

Nanobiotechnology, Synthetic Biology, and RNAI: Patent Portfolios for Maximal Near-Term Commercialization and Commons for Maximal Long-Term Medical Gain

Thomas M. Mackey

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NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi: PATENT PORTFOLIOS FOR MAXIMAL NEAR- TERM COMMERCIALIZATION AND COMMONS FOR MAXIMAL LONG-TERM MEDICAL GAIN

THOMAS M. MACKEY*

ABSTRACT.....	126
INTRODUCTION	126
I. PRESENT AND PROBABLE FUTURE SCIENTIFIC KNOWLEDGE AND TECHNOLOGICAL CAPACITIES	130
A. <i>The Present and Near Future: Incremental Progress</i>	133
B. <i>In 20-to-40 Years: Revolutionary Progress, Effecting Leaps Forward in Medicine</i>	135
1. Interim Work Towards the Probable Revolutionary Advances: Identification and Removal, or Circumvention, of Scientific and Technological Obstacles.....	135
2. Medical Leaps in 20-to-40 Years: Vastly Improved Risk Identification, Prevention, Diagnosis, and Treatment for Common and Commonly Lethal Chronic Diseases	139
II. THE EFFECTIVE USE OF PATENT PORTFOLIOS TO NAVIGATE THROUGH COMPLICATED AND UNCERTAIN LEGAL, SCIENTIFIC, AND TECHNOLOGICAL TERRITORIES	146
A. <i>The Patent Portfolio: The Main Unit of IP Value in All Three Technologies</i>	146
B. <i>Patent Thickets and Low Quality Patents: Consequences</i>	

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of Patenting Too Early, Too Many, and Too Broadly in NB/BN, Synthetic Biology, and RNAi 153

C. *Prosecuting to Maximize Patent Portfolio Value When the Pertinent Patent Law, Science, and Technology are All Uncertain and Quickly Changing*..... 157

1. *KSR Int’l Co. v. Teleflex, Inc. and Pertinent Likely Provisions of the Patent Reform Act: Effects on Patent Prosecution* 159

a. *The Heightened Obviousness Bar for Post-KSR NB/BN, Synthetic Biology, and RNAi Claims to Combinations*..... 159

b. *Possible Forthcoming Statutory and PTO Rule Changes That Would Help Further Weed Out Patent Thickets and Increase Patent Validity: Creating a One-Year Post-Grant Opposition Period, Reducing the Litigation Estoppel Effect of Inter Partes Reexaminations, and Empowering the PTO to Make Rules That Limit Continuations*..... 168

2. *Just-Now-Learning that Human Genetic Regulation is Not What We Thought: Specific Consequences for Prosecuting NB/BN, Synthetic Biology, and RNAi Patents* 170

3. *General Strategies and Tactics in Patent Prosecution that Maximize Patent Portfolio Value in NB/BN, Synthetic Biology, and RNAi*..... 172

III. *DESIGNING AND EXECUTING ROADMAPS THAT MAXIMIZE COMMERCIAL VALUE: USE OF PATENT PORTFOLIOS, LICENSES, VENTURE CAPITAL, AND ACQUISITIONS* 174

A. *Early Thorough Integrative Research Planning that Culminates in a Multi-Dimensional Modifiable Roadmap* ... 174

B. *Maintaining and Modifying the Roadmap to Maximize Commercial Value* 180

C. *Using the Patent Portfolio to Facilitate Commercial Development* 180

D. *Exclusive Licensing* 181

E. *Maximizing Patent Portfolio Value to Obtain and Maintain Venture Capital*..... 182

F. *Through the Minds of Prospective Buyers: How Pharmaceutical and Biotechnology Companies Acquire NB/BN, Synthetic Biology, and RNAi Technology* 185

IV. *OVERCOMING NEAR-TERM OVER-OPTIMISM TO REALIZE*

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 125

LONG-TERM REVOLUTIONARY GAINS: A SOBERING LOOK AT THE MODEST MEDICAL GAINS IN FIGHTING AMERICA’S TOP THREE KILLERS—HEART DISEASE, CANCER, AND CEREBROVASCULAR DISEASE..... 186

V. POLICY PRESCRIPTIONS: FURTHER WEED OUT THE PATENT THICKETS, INCREASE PATENT QUALITY, AND SHIFT THE MAIN FOCUS FROM MAXIMIZING NEAR-TERM COMMERCIALIZATION TO MAXIMIZING LONG-TERM MEDICAL PROGRESS 188

 A. *Further Weed Out the Patent Thickets and Increase Patent Quality: Why KSR and the Patent Reform Act Probably Will Not Suffice and How We Could Do More* 192

 1. Additional Changes Recommended: Prosecution History Estoppel, Improved Injunctive Relief to Deter Holdups from Trolls, and Removal of the Prior Art Limit to Reexaminations..... 192

 2. Impractical Given the Extraordinary Cross-Industry Nature of the Technologies: Extensive Industry-Specific Patent System Reform..... 193

 B. *Parallel Science and Technology Commons* 194

 1. Commons for Pertinent Upstream Basic Science and Technology: Which Commons Type for Valid and Reliable Building Block Standards in the Three Nascent Technologies? 194

 2. Which Commons Type for Very High Risk and Very Long-Term Technological Developments That Could Truly Revolutionize Medicine? 197

CONCLUSION..... 204

ABSTRACT

This Article has a dual focus: the use of patent portfolios for maximal near-term commercialization in nanobiotechnology, synthetic biology, and interference RNA, and the creation of commons for maximal long-term medical gain in these technologies. These three technologies show great promise for clinical medicine, but only in the long-term. At least twenty years of R&D will be required to overcome scientific and technological barriers to a revolutionary medical breakthrough. For near-term R&D, different routes to patent portfolio-enabled commercialization are described and prescribed. A patent portfolio theory is presented which views the portfolio as the principal unit of intellectual property value because many firms maximize scale and diversity of intellectual property protection through a careful drafting of many distinct, but related, patents. The theory is qualified by the extraordinarily valuable outlier patent that to some extent is “decontextualized,” i.e., its market value is partly independent from that of its portfolio. Patent thickets and low quality patents, as well as recent doctrinal and likely forthcoming statutory changes that should reduce these problems, are addressed. Multidimensional, modifiable roadmaps to commercialization are prescribed to meet near-term challenges. Research-based alliances (e.g., cross-university alliances), as well as exclusive licenses with start-ups, should often be considered. Plans for acquiring venture capital and developing patent portfolios that attract good acquisition offers from pharmaceutical or biotechnology companies often must also be made. Patent portfolio-enabled commercialization should be complemented by foundational commons that solidify the upstream basic science and technology building blocks for the technologies. Commons are also needed for high risk, but also potentially very high medical return, multidisciplinary and long-term R&D in these three technologies.

INTRODUCTION

This is an attempt to hit moving targets that, if captured as freeze-frames, would defy ready characterization. I predict probable developmental paths and consider feasible, though less probable, alternative developmental paths for three polymorphic nascent technologies in the life sciences: nanobiotechnology (NB/BN),¹ synthetic

1. A coherent distinction between “nanobiotechnology” (NB) and “bionanotechnology” (BN) appears exceedingly difficult. “Nanobiotechnology” may often

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 127

biology, and interference RNA (RNAi).² These three nascent technologies have enough similarities and differences in terms of patent portfolio issues, probable paths to commercial development, and promises for future medical advances to be fruitfully compared and contrasted in this Article.³ Developmental paths will evolve as congressional statutes, federal court doctrine, and U.S. Patent and Trademark Office (PTO) procedure also evolve over the coming years and decades, in part as both causes and effects of how the technologies evolve.⁴ Because of the great uncertainties involved in these evolutions, part of this Article thus focuses on a key to commercializing particular nascent life science technologies—building effective patent portfolios—under conditions of high scientific, technological, and legal uncertainty, where decision-making itself is poorly understood.⁵

The technological and scientific landscapes are even more complex than they are uncertain, although the uncertainty is a large part of the multilayered complexities in the pertinent sciences and technologies.⁶ The breadth and overlap—and potentially overwhelmingly large number—of NB/BN, synthetic biology, and RNAi patent portfolios, complex as they are, are exceeded in complexity by the broad and overlapping technologies that these portfolios could potentially cover.⁷ This second, greater complexity is exceeded still by a third: multilayered and overlapping intracellular human genetic mechanisms and epigenetic systems.⁸ The fact that our pertinent human biology is even more complex than the extremely multifarious and challenging technologies should give us some pause when we hear of potential major medical

include technology that would also be considered “bionanotechnology,” and vice versa. Because of this taxonomical difficulty and the related breadth of technology in a set that would include NB, BN, and technology in the intersection of NB and BN, “nanobiotechnology” will be defined broadly as NB and/or BN, or “NB/BN.” See *infra* Part II and note 22.

2. See *infra* Parts I, III–V.

3. See *infra* Parts I–V.

4. See *infra* Parts I–V.

5. Cf. Interview by Sean Silverthorne with Gary P. Pisano, Harry E. Figgie, Jr. Professor of Business Administration, Harvard Business School, in *Science Business: What Happened to Biotech?*, HARV. BUS. WK. (Nov. 13, 2006), available at <http://hbswk.hbs.edu/item/5503.html> (statement of Gary P. Pisano) (“[T]he business side of the [biotechnology] industry [has been] continually challenged by . . . profound and persistent uncertainty, [a] complex and heterogeneous . . . scientific knowledge base, and . . . rapid . . . scientific progress.”).

6. See *infra* Parts I, II.C.2, IV–V.

7. See *infra* Parts I–II, IV–V.

8. See *infra* Parts I, II.C.2, V.B.1.

breakthroughs, such as prophylactics or cures for cancers, coming from the technologies anytime soon.⁹

Although possible, it is not likely that such prophylactics or cures could come without a much more complete picture of the pertinent chemistry (e.g., cellular and systemic structures) and physics (e.g., pertinent quantum mechanical and classical forces and their influences on normal and pathological conditions).¹⁰ We need a deeper and more precise understanding of various cellular mechanisms and epigenetic systems (in the case of cancer, this would require, *inter alia*, a much better comprehension of the forces that promote and prevent carcinogenesis and metastasis).¹¹

In Part I, I briefly survey each of the three nascent technologies, creating overviews of likely near-term and long-term future developments. In Part II, I look at efficacious patent portfolio construction and management primarily from the standpoint of how a patent practitioner could assist a government agency, university, or start-up that is looking to develop and commercialize an NB/BN, synthetic biology, or RNAi invention. In Part III, I further examine how a practitioner could use patent portfolios to help his or her client via exclusive licensing, getting and maintaining venture capital, and becoming an attractive target for acquisition by a large pharmaceutical or biotechnology company. Intellectual property (IP) is typically one of the most valuable assets of a government agency, university, or start-up seeking to commercialize innovation in cutting edge applications in the life sciences.¹² An effective IP portfolio and a carefully planned and executed exclusive license between a government agency or university and a start-up are often crucial to receive venture capital, which has thus far been the lifeblood of most start-ups with very high input costs.¹³ New complicated technologies almost invariably involve high input costs, thus creating incentives to maximize IP protection early, broadly, and often.¹⁴ In NB/BN, synthetic biology, and, to a lesser extent, RNAi, patents that were too broad in scope were pursued and granted too early and too often to too many inventors.¹⁵

9. See *infra* Parts I, II.C.2, IV, V.B.

10. See *infra* Parts I, II.C.2, IV, V.B.

11. See *infra* Parts I, II.C.2, IV, V.B.

12. See *infra* Part III.

13. See *infra* Parts III.C–III.E.

14. See *infra* Part II.B.

15. See *infra* Part II.B in regards to nanomedicine patent applications. Cf. Raj Bawa, Editorial Commentary, *Will the Nanomedicine “Patent Land Grab” Thwart*

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 129

Many patent thickets and invalid patents either loom or already exist, creating barriers to commercialization in sectors in all three nascent industries.¹⁶ Patents that become entangled in thickets probably face formidable validity and infringement challenges if and when the pertinent technology becomes commercially viable.¹⁷ The thickets thus create barriers to gaining that commercialization in the first place, partly because venture capitalists are understandably wary of investing in a company that is likely to face patent litigation.¹⁸ Fortunately, the federal courts, Congress, and the PTO are in the process of creating changes in the law which will help weed out the thickets and increase patent quality,¹⁹ although they have not gone far enough. In Part V.A, I advocate further legal changes that could effect additional patent thicket weeding and increases in patent quality. Finally, in Part V.B, I recommend an increase in the ratio of long-term rigorous, ambitious, and publicly funded research and development (R&D) to patent portfolio-driven near-term commercial R&D in these technologies. The prescription is based mainly on projections that increasing this ratio would probably direct and expedite progress towards removing or circumventing scientific and technological obstacles to revolutionary medical applications of the technologies.²⁰ The greatest long-term prospects—in terms of public good payoffs—are the improvements in health and increases in longevity that these still largely undeveloped life science technologies could provide via high-tech and highly personalized medicine.²¹

Commercialization?, 1 NANOMEDICINE: NANOTECHNOLOGY, BIOLOGY & MED. 346, 347 (2006) [hereinafter Bawa Commentary] (stating that “[f]or more than a decade all of the world’s major patent offices have faced an onslaught of nanomedicine-related patent applications. . . . [R]esearchers, executives, and patent lawyers are making an effort to obtain broad protection for new nanoscale polymers and materials that have applications in nanomedicine.”) (citations omitted). Such problems may not be particular to these nascent technologies or even to nascent technologies in general. In the United States at least, too many low quality patents may be the general patent office norm, not the exception. See Cecil D. Quillen, Jr., *Innovation and the U.S. Patent System*, 1 VA. L. & BUS. REV. 207, 210 (2006) (arguing that “[t]he patent proliferation that results from the U.S. patent system’s current low standards for patentability and the necessity for would-be innovators to engage in defensive patenting is felt forcefully throughout the business community and among innovators. More patents mean more patent obstacles and higher costs for would-be innovators.”).

16. See *infra* Part II.B.

17. See *infra* Part II.B.

18. See *infra* Parts II.B, III.E.

19. See *infra* Part II.C.1.

20. See *infra* Part V.B.2.

21. See *infra* Parts IV, V.B.2.

I. PRESENT AND PROBABLE FUTURE SCIENTIFIC KNOWLEDGE AND TECHNOLOGICAL CAPACITIES

NB/BN, synthetic biology, and RNAi are life science technologies that, just in the last few years, have attained a large amount of public and private funding—and much patenting as well—largely because of their perceived commercial potential in many areas, most notably, pharmaceuticals. Ironically, however, there is much uncertainty—especially in medicine—as to whether any of the technologies will make any truly major advances. More fundamentally, precisely what each of these technologies is, how it will develop, and how to differentiate it from the others is also not certain. I will not attempt to differentiate “nanobiotechnology” from “bionanotechnology.”²² I will instead define nanotechnological biotechnology/biotechnological nanotechnology (NB/BN) as the interface of nanotechnology with biotechnology.²³ Nanotechnology includes nanomaterials, nanointermediates, nano-enabled products, and nanotools.²⁴ Biotechnology includes gene cloning, as well as genetic, cell, and tissue engineering.²⁵ NB/BN includes many technologies that are pertinent to either NB or BN, or

22. See *supra* note 1 and accompanying text.

23. Nanotechnology’s polymorphisms, combined with its poorly established scale definitions, create a degree of nebulosity which may be troubling for both the technology and patents related to it. See Nicholas J. Uhlir, Note *Throwing a Wrench In the System: Size-Dependent Properties, Inherency, and Nanotech Patent Applications*, 16 FED. CIR. B. J. 327, 338 (2006) (“Because nanotechnology is a rapidly evolving science, measurement standards often do not exist for the properties the technology exhibits.”). Many of these polymorphisms exist within NB/BN. Although nanobiotechnology and bionanotechnology are often used interchangeably, providing further taxonomical confusion, there also appears to be little discussion and no existing consensus on whether the terms are truly synonymous, whether it matters, and why one term is used as opposed to the other. See Nature Nanotechnology, Nature Publishing Group, Editorial, *Live Wires*, 1 NATURE NANOTECHNOLOGY 79, 79 (2006) (“[S]hould the field be called nanobiotechnology or bionanotechnology? *Nature Nanotechnology* prefers the former, and a quick search on Google confirms this by more than three-to-one. But which is correct? Are there subtle differences between the two?”). Any distinction between a nanotechnological biotechnology (NB) subset and a biotechnological nanotechnology (BN) subset may inevitably be nebulous, given the evolving states of both nanotechnology and biotechnology. Moreover, there may be many types of technology that could be classified as both NB and BN.

24. See LUX RESEARCH, THE LUX NANOTECH INDEX (2007), available at <http://www.luxresearchinc.com/pxn.php> [hereinafter LUX NANOTECH INDEX] (referring to nanomaterials, nanointermediates, nano-enabled products, and nanotools as four stages of a nanotechnology value chain).

25. See generally HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY (Sara Tenney ed., 6th ed. 2008) (1986). As with the list of types of nanotechnology just given, see LUX NANOTECH INDEX, *supra* note 24, this list of types of biotechnology represents the technology accurately, but not comprehensively.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 131

both.²⁶ RNAi—i.e., microRNA (miRNA) or short interfering RNA (siRNA)—is a fairly recently discovered means of gene silencing.²⁷

26. For example, biomolecular and biomimetic devices; biosensors; molecular motors; biomolecular fabrics; bioseparations via nanofiltration; subsets of engineered enzymes and proteins created by metabolic engineering; nanoparticle-enabled drug discovery and delivery; other nanotherapeutics and nanodiagnostics; optical semiconductors; catalysts for organic reaction; use of nanobiomimetics in nonbiological systems; and use of actin filaments in electronic circuitry. This representative list of technologies in the interface of nanotechnology and biotechnology, though longer than the representative list for either technology alone, *see supra* notes 24–25, is still far from comprehensive.

27. *See* A DICTIONARY OF BIOLOGY 42, 568-72 (Robert S. Hine ed., Oxford University Press 6th ed. 2008) (describing succinctly how RNAi evolved from antisense DNA technology and how double-stranded RNA (dsRNA) is superior to antisense single-stranded DNA (ssDNA) as a silencing tool in that dsRNA is not susceptible to degradation via DNAases). There are two RNAi sequential pathways: (1) a miRNA pathway; (i) a Dicer protein cuts precursor fragments of miRNA into shorter fragments, typically twenty-one-to-twenty-two nucleotides, (ii) a gene strand associates with an assembly of proteins, the RNA-induced silencing complex (RISC), (iii) “miRNA binds *imperfectly* to target . . . [the complementary messenger RNA (mRNA) base sequence,] causing *suppression of translation . . . but not degradation of the mRNA*”; and (2) a siRNA pathway. *Id.* at 570–71. (emphasis added). The siRNA pathway also uses a Dicer cut and RISC assembly, although, unlike with miRNA, the siRNA-RISC complex “binds to [the] target mRNA [base] sequence *completely, triggering cleavage and degradation of the mRNA.*” *Id.* at 571 (emphasis added). RNAi is described as having much promise to knockout specific genes to understand their function and for new forms of targeted gene therapy, especially in oncology. *See id.* at 571. Precursors to siRNA “originate from various sources, including virus infection, introduced transgenes, and transposons,” so it helps protect cells by targeting viral RNA for destruction and by silencing transposons. *Id.* at 571. Transposons, or transposable elements (Tn elements), are “jumping” DNA sequences that can transpose across the genome via the enzyme transposase, thus mutating genes and damaging chromosomes. The siRNA-guided silencing mechanism prevents the “jump” by destroying the complementary mRNA for transposable elements and thereby precluding the production of transposase. *See* Philip D. Zamore, *Genomic Defence with a Slice of Pi*, 446 NATURE 864, 864 (2007); GEORGE M. MALACINSKI & DAVID FREIFELDER, ESSENTIALS OF MOLECULAR BIOLOGY 364–65 (3rd ed. 1998). *See also* Gilbert Chin & Jake Yeston, *Editors’ Choice: Promoting Silence*, 317 SCIENCE 427, 427, 429 (2007) (discussing Jiang Han et al., *Promoter-associated RNA is Required for RNA-directed Transcriptional Gene Silencing in Human Cells*, 104 PROC. NAT’L ACAD. SCI. 12422 (2007)) (providing a very brief review of the capacity of RNAi to modulate gene expression by either degrading mRNA or blocking translation and reporting that siRNAs in yeast act by degrading “low-abundance nascent transcripts, rather than on the DNA.”). Chin & Yeston, *supra*. “In human cells, siRNAs directed against promoter sequences can block gene transcription. Do these siRNAs act on the promoter DNA or, as in yeast, an RNA species?” *Id.* at 429. Research also suggests that suppressing a variant of a human EF1a mRNA promoter approximately 230 base pairs upstream from this promoter reduces the ability of siRNA to induce transcriptional silencing. *Id.* When miRNA, but not siRNA, act on mRNA such that translational blocking occurs sans mRNA degradation, the degree of translational blocking may need to be proportionate to the amount of mRNA. This would be true if pertinent bacterial findings can be extrapolated to yeast (and possibly to humans), because bacterial research has found the ratio of mRNA/protein production to be constant. *See* Narendra Maheshri & Erin K. O’Shea, *Living with Noisy Genes: How Cells Function Reliably with Inherent Variability in Gene Expression*, 36 ANN. REV. BIOPHYSICS

Similarly, synthetic biology is a fairly new area of bioengineering with ambitions such as the artificial synthesis of macro-level biological systems using programmable parts or “gene switches” connected via a modular interface.²⁸ There are many technologies that intersect two of the three nascent technologies of NB/BN, synthetic biology, and RNAi, and some in the interface of all three. Some of these intersecting technologies are potentially highly salutary.²⁹ However, the three technologies are often discussed separately in both scientific literature and legal literature. These considerations support the mutual coverage and the separate categorization of the three technologies in this Article.

BIOMOLECULAR STRUCTURE 413, 418 (2006) (reviewing experiments that utilized “stochastic [*in vivo*] models of gene expression to infer . . . mRNA[] and protein dynamics . . . [from] static snapshots of protein distribution . . . [which created] steady-state protein levels . . . [that confirmed] the validity of the common assumption that protein production is proportional to mRNA levels”).

28. See, e.g., Sapna Kumar & Arti Rai, *Synthetic Biology: The Intellectual Property Puzzle*, 85 TEX. L. REV. 1745, 1746 (2007).

Synthetic biology’s long-term goals encompass such far-reaching possibilities as constructing an entirely artificial programmable genome from standard parts. . . . More immediately, synthetic biology “systems”—that is, organisms engineered with artificial metabolic pathways composed of a number of different standard parts—have produced important concrete results, including the *possibility* of unlimited supplies of previously expensive drugs for malaria.

Id. (emphasis added).

29. In the interface of NB/BN’s potential cellular applications and synthetic biology’s engineering ambitions, see, for example, Richard Jones, Thesis, *What Can Biology Teach Us?*, 1 NATURE NANOTECHNOLOGY 85, 86 (2006) (conjecturing that some physicists might want to take synthetic biology’s engineering ambition of reintroducing systemic functionality to a stripped-down host organism further by using nature’s design of the cell as a roadmap for synthesizing all of the synthetic components of the cell). See also Mitchel J. Doktycz & Michael L. Simpson, Perspective, *Nano-Enabled Synthetic Biology*, 3:125 MOLECULAR SYSTEMS BIOLOGY 1, 1–7 (2007) (arguing that the use of unique physical properties of nanoscale materials, guided by systems biology principles, permit the construction of synthetic structures with cell-like characteristics). The authors outline the research needed for the creation of nano-enabled synthetic biology. Nano-enabled synthetic biology will ultimately include hybrid systems that expand the synthetic biology toolbox, with the possible eventual realization of “synthetic systems of high functional density and cell-like complexity.” *Id.* at 7. In the interface of NB/BN and RNAi, see, for example, Robert Berry, *Dendritic Nanotechnologies, Inc.: The Keys to Nanotechnology—Precision, Scalability, and Reproducibility*, 2 NANOTECHNOLOGY L. & BUS. 175, 179–80 (2005) (arguing that dendritic polymer nanostructures would be excellent reagents for the delivery of siRNA *in vivo* and *in vitro*). In the interface of RNA generally (and thus not just RNAi) and synthetic biology, see Farren J. Isaacs et al., Review, *RNA Synthetic Biology*, 24 NATURE BIOTECHNOLOGY 545, 545–53 (2006), for a discussion of various computational and directed-evolution ambitions for engineering both more complex RNA systems and novel, diverse RNA molecules that could sense, probe, and control a variety of cellular, molecular, and large-scale systemic components, and the obstacles to realizing these ambitions.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 133

A. The Present and Near Future: Incremental Progress

Pharmaceuticals are perhaps the most promising area for all three fields. However, a distinction must be made between that which has been patented and that which has actually convinced the U.S. Food and Drug Administration (FDA) that it is safe and effective for medical use. There are frequent reports of nanotechnology drug delivery tools and nano-reformulated drugs in “existing use.”³⁰ However, in its most recent consumer update, dated July 25, 2007, the FDA states:

*Some day, you may see nanotechnology used . . . to provide new drugs that are able to reach sites in the body more effectively and at safer doses[,] create tiny sensors that detect diseases in the body far earlier than existing diagnostic tools[,] [and] manufacture incredibly small pumps that can be implanted to deliver lifesaving medications precisely to the cells and tissues that need them.*³¹

In contrast, the FDA’s list of current medical uses includes only the most mundane and apparently least risky applications, such as sunscreens and protective and glare-reducing coatings for eyeglasses.³² The FDA indirectly addresses this discrepancy, but does not clearly

30. *E.g.*, Peter Coffee, *Fads and Hype in Technology: The Sargasso Sea of “Some Day Soon,”* in LYNN E. FOSTER, *NANOTECHNOLOGY: SCIENCE, INNOVATION, AND OPPORTUNITY* 19, 28 (2006) (arguing that nanotechnology is not a fad, but a trend, as indicated by “existing uses, such as . . . drug-delivery tools”); Paul J.A. Borrn & David Berube, *A Tale of Opportunities, Uncertainties, and Risks*, 3 *NANOTODAY* 56, 57–58 (2008) (reporting both that a rapidly increasing nano-based market includes medical products such as heart valves, drug delivery systems, and imaging techniques and that nanosilver coatings are also increasingly used in products such as wound dressings and urinary catheters).

