stem cells also implies that the potential market for the CD34 purification process is significant. While this may evoke Kitchian prospect theory, the conditions under which biotech research and

206. See *CellPro*, 931 F. Supp. at 311-12; Bar-Shalom & Cook-Deegan, *supra* note 188, at 643-44. These differences reaffirm the fallacy of defining a biomolecular genus functionally when predicting the function of a biomolecule from its structure is more art than science.

207. The litigation over the CD34 patent ultimately led to the demise of CellPro and was driven by each company's interest in selling purification systems for purposes of administering purified stems cells to cancer patients. Bar-Shalom & Cook-Degan, *supra* note 188, at 638. Chemotherapy and radiation therapy, both of which are used to treat cancer patients, kill stem cells. *Id.* at 640-41. Scientists believed that purifying a patient's stems cells from tissue samples prior to cancer treatment could be used to replenish the bone marrow cells lost. *Id.* Interestingly, the demand for stem cell separation methods ultimately collapsed after scientists discovered that bone marrow transplantation had little benefit relative to its costs and toxicity. *Id.* at 655.

development occur mitigate the concerns raised by Merges and Nelson.²⁰⁸ First, patentees will have a high level of technical sophistication, suggesting that they will appreciate the value of the nonrivalrous uses of their technology. Second, patentees will have strong economic incentives to license research-tool patents because of the long period that typically exists between development of research tools and actual product development; virtually any opportunity to cultivate an early-stage source of revenue will be welcome.

This example reveals an important dynamic: the broader the range of applications for a research tool, the less likely a patent owner will be able to exploit its research potential and the greater the market-size incentives will be to make the technology broadly available. As a consequence, access to research tools of broad importance to biomedical research and development is unlikely to be restricted. Nevertheless, patent premiums still could function as *de facto* restrictions on access, although concern about this occurrence is allayed somewhat by the lack of corroborating evidence.²⁰⁹

The preceding discussion illustrates the interplay among scientific factors, economics, and legal rules. The two categories that I have identified, common-method and problem-specific research tools, provide a useful framework for analyzing whether the patenting of specific research tools exerts adverse effects on biomedical research and development. It also provides several bases for understanding why biotech patenting has not conformed as predicted in the various competing legal theories. Analysis of the underlying science reveals several mitigating factors that explain why the rapid growth in biotech patenting has not led to the negative outcomes predicted. Although these findings provide grounds for optimism about biomedical innovation and hope that dedication of data and materials to the public domain will continue, my primary objective is to advance the current understanding of biotech patent dynamics, not to advocate the kind of rose-colored vision of biotech patent policy that I have criticized the scientific community for promoting about biotechnology.

IV. CONCLUSION

The legal debate over biotech patent policy rightly has focused attention on the patenting of important biotech research tools and the threats to innovation posed by patent anticommons. However, the important influ-

208. See discussion *supra* Part I.A.

209. Walsh et al., *supra* note 5, at 331-33.

ence of biomedical science itself on biotech patenting has been notably absent from this discourse.

I have sought to remedy this oversight by developing three central points. First, the uncertainty and complexity of biomedical science help explain several important trends in biotech patenting, including recent shifts towards free public access to important classes of research tools. Second, the standard finite commons model is not representative of the essentially unbounded opportunities in biotech research that exist at this early stage of development. Further, once the premise of a finite commons is abandoned, the potential for patent anticommons to emerge largely disappears and patents on most research tools pose less of a threat than predicted. Third, I identify two central classes of biotech research tools, common-method and problem-specific, but conclude that only patents on common-method tools pose potentially significant risks to biomedical innovation. However, even these risks can be mitigated by factors, such as the existence of nonrivalrous uses, that reduce the likelihood that access will be limited.

In sum, although it would clearly be wrong to infer that biotech patenting has no adverse effects on biomedical innovation, these findings suggest that the actual risks are significantly lower and more circumscribed than many have predicted. Thus, the current legal regime works reasonably well with respect to problem-specific research tools. Potential bottlenecks, however, exist with respect to common-method research tools. In particular, despite the mitigating factors identified above, the high-stakes nature of biomedical science suggests that targeted interventions likely will be needed to address the potential threats posed by patents on critical common-method research tools that lack nonrivalrous uses.