31. Press Release, U.S. Food and Drug Administration, Consumer Update, FDA Readies for More ‘Nanoscale’ Challenges (July 25, 2007), *available at* <http://www.fda.gov/consumer/updates/nanotech072507.html> [hereinafter FDA Readies for More Nanoscale Challenges] (emphasis added).

32. [A] few cosmetic products claim to contain nanoparticles to increase the stability or modify [the] release of ingredients. Similarly[, the] FDA is aware of nanotechnology-related claims made for certain sunscreens. We are currently not aware of any safety concerns[,] but [the] FDA is planning additional studies to examine the effects of select nanoparticles on skin penetration.

U.S. FOOD AND DRUG ADMINISTRATION, *FDA AND NANOTECHNOLOGY PRODUCTS: FREQUENTLY ASKED QUESTIONS*, <http://www.fda.gov/nanotechnology/faqs.html> (last visited Nov. 07, 2008) [hereinafter FDA Statement on Whether There are Regulated Nanotech Products] (answering the question “[a]re there any FDA-regulated products currently on the market that employ nanotechnology?”).

state whether non-sunscreen or non-cosmetic uses (e.g., prescription drugs or medical devices used for medical prevention or treatment) of nanotechnology are currently marketed.³³ The contrast between apparent overstatements of the extent of present pharmaceutical applications from enthusiastic private sources and the FDA's apparent excess caution in focusing mostly on cosmetics and sunscreens may reflect source-driven agendas that lead to questions of bias. That said, most likely even very enthusiastic industry representatives would admit that technological barriers to the use of NB/BN in pharmaceuticals, at least for now, preclude revolutionary advances in treatment for often-lethal diseases. Similarly, even the FDA admits that NB/BN has an impressive future pharmaceutical potential,³⁴ although, of course, safety, efficacy, and environmental effects will have to be adequately addressed. Certainly, though a few may be on the market, FDA-approved NB/BN drug tools and nano-enabled drugs are not revolutionizing medical treatment at this time.

It is highly probable that scientific and technological barriers will also keep NB/BN from revolutionizing medical treatment in the near future. For instance, in nanoparticle-enabled gene therapy or drug delivery, pertinent science and engineering investigations tell us that we are just starting to understand the formidable limitations to precisely targeted delivery such as demonstrated size and charge-determined disruptions of polycationic organic nanoparticles on living cell membranes.³⁵ Because uses of synthetic biology and RNAi also involve

33. *Cf. id.* (“[S]everal FDA regulated products . . . employ nanotechnology. However, to date, few manufacturers of regulated products have claimed the use of nanotechnology in the manufacture of their products or made any nanotechnology claims for the finished product.”).

34. *See* FDA Readies for More Nanoscale Challenges, *supra* note 31.

35. Pascale R. Leroueil et al., *Nanoparticle Interaction with Biological Membranes: Does Nanotechnology Present a Janus Face?*, 40 *ACCTS. OF CHEMICAL RES.* 335, 336–37 (2007) (investigating how polycationic organic nanoparticles might cross a mammalian cell membrane). The authors conducted experiments that selected dimyristoylphosphatidyl choline (DMPC) as a supported lipid bilayer in a crystalline phase to see if and, if so, how this mimic of a mammalian plasma membrane might be disrupted by polycationic organic nanoparticles. *Id.* The authors were able to image “hole” or “pore” formation directly in the lipid bilayer of DMPC, generally associated with exposure to various polycationic polymer species. *Id.* at 337, 339. The nanoparticles were hypothesized to enter cells not via endocytosis or phagocytosis mechanisms, but by an adhesive or diffusive mechanism. The authors, however, concluded that “[c]learly, more studies [were] needed to fully understand the process by which nanoparticles cross the cell plasma membrane. . . . Gaining a better understanding of this mechanism has important implications for design of drug delivery, cell transfection, and gene therapy agents.” *Id.* at 341.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 135

intricate cellular and extracellular processes, they will likely face similar formidable, though often not insurmountable, obstacles to successful implementation.³⁶

B. In 20-to-40 Years: Revolutionary Progress, Effecting Leaps Forward in Medicine

1. Interim Work Towards the Probable Revolutionary Advances:

36. Cellular and extracellular obstacles to the implementation of RNAi include the limit that yet-to-be-determined standards for screening and phenotype ontology create for the use of RNAi to identify loss-of-function or gene silencing phenotypes. See Thomas Horn et al., *GenomeRNAi: A Database for Cell-Based RNAi Phenotypes*, 35 NUCLEIC ACIDS RES. D492 (DATABASE ISSUE) D496 (2007), available at http://nar.oxfordjournals.org/cgi/content/full/35/suppl_1/D492 (arguing that major unsolved challenges “in representing RNAi phenotypes . . . [include] a lack of standards on [the] minimal information . . . need[ed] . . . for small and large-scale screening approaches” and a proper descriptive ontology for cellular phenotypes). As for cellular and extracellular obstacles to the implementation of synthetic biology, see Keith E. Tyo et al., *Expanding the Metabolic Engineering Toolbox: More Options to Engineer Cells*, 25 TRENDS IN BIOTECHNOLOGY 132, 132 (2007). The artificiality of synthetic cellular solutions to many problems, including pathological cellular conditions, poses the challenge of discovering “ways to remodel highly interconnected cellular networks to add properties that are often orthogonal to . . . [their evolved] design . . .” *Id.* See also Philippe Marguet et al., *Biology by Design: Reduction and Synthesis of Cellular Components and Behaviour*, 4 J. ROYAL SOC’Y INTERFACE 607, 619 (2007) (arguing that it is critical for synthetic biology to address this question: “given the amount of cell physiology (even for highly characterized organisms such as *E. coli*) that is still poorly understood, to what extent can we standardize parts or systems with confidence?”); Ernesto Andrianantoandro et al., Review, *Synthetic Biology: New Engineering Rules for an Emerging Discipline*, 2 MOLECULAR SYSTEMS BIOLOGY 1, 1–2 (2006), available at <http://www.nature.com/msb/journal/v2/n1/pdf/msb4100073.pdf> (comparing the prospective development of synthetic biology to the actual development of computer engineering). The authors argue that, to construct biological systems, synthetic biology will have to extend engineering principles to accommodate the unique set of design problems and solutions across populations of cells. *Id.* But see J. Christopher Anderson et al., *Environmental Signal Integration by a Modular AND Gate*, 3:133 MOLECULAR SYSTEMS BIOLOGY 1, 5–6 (2007) for a report of a successful construction of a modular synthetic biology interface that integrates environmental signals. Input promoters are cleverly constructed as independent sensors of when different, often non-integrated, environmental signals (e.g., oxygen, pH, cell density, lactate, and glucose) acquire the integration necessary for specificity. Only then are the two input promoters—inputs to an AND gate—activated and swapped with outputs using the AND gate. *Id.* at 5. This swapping of inputs and outputs (the inputs and outputs being easily replaceable transcriptional signals), while preserving the AND gate behavior, is reported to demonstrate the modularity of the AND gate. *Id.* at 6. The model is also reported to require the use of a particular plasmid and fluorescent reporter system that facilitates the eventual standardization of genetic circuits connected in a series which the authors report to be “a critical approach in the design of large integrated systems consisting of multiple genetic circuits.” *Id.* See also Kumar & Rai, *supra* note 28, for some assertions of synthetic biology’s future powers if obstacles to these powers could be removed or circumvented.

Identification and Removal, or Circumvention, of Scientific and Technological Obstacles

If these three technologies, considered alone or as a group, were graded on what they will most probably deliver in the near future to patients with often-lethal diseases, such as various forms of cancer, they would receive a B-. However, if they were graded, either separately or as a totality, twenty years hence—assuming scientific, technological, legal, and funding conditions facilitate the proper research and development paths—they would receive an A+.³⁷ This is a potential

37. However, the combination of these conditions needed to foster near-optimal development is presently not in place. See recommendations for fostering near-optimal long-term development, *infra* Parts IV, V.B. If these conditions remain as they are now, my best guesstimate of the time to A+ level development in terms of medical delivery would be about forty years, or roughly double the time it would take if near-optimal conditions are put in place in the near future. Although my “twenty-to-forty-year guesstimate” for achieving revolutionary medical gain is admittedly only that, this guesstimate is preferable to stating “near-to-remote future to remote future” both because of the nebulosity of this qualitative projected range and because, considering all of the variables, I maintain that the twenty-to-forty-year time frame is still a fair guesstimate. See *infra* note 52 and accompanying text. The Ontario Medical Advisory Secretariat’s assessment of nanotechnology specialists’ projections of expected timeframes for the use of nanotechnologies in clinical patient care also may provide some credence to my guesstimate as it pertains to NB/BN. THE MEDICAL ADVISORY SECRETARIAT, ONTARIO MINISTRY OF HEALTH AND LONG-TERM CARE, NANOTECHNOLOGY: HORIZON SCANNING APPRAISAL 30 (Nov. 2006) [hereinafter ONTARIO MEDICAL NANOTECH HORIZON] (stating the following: (1) although over half “of the specialists . . . [predicted] that nano-based therapies will lead to major changes in medicine over the next [twenty] years,” “potential beneficial effects are not expected on a relatively large scale until after 2020”; (2) yet specialists were split about the extent to which unexpected obstacles might lengthen the time to viable clinical delivery; and (3) moreover, “[t]he time span between the first successes in the laboratory and general everyday application is underestimated. Potential problems include the lack of long-term stability of nanostructures and the manufacture of sufficiently large commercially viable quantities of nanotechnology products (in particular, [three]-dimensional nanostructures).”). Note as well that if the nanotechnology specialists would like to receive grants for research having potential clinical medical applications, they have a conflict of interest that may lead to negatively skewed time-frame estimates. Such considerations make a National Nanotechnology Initiative (NNI) representative’s rather broad projections of radical transformative change by 2020, unsupported by extensive factual investigation, appear particularly questionable. Cf. Mihail C. Roco, *National Nanotechnology Initiative—Past, Present, Future*, in HANDBOOK OF NANOSCIENCE, ENGINEERING, AND TECHNOLOGY 3–4 (William A. Goddard III et al. eds., 2d ed. 2007) (providing a sigmoid curve—with time (in years) as the x axis, nanotechnology outcomes as the y axis, and the years 2000–2020 as horizontal asymptotes—to represent his prediction of growth in nanotechnology outcomes until we approximate a “nano-world” in 2020). If Roco is correct and his sigmoid curve fairly accurately depicts the nanotechnology growth that will occur over the next eleven years, exponential growth should be just around the corner, especially in NB/BN because “the most dynamic component driving an accelerating path of change is the convergence of nanotechnology, modern biology, and digital revolution.” M.C. Roco, *National*

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 137

problem with “just around the corner” hype: it hides the obstacles to maximizing the development of highly promising technologies in the remote future, because it fears that revealing these obstacles will prevent near-term commercialization. Unfortunately, the near-term ventures can only hope for a succession of incremental gains along a modest, low-risk-for-investors R&D path.³⁸ Long-term development must be based on solid, publicly funded research that broadly looks at the potential scientific and technological uses of these technologies, obstacles to realizing these potential uses, and ways to eliminate or circumvent the obstacles.³⁹

Some high quality academic research on these very issues is already being done. For instance, Jacob Klein, a physical chemist at Oxford University, in commenting on his own and other “novel and important” concurrent research,⁴⁰ highlights potential clinical delivery problems in NB/BN which are associated with interactions between nanoparticle-protein corona coating and the patient’s cell. He also recommends that researchers use more sophisticated methods to measure pertinent forces.⁴¹ Several rigorous analyses highlighting barriers to

Nanotechnology Initiative—Past, Present, Future 7–8, preprint available at http://www.nano.gov/NNI_Past_Present_Future.pdf. But considering not only the nanotechnology specialist projections and the Ontario Secretariat’s description of possible problems that could delay commercial translations of lab successes reported above, but also the many studies revealing formidable obstacles to the realization of radical growth in NB/BN, discussed in this part of the Article as well as in Parts I, II.C.2, IV, and V.B, exponential growth in the near future appears overly optimistic, even under the best scientific, technological, and legal conditions.

38. See *infra* Part V.B.1.

39. See *infra* Part V.B.

40. Most notably the research of Tommy Cedervall et al. published in *Understanding the Nanoparticle—Protein Corona Using Methods to Quantify Exchange Rates and Affinities of Proteins for Nanoparticles*, 104 PROC. NAT’L ACAD. SCI. 2050 (2007).

41. Jacob Klein, *Probing the Interactions of Proteins and Nanoparticles*, 104 PROC. NAT’L ACAD. SCI. 2029, 2029–30 (2007) (arguing that nanoparticle-protein interactions that effect corona coating show great potential in nanomedicine, especially nanotoxicology). Klein also suggests that advances towards realizing this potential in nanomedicine will require more quantitative and systematic research into the corona, as well as research into how the “corona actually interacts with and affects the well-being of living cells, using, among other approaches, the highly sophisticated methodologies that have been developed to measure surface and intermolecular forces directly.” *Id.* Klein is also very complimentary of the aforementioned concurrent research by Cedervall et al. Klein interprets Cedervall’s research as showing that which proteins “win the competition” to adsorb on the nanoparticle surface depend on these parameters: interactions of their affinities to the corona, time length of the experiment, and whether available nanoparticle surface area is in excess to the protein mixture or vice versa. Klein, *supra* at 2029. Klein argues that the protein mixture should be in excess and, ideally, reflect what would occur in a “true biological situation” (e.g., mimic a

implementation have also been conducted on NB/BN, synthetic biology, and RNAi mechanisms related to targeted drug delivery and other medical interventions.⁴²

RNAi biomedical technologies could include molecular modifications that enhance compound efficacy and gene-specific RNAi targets, among other possibilities.⁴³ However, as with nanoparticle-assisted drug delivery, the use of RNAi in drug delivery faces the anticipated barrier of mistargeting.⁴⁴ Although formidable obstacles for both targeted siRNA drug delivery and gene therapy remain,⁴⁵ many

typical therapeutic or imaging concentration). *Id.* at 2029–30. Greater nanoparticle size also unexpectedly enhanced the degree of adsorption. *Id.* at 2030.

42. Regarding NB/BN, see, for example, Patrick Couvreur & Christine Vauthier, Expert Review, *Nanotechnology: Intelligent Design to Treat Complex Disease*, 23 PHARMACEUTICAL RES. 1417, 1419 (2006), for a list of many different possible NB/BN solutions to current therapeutic challenges for diseases and medical conditions including cancer, infections, metabolic diseases, autoimmune diseases, prevention of graft rejection, pain treatment, and outstanding problems in gene therapy. The authors also suggest that an inadequate understanding of how the immune system functions as a whole and the need to identify specific cell targets for more selected performance are two of the research problems that must first be solved before the NB/BN clinical solutions can be realized. *Id.* at 1440. Cf. James L. McGrath, *How Nanotechnology Will Revolutionize Bioseparations*, 30 BIOMEDICAL ENGINEERING SOC'Y BULL. 10, 10–11 (2006) (arguing that the use of nanofiltration to facilitate reliable bioseparations of “[beta-2 microglobulin] from albumin at [the] flow rates and protein levels used in blood dialysis[,]” thus reducing the need for more frequent dialysis to combat the unacceptable loss of albumin, shows great potential, while also stating “that nanofabricated membranes will eventually have the [necessary] strength and architecture” to realize this potential) (emphasis added).

43. Cf. Helmuth H.G. van Es & Gert-Jan Arts, Review, *Biology Calls the Targets: Combining RNAi and Disease Biology*, 10 DRUG DISCOVERY TODAY 1385 (2005) (arguing that RNAi biology can help identify disease-relevant genes and construct in vitro models, and that “adenoviral siRNA libraries and disease-based cellular models [can be] used [to] generate high-quality and functionally validated targets” for drug discovery).

44. See Sabrina Oliveira et al., Review, *Targeted Delivery of siRNA*, 2006:63675 J. BIOMEDICINE BIOTECHNOLOGY 1 (2006), available at <http://www.hindawi.com/GetArticle.aspx?doi=10.1155/JBB/2006/63675> (Because the functional mediators of RNAi are small interfering RNAs (siRNA), “siRNA should therefore be targeted to three levels: to the target tissue, the target cell type, and the subcellular compartment. Primary obstacles for achieving this . . . include competitive uptake by nontarget cells, excretion in urine, degradation by nucleases, and endosomal trapping.”). However, the authors describe three categories of approaches to overcoming these barriers: chemical modifications of siRNA, viral nucleic acid delivery systems, and nonviral nucleic acid delivery systems. *Id.* at 2–6.

45. E.g., *id.* at 1, 6–7; Jens Kurreck, Review Article, 2006:83757 *siRNA Efficiency: Structure or Sequence—That is the Question*, J. BIOMEDICINE BIOTECHNOLOGY 1, 1–6 (2006) available at <http://www.hindawi.com/GetArticle.aspx?doi=10.1155/JBB/2006/83757>; N. Aronin, *Target Selectivity in mRNA Silencing*, 13 GENE THERAPY 509, 513 (2006) (discussing possible toxic clinical off-target side effects of RNAi in gene therapy, such as changes in the expression profiles of the non-targeted, but hit, mRNA, effecting RNAi-induced off-target

strategies have been proposed to surmount these obstacles.⁴⁶

2. Medical Leaps in 20-to-40 Years: Vastly Improved Risk Identification, Prevention, Diagnosis, and Treatment for Common and Commonly Lethal Chronic Diseases

All three technologies have implications for various areas of medicine, most notably oncology.⁴⁷ However, for reasons that will be explained below, truly revolutionary gains in premorbid risk identification, individually tailored prophylactics, earlier and more accurate diagnoses, and more efficacious and safer treatments will be possible only after various scientific and technological barriers to implementation are eliminated or circumvented. Arguably the most promising of the three technologies from the medical perspective is RNAi, especially for cancer,⁴⁸ with particular promise noted for the

mRNA translational repression).

46. *E.g.*, Oliveira et al., *supra* note 44, at 1–7; Kurreck, *supra* note 45, at 5–6.

47. *See, e.g.*, Andrei Gartel & Eugene S. Kandel, *RNA Interference in Cancer*, 23 *BIOMOLECULAR ENGINEERING* 17, 17 (2006) (reporting that RNAi has become a potent tool for effecting changes in gene expression via siRNA to determine cellular factors in oncogenesis and tumor suppression and that RNAi aimed at oncogenes, both in vitro and in vivo, has successfully inhibited tumor cell growth); Marta Izquierdo, Review, *Short Interfering RNAs as a Tool for Cancer Gene Therapy*, 12 *CANCER GENE THERAPY* 217, 217 (2005) (discussing the following promising RNAi methods for fighting cancer: inhibiting overexpression of cancer genes, blocking cell division via interference with cyclin E and related genes, suppressing anti-apoptosis genes and thus facilitating cancer cell death, and reducing the side effects of chemotherapy by interfering with multidrug resistance genes or chemoresistance targets); Marguet et al., *supra* note 36, at 615 (describing the use of synthetic biology for cell-based cancer therapeutics made by engineering mammalian cells, including a description of one study in which melanoma patients received engineered cells by adoptive cell transfer). The authors contend that “[e]ven though only [two] out of the [fifteen] patients showed sustained regression, the work demonstrates the potential applicability of targeted therapy using engineered cells.” *Id.*

48. *See* Chia-ying Chu & Tariq M. Rana, *Translation Repression in Human Cells by MicroRNA-Induced Gene Silencing Requires RCK/p54*, 4 *PLOS BIOLOGY* 1122, 1133 (2006) (reporting different effects of deleting helicase RCK/p54, a component of RISC, depending on whether the RISC was miRISC or siRISC). Deleting RCK/p54 releases translational repression via an imperfect complementary miRNA that acts through miRISC, but this deletion does not influence the gene silencing effects of the perfect complementary siRNA that acts through siRISC. *Id.* The authors argue that this finding provides mechanistic insight, although they conclude that additional related research is needed on carcinogenesis because “most targets of miRNA have not yet been identified.” *Id.* Relatively low miRNA-induced upregulation of the RAS protein has been associated with tumorigenesis in lung cancer, altered RCK/p54 expression has been associated with the development of both colorectal tumors and chronic hepatitis C, and “perturbations of either miRNA or RCK/p54 expression levels can have deleterious consequences for the cell.” *Id.* *See, e.g.*, Gartel & Kandel, *supra* note 47; Izquierdo, *supra* note 47, at 221–24. *See also* A *DICTIONARY OF BIOLOGY*, *supra* note 27, at 570–72 (discussing the role of RISC assembly in miRNA and

treatment of pancreatic cancer⁴⁹ and breast cancer.⁵⁰ However, overlap among these technologies should foster synergistic collaborations.⁵¹

Although the maturation of NB/BN, synthetic biology, and RNAi may well lead to revolutionary gains in clinical medical intervention at some point in the next twenty-to-forty years,⁵² a comparably pertinent history of unmet promises leaves me skeptical that such gains will occur anytime sooner. Over ten years ago, telomerase inhibitors were predicted to offer great advances in cancer treatment via suppression of telomeres.⁵³ Telomeres are TTAGGG nucleotides repeated hundreds of times on the tips of linear chromosomes.⁵⁴ Each time that they divide, normal somatic cells lose telomeric DNA as a function of age both in vivo and in vitro.⁵⁵ In contrast, many cancer cells and cell lines established from cancer maintain their telomere length by telomerase, which synthesizes telomeric repeats.⁵⁶ Telomerases are special reverse transcriptases, which are enzymes that transcribe DNA from an RNA template.⁵⁷ In 1996, Michael Fossel was one of the enthusiasts of the potential of not only telomerase inhibitors to cure cancer, but also of telomerase enhancers to cure aging, in the then near future:

siRNA).

49. See, e.g., Hong Chang, Review, *RNAi-Mediated Knockdown of Target Genes: A Promising Strategy for Pancreatic Cancer Research*, 14 *CANCER GENE THERAPY* 677, 677 (2007).

50. See, e.g., Ramesh Subramanian et al., *siRNA-Mediated Simultaneous Downregulation of uPA and Its Receptor Inhibits Angiogenesis and Invasiveness Triggering Apoptosis in Breast Cancer Cells*, 28 *INT'L J. ONCOLOGY* 831, 831, 836 (2006) (reporting that the simultaneous transcriptional silencing of the "genes" that code for the UPA and UPAR proteins can indirectly trigger apoptosis in breast cancer cells).

51. See, e.g., *supra* note 27.

52. The wide time interval required for stating a projection as a more-likely-than-not probability, rather than just a possibility, reflects uncertainty about whether very good allocations of resources, facilitative IP, and regulatory regimes will be in place. In Parts IV and V, *infra*, I argue that the present heavy emphasis on the fast commercial development of applications of academic research—in the United States, at least—will create path dependencies in R&D leading to more modest gains and thus perhaps decades of unnecessary delays in achieving truly revolutionary health-related benefits from these technologies. In NB/BN, some experts predict that second generation nanodevices will be ready for clinical use as early as 2009. See *ONTARIO MEDICAL NANOTECH HORIZON*, *supra* note 37, at 9 tbl.1. But even if this should occur, it will likely be many years, if not decades, later that these nanodevices will approximate their optimal clinical efficacy.

53. See *infra* text accompanying note 58.

54. See J.W. Shay & W.E. Wright, Review, *Hallmarks of Telomeres in Ageing Research*, 211 *J. PATHOLOGY*, 114, 116 (2007).

55. See *id.* at 114, 116.

56. See *id.* at 117–19; MICHAEL FOSSEL, *REVERSING HUMAN AGING* 70 (1996).

57. See Shay & Wright, *supra* note 54, at 114.

The work on telomerase inhibitors is more advanced than the work on inducers; cancer therapy will precede therapy for aging. Two families of telomerase inhibitors are currently undergoing trials in animals. The first human trials cannot be far off: The best estimates from those working with these compounds is before 2000. A reasonable estimate is that if the rate of development continues, we will have a clinically available cure for most cancers by the year 2005 or soon thereafter. . . .

. . . .

Treating aging with telomerase inducers would slightly increase our chances of acquiring cancer[,] but we would also treat ourselves with a telomerase inhibitor to kill cancers before commencing telomerase therapy [for aging].⁵⁸

It is now shortly after Fossel's predicted year for the "cure for most cancers," but there still is no cure for any cancer, via a telomerase inhibitor or any other method (nor is there a cure for aging).⁵⁹ These additional historical reminders should help suppress excess hype about translating the great promise that RNAi transcriptional and translational silencing mechanisms have displayed in the lab to great successes with either miRNA or siRNA in treating cancer patients in the near future:

RNA interference has joined the family of gene-regulation tools that already includes anti-sense RNA, ribozymes, and triplex-forming oligos. Each of these [new] methods at the time of its emergence was viewed as a near-universal solution to gene inactivation problems. However, the discrepancy between "promise and reality," as well as the "growing pains" of empirically discovered limitations and artifacts inspired a much more balanced view of these techniques. In the face of the growing popularity of experimental RNAi, one cannot help but wonder what its limitations will be. So far, the issue of target-

58. FOSSEL, *supra* note 56, at 162–63.

59. Nonetheless, regarding malignant cancer at least, Fossel certainly appears to have been on the right track. See Shay & Wright, *supra* note 54, at 118 tbl.1, 119 (reporting aggregate ratios of (tested positive for telomerase activity)/(total tested) from hundreds of studies over a recent five year period which examined the presence of telomerase activity in different tissues—(1) normal tissue (367/2350); (2) preinvasive cancer (410/1391); and (3) malignant cancer (3615/4304)—and arguing that "[s]ince telomerase activity is detected in almost all advanced tumours [sic], the use of telomerase inhibitors may provide an effective and novel approach to cancer therapy").

specific versus off-target effects is the most commonly recognized problem of this approach. . . .

. . . .

Importantly, “the nonspecific effects on gene expression are dependent upon siRNA concentration in a gene-specific manner.” Therefore, it is possible that the non-specific effects of a studied siRNA and a randomly chosen “control” duplex could differ substantially only because the two were delivered to the target cells with different efficiencies, have different intracellular stability, etc.

. . . .

Unfortunately, the use of a single specific siRNA and a single “targetless” control siRNA predominates in the literature. . . . [W]e expect that more stringent controls . . . will become the accepted norm. . . .

. . . .

. . . While the general significance of microRNAs in oncology has been recognized,⁶⁰ a tremendous amount of work is still required to produce a complete list of these molecules encoded in [the] human genome, as well as to determine the biological functions of each one of them. . . .

. . . .

We expect that miRNA implicated as oncogenes will become targets of therapeutic intervention. . . . Also, we will certainly see gene therapy attempts aimed at restoring the tumor suppressive miRNAs that are lost in cancer. . . .

. . . .

. . . The attempts of siRNA-based therapy are certainly not far away, [sic] however, they would face the same problem as the preceding technologies: how to efficiently deliver the active sequence to a specific target in a body without side effects.^{61,62}

60. One example of the specific oncological significance of miRNA is the aforementioned association between miRNA-induced upregulation of the RAS protein and lung cancer. See Chu & Rana, *supra* note 48.

61. Ironically, one possible side effect is facilitating carcinogenesis: “Viral or nonviral vectors transfect cells, allowing researchers to bypass systemic delivery challenges. Integrated expression systems run the risk of producing cancer, however, and so are highly experimental.” Charlie Schmidt, News Feature, *Negotiating the RNAi Patent Thicket*, 25 NATURE BIOTECHNOLOGY 273, 275 (2007).

62. Gartel & Kandel, *supra* note 47, at 28–30 (citations omitted). There are many anticipated barriers to efficacy, such as the mistargeting reported by Gartel & Kandel. Another researcher also reports the irony that first generation RNAi drugs, based on promising preclinical data, may be efficacious, but for “the wrong reasons”—i.e., reasons unrelated to gene silencing—thus potentially retarding further RNAi development:

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 143

In addition to reminding ourselves that predicted timelines for medical applications of biotechnology have frequently gone unmet, we should also find sobering recent research at the ENCYCLOPEDIA OF DNA ELEMENTS (ENCODE) consortium and elsewhere which calls into question many basic assumptions about DNA, RNA, and protein regulation, creating a regulatory picture that is far more intricate and multilayered than was long-assumed.⁶³ One possible consequence of the

This is because of the potential for nucleic acids to stimulate innate immune responses, which are known to be capable of antiviral, antiangiogenic, and anticancer activities. . . . [T]he concept of therapeutic “isiRNAs,” that is, siRNAs combining potentially synergistic gene silencing and immune-stimulatory activities, has been discussed. It would certainly not be the first time, or even surprising, to find drugs to be safe and efficacious, but working through an unanticipated mechanism of action. Yet the realization that early RNAi drugs may have been clinically successful because of these nonspecific effects rather than gene silencing may negatively impact the perceived value of the RNAi platform, both because these responses increase development risk and because there would be no need to buy expensive RNAi IP when access to immune-stimulatory nucleic acids may be obtained for much less.

Dirk Haussecker, Review, *The Business of RNAi Therapeutics*, 19 HUMAN GENE THERAPY 451, 459–60 (2008) (citations omitted).

63. See The ENCODE Project Consortium, *Identification and Analysis of Functional Elements in 1% of the Human Genome by the ENCODE Pilot Project*, 447 NATURE 799, 799–80 (2007) [hereinafter ENCODE PILOT PROJECT] (reporting the following among many unanticipated findings of research on 1% of the human genome: (1) pervasive transcription, with many transcripts linking distal regions with known protein coding sequences; (2) newly identified non-coding transcripts, some of which overlap with chromatin structure and protein-coding transcripts while others are in regions previously thought to be transcriptionally silent; (3) chromatin structure predicting the timing of DNA replication, while chromatin accessibility and histone modification patterns predict the presence and activity of transcription start sites; (4) the identification of several new transcription start sites that were surrounded by regulatory sequences with no upstream locational bias; (5) much variation itself in the sequence variability of both the functional elements and the likelihood that these elements were located in a structurally variable genomic region; and (6) lack of constraint of many functional elements across evolution, suggesting that there is a large pool of biochemically active, but neutral elements that provide no benefit to the organism). Elizabeth Pennisi summarizes some of the most surprising results of this and related research. Elizabeth Pennisi, News of the Week, *Genomics: DNA Study Forces Rethink of What It Means to Be a Gene*, 316 SCIENCE 1556, 1556–57 (2007) (stating that the research reveals an extremely different picture of DNA, RNA, protein, and their interactions than the one that scientists have assumed for decades). All of the following long-held assumptions appear to be wrong: (1) *DNA is compact*. No, human genes can be sprawling. (2) *Much of the transcribed DNA is translated*. Again, no, because although protein-coding DNA comprises 2% of the genome, 80% of the bases are being expressed. (3) *Not much untranslated DNA turns up as transcribed-only regulatory RNA*. On the contrary, this is the fate of a huge amount of untranslated DNA. Ms. Pennisi reports that these findings, combined with unexpected distributions of exons and promoters, suggest that “a multidimensional network regulates gene expression . . . [and] that because of this complexity, [some] researchers . . . [believe that] RNA transcripts[, not DNA transcripts, should be viewed] as the fundamental

unanticipated huge amount of expressed, non-coding DNA transcribed as regulatory non-coding RNA (ncRNA) is creating a multi-transcriptional knockout from a single RNAi sequence.⁶⁴ ENCODE and related recent research reveal enormously complex specific and global interconnectivities between metabolism, mRNA abundance, transcription, translation, protein production, and static architecture,⁶⁵

functional units of genomes.” *Id.* See Thomas R. Gingeras, Perspective, *Origin of Phenotypes: Genes and Transcripts*, 17 GENOME RES. 682, 683 (2007) (arguing that “a by-product of these [recent] studies [is] the unanticipated, but unanimous conclusion” that there is a huge amount of expressed DNA that never turns up in proteins). Gingeras states that it has been suggested that we temporarily refer to the large collection of newly identified putative non-protein coding transcripts as “transcripts of unknown function” (TUFs) until they are better understood. *Id.* See also Mark B. Gerstein et al., Perspective, *What is a Gene, Post-ENCODE? History and Updated Definition*, 17 GENOME RES. 669, 676 (2007) (proposing, in light of the diverse regulation and pervasive transcription highlighted by ENCODE, this newer, more inclusive definition of a gene which expands on the idea that genotypes make phenotypes: “A [gene is a] genomic sequence ([either] DNA or RNA) directly encoding functional product molecules. . . .”). This assumes, at the molecular level, that phenotype relates to biochemical function, because this assumption comports with earlier concepts of a gene. *Id.* at 679. If several functional products share overlapping regions, a gene is then the distinct union of all overlapping genome sequences coding for final RNA or protein products. *Id.* at 676–77. Nonetheless, Gerstein et al. suggest that defining “function” within their “gene” definition could be at best challenging and at worst impossible: “High-throughput biochemical and mutational assays will be needed to define function on a large scale. . . . However, we probably will not be able to ever know the function of all molecules in the genome.” *Id.* at 679.

64. See, e.g., Alex Gaither & Vadim Iourgenko, *RNA Interference Technologies and Their Use in Cancer Research*, 19 CURRENT OPINION ONCOLOGY 50, 50–53 (2006) (discussing the use of RNAi to knockout genes associated with neoplastic growth).

65. See, e.g., Yohann Grondin et al., *The Correlation Between Architecture and mRNA Abundance in the Genetic Regulatory Network of Escherichia Coli*, 1:30 BMC SYSTEMS BIOLOGY 1, 5 (2007) (agreeing with ENCODE, the authors found that “[m]any factors intervene in the dynamics of gene regulation,” including both “local factors such as the sequence specificity of the transcription factor DNA binding site and global ones such as the structural organization [sic] of the chromosomes”). Grondin et al. also found “a significant correlation between architecture and mRNA” which they speculated to be due to selective pressure to produce both enough regulator for phenotype production, but not too much regulator because that would require “more regulator to be eliminated in order to generate another phenotype.” *Id.* (citations omitted). The regulation is effected by DNA-binding transcription factor proteins encoded by certain mRNA. Grondin et al.’s findings also suggest a “significant correlation between the number of genes regulated by a transcription factor and the abundance of mRNA that encode for this transcription factor.” *Id.* See also Daniel H. Lackner et al., *A Network of Multiple Regulatory Layers Shapes Gene Expression in Fission Yeast*, 26 MOLECULAR CELL 145, 145–54 (2007) (conducting a translational profile of *S. pombe* cells which found multiple complex and unexpected genome-wide relationships between transcription and translation, as well as between translation and mRNA polyadenylation). Specific findings included these: (1) a positive correlation between mRNA length and translational efficiency which puzzled the authors because mRNA is inversely correlated with several other independent measures of translational efficiency; (2)

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 145

with newly discovered ncRNA playing key regulatory roles under both normal and pathological conditions.⁶⁶ Answering such a dauntingly large and diverse range of complex, but important questions about the human genome will also require improved methodologies.⁶⁷ Thus, despite some patenting and some substantial technological developments, the mechanisms of RNAi cannot be truly understood at present because RNAi has to fit within this multilayered “portfolio of biology puzzles” which will require much additional investigation.⁶⁸

deadenylation dynamics could explain “potentiation,” that is, “[i]ncreased transcription would temporarily increase the proportion of long-tailed mRNAs, which in turn would lead to increased translation,” which would provide an elegant global link between transcriptional and translational change; (3) the strong possibility that intracellular mechanisms and extracellular systems are congruent, if not coordinated, multilayered means of regulating protein production; and (4) transcriptional and translational efficiencies may be correlated, though not causally linked, due to “independent evolutionary selection at different levels of regulation.” *Id.*

66. Cf. Aldo Pagano et al., *New Small Nuclear RNA Gene-Like Transcriptional Units as Sources of Regulatory Transcripts*, 3 PLOS GENETICS 0174, 0175 (2007) (studying the particular ncRNAs synthesized by RNA polymerase III which the authors hypothesize play key roles in regulating protein-coding genes synthesized by RNA polymerase II).

67. Cf. Bradley E. Bernstein et al., Review, *The Mammalian Epigenome*, 128 CELL 669, 677–78 (2007) (reviewing the pertinent literature, emphasis is placed on methodological advances needed to answer many diverse and immensely complex epigenomic questions, with the conclusion that the enormity of the challenge should nonetheless not deter research because “a concerted effort toward understanding the [human] genome would ultimately be rewarded with a far richer understanding of how the genetic code is made manifest across an incredibly varied background of developmental stages, tissue types, and disease states”).

68. Cf. Chu & Rana, *supra* note 48, at 1133–34 (Cautioning that while their findings, combined with the results of previous research, “suggest an intriguing role for miRNA function in development and carcinogenesis[,] . . . most targets of miRNA have not yet been identified. . . . What determines the balance between active translation and repression of mRNAs targeted by miRISC, and how cells control the specificity of this repression, are key directions for future investigation.”); Zain Paroo et al., Review, *Biochemical Mechanisms of the RNA-Induced Silencing Complex*, 17 CELL RES. 187, 189, 192 (2007) (After listing and analyzing numerous broad unanswered questions regarding biochemical mechanisms of RNAi—e.g., “[w]hat are the biochemical functions of genetically identified RNAi components,” “[h]ow is RISC activity regulated”—the authors conclude that uncovering the “influence of cellular signaling pathways on RISC activity and the contribution of RNAi to physiological processes are [sic] critical in understanding the importance of small regulatory RNAs in biology and disease.”).

II. THE EFFECTIVE USE OF PATENT PORTFOLIOS⁶⁹ TO NAVIGATE THROUGH COMPLICATED AND UNCERTAIN LEGAL, SCIENTIFIC, AND TECHNOLOGICAL TERRITORIES

A. *The Patent Portfolio: The Main Unit of IP Value in All Three Technologies*

Universities and government agencies with innovations in nascent life science technologies, such as NB/BN, synthetic biology, or RNAi, which have near-term applications, often build and maintain patent portfolios to help them get good exclusive licensing deals with start-ups that show promise for commercial development. The university/government agency-start-up alliance can then further develop the portfolio to get and keep venture capital, with the hope that the start-up or the portfolio itself will mature into a lucrative acquisition target for a large pharmaceutical or biotechnology company. Patent portfolio theory provides considerable explanatory power for how patenting fits into commercial decision-making in all three technologies.⁷⁰ The theory explains, at least in part, each of the following: (1) the prevalence of heavy, early, and broad patenting; (2) why government agencies, universities, and start-ups that obtain

69. I say “patent,” not “IP” portfolios, because virtually all NB/BN and RNAi inventions will be patented. Although it is possible that some synthetic biology inventions will be governed by copyright law, Kumar and Rai, in examining the constraints of statutory construction, current practice in synthetic biology, and policy concerns, are skeptical that this will be the case. See Kumar & Rai, *supra* note 28, at 1763–64.

Synthetic biologists might argue that strings of DNA bases are comparable to source code and that DNA strings could therefore also be covered by copyright.

Unlike software, however, the products of synthetic biology are not discussed . . . in the [copyright] statute. Thus, a court that . . . wished to find that material copyrightable would have to do so by analogy. Additionally, even if courts were willing to make such an analogy, [17 U.S.C. § 101, the statute defining what is copyrightable] . . . requires expressive choices. . . .

The construction of DNA sequences using base pairs that do not exist in nature might allow significant room for expressive choice. . . . However, most synthetic biologists working today, including those at MIT, are working within the confines of the existing genetic code. This code constrains the expressive choices that they make, making copyright protection less likely.

Beyond formal legal doctrine lies a set of policy concerns [given that patent rights are available, adding an entirely new type of right might hurt innovation].

Id. (citations omitted).

70. See generally Gideon Parchomovsky & R. Polk Wagner, *Patent Portfolios*, 154 U. PA. L. REV. 1, 1 (2005) (making a somewhat similar, though more thorough and generally applicable argument than the one I am presenting only for three technologies, that is, that the patent portfolio represents the “true value of patents”).

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 147

attractive exclusive licensing agreements typically have patent portfolios with many diverse, but distinct, patents—the collective power of the patents in the portfolio gives the portfolio leveraging might that is largely independent of the value of any patent; (3) the diversity of claims patented by a university or start-up company—the diversity maximizes the range of related activity on which the university investigators or start-up company can construct and develop research; (4) both the high diversity and high quantity of patents in successful portfolios give the patentee an insurance that is especially valuable where, as in all three of these technologies, the pertinent science, technology, and law are all highly uncertain and quickly evolving, that is, an insurance against determinations of individual patent invalidity, infringement, or lack of commercial value;⁷¹ and (5) the incentives for patent thicket formation, as well as the associated increased risks of holdup and bargaining failure, validate the concerns of some IP scholars that the worsening patent thicket problem has increased the costs of innovation.

Nonetheless, Robert Merges, a skeptic of the idea that software patent portfolios are produced primarily for “defensive purposes” with insufficient care given to individual patents, conducted an empirical study in the software industry which reported high correlations between at least some proxies of correlates of prosecution effort and firm success.⁷² Although my Article is interested in natural science patents, not software patents, Merges’ critique, though industry-specific, could perhaps be generalized as an argument for the perceived greater relevance of individual patents vis-à-vis patent portfolios.

I will first explain why I do not find Merges’ empirical critique of portfolio theory compelling, then distinguish my portfolio theory

71. Regarding the potential litigation protection of nanotechnology patent portfolios, compare R. Douglass Moffat, *Public Markets and Nanotechnology Companies*, in LYNN E. FOSTER, *NANOTECHNOLOGY: SCIENCE, INNOVATION, AND OPPORTUNITY* 61, 61–62 (2006).

At this stage of nanotechnology development . . . intellectual property platforms based on broad patents (often coming from academia) are the main assets behind many companies. The applicability of this . . . [technology] could cut across many markets and applications. Some firms have amassed broad IP by taking a portfolio approach to early-stage commercialization. . . . Such diversification . . . makes sense not only from a scientific point of view but also to lessen risks associated with potential patent litigation. The patent landscape in nanotech might be likened to the gold rush days, with [many] overlapping claims.

72. Robert P. Merges, *Patents, Entry and Growth in the Software Industry* 1, 23 (Aug. 1, 2006) (unpublished manuscript, available at <http://ssrn.com/abstract=926204>).

somewhat from that of Gideon Parchomovsky and R. Polk Wagner. Even assuming, arguendo, that the serious methodological and analytical problems in Merges' study⁷³ could be remedied in either a revision of his manuscript or a subsequent study such that better support is provided for his hypothesis that prosecutorial effort on individual patents fosters firm success, aggregate effort applied to patent portfolios could foster even greater firm success. In fact, Merges admits that his study is consistent with this hypothesis:

[T]he results for the total number of patents held by the firm . . . are somewhat puzzling. Only the square of this number is significant. This latter result suggests that the size of a firm's patent portfolio does have an effect on the firm's success, one that increases in magnitude nonlinearly with the size of the portfolio.⁷⁴

Merges' study *at most* implies that the value of individual patents is not negligible, which does not preclude the possibility that their value is often far exceeded by that of the portfolios that they comprise. The nonlinear relationship that Merges found (again, assuming arguendo that this relationship would persist after the methodological and analytical problems were remedied) could be due to the presence of

73. *Id.* at 16–37. The study has at least two analytical flaws: (1) causal inferences are at least implied from individual correlates between proxies of prosecutorial effort and firm growth for firms of various sizes, without any indication that *ceteris paribus* conditions have been met; and (2) no rationale for choosing various proxies of prosecutorial effort is given. The study also has at least three methodological flaws: (1) correlational coefficients and T values are provided without indicating precisely which tests are used; (2) If the Pearson r and a one-way T test were used, there is no indication that Kolmogorov-Smirnov or other tests for normal distribution were used, which is particularly problematic given that,

patent counts exhibit relatively large means and heavy upper tails[, which] . . . usually indicates the presence of overdispersion that is consistent with the presence of both observed and unobserved heterogeneity. It may also reflect the presence of outliers that cannot be easily modeled by assuming smoothly distributed unobserved heterogeneity. The consequences of these features of data for alternative modeling strategies deserves further investigation because the regression models based on several popular discrete distributions are unsuitable.

Jie Q. Guo & Pravin K. Trivedi, *Flexible Parametric Models for Long-Tailed Patent Count Distributions*, 64 *OXFORD BULL. ECON. & STAT.* 63, 63 (2002); and (3) data from several privately held firms was not used because “erroneously identical numbers [were] reported for revenues and employees from year to year. In such instances where firm data appeared suspect, a new company was randomly selected to sample.” Merges, *supra* note 72, at 18. These several replacements could have introduced selection bias.

74. Merges, *supra* note 72, at 21.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 149

outliers, which would be consistent with my qualified portfolio theory that I will now describe.

There are different versions of patent portfolio theory. My version is that the value of a large and distinct, but related, group of patents often functions as something of a super-patent, high in scale,⁷⁵ diversity,⁷⁶ and quantity,⁷⁷ as previously described by Parchomovsky and Wagner. However, I also find Parchomovsky and Wagner's description of an inverse relationship between individual patent value and the number of patents in a portfolio⁷⁸ imprecise. Parchomovsky and Wagner view quantity of patents in a portfolio as a mitigation of the tradeoff between diversity and scale, as well as an explanation of the apparent paradox that firms acquire individual patents at costs that exceed their individual values.⁷⁹

I mostly agree that the pertinent firm benefit in a cost-benefit comparison is the marginal value that the additional patent is expected to add to the portfolio compared to the marginal cost of acquiring the patent, but, unlike Parchomovsky and Wagner,⁸⁰ I do not infer virtual irrelevance of individual patent value in patenting decisions from this portfolio-level cost-benefit assessment. Parchomovsky and Wagner state that “[t]he overwhelming majority of patents have no value whatsoever, and of those that have value, it is nearly impossible to determine *ex ante*,”⁸¹ although they do not provide a very compelling argument to support this assertion. Certainly, a major innovative breakthrough with clearly foreseeable substantial clinical medical applications would have a high probable value *ex ante*. Parchomovsky and Wagner also do not adequately address the possibility of an individual prospective or actual patent or claim of such high value that to some extent it “transcends the portfolio” as measured by the disproportionate attention the patent or claim receives from the patent applicant or patentee and his or her competitors. Their statement that although “individual patents may be of great independent value to their inventors[,] . . . [i]nventors can increase the value of such patents by

75. Parchomovsky & Wagner, *supra* note 70, at 31–37.

76. *Id.* at 37–41.

77. *Id.* at 42–43.

78. *See id.* at 42.

79. *Id.*

80. *See id.* at 42–43 (asserting that under patent portfolio theory, patenting decisions are made with virtually no consideration of the value of individual patents).

81. *Id.* at 5 (emphasis added).

constructing a portfolio around them”⁸² implicitly dismisses this transcendent possibility, even though the distribution of the value of patents is apparently quite skewed.⁸³

Perhaps an analogy between coaching a successful professional football team and obtaining and maintaining a successful patent portfolio is apt.⁸⁴ Although the ultimate value of the 2007 New England Patriots was their collective and coordinated breadth and depth of skills, coaching attention paid to individual players was proportionate to overall pertinent coordinated skill breadth and depth.⁸⁵ Thus, to extend the analogy, perhaps in an NB/BN, synthetic biology, or RNAi portfolio, there is a key Tom Brady quarterback patent within which there is also a key throwing method claim. Much attention will be paid to prosecuting that patent, with special care given to the written description, enablement, and claim drafting for the throwing method. That does not mean that the portfolio of coordinated skills taken as a totality is not the best predictor of team success. The value of the throwing method claim should thus be viewed primarily, though not

82. *Id.* at 9.

83. See Mark A. Lemley & Carl Shapiro, *Probabilistic Patents*, 19 J. ECON. PERSP. 75, 80 (2005) [hereinafter Lemley & Shapiro, *Probabilistic Patents*] (reporting that “the top [one] percent of patents [are] more than [one] thousand times as valuable as the median patent.”).

84. This analogy is used partly because pertinent natural science firms do not put their patent portfolio evolutions on display with explanatory footnotes. Moreover, because of the nascent nature of NB/BN, synthetic biology, and RNAi, firms have not yet gone through their patent life cycles to allow for retrospective analysis. In addition, professional athletics teams are well-known, allowing for rather transparent analogies. Although there are obvious pertinent differences between professional athletics teams and life science firms, there are many pertinent similarities as well, such as possible high commercial value that depends at least partly on prudent planning to maximize the probability of success.

85. Note that I said 2007 New England Patriots, not 2007–2008 New England Patriots; the Patriots certainly appeared invincible in 2007, but the New York Giants victory over the Patriots in the 2008 Super Bowl proved that the Patriots could be beaten. The lesson for near-term patent portfolio enabled commercialization may be that even the most promising commercial ventures can backfire. Cf. Ann Thayer, Latest News, *Harvard Licenses Nanotech Patents: Nano-Terra Gets Whitesides Nanofabrication Portfolio*, 85 CHEMICAL & ENGINEERING NEWS, June 11, 2007, at 14, [hereinafter Thayer, *Harvard Licenses Nanotech Patents*] (arguing that Nano-Terra, a start-up that licensed an extremely promising patent portfolio from Harvard in 2007, may be analogous to Nanosys, another nanotechnology start-up founded in 2001 by Harvard chemistry professors Charles M. Lieber and Hongkun Park, among others). Nanosys is reported to have had a similar approach to Nano-Terra for commercializing nanotechnology and to have about 500 patents and patent applications, many licensed from Harvard, Columbia University, MIT, and the University of California. Like Nano-Terra, Nanosys’ scientific connections and IP attracted investors, only to disappoint them when it called off a \$100 million stock offering in 2004. *Id.*

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 151

entirely, within the context of the Tom Brady quarterback patent. The patent in turn should be viewed primarily, though not entirely, within the context of the New England Patriots firm capital. I say not entirely, because this particular throwing method claim and this particular Tom Brady quarterback patent alone would have a high market value for many teams, and thus neither has a negligible value divorced from the Patriot portfolio.

Moreover, such particularly important individual patents and claims can play distinct decontextualized roles, especially when they are even more exceptionally valuable vis-à-vis the team. Team size, like quantity of patents in the portfolio, does have the effect of greatly reducing this possibility of the extraordinarily valuable outlier dwarfing the portfolio such that the value of the portfolio could be viewed as more dependent on it than vice versa. Thus, in a sport such a football, where team size is large, player value is more contextualized. In a sport such as basketball, with a maximum team size of twelve, the exceptional outlier like Michael Jordan of the 1995 Chicago Bulls can have a value that exceeds that of the remainder of the team. The team's greater dependence on him than vice versa could be calculated by the probable difference that he alone made to the team's exceptional performance.⁸⁶ Thus, ceteris paribus, the probability of an extremely valuable outlier patent or claim may vary inversely with the respective number of patents or claims in the portfolio. Extremely valuable outlier patents or claims are probably rare in start-up firms with large patent portfolios, but there certainly are dominant patents and claims with effects that exceed, if not dwarf, the composite effects of patents and claims in the remainder of their portfolios.

The very small percentage of utility patents that are litigated—or even enforced throughout their potential twenty-year term⁸⁷—suggests that the “extraordinary outlier” is rare indeed. Thus, my view is that

86. For example, but for Michael Jordan, it is very unlikely both that the team would have won a record seventy-two games in the regular season and that the team would have dominated the competition in the postseason.

87. See John R. Allison et al., *Valuable Patents*, 92 GEO. L. J. 435, 437 (2004); Lemley & Shapiro, *Probabilistic Patents*, *supra* note 83, at 75 (2005) (stating that the empirical evidence indicates that of the 200,000 patents issued each year, 1.5 percent are litigated and 0.1 percent are litigated to trial); SUZANNE SCOTCHMER, *INNOVATION AND INCENTIVES* 202–03 (2004) (discussing two studies of biotechnology patent litigation rates, one finding six per 100 biotech patents litigated, the other finding 1.9 per 100 biotech patents litigated). The study reporting a 1.9/100 biotech patent litigation rate also reported that the litigation was concentrated in “high-value patents,” which is consistent with the extraordinarily valuable outlier that qualifies my patent portfolio theory.

there are a few individual patents and claims of a distinct, high worth that to some extent transcends the worth of the portfolios that contain them. This qualified portfolio theory appears more credible than Parchomovsky and Wagner's categorical portfolio theory that makes individual patent irrelevance the predominant effect of maximizing portfolio diversity and scale via within-portfolio high quantity patenting that mitigates the scale-diversity tradeoff. The relatively few utility patents that are either litigated or enforced throughout the maximum twenty-year patent term is consistent with my qualified portfolio theory because, while my theory makes the portfolio the primary unit of value, the theory also allows for extraordinarily valuable individual patents to be carefully and vigorously protected via litigation and maximum term enforcement. While no doubt there are many other considerations, these considerations nonetheless appear to make a qualified portfolio theory more credible than an absolute portfolio theory.

The rarity of litigation and full-term enforcement also create additional problems for Merges' prosecution effort-based critique of portfolio theory. The most notable problem is the strong possibility that this effort reflects *ex ante* ignorance about portfolio value more than it does the pursuit of individualized, rather than portfolio-based, approaches to commercialization. Once proportionate patent and claim value in the portfolio as it pertains to more global commercialization, research, and development prospects become clear, low attention to the vast majority of individual patents is correctly predicted by my qualified patent portfolio theory.

There are scholars who do not attempt to refute the apparent paradox that firms acquire individual patents at costs that exceed their individual values, although unlike Parchomovsky, Wagner, and myself, they also do not use patent portfolio theory to explain the apparent paradox. The following are among the theoretical alternatives to patent portfolio theory presented as explanations: patents as signals, patents as internal metrics, the lottery theory of patents, and defensive patenting. However, Parchomovsky and Wagner effectively critique each of these alternatives to patent portfolio theory.⁸⁸

88. See generally Parchomovsky & Wagner, *supra* note 70. Most persuasive among their critiques are the following. First, signaling theory—patents signal to third parties information about the patented invention and patenting firm—fails to explain the patent paradox, because if the expected value of individual inventions is low, “it is not clear how information about individual . . . [patents] is valuable to third parties.” *Id.* at 21–22. Second, internal metrics theory—patents serve an intra-firm purpose, that is, measuring employee productivity—also fails to explain the patent paradox. “Given the low private value of

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 153

Moreover, the key value of patent portfolios is emphasized not only by scholars such as Parchomovsky and Wagner, but also by practitioners.⁸⁹ Looking at the three technologies under discussion, I will now show how portfolio-driven over-patenting contributes to both thickets and low quality patents. Later, I will show the extensive exclusive licensing predicted by patent portfolio theory.

B. Patent Thickets and Low Quality Patents: Consequences of Patenting Too Early, Too Many, and Too Broadly in NB/BN, Synthetic Biology, and RNAi

In various technology sectors in NB/BN, synthetic biology, and, to a lesser extent, RNAi, patents that were too broad in scope were pursued and granted too early and too often to too many inventors. In various sectors in all three technologies, universities have been frequent participants in this rush to patent many broad patents early. Several factors foster thickets and low quality patents in these technologies: (1) the complexities of the technologies; (2) insufficient attention to

patents, it seems problematic to equate patent filings with successful job performance.” *Id.* at 22–23. Third, defensive patenting theory—patents are “bargaining chips to negotiate with competitors and to secure certain niches in the marketplace”—is only partly correct, because the portfolio can act not only as shield, but also as sword, that is, defensive patenting theory ignores “offensive uses conferred with patent rights.” *Id.* at 26–27. Fourth, lottery theory—patents are generally of very low value, but “a few are of such great financial consequence that they provide a sufficient incentive to inventors to obtain patents, based on the infinitesimal hope of receiving an extremely high payoff”—assumes that inventors are “so risk-seeking that they are willing to engage in an activity with a negative expected value. However, the standard assumption in the patent literature . . . is that investors are actually risk-averse.” *Id.* at 24–25. I would add the following critique of lottery theory: although my qualified portfolio theory allows for the exceptionally valuable outlier claim or patent as an exception to the generality that patents are purchased at costs that exceed their projected and actual worth, I reason that this allows for fairly rare, intense, individualized protection via careful prosecution, litigation, and full-patent term enforcement. This protection is due to probable exceptional ex ante worth, probable or known exceptional ex post worth, or both. The protection is not lottery-like gambling, either ex ante or ex post, on the very improbable existence of an outlier claim or patent of exceptional worth.

89. In NB/BN, see, for example, Chinh H. Pham & Charles Berman, *Intellectual Property Policy and Impact*, in LYNN E. FOSTER, *NANOTECHNOLOGY: SCIENCE, INNOVATION, AND OPPORTUNITY* 105, 106 (2006) (Lawyers Pham and Berman argue that a patent portfolio should “minimize the gaps that competitors can design around” and that the “challenge of creating a strong and solid portfolio is equally applicable to the field of nanotechnology.”). See also Bruce S. Itchkawitz, *Developing an Effective Patent Portfolio*, 3 *NSTI-NANOTECH* 344 (2006); Albert P. Halluin & Lorelei P. Westin, *Nanotechnology: The Importance of Intellectual Property Rights in an Emerging Technology*, 86 *J. PAT. & TRADEMARK OFF. SOC’Y* 220, 226 (2004) (contending that “the key to the success of many emerging technology companies will be how well-managed their intellectual property portfolio is”).

individual patents by some patent practitioners; (3) the perceived need to claim as much new turf as soon as possible to defend against others rushing in to patent portions of the nascent field which could possibly be viewed as within the scope of one's specification;⁹⁰ and (4) the burden on overworked and undertrained patent examiners.

A thicket is not equivalent to a group of invalid patents, infringing patents, or both. In a thicket, numerous inventors can hold valid patents that nonetheless create a high density of patent protection for potential commercial products or services.⁹¹ However, this distinction between thicketing as a barrier to commercialization and other legal and technological barriers to commercialization does not mean that the two are mutually exclusive. Some patents in a portfolio may add to thicket density, while others in the portfolio may be infringing overlaps or be invalid because of lack of utility, an inadequate written description or enablement in the specification, or claim indefiniteness. Obviousness, post-*KSR*,⁹² is another major hurdle to their validity. Patent thickets could thus lead to various transaction costs that stymie innovation and development.⁹³

Nonetheless, some commentators paint a picture of an uncluttered biotechnology patent landscape. This view has been based on the commonsensical argument that anticommons thicketing should be viewed as the ratio of the number of patents in the field to the breadth

90. See Halluin & Westin, *supra* note 89 at 226–27. See also Bawa Commentary, *supra* note 15, at 346–49. Cf. Raj Bawa et al., *Protecting New Ideas and Inventions in Nanomedicine with Patents*, 1 *NANOMEDICINE: NANOTECHNOLOGY, BIOLOGY, AND MED.* 150, 155 (2005) [hereinafter Bawa et al., *Protecting Nanomedicine*] (expressing concern that the proliferation of broad patents in nanotechnology could ultimately require litigation to untangle, “especially if sectors of nanomedicine become financially lucrative,” and reporting a classic patent thicket already “developing in the area of single-walled carbon nanotubes”).

91. See Gavin D. George, Note, *What is Hiding in the Bushes? eBay's Effect on Holdout Behavior in Patent Thickets*, 13 *MICH. TELECOMM. & TECH. L. REV.* 557, 557 (2007) (defining a patent thicket as existing “where there are numerous different firms holding patents that are legally and technologically distinct, but overlap to cover a much smaller number of actual or potential commercial products”).

92. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007).

93. See Helen M. Berman & Rochelle C. Dreyfuss, *Reflections on the Science and Law of Structural Biology, Genomics, and Drug Development*, 53 *UCLA L. REV.* 871, 902 (2006) (arguing that the problems with biotechnology patents of broad scope are clear, namely, difficulties in negotiating thickets of rights which effect inefficient exploration of some areas of research, while also precluding the encouragement needed to solicit second-comers to find new uses that build on patents in the thickets); Bawa et al., *Protecting Nanomedicine*, *supra* note 90 (contending that the end result of the proliferation of nanotechnology patents that lead to thickets is “a drag on the innovation process itself”).

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 155

of the field.⁹⁴ A thicket of course does denote high population density, not just high population or high population growth. Thus, given the breadth of all three fields, reports of industry-wide heavy patenting in NB/BN, synthetic biology, or RNAi do not cause as much concern as do reports of the issuance of many patents in fairly narrow sectors within the fields. Unfortunately, however, there have been reports of thickets in fairly narrow sectors in all three fields: for example, in NB/BN, single-walled carbon nanotubes;⁹⁵ in synthetic biology, DNA-binding proteins;⁹⁶ and in RNAi, clinical medical therapeutics.⁹⁷ Reportedly more cautious PTO examinations of RNAi patent applications may make thicketing less of a problem in RNAi.⁹⁸ Yet the issuance of the first RNAi target-specific patent to Sirna Therapeutics—covering *any* chemically modified siRNA that targets the KK-gamma gene (implicated in several diseases including asthma, arthritis, and cancer)⁹⁹—is viewed by one industry insider as overly broad.¹⁰⁰

The problem of many overbroad patents is of particular concern—especially in NB/BN—among foundational patents. One worry is that such patents could stymie development by reducing access to foundational building blocks.¹⁰¹ Even in synthetic biology where

94. *E.g.*, David E. Adelman & Kathryn L. DeAngelis, *Patent Metrics: The Mismeasure of Innovation in the Biotech Patent Debate*, 85 TEX. L. REV. 1677, 1682 (2007) (arguing that an anticommens cannot be inferred only from a high number of patents in an industry, because one must also consider the breadth of the industry).

95. *E.g.*, Bawa et al., *Protecting Nanomedicine*, *supra* note 90. *Cf.* Pham & Berman, *supra* note 89, at 113.

If the USPTO were to allow broad patent claims it would restrict innovation by allowing a few major players to control a large share of the field and crowd out small, innovative players[;] . . . in some areas a restriction on innovation may soon be created. This [may] be especially true for inventions involving carbon nanotubes. There are currently an abundance of issued patents, many of which may be overlapping in scope.

96. *E.g.*, Kumar & Rai, *supra* note 28, at 1758–60.

97. *E.g.*, Schmidt, *supra* note 61, at 273–75.

98. *See id.* at 273.

99. *Id.* at 275. *See also* U.S. Patent No. 7,022,828 (filed May 28, 2002) (issued April 4, 2006).

100. Schmidt, *supra* note 61, at 275 (quoting an anonymous industry insider: “[w]e’re sure the siRNA community will address these kinds of patents and unite to stop them”). This insider also predicted “fierce fighting among companies when it comes to these [target-specific] patents; this will be a future battlefield.” *Id.* (alteration in original).

101. *Cf.* Ted Sabety, *Nanotech Innovation and the Patent Thicket: Which IP Policies Promote Growth?*, 1 NANOBIOTECHNOLOGY L. & BUS. 262, 275–76, 278–79 (2004) (arguing that because the cluttered patent landscape of nanotechnology resembles that of the radio industry and that the government-compelled creation of RCA to pool radio patents may have prevented thicket-induced slowed production, the government should proactively intervene

commons of standard building blocks have been created,¹⁰² at least one broad foundational synthetic biology patent has been issued.¹⁰³ One scholar contends that “even assuming appropriate enforcement of foundational patents, a proliferation of patents on basic parts and devices could create transaction-cost-heavy thickets or ‘anticommons.’”¹⁰⁴

Prior to PTO’s creation of a nanotechnology art division,¹⁰⁵ nanotechnology patent practitioners often claimed that allegedly nano-ignorant patent examiners were entirely responsible for the issuance of invalid nanotech patents, although the practitioners also commended PTO attempts to remedy the alleged ignorance.¹⁰⁶ In contrast, some academics alleged that practitioners pursued the maximal value of patent portfolios—or simply patented early, broadly, and often—with each new patent reducing the risk of a later validity or infringement challenge.¹⁰⁷

The likely truth is that both examiner nano-ignorance and practitioner pursuit of maximum patent portfolio value effected less-thorough-than-needed drafting of many individual claims and the written description or the enablement parts of the specifications. The lack of thoroughness caused the issuance of many overbroad and/or overlapping NB/BN patents, many of which were foundational. However, it is also probably true that neither the examiners nor the practitioners deserve blame. The examiners were extremely overworked and not specifically trained in NB/BN, which may excuse

in nanotechnology by creating publicly funded foundational patents).

102. See, e.g., Kumar & Rai, *supra* note 28, at 1763–65 (discussing synthetic biology commons, including one at MIT, and one at Biological Innovation for Open Society (BIOS), the latter being a patent-based commons). The MIT Registry contains more than two thousand standardized parts; “[t]he MIT scientists involved with the Registry . . . are sufficiently concerned that they have created a ‘BioBricks Foundation’ that might serve to coordinate a synthetic biology commons.” *Id.*

103. See U.S. Patent No. 6,774,222 (filed Dec. 15, 2000) (covering molecular computing elements, gates, and flip-flops).

104. See Kumar & Rai, *supra* note 28, at 1747.

105. See PATENT AND TRADEMARK OFFICE, U.S. DEPARTMENT OF COMMERCE, CLASSIFICATION ORDER 1850 (2005), available at <http://www.uspto.gov/web/offices/opc/documents/1850.pdf>.

106. E.g., MORRISON AND FOERSTER, LEGAL UPDATES AND NEWS, COMMERCIALIZING NANOBIO PRODUCTS: AN OVERVIEW OF LEGAL ISSUES AND REGULATIONS (2004), <http://www.mofo.com/news/updates/files/update1366.html> (last visited Nov. 8, 2008).

107. See, e.g., Parchomovsky & Wagner, *supra* note 70, at 33–36.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 157

them of some nano-ignorance.¹⁰⁸ The practitioners were also obligated to both their firms and their clients to provide the greatest overall value to their clients in a highly competitive new technology where patent portfolio value was the best approximation of that value. The responsibility to fix the system needed to come from outside observers, such as academics who can afford to be disinterested, as well as Congress and the federal courts. It is thus most heartening that academics, legislators, and judges have worked towards ways to reduce patent thickets and increase patent quality. I will now describe how particular doctrinal, statutory, and PTO rule changes may help reduce the patent thickets and increase patent quality, as part of an assessment of the changing legal, scientific, and technological landscapes. I will also describe challenges that these landscapes create for practitioners seeking to maximize patent portfolio value.

C. Prosecuting to Maximize Patent Portfolio Value When the Pertinent Patent Law, Science, and Technology are All Uncertain and Quickly Changing

In this section, I will address patent prosecution challenges in all three fields that are experiencing rapid and uncertain legal, scientific, and technological changes. I will focus first on how the higher obviousness bar effected by *KSR* and its Federal Circuit progeny,¹⁰⁹ as

108. See Uhler, *supra* note 23, at 341. The multidisciplinary nature of the field also appears to have made adequate examiner training in nanotechnology an arduous task. Because the novelty of many nanotechnology inventions inheres in their unusual and/or size-dependent properties, the applicant's capacity to be his or her own lexicographer encourages one to define the inventions by property limitations over the prior art oneself. The definiteness requirement for validity thus puts the examiner in the position of evaluating the metes and bounds of nanoproperties that complicate the claim's relationship to the prior art. See *id.* at 345. Moreover, "in any given nanotech case, the chance that an examiner will possess practical knowledge of the relevant technology is small. Thus, examiners will more likely fail either to appreciate the significance of the properties exhibited by nanotechnology, or to recognize these properties or their equivalents in the prior art." *Id.* at 341.

109. Prior to *KSR*, there was a growing concern that both rejection rates during prosecution and invalidity determinations during litigation were too low, largely because the obviousness bar had become too low. Regarding invalidity determinations during litigation, see, for example, Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L. J. 1155, 1156 (2002) (stating that "[i]n biotechnology cases, the Federal Circuit has bent over backwards to find biotechnolog[y] inventions nonobvious, even if the prior art demonstrates a clear plan for producing the invention"). But see generally Christopher A. Cotropia, *Nonobviousness and the Federal Circuit: An Empirical Analysis of Recent Case Law*, 82 NOTRE DAME L. REV. 911 (2007) (reporting, while the *KSR* decision was pending, various results from his statistical study of Federal Circuit obviousness

well as likely components of the Patent Reform Act, will make some pertinent patent prosecutions less certain and some pertinent patent validity challenges less risky.

determinations from January 1, 2002 to December 31, 2005 from which he inferred both that it is likely that the Federal Circuit has no bias towards nonobviousness and that, overall, the “suggestion test,” or the TSM test, plays a small role in its obviousness determinations). However, his statistical analysis has the following limitations which preclude support for either inference. First, by temporally truncating the population parameter to four years, Cotropia obtained a total population of 102 patents. Cotropia contends “while information from the 1980s and 1990s is nice, the focus of the current debate is on the Federal Circuit’s recent jurisprudence. It matters little what the court’s take on nonobviousness was twenty years ago.” *Id.* at 927. But on the previous page he seems to contradict this blithe justification for his temporal truncation—“the population of this study can be used to predict the ‘population of all past and future . . . decisions[.]’”—implying that the validity of the study’s findings could be checked by how they predict populations from the 1980s and 1990s. *Id.* at 926 (alteration in original). Moreover, including the earlier patents would have allowed for trend analyses. Most importantly, the earlier patents would have increased the subpopulation sizes, thus increasing a type of statistical power, that is, the improbability of committing a β error in subpopulation comparisons. Consider the 0.1668 p-value for the Fisher’s Exact Test which Cotropia obtained by comparing the Federal Circuit’s obviousness determinations of appeals from lower court infringement cases with the determinations in the lower courts. *Id.* at 933. If he had included the early patents to increase the N, the differences most likely would have resulted in a p-value of less than 0.05. Second, Cotropia contends that, because nonobviousness is a fact-intensive inquiry, it is difficult to determine whether a decision is incorrect. *Id.* at 929. Although Cotropia states that such fact-intensive inquiry does not appear possible on a large scale, by reducing his population parameters to obtain only 102 patents, his own inquiry is medium-scale at best. Despite lack of knowledge of the underlying facts, he tacitly assumes throughout the study, by testing repeatedly for deviations from a 50% obviousness determination rate, that this rate indicates lack of bias regarding obviousness. *See, e.g., id.* at 931–33. An analysis of the underlying facts and pertinent statutory and case law could have indicated a point much higher or lower than this for any subpopulation comparison. Thus, because Cotropia fails to place the data in its proper underlying factual context, his inferences about the statistical significance of his data are invalid. The absence of facts, combined with this assumed null hypothesis (i.e., judge tacitly assumed unbiased if obviousness determinations are 50%), also creates a lack of internal validity because the facts are confounders and hence his statement that “[s]tatistical testing supports this causal observation” is false. *Id.* at 948. Third, Cotropia’s differential treatment of decisions where all claims in a patent were determined valid or invalid (he operationally defined the totality of the claims as one “patent”) vis-à-vis decisions where some of a patent’s claims were determined valid and others determined invalid (he operationally defined the valid and invalid ones as two distinct “patents”) introduced at least some systematic bias. *See id.* at 925. Perhaps if he had supplemented this approach with analyses of claims only, he could have compared resulting differences in ways that would have detected the extent to which this bias alone invalidated the study, notwithstanding all of its other aforementioned limitations. These limitations are stated in detail not only to support the proposition that Cotropia’s data does not afford him the inferences that he draws from it, but also to highlight just some of the many methodological problems that can occur in patent metrics. In addition, a second proposition is supported, that is, that patent metrics studies should be designed, conducted, and analyzed with extreme care.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 159

1. *KSR Int'l Co. v. Teleflex, Inc.* and Pertinent Likely Provisions of the Patent Reform Act: Effects on Patent Prosecution

a. *The Heightened Obviousness Bar for Post-KSR NB/BN, Synthetic Biology, and RNAi Claims to Combinations*

KSR Int'l Co. v. Teleflex, Inc. heightened the obviousness bar with a unanimous Supreme Court opinion¹¹⁰ that serves as both an ex ante (i.e., pre-issuance) prosecutorial bar on obvious patent application claims and an ex post (i.e., post-issuance) weeder of obvious patent claims. According to the Federal Circuit's teaching, suggestion, or motivation (TSM) test for obviousness under 35 U.S.C. § 103, an invention is obvious if a hypothetical "person having ordinary skill in the art" (PHOSITA) would have found a teaching, suggestion, or motivation to combine prior art references to make the invention. However, in April 2007, the Supreme Court held in *KSR* that the Federal Circuit's use of the TSM test was too rigid because it required that the prior art address the particular problem that the patentee sought to solve.¹¹¹ *KSR* held that the obviousness PHOSITA would not be confined to consider only the elements designed to solve the problem because "[c]ommon sense teaches . . . that familiar items may have obvious uses beyond their primary purposes. . . ."¹¹² *KSR* thus raised the obviousness bar to patent validity.

However, *KSR* also held that intensive, explicit analysis is often required to determine if there is an apparent reason to combine known elements as manifested in a combination.¹¹³ Obviousness is not proven merely by identifying in the prior art all of the elements of an invention.¹¹⁴ Nonetheless, the Court maintained that teachings themselves need not be explicit and that a court should account for the inferences and creative steps that the obviousness PHOSITA would make.¹¹⁵

Cautioning against "overemphasis on . . . published articles [or] the explicit content of issued patents," the Court opined that when there is little discussion of obvious combinations, "it often may be the case that market demand, rather than scientific literature, will drive design

110. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1733 (2007).

111. *Id.* at 1741–42.

112. *Id.* at 1742.

113. *Id.* at 1740–41.

114. *Id.* at 1741.

115. *Id.*

trends.”¹¹⁶ Design incentives and other market forces could be available in a different field or endeavor.¹¹⁷ Likewise, if a technique used to improve one device would be recognized by the obviousness PHOSITA as likely to improve similar devices in the same way, this recognition would make the technique obvious unless the actual application of the technique would be beyond the obviousness PHOSITA’s skill.¹¹⁸ However, this prescription for inquiries into sources other than published articles and issued patents was counterbalanced with an emphasis on multiple patent review: “Often, it will be necessary for a court to look at the interrelated teachings of multiple patents. . . .”¹¹⁹ Thus, the Court emphasized the need for an expanded obviousness analysis based on more patent and publication-related information, as well as more non-patent and non-publication-related information. This emphasis on an expansive inquiry came with a related warning not to transform the general principle underlying the TSM test and *Graham* into a rigid rule that limits obviousness inquiry, although, if such rigidity was eschewed, both the TSM test and *Graham* could still be useful in an obviousness analysis otherwise correctly applied.¹²⁰ The Court argued that *Graham* itself prescribed a broad obviousness inquiry,¹²¹ and that the material issue is “the objective reach of the claim.”¹²²

Stating bluntly that “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton,”¹²³ the Court, contrary to the Federal Circuit, opined that proof that a combination was “obvious to try” could make a claim for the combination obvious.¹²⁴ “Obvious to try” can be shown by design need or market pressure to solve a problem for which there are finite, predictable solutions that the obviousness PHOSITA would have reason to pursue and could anticipate a successful pursuit.¹²⁵

116. *Id.*

117. *Id.* at 1740.

118. *Id.*

119. *Id.*

120. *Id.* at 1741. *See also* *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966).

121. *KSR*, 127 S. Ct. at 1739.

122. *Id.* at 1742.

123. *Id.*

124. *Id.*

125. *Id.* Recall also that *KSR* stated that market and design forces can come from a different field altogether and can involve a claimed technique for a device that is different, though similar, if the obviousness PHOSITA would have recognized using that technique to make the similar device, and it was within his or her technical skill to make it. *See id.* at 1740. Considered with statements made in *KSR* linking design and market forces to making

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 161

The plethora of polymorphisms and multidisciplinary nature of NB/BN and, to a lesser extent, synthetic biology and RNAi, will make defining the obviousness PHOSITA for many inventions in these fields difficult.¹²⁶ Subsequent to *KSR*, the Federal Circuit in *Daiichi Sankyo v. Apotex, Inc.* defined PHOSITA for an obviousness determination narrowly as one of two types of specialists, rather than the general practitioner used by the district court.¹²⁷ The narrow definition caused the Federal Circuit to overrule the district court on the question of obviousness.¹²⁸ The *Daiichi Sankyo* court's obviousness determination

something "obvious to try," if there are a finite number of predictable solutions and the obviousness PHOSITA would have anticipated a successful pursuit, these other statements suggest that the finite, predictable solutions need not have been for the device claimed or even in the same technical field.

126. Note that the PHOSITA legal construct is the hypothetical objective reference person for not just obviousness analysis, but also utility, written description, enablement, and claim definiteness analysis (thus making PHOSITA definitions essential to many determinations of claim validity), as well as claim construction in infringement cases. Although this is not the prevailing current doctrine, the range of obviousness PHOSITA candidates should be commensurate with the best estimate for the variance from the level of ordinary skill among practitioners in the art. For instance, if there is an extremely wide range of skill in a well-defined art, then there are many candidates who would fit within the "normal range of skill" and thus could be said to possess "ordinary skill." The converse logic applies when the range of skill is much narrower, leading to a much greater constriction of who should count as possessing "ordinary skill." Note, however, that there is more than one PHOSITA per claim and that this logic as it pertains to innovative skill would not apply to the written description or enablement PHOSITA. Burk & Lemley, *supra* note 109, at 1185–90. The Federal Circuit has varied its PHOSITA constructions depending on the analytic task required; for example, the PHOSITA for obviousness purposes has been constructed to be,

not an especially inspired problem solver, as she is imagined to remain stuck in the rut of conventional thinking. But the obviousness PHOSITA is still someone who is trying to solve new problems. By contrast, the PHOSITA of the first paragraph of section 112 shows no such innovative tendency, but is simply a user of the technology.

Id. at 1190 (citations omitted). Thus, the level of "ordinary innovative skill within an art" and, if I am correct, variance from this level of ordinary innovative skill, should be highly pertinent in determining PHOSITA for obviousness analysis, but impertinent for written description or enablement analysis.

127. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256–59 (Fed. Cir. 2007) (considering that the inventors of a compound to treat ear infections were specialists in drug development and ear treatments, not general practitioners or pediatricians, and that the specification was directed to the same sort of expert, the Federal Circuit determined that the district court erred in accepting a general practitioner or pediatrician as the PHOSITA for an obviousness analysis, for the appropriate PHOSITA was either a scientist engaged in developing pharmaceutical formulations and treatment methods for the ear, or a medical professional who treats ear infections and is trained in pertinent pharmaceutical formulations for the ear).

128. Given its narrowing of the obviousness PHOSITA to one of two types of

was thus ultimately driven by its narrow PHOSITA definition.

The patent prosecutor in a highly complex technology like any of the three fields here may thus be caught in something of a bind. On the one hand, he or she must attempt to avoid a 35 U.S.C. § 112, ¶ 1 written description rejection by making the written description precise enough for this PHOSITA to know that the inventor was in possession of the claimed invention at the time of the application. On the other hand, he or she must also try to avoid a 35 U.S.C. § 103(a) rejection by keeping the written description from being so precise that it leads to a very narrow obviousness PHOSITA and a holding that the invention is obvious. There will often be yet another major consideration—enablement under 35 U.S.C. § 112, ¶ 1—that tips the scales towards precision. For the enablement PHOSITA to be able to make the invention, enablement must include precise language, ideally with clear links to both the written description and the claims, thus implying that all three should be written precisely. This may create an additional risk of an obviousness determination, post-*KSR* and post-*Daiichi Sankyo*, but it will not necessarily create a much greater risk. On the other hand, considering the complexity of the three fields, deliberate vagueness could greatly risk an enablement rejection. Thus, as usual, it is better to err on the side of being too precise than not precise enough.

Precision and thoroughness are key for prosecutors, examiners, and judges alike. Implicit in *KSR*'s emphasis on secondary characteristics is the need to apply the TSM test, if at all, in an expansive and flexible manner. The Court's construction of an obviousness PHOSITA with not just ordinary skill, but common sense and ordinary creativity, prescribes thorough fact-based investigation. Although ultimately a legal determination, obviousness, of course, often also requires a very fact-intensive inquiry. When the Court opines that an obviousness determination often necessitates examining multiple patents, not just the most clearly relevant patents and printed publications,¹²⁹ as well as market forces and design trends,¹³⁰ the Court is basically saying, do *not* truncate the factual inquiry because many facts aside from what may appear at first review to be the most pertinent prior art and printed publications may be relevant. Note that the many polymorphisms in

specialists, the Federal Circuit determined that a reasonable jury could only find that either specialist would have seen the invention as obvious and thus it was obvious as a matter of law. *Id.* at 1257, 1259.

129. *KSR*, 127 S. Ct. at 1742.

130. *Id.* at 1740.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 163

NB/BN, synthetic biology, and RNAi, even if they are not combinations, may still be products of interdisciplinary research and thus, in patent prosecution and patent validity litigation, be especially likely to require a thorough examination of information culled from various sources.¹³¹

Although it may be troubling for the patent prosecutor with a debatably non-obvious invention in any of the three fields, from a policy perspective, *Daiichi Sankyo* is another helpful weeder of invalid claims. The narrowness of the obviousness PHOSITA in *Daiichi Sankyo* would appear to require, for instance, that the obviousness PHOSITA pertaining to virtually all NB/BN be a person of ordinary skill in the pertinent interdisciplinary niche within nanotechnology and biotechnology. Such a person in one's exact subdiscipline is, inter alia, far more likely to find one's claim obvious than is a "general nanotechnologist" of ordinary skill.¹³² Returning to the perspective of patent prosecution, *Daiichi Sankyo* appears to make O'Neill et al.'s encouragement of nanotechnology inventors and researchers to work closely with their patent agents and attorneys to provide "thorough specification[s] that disclose[] all reasonable variations of their nanotech[nology] inventions"¹³³ even more compelling by mitigating the obviousness concerns associated with my precision prescription above. In doing so, the applicant fosters a broad construction of the obviousness PHOSITA. Thus, patent prosecutors are best served by making the enablement, claim(s), and written description precise, while also emphasizing in the written description the breadth of the pertinent arts.

The high level of ordinary skill in NB/BN, synthetic biology, and RNAi could, following *KSR* and *Daiichi Sankyo*, make the invention

131. Cf. Stephen J. MacKenzie, *Supreme Court's KSR v. Teleflex Decision* (2007), <http://www.wcsr.com/default.asp?id=118&objID=241&print=1> (last visited Oct. 11, 2008) (arguing, in the context of *KSR*'s effects on litigation, "[i]n chemical, electrical, and biotechnology cases, a more in depth obviousness analysis may be needed since predictability of results may not be easily apparent, the function of known prior art elements usually changes when chemically combined, and the background knowledge of a person of ordinary skill in the art may span several disciplines").

132. *Daiichi Sankyo* may outdate some previous commentary on the enablement challenge that assumed that the PHOSITA would be broadly defined as a nanotechnologist of ordinary skill. Leonard P. Diana, et al., *Untangling the Nanothreads Between the Enablement and Written Description Requirements*, 4 *NANOTECHNOLOGY L. & BUS.* 41, 47 (2007) (contending that despite very high knowledge and expertise in nanotechnology, a PHOSITA would have, paradoxically, relatively low knowledge and expertise because of nanotechnology's highly interdisciplinary nature).

133. Sean O'Neill et al., *Broad Claiming in Nanotechnology Patents: Is Litigation Inevitable?*, 4 *NANOTECHNOLOGY L. & BUS.* 29, 39 (2007).

appear more predictable and technologically feasible compared to what was known at the time of the invention. Prior to *KSR*, in the 1990s at least, the probability that federal district courts would find a claim obvious appears to have varied inversely with the complexity of the art.¹³⁴ Because of their generally greater complexity, biotechnology claims may have been less likely to be held obvious in this decade, even when the inventions involved relatively minor additions to the prior art. However, *KSR*'s holding that if an invention is "obvious to try," it is obvious under 35 U.S.C. § 103, even absent identification of the problem or any written prior art, will probably make similar, relatively minor additions to the prior art in NB/BN, synthetic biology, or RNAi claims more likely to be held obvious.

In regards to the three fields addressed in this Article, there have been several cases in biotechnology that are related to synthetic biology and RNAi, and a few cases related to some form of NB/BN as well. However, thus far, there has been only one case that specifically addressed a nanotechnology patent and no cases that have specifically addressed a synthetic biology or RNAi patent. In the sole nanotechnology case, *In re Kumar*, the Federal Circuit vacated and remanded the Board of Patent Appeals and Interferences' (BPAI) determination that several claims in a patent application for aluminum oxide particles of submicron size were obvious.¹³⁵ The Federal Circuit rejected the BPAI's own identification for the first time of underlying particle size values (i.e., the size values had been previously identified by no one, including no party during prosecution or the BPAI appeal) to make an obviousness determination. The court stated that if an obviousness rejection "is based on overlapping values in the prior art, identification of the values deemed to overlap is material to the rejection. In this case[,] the overlapping values were identified for the first time in the decision of the Board, and are not themselves set forth in . . . any . . . reference."¹³⁶ The Federal Circuit remanded the case for

134. Cf. Sean M. McEldowney, *New Insights on the "Death" of Obviousness: An Empirical Study of District Court Obviousness Opinions*, STAN. TECH. L. REV., July 2006, ¶¶ 22, 41, available at <http://stlr.stanford.edu/pdf/McEldowney-Obviousness.pdf> (reporting from his empirical study of 321 published federal district court opinions (the study is limited in that it did not look at Federal Circuit opinions) that reached the question of obviousness on 407 utility patents). Although complexity of the art was not associated with an obviousness holding in the 1970s, it was in the 1990s; "simple patents [were] more likely than complex patents to be invalidated as obvious in the 1990s." *Id.*

135. *In re Kumar*, 418 F.3d 1361, 1361 (Fed. Cir. 2005).

136. *Id.* at 1367.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 165

the declarants to provide additional information, armed this time with the BPAI's identification of overlapping numerical values.¹³⁷

However, *KSR*, with its emphasis on the problem not having to be spelled out for the obviousness PHOSITA, may at least partly eclipse *Kumar*. *KSR* emphasized that this PHOSITA has not only ordinary skill in the art, but also ordinary creativity¹³⁸ and common sense.¹³⁹ An issue post-*KSR*, for a case such as *Kumar*, would thus seem to be not whether the numerical values generated by the examiner, the BPAI, or federal judge were ever before the applicant, but rather, whether the obviousness PHOSITA would have used ordinary skill, common sense, and ordinary creativity to derive the same finite overlapping range. *KSR* would not appear to require this PHOSITA to have been presented with the numerical values.

Kumar also criticized the BPAI for mishandling the declarative evidence and applying the incorrect enablement test for obviousness.¹⁴⁰ *Kumar* stated that the correct test is whether the prior art enabled the obviousness PHOSITA to make and use the invention. That is, would a patent reference have enabled this PHOSITA to produce particles of the size and distribution claimed by *Kumar*?¹⁴¹ Although if the prior art is enabling, it "teaches," making the invention obvious, if the prior art is not enabling, it may or may not "teach away." "Teaching away" is a form of secondary evidence involving unexpected results that *KSR* discussed as being valuable in establishing non-obviousness.¹⁴² Thus, in nanotechnology patent applications, prosecutors should emphasize unexpected results, especially size-dependent unexpected results due to quantum effects and the absence of an enabling method of producing nanoscale materials with certain properties. Demonstrating such unexpected results would still show non-obviousness post-*KSR*. Prosecutors should also emphasize the value of declarative teaching away evidence of uncited art post-*KSR*.

Regarding post-*KSR* obviousness issues with chemical and biotechnology claims that may be pertinent to synthetic biology and RNAi inventions, the following statement and prediction are probably correct: "A virtually *per se* rule of patentability for new biotechnology

137. *Id.* at 1369.

138. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007).

139. *See id.*

140. *See In re Kumar*, 418 F.3d at 1368-69.

141. *Id.* at 1369.

142. *KSR*, 127 S. Ct. at 1740.

entities is set in the 1995 *Deuel* case. *Deuel* has been the subject of heavy criticism [in] the scholarly community. . . . It may be expected that in the wake of *KSR* there will be a renewed challenge to the viability of *Deuel*.¹⁴³ Just weeks after *KSR*, in *Ex Parte Kubin*, relying on *KSR*'s "obvious to try" reasoning, the BPAI took a direct shot at *Deuel*.¹⁴⁴ *Deuel* had held that prior art DNA cloning methods and a partial amino acid sequence for a protein encoded by the disputed patented DNA did not suffice to make that DNA obvious.¹⁴⁵ But then, just weeks after *Kubin*, in another case, *Takeda Chemical Industries*,¹⁴⁶ the Federal Circuit rejected an argument analogizing "obvious to try" to *KSR*. However, *Takeda Chemical Industries* should not be misinterpreted as either an implicit rejection of *Kubin* or an implicit reaffirmation of *Deuel*; it was neither, fitting in nicely with not only *Kubin*, but also *Pfizer*¹⁴⁷ and *KSR*. Unlike in *Kubin*, *Pfizer*, and *KSR*, the invention in *Takeda Chemical Industries* was one of "millions of possibilities" among the pertinent options.¹⁴⁸ Clearly, when *KSR* said that there should be

143. Harold C. Wegner,

KSR-Induced PTO Obviousness Practice Changes, 20-21 (2007), available at [http://www.patenthawk.com/blog_docs/070529_KSR_PTO_Obviousness_Practice_\(Wegner\).pdf](http://www.patenthawk.com/blog_docs/070529_KSR_PTO_Obviousness_Practice_(Wegner).pdf) (discussing *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995)).

144. *Ex parte Kubin*, Application No. 09/667,859, 8-9 (B.P.A.I. 2007) (precedential opinion).

145. *In re Deuel*, 51 F.3d. at 1558-59.

146. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

147. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

148. *Ex Parte Kubin* held that a rejected claim to a nucleic acid sequence encoding a cell surface marker protein was obvious because there was a limited number of ways to isolate the protein that the obviousness PHOSITA would have had reason to try, expecting at least one to be a success. *Ex parte Kubin*, Application No. 09/667,859 at 9. In *Takeda Chemical Industries*, the Federal Circuit held that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indust.*, 492 F.3d at 1357 (emphasis added). The Federal Circuit therefore rejected the appellant's "obvious to try" argument because it failed to show how the obviousness PHOSITA would have chosen the prior art compound to modify the compound from the "hundreds of millions of possibilities." *Id.* In addition to these two post-*KSR* cases, in *Pfizer*, decided shortly before *KSR*, the prior art also gave the obviousness PHOSITA far-fewer-than-astronomical options in a genus—fifty-three acceptable anions—from which to select a few, including the claimed anion. *Pfizer*, 480 F.3d at 1363. The question of "limited options" often appears as a decisive motif running through what may otherwise be seen as disparate opinions. Prosecutors may often wish to preempt an "obvious to try" rejection by emphasizing in the written description the uncertain feasibility, multitude, and diversity of options that existed at the time of the invention, using the prior art, declarations, and valid and reliable evidence of design needs or market pressures. The prevalence and prominence of "limited options" motifs in all of these opinions on

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 167

limited options, the Court did not intend the finite limit to be so astronomical. In *Kubin*, *Pfizer*, and *KSR*, in contrast, there were truly limited options.¹⁴⁹

Given the potential of all three nascent technologies to enable more precise drug delivery, one wonders if *KSR* will have a warming or chilling effect on large pharmaceutical and biotechnology companies that have been somewhat risk-averse regarding these technologies. These companies have preferred not to develop the technologies internally, but instead acquire the start-ups with the most promising or “disruptive” patent portfolios.¹⁵⁰ This question may be commercially critical for particular government agencies and university inventors, as well as their start-up exclusive licensees, because pharmaceutical patent expirations will also cause the drug market to open considerably in the near future.¹⁵¹

Many pharmaceutical and biotechnology companies look to make what they can of combinations, new uses, or new methodologies related

obviousness make such work important as part of a thorough and careful written description.

149. Some commentators have nonetheless misinterpreted *KSR* in criticizing *Kubin*. See, e.g., Eric K. Steffe & Elizabeth J. Haanes, *Patent Board Challenges Federal Circuit to a Duel*, IP LAW 360, July 27, 2007, at 3, <http://64.237.99.107/media/pnc/4/media.354.pdf>.

(criticizing *Kubin* for not providing “any identified predictable solutions, let alone a finite number of identified, predictable solutions to the problem. Where *KSR* may have opened the door, nothing in the *KSR* opinion mandated dispensing with the need for at least *some structural similarity* in the prior art.”) (emphasis added). But *Kubin* argues compellingly that because combining the prior art references would have led to a limited number of *conventional methods* for isolating the claimed cDNA for producing a protein implicated in the human immune system and various human diseases, the obviousness PHOSITA would have a motive to try these methods with the reasonable expectation that at least one method would be a success. *Kubin* effectively relies on *KSR*’s statement that where there are a finite number of *identified, predictable solutions* within the obviousness PHOSITA’s technical grasp and he or she has a motive to solve the problem and reason to anticipate success, the success was due to common sense and ordinary skill and thus obvious to try. See *Ex parte Kubin*, Application 09/667,859, at 8-9; *KSR Int’l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007). Ordinary common sense, ordinary creativity, and flexible and expansive obviousness inquiries were strong motifs running through *KSR*. Requiring identification of a particular similar structure in the prior art—when the obviousness PHOSITA could use ordinary common sense and ordinary creativity to combine the prior art references that included limited conventional methods one of which would most likely solve the problem—imposes precisely the sort of narrowness and rigidity that *KSR* rejected for obviousness determinations.

150. See MICHAELA PLATZER, NATIONAL VENTURE CAPITAL ASSOCIATION, PATIENT CAPITAL: HOW VENTURE CAPITAL INVESTMENT DRIVES REVOLUTIONARY MEDICAL INNOVATION 9 (2006) (reporting that “many large pharmaceutical and life science corporations consider young, venture backed companies to be their de facto R&D pipelines. For this reason, venture-backed companies often are acquired for their disruptive technologies by these larger organizations”).

151. See Bawa et al., *Protecting Nanomedicine*, *supra* note 90, at 154.

to known drugs, however, pursuing “extended patent coverage for their key commercial products” as part of their “Patent Life Cycle Management[] [strategy to] maximize[] [the] profitability of drugs.”¹⁵² *KSR* could certainly be applied to challenge such extensions as obvious, particularly by combining its “obvious to try” analysis¹⁵³ with the reasonable probability of success analysis in not only *KSR*,¹⁵⁴ but also *Pfizer*.¹⁵⁵ However, the chilling effect of such prospective challenges on these companies is unlikely to be very big precisely because the companies are already risk-averse. These companies often acquire start-ups with portfolios that include highly valuable patents and claims on somewhat “disruptive technology” where “unexpected results” and other “secondary indicia of non-obviousness” can be convincingly shown.¹⁵⁶ Thus, if NB/BN, synthetic biology, or RNAi offers a combination, new use, or new method for a drug with an expiring patent, and the risk-averse drug company is willing to acquire the patent portfolio containing the combination, use, or method allowing for an extension of patent coverage, the extension would probably withstand an obviousness challenge.

b. Possible Forthcoming Statutory and PTO Rule Changes That Would Help Further Weed Out Patent Thickets and Increase Patent Validity: Creating a One-Year Post-Grant Opposition Period, Reducing the Litigation Estoppel Effect of Inter Partes Reexaminations, and Empowering the PTO to Make Rules That Limit Continuations

In addition to the case law discussed in the previous section, at least two components of the House version of the Patent Reform Act, the Senate version of this act, or both,¹⁵⁷ and a third reform proposed by the PTO,¹⁵⁸ are likely to be effective ex post patent thicket weeders and

152. See Steven R. Ludwig & Matthew E. Kelley, *Pharmaceutical Patent Life Cycle Management After KSR International v. Teleflex*, VENABLE LLP, May 2007, at 1, available at <http://www.venable.com/docs/pubs/1684.pdf>.

153. See *KSR*, 127 S. Ct. at 1742.

154. See *id.*

155. See *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364–65 (Fed. Cir. 2007).

156. Cf. PLATZER, *supra* note 150.

157. The House version has passed. See Patent Reform Act of 2007, H.R. 1908, 110th Cong. (as passed by House, Sept. 7, 2007). The Senate is still debating its version. Compare Patent Reform Act of 2007, S. 1145, 110th Cong. (as reported by S. Comm. on the Judiciary, Jan. 24, 2008), with Patent Reform Act of 2008, S. 3600, 110th Cong. (as referred to S. Comm. on the Judiciary, Sept. 25, 2008).

158. Changes to Practice for Continuing Applications, Requests for Continued Examination Practice, and Applications Containing Patentably Indistinct Claims, 71 Fed.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 169

patent quality enhancers: (1) creating a one-year post-issuance period when validity challenges can be made without incurring the expense associated with reexamination or litigation;¹⁵⁹ (2) reducing the litigation estoppel effect of *inter partes* reexaminations;¹⁶⁰ and (3) empowering the PTO to limit continuations.¹⁶¹ Allowing one year for post-issuance validity challenges at the PTO would spare potential challengers the monetary expenses, opportunity costs, and lengthy periods of uncertainty often associated with lawsuits and, to a lesser extent, reexaminations.¹⁶² Striking the estoppel language “could have raised” from “raised or could have raised” in 35 U.S.C. § 315(c) could also make *inter partes* reexamination a more frequent choice for a validity challenger who also wants to preserve litigation options.¹⁶³ The first two

Reg. 48 (proposed Jan. 3, 2006) (to be codified at 37 C.F.R. pt. 1) [hereinafter PTO Proposed Limit to Continuations as a Matter of Right].

159. See H.R. 1908, sec. 6(f)(1), §§ 321–22; S. 1145, sec. 6(e)(1) §§ 321–22. *But see* S. 3600, sec. 5(c). The more recent Senate Bill creates a more complicated two-period post-grant challenge system. During the first nine-month post-grant period, petitions to cancel claims as unpatentable under 35 U.S.C. § 282(b)(2) or (3) may be made. S. 3600, sec. 5(c), § 321(b). During a second post-grant period, commencing the later of nine months after issuance (or reissuance) or the termination of a first-period proceeding, petitions may be made based on prior art in patents or printed publications to cancel claims as unpatentable under 35 U.S.C. § 102 or § 103. S. 3600, sec. 5(c), § 321(c).

160. See H.R. 1908, sec. 6(d). *But see* S. 1145, sec. 6(a); S. 3600, sec. 5(b)(1). In contrast to the House version, both Senate versions would eliminate *inter partes* reexaminations, leaving in their stead only the post-grant review procedures referenced in the previous footnote. See S. 1145, sec. 6(e); S. 3600(c), sec. 5(c).

161. See PTO Proposed Limit to Continuations as a Matter of Right, *supra* note 158, at 48–49. *But see* *Tafas v. Dudas*, 511 F. Supp. 2d 652 (E.D. Va. 2007) (presenting a successful challenge of the PTO’s proposal which effected a preliminary injunction on implementing the proposal). However, the PTO’s appeal of *Tafas* is currently pending at the Federal Circuit. Press Release, U.S. Patent and Trademark Office, USPTO Identifies New Applicability Date of Certain Provisions in “Claims and Continuations” Final Rule (Aug. 4, 2008), available at <http://www.uspto.gov/web/offices/com/speeches/08-33.htm>.

162. In addition to reducing the ex post expense of a validity challenge, the one-year period for post-issuance validity challenges at the PTO may also indirectly reduce hindsight bias if the obviousness issue is then taken to the Federal Circuit. *The Supreme Court, 2006 Term—Leading Cases*, 121 HARV. L. REV. 375, 383 (2007) (concurring with fellow scholars’ prescriptions for post-grant PTO review). The law review editors argued that a more robust review would not only alleviate concerns about overissuance, but could also proactively combat judge hindsight bias by providing independent obviousness assessments by both the examiner and pertinent experts during the review. *Id.* If the obviousness issue remains unresolved, post-*KSR*, a judge employing common sense might be more likely to defer to the PTO’s robust review. *Id.*

163. Cf. JULIE A. HEDLUND, THE INFORMATION TECHNOLOGY AND INNOVATION FOUNDATION, PATENTS PENDING: PATENT REFORM FOR THE INNOVATION ECONOMY 11 (2007), available at <http://www.itif.org/files/PatentsPending.pdf> (arguing that this estoppel language made third parties reluctant to use *inter partes* reexaminations even after Congress

changes listed above would also allow third parties to participate more in patent examination and review, which scholars providing in-depth analyses of possible reforms to the patent system have recommended.¹⁶⁴

The last change listed—empowering the PTO to limit continuations—would encourage the rigorous initial prosecution of claims, by discouraging the filing of what could be an endless series of continuation-in-part applications (CIPs). Such CIPs can perpetually broaden claims so long as each new CIP's claims are supported by the initial specification in a 35 U.S.C. § 112, ¶ 1 sense and otherwise comply with pertinent provisions of 35 U.S.C. § 120 and 37 C.F.R. § 1.78. Having a CIP as a virtually certain prosecutorial option can thus add both sloppiness and perpetual uncertainty to ultimate claim scope. Allowing the PTO to restrict continuations may reduce a patentee's ability to protect all variations of its combination product. However, obviousness doctrine, rejuvenated by *KSR* and its Federal Circuit progeny, will protect against many attempts to design around initially claimed combinations with distinct, but obvious, derivatives.

2. Just-Now-Learning that Human Genetic Regulation is Not What We Thought: Specific Consequences for Prosecuting NB/BN, Synthetic Biology, and RNAi Patents

As noted in Section II.B.2, new research at ENCODE and elsewhere convincingly shows that much of what we have long thought was true about nucleic acid regulation of protein production and activity at the mammalian cellular and extracellular levels is incorrect. ENCODE et al. could have effects on the written description, utility, enablement, and definiteness of nucleotide and amino acid sequence patents. At first blush, most troubling for prospective patentees of sequences would appear to be continuing to establish utility under 35 U.S.C. § 101. The

had allowed for appeals to the Federal Circuit).

164. *E.g.*, Adam B. Jaffe & Josh Lerner, *Innovation and Its Discontents*, 1 *CAPITALISM & SOC'Y* 17, 22-23 (2006) (arguing compellingly that because the presumption of patent validity is necessary to reduce start-up precariousness that can deter investment, this presumption must remain, but that this presumption must also be made reasonable by an increase in patent quality effected by a change in the rules associated with *inter partes* reexamination). If all parties are given meaningful opportunity to request reexamination on the basis of any relevant facts they have—with an opportunity to appeal and make any argument later in court not specifically made in the reexamination—then this presumption might become reasonable, because the greater attractiveness of *inter partes* reexamination, backed up with meaningful possible appeal, means a patent must either withstand a rigorous post-issuance test, be of too trivial worth for its validity to matter, or be too clearly valid to elicit a third party challenge. *Id.*

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 171

need for a specific, substantial, practical, and credible utility could certainly be difficult to meet if many of the most basic roles that the sequence was long thought to play are called into question.¹⁶⁵ Moreover, calls from scientists for a highly accessible genetic commons that extends upon the genomic commons created by the Human Genome Project,¹⁶⁶ combined with the Federal Circuit's most likely no-longer-tenable discrete definition of "a gene" as "a chemical compound, albeit a complex one,"¹⁶⁷ makes one wonder if patent law regarding the regulation of nucleotide sequences needs a major overhaul. In addition to concerns about whether the sequences as we now understand them meet the utility requirement of § 101, there are science policy issues,¹⁶⁸ as well as concerns about whether the definiteness requirement of § 112, ¶ 2 is met, given the current uncertainty regarding just what a gene is. Until the mechanisms controlling human transcription and translation—and their extracellular regulating links that allow for genome-wide and proteome-wide extraordinarily complex, seemingly multiple context dependent determinants of phenotypes which were found in the research at ENCODE et al.—are far better understood, this uncertainty will persist.

Consider the possible definiteness problems associated with claim one of Verdezyne's recent patent licensed to the University of California. The claim is putatively for "[a] method of synthesizing a DNA sequence encoding a polypeptide" which involves iterative DNA deconstruction and reconstruction via globally optimized division,

165. Cf. Posting of Kevin Noonan to Patent Docs, *What's ENCODE'd in Your Genome Isn't a Collection of Genes*, http://patentdocs.typepad.com/patent_docs/2007/06/whats_encoded_i_1.html (June 18, 2007, 22:51 EST) (arguing that because ENCODE implies that the traditional definition of the mammalian gene as a discrete template for translation is wrong because transcription is more generalized, the utility of Express Sequence Tags (ESTs), which were thought to be differentially expressed in tissue, and thus, reflect an event specific to a cell, tissue, or organ, is, "at best, highly questionable").

166. Cf. Roger D. Klein, Editorial, *Gene Patents and Personalized Medicine*, 4(3) PERSONALIZED MED. 237, 239–40 (2007) [hereinafter Klein, *Gene Patents*] (Contending that "the heritable and somatically acquired genetic traits influencing most drugs' physiologic effects are likely to be polygenic. In the future, the inherent encumbrances that gene-related patents impose . . . [are likely to] be magnified, as advancing knowledge necessitates the acquisition and integration of information regarding possible variants in multiple genes that act in concert[.]" while implying that an expansion of patent-eligible subject matter to include medically related genotype-phenotype correlations would also deter this necessary acquisition and integration.)

167. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991), cert. denied, 502 U.S. 856 (1991).

168. See, e.g., Klein, *Gene Patents*, supra note 166, at 238–40.

thermodynamically controlled self-assembly, and reconstitution.¹⁶⁹ First, forget ENCODE et al.'s research for a second. The claim's apparent excess breadth—exacerbated by the use of the open-ended word “comprising” in the first claim upon which the next forty claims depend¹⁷⁰—could make it vulnerable to a written description challenge¹⁷¹ and/or an infringement challenge. Now recall that ENCODE et al.'s findings imply that nucleotide sequence expression culminating in particular amino acid sequences is highly variable.¹⁷² If this implication is correct, then claim one of Verdezyne's patent could possibly be vulnerable to a definiteness challenge due to an inherent ambiguity in the phrase “encoding a polypeptide” because the method may not encode a polypeptide under all conditions. On the other hand, because claims are given their broadest reasonable construction “in light of the specification as it would be interpreted” by the definiteness PHOSITA,¹⁷³ courts could find this variability acceptable if the method encodes a polypeptide under at least one condition and, considering the specification, this PHOSITA would construe the method as encoding the polypeptide.

3. General Strategies and Tactics in Patent Prosecution that Maximize Patent Portfolio Value in NB/BN, Synthetic Biology, and RNAi

Given both the thickets looming in various sectors in all three technologies and the breadth of scientific and legal uncertainty,¹⁷⁴ patent prosecutors in any of these technologies must do extensive and intensive searches of both the printed prior art and the evolving state of the art prior to actual prosecution. Such thorough research is needed to ensure that the specification includes as broad and precise a written description of the art and as clear and thorough an enablement for the claims as possible. *KSR* makes it imperative that claims be crafted to avoid excess breadth vis-à-vis both the prior art and all non-prior art

169. U.S. Patent No. 7,262,031 (filed May 21, 2004).

170. “A method of synthesizing a DNA sequence encoding a polypeptide, comprising . . .” ‘031 Patent claim 1.

171. Unless the claim was accompanied by a highly pertinent and broad written description.

172. See ENCODE PILOT PROJECT, *supra* note 63.

173. *In re Am. Acad. Sci. Tech Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

174. Although legal uncertainty persists, it appears much more likely—given *KSR*, its BPAI and Federal Circuit progeny, and both the House and Senate versions of the Patent Reform Act—that the cumulative impact of legal changes affecting prosecution will lead to more, not fewer, hurdles to establishing and proving patent validity.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 173

knowledge culled outside of printed publications and patents (especially information pertaining to market forces and design incentives).

However, maximal valid breadth by definition is not excessive. Thus, the prosecutor should obtain the broadest claims—considered collectively as parts of a much greater whole that is one’s ultimate patent-related focus, i.e., the patent portfolio—that one’s other patents, the prior art, outside knowledge, and the specification will allow.¹⁷⁵ Maximal patent protection means careful portfolio building with many broad, non-overlapping patents that maximize diversity and magnitude of protection in (a) particular area(s) of the technology. Although CIPs and other continuations may be limited by new PTO rules,¹⁷⁶ neither these rules nor the House or Senate version of the Patent Reform Act does away with broadening reissues, which could be filed within two years of issuance¹⁷⁷ to prevent potential competitors from designing around one’s inventions. Claiming less than maximal valid specification breadth prevents optimal portfolio-level patent magnitude and diversity and inadvertently invites claims for designs around inventions protected by the portfolio. Such inadvertent invitations will almost certainly be accepted in the three intensively and extensively patented technologies discussed here. In addition, note that the Patent Reform Act may also eliminate “interferences.”¹⁷⁸

Regardless of the ultimate status of “interference” or “prior inventor challenges,” litigating challenges will continue to be expensive distractions from patent portfolio buildup in alliance with business and science development.¹⁷⁹ Moreover, although this will be addressed more fully in the next part of this Article, the quality of further development and the value of an ultimate acquisition by a large pharmaceutical or

175. Considering also that the claims must be given the broadest reasonable interpretation that the definiteness PHOSITA, after assessing the specification, would give them. *In re Am. Acad. Sci. Tech Ctr.*, 367 F.3d at 1364.

176. *See supra* Part II.C.1.b.

177. 35 U.S.C. § 251 (2000).

178. Both House and Senate versions replace “interference proceedings” with “derivation proceedings.” H.R. 1908, sec. 3(j); S. 1145 sec. 3(j); S. 3600, sec. 2(j). However, under all current versions of the Act, the PTO Director could nonetheless still institute a proceeding under 35 U.S.C. § 135(a) when a dispute arises between different individuals regarding the right to patent the invention under 35 U.S.C. § 101. H.R. 908, sec. 3(i)(a)(C); S. 1145, sec. 3(i)(a)(1); S. 3600, sec. 2(i)(a)(1).

179. *Cf.* Roger C. Hahn, *The Evolving Landscape of Patenting Biotech Inventions: Terra Firma or Terra Incognita?*, 30 *BIOMEDICAL ENGINEERING SOC’Y BULL.* 7, 9 (2006) (“A huge drain on resources is required to resolve patent disputes once they have initiated in comparison to the modest costs required in building an effective IP portfolio.”).

biotechnology company will be largely driven by real *and perceived* patent portfolio quality. Validity and infringement battles can make a start-up appear unstable to licensees, venture capitalists, and potential exit companies that could acquire the portfolio, albeit in a much more developed form.

III. DESIGNING AND EXECUTING ROADMAPS THAT MAXIMIZE COMMERCIAL VALUE: USE OF PATENT PORTFOLIOS, LICENSES, VENTURE CAPITAL, AND ACQUISITIONS

A. *Early Thorough Integrative Research Planning that Culminates in a Multi-Dimensional Modifiable Roadmap*

The composition of an effective roadmap for these three technologies should usually begin at the point that commercialization appears to be a realistic possibility. At that point, business executives and consultants as well as IP and other legal advisors in a government agency, university (typically in or associated with the technology transfer office of the agency or university), or start-up company where these innovations will most likely occur should begin to collaborate on a route to commercial success.¹⁸⁰

Among the many considerations is whether a research-based alliance—e.g., a cross-government agency or cross-university alliance—via the Cooperative Research and Technology Enhancement (CREATE) Act should be formed. The benefit of such an alliance is that it would reduce patent-related competition and the possibility of an obviousness rejection¹⁸¹ if two research teams in separate government agencies or universities are engaged in parallel research and care is taken to realize CREATE's capacity to circumvent this rejection.¹⁸²

180. Cf. Posting of John D. Carroll to Fierce Biotech, *Nanotech is Promising, but Faces Hurdles*, <http://www.fiercebiotech.com/node/8774/print> (Sept. 21, 2007 6:59 EST) (reporting that although the efficient manufacture of nanotherapeutics will be difficult, small companies have the flexibility to produce innovations for new therapies). *Id.* Market demands, however, would require the involvement of large pharmaceutical companies. This is consistent with a trend towards initial innovation occurring in small companies that are subsequently acquired by large ones.

181. See 35 U.S.C. § 103(c) (2000).

182. *OddzOn Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1403–04 (Fed. Cir. 1997) (“[S]ubject matter derived from another not only is itself unpatentable to the party who derived it under § 102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable to that party under a combination of §§ 102(f) and 103.”). Compliance with this holding is essential. Prior art only under § 102(f) that was not commonly owned by both research teams at the time of the invention is not disqualified as

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 175

Enhanced cross-fertilization, collaboration, and consolidation of scientific and technological forces are all likely benefits. However, reduction of troll-like holdup by the other agency or university is an unlikely benefit. Although neither the agency nor the university may be a manufacturing entity in the traditional sense, it is also true that neither is the idle extractor of rent that makes for a troll.¹⁸³

Another major consideration is the probable market value of innovations given numerous factors that are to varying degrees technology-specific and even technology type-specific.¹⁸⁴ The assessment of probable market value is necessarily speculative, but should nonetheless be pursued to generate best educated guesses for incipient roadmap construction. It is essential to consider all reasonably possible roadblocks on various anticipated routes toward commercialization. Foreseeable possible roadblocks include: (1) scientific ignorance (e.g., unsolved pertinent puzzles uncovered by ENCODE and other research); (2) failure of future research to surmount or circumvent anticipated¹⁸⁵ and unanticipated¹⁸⁶ technological barriers; (3) barriers created by technology-type concentrations of patent thickets;¹⁸⁷ (4) pertinent known and unknown distributions of patent ownership which could stymie licensing negotiations and

prior art under § 103(c) (and thus not under §§ 103(c)(2) and (c)(3)). *Id.* Thus, information not contained in printed publications and patents, yet available outside the university, government agency, or start-up prior to collaboration, would not be disqualified as prior art. Patent prosecutors must coordinate the full disclosure of information from both groups when forming a joint research agreement under CREATE.

183. See Marc A. Lemley, *Are Universities Patent Trolls?* 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 611, 629–30 (2008).

184. *Cf.*, e.g., Bawa Commentary, *supra* note 15, at 346 (discussing factors specific to nanomedicine).

Several variables will determine whether advances in the laboratory will translate into multiple opportunities for the consumer. Early-stage nanomedicine commercialization will be hampered by large-scale production challenges, high production costs, the public's general reluctance to embrace innovative medical technology without real safety guidelines, a scarcity of venture funds, few near-term commercially viable products, a well-established micrometer-scale industry, the pharmaceutical industry's reluctance to embrace nanomedicine, and the absence of clear regulatory guidelines.

185. Just one of many expected barrier types: barriers to effective nucleic acid sequence target delivery in RNAi.

186. New pharmaceuticals and other new medical interventions both have long histories of unanticipated adverse clinical side effects, including, perhaps most notoriously, the lethal side effect of gene therapy for an eighteen-year-old man receiving the therapy in a clinical trial. See Couzin & Kaiser, *infra* note 289.

187. For example, in NB/BN, an apparent thicket in single-walled carbon nanotubes. See Bawa et al., *Protecting Nanomedicine*, *supra* note 90.

discourage venture capital;¹⁸⁸ (5) thickets effected by clusters of patent expirations;¹⁸⁹ (6) environmental and safety concerns regarding biological pharmaceuticals;¹⁹⁰ (7) the number of pending and issued patents on similar inventions as part of a review of competitors' patent portfolios;¹⁹¹ and (8) repeated citation by others of potential unlicensed competitor patents as signs of their licensing potential.¹⁹²

Once these roadblocks are considered, additional pertinent prior art, market forces, and design incentives should be reviewed, and all possibly valid, non-infringing, and commercially valuable patents that could be obtained for one's inventions should be identified.¹⁹³ It may seem premature to begin working on a modifiable roadmap of such complexity based in no small part on estimated prospective patent values, based in turn on preliminary research only, with not a single actual provisional or national patent application yet filed. However, envisioning the entire commercialization process extremely early gives the process some initial direction and identifies precisely what must be done when using deadlines that are as ambitious as current conditions allow. Although these timeframes are modifiable, strong incentives should be built to meet them; speed of development is of course impressive to licensees and venture capitalists, as well as pharmaceutical

188. Cf. Mark A. Lemley & Carl Shapiro, *Patent Holdup and Royalty Stacking*, 85 TEX. L. REV. 1991, 1992-93 (2007) [hereinafter Lemley & Shapiro, *Patent Holdup*].

The threat that a patent holder will obtain an injunction that will force the downstream producer to pull its product from the market can be very powerful. These threats can greatly affect licensing negotiations, especially in cases where the injunction is based on a patent covering one small component of a complex, profitable, and popular product.

189. Regarding expirations of pharmaceutical patents, compare Bawa et al., *Protecting Nanomedicine*, *supra* note 90, at 154, for an argument that commercialization in nanomedicine will be driven partly by the expiration of drug patents.

190. Cf. K. John Morrow Jr., *Gauging Nanobiotech's Promise Realistically: Biotech and Pharma Firms are Taking a Wait-and-See Approach*, 26 GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Dec. 1, 2006, available at http://www.genengnews.com/articles/chitem_print.aspx?aid=1953&chidl=2 [hereinafter Morrow, *Gauging Nanobiotech's Promise*] (reporting the concerns of representatives of industry and investment management firms that potential environmental and health hazards of nanotechnologies have not been adequately assessed).

191. Cf. Pham & Berman, *supra* note 89, at 113 (stating that the patent system can be a marker of innovation, with numbers of issued patents and pending patent applications helping one ascertain potential competitors and "the relative positions of intellectual property").

192. Cf. *id.* at 114.

193. Cf. Couvreur & Vauthier, *supra* note 42, at 1440 (arguing in the context of nanotechnology that successful collaboration requires managing IP very carefully at the beginning of the business relationship).

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 177

and biotechnology companies considering acquisition targets.

The first very-near-future deadline should then be set for the formation of a multidimensional, modifiable roadmap for maximal commercial development. Such a roadmap could include the following: (1) projected pertinent scientific developments, with evaluations of different developmental paths in turn linked to probability estimates of “conditions precedent,” that is, path-dependent necessary conditions for the developments to occur; (2) projected technological developmental trajectories as effects of the scientific developments in one above; (3) projected technological developmental trajectories that are not effects of the scientific developments in one above; (4) projected evolution of pertinent patent law; (5) projected evolution of pertinent food and drug law;¹⁹⁴ (6) projected evolution of pertinent environmental law;¹⁹⁵ (7) identification of IP issues generally, most notably any pertinent innovations in synthetic biology that should be subject to copyright law, not patent law;¹⁹⁶ (8) projected patent portfolio formation and evolution as effects of attempts to maximize scale and diversity considering one through six above as well as the preliminary research on roadblocks discussed in Part II.C.3; (9) identification and evaluation of pharmaceutical and biotechnology companies that may want to acquire a projected patent portfolio at some defined date (e.g., exactly five years hence); (10) identification and evaluation of current and future public funding as well as various possible future sources of venture capital; and, if this commercial roadmap should occur in a government agency or university, rather than a start-up, (11) identification and evaluation of possible start-ups for exclusive licensing negotiations (with a near-future deadline for determining how to proceed with a first choice potential licensee).

Much, if not all, of this information will be difficult to quantify via

194. Cf. PLATZER, *supra* note 150, at 5 (“Life science start[-]up companies face special challenges given the high degree of risk and the cost and time it takes to bring these innovative health care therapies and technologies to the marketplace. An unpredictable regulatory environment weighs heavily in the calculation of investment risk in a new technology.”).

195. Cf. Albert C. Lin, *Size Matters: Regulating Nanotechnology*, 31 HARV. ENVTL. L. REV. 349 (2007) (recommending, because risks are uncertain yet potentially huge, notification and labeling for all nanomaterials and additional screening, bonding, and monitoring for free form nanomaterials). Thus, the uncertainty of regulatory approval is compounded by the uncertainty as to what regulations will be in effect when particular nanomaterials are putatively ready to be commercialized. *Id.*

196. Although recall that it appears unlikely that synthetic biology will be subject to copyright. See Kumar & Rai, *supra* note 28, at 1763–64.

probability estimates, although best educated guesses should be provided with estimated confidence intervals.¹⁹⁷ In addition, scientific, technological, and legal uncertainties that defy categorical probability analysis may be quantified via traditional analysis of set intersection, possibility analysis that allows for gradation of set membership, or both.¹⁹⁸ The great degree of uncertainty regarding technological growth could also allow for contingency plans based on possible obsolescence.¹⁹⁹

197. For example, the probability that technological development x will occur by a future date could be presented as a probability, $p(x)$, with a probability of the probability estimate being correct presented as its confidence interval. This probability of a probability, $p(p(x))$, represents the likelihood that the probability measurement is correct and is thus a gauge of “certainty,” $c(x)$, that is, “predictive power.” Maximal predictive power would exist when $c(x) = 1$, that is, when $p(x) = 0$ or 1 and when $p(p(x)) = 1$, because complete certainty would exist when one both predicts that x will either happen ($p(x) = 1$) or not happen ($p(x) = 0$) and one also has complete confidence in this prediction ($p(p(x)) = 1$, $CI = 0$). On the other end of the continuum, absence of predictive power would exist when $c(x) = 0$, that is, when $p(x) = 0.5$ and $p(p(x)) = 0$, because maximal *uncertainty* would occur when one has no reason to believe that x will either happen or not happen ($p(x) = 0.5$), nor any reason to believe in any particular probability of x happening ($p(p(x))=0$, $CI = 1$). Thus, under maximal certainty, $p(x) = 0$ (0, 0) or 1 (1,1); under maximal uncertainty, $p(x) = 0.5$ (0,1). Put differently, one’s probability that a technological development will occur by a future date is a subjective assessment that reflects one’s *perceived knowledge of what is likely to happen*. Thus, for instance, given all that one knows about the science, technology, and law that could affect R&D in synthetic biology, one might predict how likely it would be for a eukaryotic cell to be completely synthesized from scratch in twenty years. In contrast, one’s probability of the probability that the eukaryotic cell will be synthesized then is one’s *perceived knowledge of the degree to which one’s knowledge of pertinent science, technology, and law is complete*. Thus, if the second-order probability is low, one lacks confidence, due to perceived ignorance, that the first-order probability is correct. Thus, a second-order probability could be calculated to determine the extent of additional research one might need to do to minimize this ignorance. The many rapidly evolving dimensions on the roadmap require that it be designed so that it can be modified when one or more projected dimensions miss the mark. However, much effort may be required to minimize uncertainty at the start, because initial investments can be modified only to a point without uprooting technological developments. Initial investments may effect entire sequences of additional investments which anticipate that the technological developments will follow paths that approximate their initial projected trajectories. Cf. SCOTCHMER, *supra* note 87, at 56–57.

[N]ot all ideas for innovations are known when investment decisions must be taken, and thus there can be regret. Any investment has the potential to set in motion a whole sequence of related investments that will entrench a technology. . . . The right interpretation of efficiency must account for options on expected future development. Since the future path of development has a stochastic element, the decision maker must have a subjective view of what is likely to happen, and with what probabilities, and then calculate economic welfare as an expected value. If this seems too demanding, try to formulate an alternative. Compared to what?

Id.

198. For a seminal discussion of possibility analysis, see L.A. Zadeh, *Fuzzy Sets*, 8 INFO. & CONTROL 338 (1965).

199. Cf. JACK ULDRICH, INVESTING IN NANOTECHNOLOGY 251 (2006) (arguing that

Even when obsolescence appears improbable, if it also seems reasonably possible, given that utility patent protection begins with the date of issuance and ends twenty years from the date of application,²⁰⁰ obsolescence should be addressed for the degree to which it is expected to reduce the patent portfolio's exit value at acquisition.

At first, the best plan is to increase patent portfolio magnitude and diversity in a specific market, with a large number of distinct, but related patents that mitigate the intra-market magnitude-diversity trade-off. The importance of market specialization at the incipient development phase in a start-up has been particularly noted in nanotechnology.²⁰¹ Premature cross-market development is generally cost-prohibitive. The small size of most nanotechnology start-ups, despite the potential cross-market applicability of their technology, makes incipient developmental efforts across markets overextensive.²⁰² Even in nanomedicine, where companies are developing a wide range of apparatuses, manufactures, and methods,²⁰³ small start-up size necessitates development in one nanomedical market only. As the nanomedical start-up matures, cross-market diversification would become more feasible, allowing for additional mitigation of the risks created by long R&D timelines, FDA²⁰⁴ and EPA²⁰⁵ hurdles, and possibly unforeseeable hurdles. The unforeseeable hurdles could include limited niche marketability due to unanticipated side effects with many patients as well as other limits to clinical use due to expense, causing third-party payer non-coverage

various nanoscale products and devices such as carbon nanotubes, nanoparticles, and quantum dots could have very short commercial lives, because although they may fetch a premium price at first, prices may drop as production scale increases and more competitors get into the field, allowing for both upgrades and entirely new products and services).

200. 35 U.S.C. § 154(a)(2) (2000).

201. ULDRICH, *supra* note 199, at 21 (arguing that nanotechnology start-ups "should be able to subcategorize the specific market [that] they are about to enter (e.g., electronics, tools, biotechnology)").

202. *Cf. id.* at 21–22 (arguing that although a nanotechnology company often has potential applications in many markets, market realities dictate that it focus on one field first and develop a specific product for that market because nanotechnology companies, especially the small start-ups, need strategic focus to succeed).

203. See Bawa et al., *Protecting Nanomedicine*, *supra* note 90, at 156.

204. See, e.g., NANOTECHNOLOGY TASK FORCE, U.S. FOOD AND DRUG ADMINISTRATION, NANOTECHNOLOGY 19–28 (2007), available at <http://www.fda.gov/nanotechnology/taskforce/report2007.html>.

205. See, e.g., Press Release, U.S. Environmental Protection Agency, EPA Invites Public Participation in Development of Nanotechnology Stewardship Program (Dec. 18, 2006), available at <http://yosemite.epa.gov/opa/admpress.nsf/a883dc3da7094f97852572a00065d7d8/0edb5f39e2ed3c428525720b00629872!OpenDocument>.

because the nanomedical intervention is not substantially superior to much cheaper therapeutic options.

B. Maintaining and Modifying the Roadmap to Maximize Commercial Value

Once the roadmap is created—because it depends on the eleven dynamic variables in Part III.A²⁰⁶—it should be frequently viewed for adjustment in research, development, and business emphases, from the pre-exclusive licensing stage down the road to acquisition. The roadmap—and the patent portfolio within it which will often be a dominant force in determining routes toward exclusive licensing, financing, and acquisition—must be viewed as dynamic entities. Virtually constant attention and frequent, though not major, changes in direction should be expected depending on existing and projected changes in these entities. Although radical directional change could connote instability that would often reduce anticipated commercial gains, more modest fine-tuning projects an impressive degree of diligence that would bode well for commercialization.

C. Using the Patent Portfolio to Facilitate Commercial Development

Building and maintaining patent portfolios with many non-overlapping patents which maximize both magnitude and diversity is but one part—albeit a crucial part—of the legal enablement of commercial development in NB/BN, synthetic biology, and RNAi.²⁰⁷ The patent portfolio must be part of an integrated legal and commercial strategy with well-defined developmental paths clearly plotted on the multidimensional roadmap.²⁰⁸ The leveraging power of the portfolio in

206. See *supra* Part IV.A.

207. Cf. Michelle Dipp et al., *Keeping It Real With Investors*, *BIOENTREPRENEUR* (2006), available at http://www.nature.com/bioent/building/financing/012006/pf/bioent899_pf.html (arguing that IP fosters start-up transition from birth to growth, seed money is needed for initial patent applications and licenses to ensure a strong IP position, small start-ups must have the tools to defend their IP from infringers of all sizes, and no industry depends on IP as much as the life sciences industry).

208. Cf. Gabor Garai & Andrew S. Baluch, *Integrated Legal Strategies for Combination Biomedical Products*, *THE PULSE*, April 2007, at 3, available at http://www.foley.com/files/tbl_s31Publications/FileUpload137/4046/ThePulse_April07.pdf. Just as a nanotechnology combination product unites these three physical components—drug, device, biologic—so too are the regulatory, intellectual property (IP), and business law issues increasingly related with regard to the legal aspects of these products. To succeed in the marketplace, the innovators of combination products must be armed with an integrated legal strategy.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 181

the context of the multidimensional roadmap to commercialization can be formidable.²⁰⁹ However, because patent clusters have already formed in sectors within all three technologies, navigating these clusters will often be crucial for exclusive licensing,²¹⁰ financing,²¹¹ and commercial and technological maturation into an attractive acquisition target.²¹²

D. Exclusive Licensing

Investor analysts have stressed the value of strategic partnerships in these emerging technologies.²¹³ Although exclusive licensing (often between university innovators and start-ups that can build on the innovations) has become an increasingly attractive first step to commercialization, “holdups” that potentially stymie innovation can exact a considerable toll.²¹⁴ Thus, it is imperative to try to foresee potential holdups and ascertain if an attempt at a non-obvious anticipatory design-around is needed. A non-obvious design-around would effectively circumvent the claims in the potential holdup.

Similar mitigation strategies are an important part of the bilateral bargaining between a university (or government agency) patentee and a start-up exclusive licensee. If it has downstream rivals, “an early

209. Cf. Schmidt, *supra* note 61, at 273.

210. Presumptively valid and broad patent protection in any of these technologies can be the key ingredient to obtaining a good licensing deal. For instance, Sirna’s broad patent portfolio in RNAi made it very attractive for Merck—which, like many pharmaceutical companies, has generally been very cautious about licensing or acquiring patent portfolios in these new technologies—to license the portfolio. *See id.*

211. Cf. Bawa et al., *Protecting Nanomedicine*, *supra* note 90, at 156 (Asserting that patents are critical for start-up financing: “investors are unlikely to invest in a start-up that has failed to construct adequate defenses around its intellectual property. In fact, patents generally precede funding from a venture capital firm.”).

212. Cf. Bawa Commentary, *supra* note 15, at 346 (Arguing that investors in nanomedicine and pharmaceutical companies consider patent issues to be among the most important issues that they will consider in evaluating a prospective investment).

213. Regarding nanotechnology for instance, see ULDRICH, *supra* note 199, at 27: “[b]ecause many nanotechnology start-ups are small, they will need assistance in getting their product to market. For this they will often need partners.”

214. Cf. Kumar & Rai, *supra* note 28, at 1758 (“[A] crowded patent landscape creates the possibility of ‘holdup’ by a previously unknown patent holder who emerges only after others have invested large sums of money . . . to the extent that patent rights holders rely upon reach-through royalties to secure revenue, standard economic theory predicts that product output by the improver will be suboptimal.”) (citations omitted). However, trolls do not just holdup big companies with deep pockets: “Start-up companies are easy targets for holders of weak patents of ambiguous scope because of the fragility of their funding and the time-sensitivity of their business plan.” Peter S. Menell, *A Method for Reforming the Patent System*, 13 MICH. TELECOMM. & TECH. L. REV. 487, 507 (2007).

licensee will actually *benefit* from agreeing to conditions that will preserve the patent holder's position in subsequent negotiations with other downstream firms, since the early licensee benefits if subsequent licensees (its rivals) must pay higher royalties."²¹⁵ Several high profile exclusive licensing deals between universities and start-ups in all three technologies imply that these deals are one of the preferred first commercial moves for many universities with promising near-term innovations.²¹⁶

E. Maximizing Patent Portfolio Value to Obtain and Maintain Venture Capital

Virtually all start-ups in these three research-intensive fields will need venture capital, and the number of patents, combined with the magnitude and diversity of patent protection, are key to getting that venture capital. Though widely recognized as critically important, getting venture capital is by no means easy to get, and even if a start-up receives venture capital, success is not guaranteed. A large percentage of biotechnology start-ups have not had a successful exit either as an

215. Lemley & Shapiro, *Patent Holdup*, *supra* note 188, at 2007. See also Garai & Baluch, *supra* note 208, at 4 (“[E]ach additional license will decrease the manufacturer’s incentive to market the combined [biomedical] product. . .”).

216. Examples of major exclusive licensing deals in all three fields in the past two years include the following. First, in synthetic biology, Condon Devices exclusively licensed synthetic biology technology for “its platform to design, construct and assemble large strings of oligonucleotides.” Ken Howard Wilan, *Commercializing Synthetic Biology*, *BIOENTREPRENEUR* (2005) (reporting that Jay Keasling, UC-Berkeley Professor of Bioengineering and Chemical Engineering, formed two synthetic biology start-ups—not only Condon Devices, but also Amyris Biotechnologies—the latter receiving \$12.5 million from OneWorldHealth, a non-profit pharmaceutical company in San Francisco). Second, in RNAi, Merck became the exclusive licensee of Sirna’s broad RNAi patents through its purchase of Sirna. See Schmidt, *supra* note 61, at 273. Third, in nanotechnology, Harvard exclusively licensed chemist George Whitesides’ patents to Nano-Terra. Thayer, *Harvard Licenses Nanotech Patents*, *supra* note 85. For an economic take on this trend, see SCOTCHMER, *supra* note 87, at 236.

An exclusive license insulates the licensee from competition, and the resulting monopoly profit can be shared with the university through the fees. Nonexclusive licenses are usually reserved for situations where the university perceives it has no other choice—for example, where [additional] industrial users threaten to challenge or design around the university’s patents. . . . [Seventy-four] percent of university licensing offices “almost always” grant sponsors the right to negotiate exclusive licenses.

Yet Scotchmer also asserts in a footnote on the same page that this “distinction between exclusive and nonexclusive licensing is a bit artificial, since the profit advantage of exclusive licens[es] can often be achieved with nonexclusive licenses and high royalties.” *Id.* at 236 n.7.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 183

initial public offering or as an acquisition.²¹⁷ NB/BN has experienced much growth, but continued rapid development is threatened by patent thickets that either already exist or are looming throughout nanotechnology, though particularly in NB/BN. Combine the thicket problem with the high concentration of venture capital within nanotechnology,²¹⁸ and one may expect a high rate of failure among NB/BN start-ups as well. However, a high failure rate does not mean that those few that eventually exit successfully will not succeed very well. Given the enormous potential in all three technologies, the most promising companies will be acquired for lucrative sums. Being one of the successful few will still be extremely difficult. A strong patent portfolio that indicates to venture capitalists that a company is *relatively* low risk for an unsuccessful exit within seven years may often be a necessary, but not a sufficient, condition for success.²¹⁹

The greatest financing challenge for NB/BN, synthetic biology, and RNAi may be in medical applications outside of a highly promising drug delivery patent, because of the caution shown by biotechnology and pharmaceutical companies, as well as much uncertainty in FDA regulatory approval and clinical utilization.²²⁰ Nonetheless, despite their cautious approach to acquisitions, established biotechnology and pharmaceutical companies increasingly engaged in them from 1998 to 2006.²²¹ These companies have pursued the safest route with these

217. Thus, as critically important as venture capital is as a step towards a successful exit, it is only that; there is no guarantee that one will make the exit. Cf. GARY P. PISANO, *SCIENCE BUSINESS: THE PROMISE, THE REALITY AND THE FUTURE OF BIOTECH* 162 (2006) (drawing an analogy between raising capital in biotech and getting an official number for the Boston Marathon; it can be tough to qualify, but tougher still to do well in the race).

218. Ann M. Thayer, *Nanotech Investing*, 83 *CHEMICAL ENGINEERING NEWS*, May 2, 2005, at 1 (reporting that 10% of the more than 1,200 nanotechnology-related start-ups worldwide have received venture capital, “and just 10% of those have received more than one round of funding”; thus, if this report is accurate, just [twelve] of these start-ups have received two or more rounds of venture capital funding).

219. Cf. ULDRICH, *supra* note 199, at 246.

[M]ost investors have limited patience. Many of the [nanotechnology] companies listed in this book are the recipients of venture capital. Venture capitalists are typically willing to give a company anywhere between three and seven years to prove they can either be a viable acquisition target or succeed on the public market. If companies cannot demonstrate progress toward these established goals, funding is going to become increasingly difficult to obtain.

220. Regarding the uncertain but possibly very large health (as well as environmental) risks of nanomaterials, see generally Lin, *supra* note 195.

221. Cf. Nixon Peabody LLP, *Nixon Peabody LLP Attorneys Speak at BIO International Convention*, May 3, 2007, http://www.sixbey.com/publications_detail3.asp?ID=1817 [hereinafter AGE OF ACQUISITION]

highly promising, yet also highly uncertain, technologies. Instead of doing the R&D themselves, they have entered into licensing agreements, relying on government and academic research, and waiting until the regulatory climate becomes clearer.²²² Because many drug patents are set to expire soon,²²³ drug development—despite all of the potential R&D hurdles—is one of the *relatively* safer bets in all three technologies for government, university, and start-up investment. An increasing percentage of total venture capital is given to life sciences companies.²²⁴ This trend most likely reflects not only the near-term expiration of many drug-related patents in these technologies which fuels drug development, but also the lack of direct investment from major pharmaceutical and biotechnology companies that prefer instead to rely on government-or-university-to-start-up de facto research pipelines.

Nonetheless, probably the most commercially promising exclusive licensing deal of 2007—Harvard’s licensing of George Whitesides’ nanotechnology patents to Nano-Terra—will apparently require no venture capital.²²⁵ Nano-Terra and Harvard will co-own the technology, which is already licensed to several large established private companies, as well as the Department of Defense.²²⁶ This may be because Whitesides previously helped create three biotechnology companies with “a combined market value of nearly \$20 billion”²²⁷ and is also a highly esteemed expert in nanotechnology.²²⁸ Without a combination of proven business acumen and scientific expertise, researchers in government agencies, universities, and start-ups should not count on being able to bypass venture capital like Harvard and Nano-Terra

(reporting that firm attorney Philip Taub would be moderating a conference panel “*The Age of Acquisition: Business Strategies for Biotech Companies.*”) (emphasis added).

222. Cf. Morrow, *Gauging Nanobiotech’s Promise*, *supra* note 190.

223. See Bawa et al., *Protecting Nanomedicine*, *supra* note 90, at 154.

224. LUX NANOTECH INDEX, *supra* note 24 (reporting that venture capital investment in the life sciences increased from 13% to 28% of total venture capital investment).

225. Having licensed more than fifty patents from Harvard, “Nano-Terra has not raised venture capital; instead, its founders and employees, along with advisors and Harvard University, own the company.” Jeffrey Carbeck, Nano-Terra, Inc., Nano-Terra, A Scientist’s Approach to Commercializing Science, Presentation at the AIChE 2007 Annual Meeting (Nov. 7, 2007) (abstract available at http://aiche.confex.com/aiche/2007/preliminaryprogram/abstract_100463.htm).

226. Thayer, *Harvard Licenses Nanotech Patents*, *supra* note 85.

227. *Id.*

228. Barnaby J. Feder, *Harvard is Licensing More Than 50 Patents to a Nanotechnology Start-Up*, N.Y. TIMES, June 4, 2007, available at http://www.nytimes.com/2007/06/04/technology/04nano.html?_r=1&oref=slogin.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 185

apparently will be able to do. Moreover, much uncertainty persists with even the most commercially promising start-ups such as Nano-Terra, as seen by the disappointments of some other seemingly very promising similar start-ups.²²⁹

F. Through the Minds of Prospective Buyers: How Pharmaceutical and Biotechnology Companies Acquire NB/BN, Synthetic Biology, and RNAi Technology

Merger and acquisition activity—especially acquisition activity—has increased sharply in the biotechnology and pharmaceutical industries over the last few years, leading some industry analysts to refer to these times in the life science industry as an “age of acquisition.”²³⁰ Although making a patent portfolio an attractive acquisition target may appear to be elusive because of many firm-specific factors,²³¹ the generalization that companies can be expected to be risk-averse, with calculated and cautious purchases built on solid patent portfolios, nonetheless holds.²³² A corollary to the risk-averse nature of these companies is that they would like to increase the acquisition risks that face their competitors, which they can do by dominating a nascent market, as long as the barriers to entry that such increased risks create do not run afoul of antitrust law.²³³

229. See, e.g., Thayer, *Harvard Licenses Nanotech Patents*, *supra* note 85.

230. See AGE OF ACQUISITION, *supra* note 221.

231. See James Mittra, *Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance Behaviour of Large Firms*, 19 TECH. ANALYSIS & STRATEGIC MGMT. 279, 279 (2007) (reporting that the present preferred balance in the pharmaceutical industry between in-house R&D and externally sourced knowledge is due to numerous very firm-specific factors).

232. Regarding nanomedicine, compare Kostas Kostarelos, Editorial, *Establishing Nanomedicine*, 1 NANOMEDICINE 259, 260 (2006), reporting that although quite a few big pharmaceutical companies like the ideas and technologies in nanomedicine, because they consider most nanomedicine companies early stage and high risk, these pharmaceutical companies are fitting nanomedicinal technologies into their pre-established markets.

233. Cf., Mark Hollmer, *News In-Brief: Merck Establishes a Foothold in RNAi*, 25 NATURE BIOTECHNOLOGY 9, 9 (2007). Although Hollmer does not specifically address antitrust issues, he does discuss Merck's exclusive licensing of a broad RNAi patent portfolio that may help the large pharmaceutical company dominate the nascent industry by excluding competitors from a large percentage of the new technological turf. If the percentage of turf excluded gets too high, it is possible that Merck could obtain a monopoly. Excessive anti-competitive effects of broad patent portfolios could thus create antitrust problems.

IV. OVERCOMING NEAR-TERM OVER-OPTIMISM TO REALIZE LONG-TERM REVOLUTIONARY GAINS: A SOBERING LOOK AT THE MODEST MEDICAL GAINS IN FIGHTING AMERICA'S TOP THREE KILLERS—HEART DISEASE, CANCER, AND CEREBROVASCULAR DISEASE²³⁴

Emphasis on the great medical potential of NB/BN, synthetic biology, and RNAi threads its way through NNI, NIH, and other U.S. government institute reports,²³⁵ academic projections of medical applications, and emerging growth company and venture capitalist hype. Although this potential is indeed great, it will not be realized anytime soon. Do not expect radical reductions in the incidence, prevalence, and mortality rates for the three most common causes of death in the United States—heart disease, cancer, and cerebrovascular disease—anytime in the next twenty years. NB/BN, synthetic biology, RNAi, and other new biotechnologies all promise great breakthroughs in our fights against these and other chronic diseases. Realizing this promise, however, will most likely require major advances in not just the technologies, but also, *inter alia*, better comprehension of complicated multilayered cellular, molecular, extracellular, and system-wide (e.g., genome-level, proteome-level) human biology. Thus, it is highly unlikely that any of the three technologies will realize this great promise in the next twenty years. Moreover, there is no guarantee that anticipated and/or unforeseen barriers to safe and efficacious medical intervention will not contraindicate the use of all of these technologies even in the remote future. We must proceed with equal parts vigorous enthusiasm and rigorous skeptical inquiry into what could go wrong. Presently, optimism is not sufficiently tempered by skepticism and rigorous searches for obstacles to implementation and ways to overcome these obstacles.

What have we seen in the last forty years? In the 1960s, we heard that a “cure for cancer” was imminent, but, despite huge funding, there is still no cure, although ironically, unjustified hype appears to continue

234. NATIONAL CENTER FOR HEALTH STATISTICS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, HEALTH, UNITED STATES 109 fig.20 (2007) (displaying tabular data that show heart disease, cancer, and stroke to be the first, second, and third most common causes of death, respectively, in the United States for every decade from 1950 through 1980, every five years from 1985 through 1995, and every year from 1996 through 2004).

235. The FDA being a notable and predictable exception. See, for example, the FDA's guardedly optimistic language regarding the uses of nanotechnology. See FDA Statement on Whether There are Regulated Nanotech Products, *supra* note 32. Canada may be a bit different. See ONTARIO MEDICAL NANOTECH HORIZON, *supra* note 37, at 12.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 187

unabated.²³⁶ In the 1980s, the biotechnology hype also promised monumental changes in treatment for various genetic disorders. In the 1990s, gene cloning identified all sorts of targets for intervention with many deadly chronic diseases, but again the deadliest three—heart disease, cancer, and cerebrovascular disease—remained major lethal threats. We did not fully anticipate the obstacles to interventions such as gene therapy. Although there are reports that “[n]anotechnology has been increasingly utilized to enhance bone tissue engineering strategies,”²³⁷ tissue engineering, though very promising, has not yet been used extensively in medicine. Unfortunately, when trying to develop and market complicated new technology—or when trying to

236. See George L. Gabor Miklos & Phillip J. Baird, *The Latest Surge in the War on Cancer; Tour de Force or Tour de Farce?*, posted by Otis to You Bet Your Life, http://barnesworld.blogs.com/barnes_world/2007/03/george_l_gabor_.html (March 05, 2007, 3:00 EST) (arguing that The Cancer Genome Alliance (TCGA) is making completely unwarranted promises of potential applications of the data to personalized medicine, with a representative of the National Cancer Institute even promising that all suffering and death from cancer will be eliminated by 2015). Miklos and Baird argue that the data TCGA is collecting appears irrelevant to the individualized clinical genetics of cancer where the key outstanding question is “[h]ow do we sort the mutations of very different types which may produce a clinical outcome in the unique genetic and epigenetic background of that particular individual[?]” *Id.* The authors contend that the effectiveness of drug treatment for individual cancers is determined by a genomically heterogeneous cell population consisting of imbalanced genomes at both the genetic and epigenetic levels, necessitating better systems-level understanding of the differences to predict therapeutically relevant outcomes. *Id.* This implies that the billions of dollars of public money that will be invested in single gene pair mutations, without genome-level multivariate systemic analysis, may be tragically wasted. They see TCGA as built on the false premise that the mutational signature of the bulk tumor is congruent to that of its metastatic derivatives and thus offers illusory hope of a personalized therapeutic application built on bulk tumor, rather than stem cell population, information. The stem cell population information, the authors contend, would “still offer some hope.” *Id.* However, Miklos and Baird’s criticism appears excessively harsh and not entirely valid, given that other researchers believe that TCGA is providing us with remarkably valuable information. See, e.g., W.C. Cho, Review, *A Future of Cancer Prevention and Cures: Highlights of the Centennial Meeting of the American Association for Cancer Research*, 19 ANNALS OF ONCOLOGY 205, 205 (2008). The complexity of carcinogenesis is reflected in ongoing debates regarding the roles that mutations might play in cancer and thus the potential of targeting mutations in oncotherapy. Compare Lawrence A. Loeb et al., Point-Counterpoint Review, *Cancers Exhibit a Mutator Phenotype: Clinical Implications*, 68 CANCER RES. 3551, 3551 (2008) (arguing that cancer cells have a mutation rate that exceeds that of normal cells and thus inhibiting mutator pathways could prevent cancer) with I. Walter Bodmer, Response, *Cancers Exhibit a Mutator Phenotype: Clinical Implications*, 68 CANCER RES. 3551, 3557 (2008) (criticizing this mutator phenotype hypothesis because natural selection would confer no advantage to Loeb et al.’s “unexpanded random mutations,” and therefore, they will rarely occur in the tumor and are “irrelevant for the overall biology of the tumor”).

237. Kyobum Kim & John P. Fisher, *Nanoparticle Technology in Bone Tissue Engineering*, 15 J. DRUG TARGETING 241, 241 (2007).

secure funding from Congress—there can be much pressure to look rigorously for how things could work to satisfy potentially wary funding sources, but there is often less pressure to examine rigorously all that could go wrong.

Some of what will go wrong will only be discovered via experimentation, but some of it can be anticipated. If we are truly more interested in long-term medical gains than short-term financial gains, we must be hyper-vigilant about investigating obstacles to major developments and how we could best overcome or circumvent them. Unfortunately, this is outside the tactical and strategic thinking that frames the work of most commercial researchers, executives, and investors. As I will argue in Part V.B.2, this requires an idealistic public commitment to long-term sophisticated research.

Also recall the many surprising findings pertinent to regulation of protein expression, reported by ENCODE and others, described in Part I.B.2, which implicate both mechanistic biology and systems biology. NB/BN, synthetic biology, and RNAi will thus need to coordinate their technologies with forthcoming basic research that elucidates the implications of the surprising new findings to realize revolutionary clinical gains in heart disease, cancer, and cerebrovascular disease.²³⁸ Intracellular mechanisms are sources of much of the planned targeted clinical intervention in all three technologies discussed in this Article.²³⁹ Accurate higher-level systemic analysis is also essential for pertinent clinical developments in synthetic biology.²⁴⁰ Sorting out the many diverse and intertwined cellular and extracellular surprising new findings pertinent to normal and pathological human conditions will of course take much time.

V. POLICY PRESCRIPTIONS: FURTHER WEED OUT THE PATENT THICKETS, INCREASE PATENT QUALITY, AND SHIFT THE MAIN FOCUS FROM MAXIMIZING NEAR-TERM COMMERCIALIZATION TO MAXIMIZING LONG-TERM MEDICAL PROGRESS

Heraclitus made two pertinent prophetic points 2500 years ago: “[a] thing’s (the world’s) real constitution has a tendency to conceal itself”

238. Regarding cancer, see, for example, Pagano et al., *supra* note 66, at 0181–82 (finding down-regulation of 21A endogenous ncRNA in tumor cell lines and concluding that the role that this newly discovered transcript plays in tumor cell proliferation needs further investigation).

239. See *supra* Part I.B.2.

240. See *supra* Part I.B.2.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 189

and “lovers of wisdom ought very much to be enquirers into many things.”²⁴¹ ENCODE et al.’s new picture of mammalian regulation of protein expression is contrary to many decades-old assumptions. This is a picture of nucleic acid and amino acid sequences involved in extraordinarily complex multilayered regulatory phenotypic controls from the level of the small sequence all the way up to the genome and proteome.²⁴² Considering this complexity—and considering too that gene therapy has yet even to approximate the ground-breaking clinical success it was promised to be²⁴³—one must approach the great medical promises of these nascent technologies with a healthy dose of skepticism.

This pithy 1808 rhyme from Walter Scott’s poem *Marmion* is also prophetic: “Oh! what a tangled web we weave [w]hen we first practi[c]e to deceive!”²⁴⁴ This prophecy applies doubly. One tangled web is a huge, broad, and often-overlapping group of patent portfolios.²⁴⁵ This web ostensibly protects innovations derived from an even more tangled web of overlapping mammalian biophysics, bioengineering, biochemistry, and cell and molecular biology which applies to NB/BN, synthetic biology, and RNAi.²⁴⁶ The following is clear in these three nascent technologies: to varying degrees, all have thickets, invalid patents of indefinite claim scope (with related inadequacies in the written descriptions), and potentially infringing patents of broad claim scope.²⁴⁷ These thickets, invalid patents, and potentially infringing patents threaten to stymie commercial development via massive litigation.²⁴⁸

If the patent portfolio is critical to the commercial development of

241. HERACLITUS, *FRAGMENTS: A TEXT AND TRANSLATION*, 29, 71 (T.M. Robinson trans., Univ. of Toronto Press 1987).

242. *See supra* Part I.B.

243. Not only has it not been a ground-breaking clinical success, gene therapy has had at least one very high-profile lethal failure. *See* Couzin & Kaiser, *infra* note 289.

244. WALTER SCOTT, *MARMION* 205 (William J. Rolfe ed., The Riverside Press 1913) (1808).

245. *See supra* Part II.B.

246. *See supra* Part I.B.

247. *See supra* Part II.B.

248. *Cf.* Giovanni Dosi et al., *Knowledge, Competition and Innovation: Is Strong IPR Protection Really Needed for More and Better Innovations?*, 13 *MICH. TELECOMM. & TECH. L. REV.* 471, 477 (2007) (contending that the literature on cumulative, sequential, and complementary technological progress indicates that if technological opportunities for firms are not mutually independent, patents can cause holdup phenomena, such as patent thickets and anticommons and, in the long-term, deter innovation).

NB/BN, synthetic biology, and RNAi,²⁴⁹ an important policy question is whether it should have such critical importance. Important related questions are whether patent portfolios, considered both within each technology and across two or more of the technologies, are likely to hinder or facilitate the best types of growth in the technologies. In this part of the Article, I argue that the quality of patent portfolios can be improved—and the risk of patent thickets and low quality patents stymieing commercialization consequently reduced—via various reforms in patent law and patent examination procedure and review. However, I also argue that these reforms will not suffice to facilitate near-optimal medical progress for two main reasons. First, upstream building blocks and other basic foundations, such as research tools, need to be broadly accessible via scientific and technological commons. Second, the most promising research is also very risky, expensive, and long-term, which makes it unsuitable for collaborative government agency or university-start-up-big pharma/biotech developmental pipelines and the securing of a reliable finance source. This latter fact is largely due to the daunting interconnected complexity of cellular, extracellular, and metabolic mechanisms, higher-level biological systems, and clinical medical translational problems. These problems include barriers to creating fairly precise links between basic laboratory science, animal experimentation, and clinical trials with humans. Nonetheless, such fairly precise translations will be needed for the most ambitious innovations that will make leaps, rather than incremental steps, toward revolutionary advances in medical diagnostics, prevention, and treatment.

This is how we might further untangle the patent web and increase patent quality. Although not in itself a panacea, the untangling will at least afford us more valid, secure, and non-infringing patent portfolios. Three related statements from Albert Einstein—“[o]ut of clutter, find simplicity”; “[f]rom discord, find harmony”; and “[i]n the middle of difficulty lies opportunity”²⁵⁰—apply as well. Findings from ENCODE et al. strongly imply that intracellular and extracellular regulations of phenotype production are linked via extraordinarily intricate, variable, and multilayered connections.²⁵¹ The technological boundaries between BN and NB, as well as between NB/BN, synthetic biology, and RNAi

249. See *infra* Part II.A.

250. ALBERT EINSTEIN, *THE EXPANDED QUOTABLE EINSTEIN* 322 (Alice Calaprice ed., 2000).

251. See *supra* Part I.B.

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 191

are also blurred because of complexities and uncertainties, in addition to categorical overlap.²⁵² The patent portfolio in itself is not problematic, so much as the ease of getting patents and building a commercially valuable portfolio that may nonetheless contain invalid or infringing patents. The low value of most individual patents vis-à-vis patent portfolios is a large part of the problem, and the market alone is unlikely to create the necessary incentives to fix it.²⁵³ Nonetheless, one must also be wary of the formation of commons for reasons that ostensibly promote the public good, but are in actuality a close cousin of “regulatory capture,” that is, a way for people who already possess patents to reduce the patenting potential of future competitors.²⁵⁴

A much more finely tuned balance between private patent protection and public incentives for inventions could facilitate truly major medical progress in the next twenty years. Private patent protection must be guided by additional changes in patent law.²⁵⁵ Commons are necessary for upstream building blocks to secure the foundation of valid and reliable basic science and technology.²⁵⁶ Governmentally and philanthropically funded prizes for cures or preventions for diseases would be salutary supplements to particular reforms in patent law and examination procedure and the proper creation and maintenance of parallel commons.²⁵⁷ There is no panacea

252. See *supra* Part I.A.

253. Compare Parchomovsky & Wagner, *supra* note 70, at 60 (“Perhaps the most important prediction enabled by the portfolio theory is that the current patent intensity (patents obtained per research dollar) should not be expected to drop dramatically—at least absent the intervention of other major factors, such as substantive legal changes.”) with Lemley & Shapiro, *Probabilistic Patents*, *supra* note 83, at 82 (reporting that voluntary arrangements can occur between established incumbents with a shared incentive to clear out a patent thicket by signing broad cross-licenses). In nascent fields like the three discussed in this Article where new start-ups own much of the patents, however, there are no established incumbents.

254. Cf. Kumar & Rai, *supra* note 28, at 1747 (reporting, in the context of synthetic biology, “the attempt by individuals to use intellectual property rights to create a ‘commons,’ just as [the] developers of free and open-source software use the leverage of software copyrights to impose requirements of openness on future programmers—requirements greater than those attaching to a public domain work”).

255. See *infra* Part V.A.1.

256. See *infra* Part V.B.1.

257. See Joseph E. Stiglitz, Editorial, *Scrooge and Intellectual Property Rights: A Medical Prize Fund Could Improve the Financing of Drug Innovations*, 333 BRITISH MED. J. 1279, 1279–80 (2006) (recommending government-funded prizes for cures to diseases—such as malaria—that primarily affect third world countries because there are insufficient incentives for the commercial development of cures for these diseases). See also SCOTCHMER, *supra* note 87, at 39, 41–42 (providing an economic analysis of two types of

for either the somewhat chaotic patent portfolio landscape or long-funded but still refractory killers such as our country's most common: heart disease, cancer, and cerebrovascular disease. Nonetheless, there is much more that we can and should do.

*A. Further Weed Out the Patent Thickets and Increase Patent Quality:
Why KSR and the Patent Reform Act Probably Will Not Suffice and
How We Could Do More*

1. Additional Changes Recommended: Prosecution History Estoppel,
Improved Injunctive Relief to Deter Holdups from Trolls,²⁵⁸ and
Removal of the Prior Art Limit to Reexaminations

The Supreme Court and Congress are both to be lauded for initiating reforms that should help weed out overbroad and potentially overlapping patents from thickets and thickets-in-the-making in all three technologies. But considering the expense and the retardation of development that thickets effect, the federal courts and Congress should go farther. IP scholars have recommended several promising ex ante and ex post legal changes that deserve greater consideration from judges and legislators. Prosecution history estoppel, which could force patent applicants to produce sufficient information about their patented invention at an early stage, is a promising ex ante recommended change.²⁵⁹ Removing the prior art limit to reexaminations (the removal being somewhat like extending to reexaminations *KSR*'s prescription that obviousness inquiries be expansive and thus may need to consider more than just the prior art) and providing injunctive relief to reduce patent trolls²⁶⁰ are both very promising ex post recommended changes.

prizes as alternatives to patents—"targeted prizes," which are directed ex ante at well-known needs that originate with sponsors, and "blue sky prizes," which are directed ex post at the value of the innovation—and arguing that "[t]he advantage of prizes over patents is that they can avoid the deadweight loss of proprietary pricing").

258. Although injunctive relief proposals have been very seriously considered, it now appears unlikely that injunctive relief will be a major component of the Patent Reform Act that eventually passes to become law. See H.R. 1908; S. 1145; S. 3600.

259. See Parchomovsky & Wagner, *supra* note 70, at 10, 69–71.

260. See Mark A. Lemley, Patent Reform Legislation—Public Comments on Substitute HR 2795 and the Role of the Antitrust Modernization Commission, Testimony Before the Antitrust Modernization Commission 7–9 (Oct. 24, 2005), available at http://govinfo.library.unt.edu/amc/commission_hearings/pdf/statement_Lemley.pdf. *But cf. id.* at 1–2 (arguing that while abusive patent litigation is reported by innovators in semiconductor, computer, Internet, and telecommunications, it is not a problem for the medical device, biotechnology, and pharmaceutical industries because of differences in the two types of industries). Lemley states, "pharmaceutical patents are more likely to cover a

2. Impractical Given the Extraordinary Cross-Industry Nature of the Technologies: Extensive Industry-Specific Patent System Reform

Some scholars have noted that patent problems are often industry-specific, with divergence most common between biotechnology and pharmaceutical patents and software patents, leading some to question whether the patent system should be tailored to such differences.²⁶¹ Category-specific patent rules may be both feasible and desirable for some types of patents, such as business methods patents and software patents.²⁶² However, even if nanotechnology is limited as it has been here to NB/BN, because NB/BN often incorporates computer science and other fields, it would oversimplify this interdisciplinary technology to place it in a single natural science category.²⁶³ Similarly, synthetic biology involves code-driven information, which makes it, somewhat like bioinformatics, an awkward exclusive fit in biotechnology.²⁶⁴ Only RNAi could possibly be placed exclusively in a biotechnology category, but because of potential salutary synergies between RNAi and both

whole drug, rather than one of 5,000 different components of a semiconductor chip.” *Id.* This perception may indeed be common and thus explain why many in the computer industry have supported the most recent patent reform proposals, while many in the life sciences industry have not. *See also* Robert E. Thomas, *Vanquishing Copyright Pirates and Patent Trolls: The Divergent Evolution of Copyright and Patent Laws*, 43 AM. BUS. L. J. 689, 693 (2006) (“Large biotechnology, medical, and pharmaceutical companies (biotech/pharma) do not face the same threat that their info-tech counterparts face. This lack of cohesiveness has likely delayed or prevented the passage of some of the proposed patent reforms.”). However, nascent multidisciplinary technologies such as the three discussed here—especially synthetic biology—straddle the computer/life sciences dichotomy. *Cf.* Arti Rai & James Boyle, *Synthetic Biology: Caught Between Property Rights, the Public Domain, and the Commons*, 5 PLOS BIOLOGY 0389, 0389-90 (2007) (“Intellectual property law in the U[.][S.][.] has already had difficulty incorporating the revolutionary technologies from which synthetic biology draws inspiration—biotechnology and computers.”). Given the multitude and diversity of patents, as well as patent thickets, in these three nascent technologies, it is very possible that, by the time many of the innovations covered by patents in the technologies become commercially viable, injunctive threats from trolls could be problematic for these patents too.

261. *See, e.g.*, Menell, *supra* note 214, at 496–501 (noting many distinctions between these two broad categories of patents).

262. *See id.* (arguing that software and business methods patents both pose particular problems that warrant specific reforms tailored to these categories).

263. *See* Rai & Boyle, *supra* note 260. *See also supra* text accompanying note 259. Regarding NB/BN, compare NCI Alliance for Nanotechnology in Cancer, Nat’l Cancer Inst., *Where Science and Law Meet*, MONTHLY FEATURE, Oct. 2006, at 2, available at http://nano.cancer.gov/news_center/monthly_feature_2006_oct.asp, and the statement “the filing of a nanotechnology patent often involves a team of scientists representing many scientific disciplines collaborating on a technology comprising multiple components, each of which might require multiple IP licenses.”

264. *Cf.* Rai & Boyle, *supra* note 260, at 0391.

NB/BN and synthetic biology,²⁶⁵ even RNAi does not support the argument for category-specific reform.²⁶⁶ Category-specific reform could also add a burdensome bureaucratic layer to pertinent patent analysis.

B. Parallel Science and Technology Commons

1. Commons for Pertinent Upstream Basic Science and Technology: Which Commons Type for Valid and Reliable Building Block Standards in the Three Nascent Technologies?

Broad foundational patents have been reported to slow growth in many industries.²⁶⁷ Research at ENCODE and elsewhere reveals the need for a more accurate and deeper understanding of human biology. This understanding is one of the most important foundational knowledge bases in all three nascent technologies.²⁶⁸ In synthetic biology, unlike in NB/BN, many of the building blocks have been kept in commons.²⁶⁹ However, although building parallel commons could provide an effective thicket prophylactic, the commons in synthetic biology in themselves have thus far not deterred thickets.²⁷⁰ The absence of successful patent pools in the life sciences is also cause for concern.²⁷¹

One promising solution is to obtain statements of non-assertion from other patentees in patent-based commons such as the Registry of Standardized Biological Parts at MIT, especially considering that many of the innovations in NB/BN, synthetic biology, and RNAi will be made in academia and government.²⁷² Another good idea is for MIT to “open the Registry to any owner that promised to donate its parts to the public

265. *See supra* note 29.

266. Moreover, even where Menell seeks categorical reform—software and business patents—he states that the boundaries of these patents are inherently ambiguous. Menell, *supra* note 214, at 506. Although he implies that this ambiguity is primarily a reflection of claim indefiniteness created by inadequate prosecution, *see id.*, there are also disciplinary boundary problems in software or business methods made to achieve biotechnology goals.

267. *See, e.g.*, Rai & Boyle, *supra* note 260, at 0390 (arguing that considerable evidence from virtually every important industry in the twentieth century reveals that broad patents on foundational research can retard industry growth).

268. *See supra* Part I.B.

269. *See* Rai & Boyle, *supra* note 260, at 0391.

270. *Cf.* Kumar & Rai, *supra* note 28, at 1768 (“Even in its nascent state, the synthetic biology research space is filled with proprietary rights.”).

271. *See id.*

272. *Cf.* Rai & Boyle, *supra* note 260, at 0391 (stating that because many of the MIT registry patents are owned by academia and government, statements of non-assertion in the registry would be “a salutary development and a comfort to those working on the registry”).

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi 195

domain after some fixed number of years.”²⁷³ The synthetic biology commons should be extended to interfaces between synthetic biology and other technologies, especially NB/BN and RNAi (as well as correlational research linking genotypes to phenotypes²⁷⁴). Because of the cross-disciplinary nature of these technologies, many of the grants that fuel the research that feeds the commons should likewise be cross-disciplinary.²⁷⁵ However, the highly contentious disputes over the degree to which foundational genomic information should be preserved in a scientific commons suggest that attempts to expand or add foundational commons pertinent to the three nascent technologies discussed here would meet stiff resistance.²⁷⁶

273. Joachim Henkel & Stephen M. Maurer, News and Views, *The Economics of Synthetic Biology*, 3:117 MOLECULAR SYS. BIOLOGY 1, 4 (2007) (acknowledging that this prescription assumes that the MIT Registry will remain “the world’s premier focal point for recording and sharing parts information”). The authors nonetheless argue that this is a safe assumption for two reasons. First, “scientific databases . . . almost always follow a winner-take-all dynamic in which frontrunners become larger and more entrenched over time.” Second, the risk of would-be monopolists trying to build their own proprietary databases to challenge the Registry is manageable because “[f]or every company that wanted to monopolize parts data, there would be several others trying to block it. The Registry would almost certainly receive their support.” *Id.*

274. *Cf.* Klein, *Gene Patents*, *supra* note 166 (stating that “it is in the public interest that our courts do not expand patent-eligible subject matter to include ownership of medically related genotype-phenotype correlations”).

275. *Cf.* PISANO, *supra* note 217, at 188–89.

There is deep knowledge within specific disciplines (e.g., chemistry, genomics), but less knowledge that helps us understand connections across disciplines. . . . Part of the problem may . . . be due to the grants funding process, which tends to reward investigators for narrow, well-defined research projects. . . . The current peer review process for grants . . . can . . . create barriers to cross-disciplinary work. . . . Critics of the grants process point to the “war on cancer” as an example of how funding can divert researchers from the most important problems. According to one account, while metastatic processes lead to about [ninety] percent of all cancer deaths, less than 0.5 percent of National Cancer Institute study proposals made between 1972 and 2004 focused primarily on metastasis.

Sara Boettiger & Alan B. Bennett, *Bayh-Dole: If We Knew Then What We Know Now*, 24 NATURE BIOTECHNOLOGY 320, 321 (2006) (arguing that because NIH’s promotion of its guidelines to license nonexclusively and make widely available upstream research tools primarily used for discovery rather than products in themselves has fostered access to upstream technologies, this promotion should serve as a model for other federal agencies to emulate).

276. Different perceptions on the critical need to preserve the scientific commons in genomics for, inter alia, the creation of standard building blocks perhaps explains reports of “vigorous, sometimes even vicious, fight[s]” where public investment has been both high and high-profile (e.g., Human Genome Project). Robert Cook-Deegan, *The Science Commons in Health Research: Structure, Function, and Value*, 32 J. TECH. TRANSFER 133, 136 (2007), available at <http://www.springerlink.com/content/782310p623282449/fulltext.pdf>. In

To counter this resistance, it is important to emphasize that the commons would not replace, but rather complement, commercial development via synergistic feeding of increasingly accurate basic science and technology.²⁷⁷ Moreover, universities may not need the patenting and licensing revenue that results from placing a disproportionate emphasis on such commercial development. Even if university patenting and licensing suffer because some researchers move away from near-term commercializable research, universities will not

examining the competition between public and private gene data provision, Cook-Deegan himself forcefully argues that the latter option has been highly problematic for basic research because of constraints on private gene sequences which effectively delayed access to the sequences until after patents issued or companies published the sequencing information. Cook-Deegan reports that these revelations via patenting or publication happened only if it was in the companies' commercial interests. *Id.* at 142. See also Tanuja V. Garde, *Supporting Innovation in Targeted Treatments: Licenses of Right to NIH-Funded Research Tools*, 11 MICH. TELECOMM. & TECH. L. REV. 249, 284 (2005) (arguing that while limited access to upstream molecular biology research tools could stifle innovation, weakening patent rights could also reduce the rate of innovation, thus implying a suboptimal innovation tradeoff, although she offers a way around the tradeoff for NIH-funded upstream tools: licenses of right provisions in grant funding). In nanotechnology, Ted Sabety contends that government-funding agencies should position seminal upstream foundational patents. See Sabety, *supra* note 101, at 279.

277. See Ron A. Bouchard, *Balancing Public and Private Interests in the Commercialization of Publicly Funded Medical Research: Is There a Role for Compulsory Government Royalty Fees?*, 13 B. U. J. SCI. & TECH. L. 120, 136-37 (2007) (stating that the power of innovation and market-stimulated research is widely viewed as stemming from a strong open basic science base). Cf. Misha Angrist & Robert M. Cook-Deegan, *Who Owns the Genome?*, 11 THE NEW ATLANTIS 87, 96 (2006), available at <http://www.thenewatlantis.com/docLib/TNA11-AngristCook-Deegan.pdf>.

[I]t is also possible that the gathering enthusiasm for "open and collaborative" research, even in the private sector, signals an inflection point. Perhaps we have moved beyond the impassioned rhetoric of public *versus* private; perhaps we no longer regard the human genome as either "the common heritage of all mankind" immune from IP rights or as a Wild West for speculative patents and endless court fights.

The ultimate fate of genomic research—who (if anyone) owns, pays for, and innovates with genomic information—won't be known for decades. But we are increasingly moving beyond the two-dimensional modes of thinking that characterized the early days of biotechnology. Legions of genome scientists (Craig Venter among them) now promote patenting and commercialization in some areas, such as protein-based drugs, while simultaneously promoting open science and expressing hostility to restrictive patents in others, such as software and raw data.

Cf. PISANO, *supra* note 217, at 188 (arguing that basic R&D can reduce risk for downstream commercialization by generating knowledge that reduces uncertainty and, thus, "[a]ny strategies or policies at the university level (such as exclusive licensing) that discourage or inhibit the broad flow of basic scientific information are clearly problematic"). Recall from Part IV.D, *supra*, that exclusive licensing appears to be a likely stop on the route to commercialization for many developments in the three nascent technologies.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI* 197

suffer too much financially because they have many other ways to market their knowledge.²⁷⁸

2. Which Commons Type for Very High Risk and Very Long-Term Technological Developments That Could Truly Revolutionize Medicine?

Unclear or excessive patent claim scope is in part due to the ease of obtaining patents of dubious value such that many companies can tout huge and varied patent portfolios without attending to individual patents or claims except those of exceptional worth.²⁷⁹ Massive litigation effecting patent deadlock may well be prevented by the collective efforts of government agencies, universities, start-ups, venture capitalists, and established pharmaceutical and biotechnological firms, as well as the PTO, Congress, and the federal courts. But even if this should occur, patent portfolio-enabled commercialization will not lead to huge medical advances, because none of the researchers, developers, and enablers of commercialization has sufficient incentive to produce the resources needed for long-term investments where the payoff is highly uncertain but potentially huge.²⁸⁰

The infeasibility of creating a viable commercial development plan for the most promising long-term medical gains that could well be enabled by much more advanced forms of these technologies makes the near-term university-start-up-venture capital-acquisition commercial R&D pipeline appear inadequate. There is talk of creating longer-term commercial partnerships, but with no probable revolutionary output for at least twenty years, incentives to sever such partnerships on truly revolutionary projects will be hard to counter. Venture capitalist

278. See Robert E. Litan et al., *Commercializing University Innovations: A Better Way* 8-9 (Nat'l Bureau of Econ. Res. Working Paper No. 407, 2007), available at http://www.kauffman.org/pdf/NBER_0407.pdf (arguing that universities transfer information, materials, equipment, instruments, human capital, networks, and prototypes a variety of ways, patenting and licensing being just one and not necessarily the most economically valuable way).

279. See *supra* Part II.B.

280. Cf. PISANO, *supra* note 217, at 190.

[T]he [IP] monetization mind-set [in universities] . . . increasingly influences licensing and disclosure policies . . . that may inhibit the broad flow of critical scientific information. These policies are aimed at maximizing university licensing revenues and equity returns rather than maximizing the contribution to the scientific commons. A shift in mentality and policies is needed. Over the long term, the continued scientific advance of biotechnology and improving the prospects for commercially successful R&D requires greater emphasis on the scientific commons.

demand for a commercial success within seven years will create path dependencies, and associated path dependency-created science and technology capacity limits will foster modest fixes to the large and diverse range of technological problems.²⁸¹ There is also talk of strong companies—perhaps Nano-Terra being a good prototype, given its apparent lack of a need for venture capital and its co-ownership of IP with Harvard—making revolutionary breakthroughs via an accumulation of incremental advances, each building on previous successes. But even the most well-financed and prestigious near-term commercial alliances, such as Harvard-Nano-Terra, will create restrictive path dependencies based on the research investments needed for successful commercialization. Because the best medical gains from all the technologies will require basic and translational research on scientific and technological paths too ambitious to converge with near-term commercial paths, publicly funded collaborative commons is recommended.²⁸²

281. Cf. SCOTCHMER, *supra* note 87, at 58 (Arguing that even if a better idea was known to occur at some point in the future, in a competitive market “delay is costly[, and] if the delay is . . . too long, then the better idea is not worth waiting for”). But venture capitalists would have you believe otherwise. See PLATZER, *supra* note 150. Platzer’s analysis, funded by the National Venture Capital Association, though it also contains valuable and valid insights, predictably overstates the risks venture capitalists will take in funding medical R&D: “[M]any . . . venture backed discoveries are so revolutionary that they disrupt markets and industry segments.” *Id.* at 9. Truly revolutionary *clinical medical* breakthroughs from any of these technologies are too uncertain and too far down the road for a “capitalist venture.” This is implied by a recent informed commentary about business prospects for RNAi. See, e.g., Haussecker, *supra* note 62, at 459.

A basic principle of economics is the inverse relationship of risk and return. The fact that market caps of individual biotechs with little more to show than a single approved drug may easily exceed that of all the pure-play RNAi therapeutics companies combined, reflects the risk, but also the time involved in realizing the therapeutic promise of RNAi.

Above all, it is the science that matters most. The delivery challenge is often cited and despite a growing literature on delivery to the brain, bone, spleen, cancers, and other targets, it is still uncertain which technologies will be able to combine safety and efficacy.

This is also implied by a cautionary analogy to prospects in nanomedicine. See K. John Morrow et al., *Recent Advances in Basic and Clinical Nanomedicine*, 91 *MED. CLINICS N. AM.* 805, 818 (2007) (citations omitted).

[M]onoclonal antibodies, one of the most significant scientific developments of the latter twentieth century. Discovered in 1975, antibodies were widely believed to hold great promise as cancer therapeutics, yet the early years of discovery were marked by many failures in clinical trials. It was only after billions of dollars in research and many frustrations that successful antibody products appeared twenty years later.

282. Cf. UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE, REPORT TO

2009]NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAI 199

Although promises of too much too soon over-hyped all of the technologies, the problem is not so much over-hype, because all of these technologies do indeed promise truly revolutionary clinical medical gains as soon as twenty years from now, as it is understating the known and unknown potential barriers to the R&D progress needed to realize the revolutionary gains. Given the multitude and diversity of these unknowns—and track records in both medical biotechnology and chronic disease medicine of not fulfilling promises according to schedule (in some cases, decades-old deadlines have passed with promised medical gains still not made)²⁸³—it appears likely that the best route towards changing this state of affairs is a major, ambitious public commitment built on these three and related technologies. We should promise major gains in prevention and treatment for our main killers—especially the top three: heart disease, cancer, and cerebrovascular disease—in twenty years, up the funding for public research, and make an unprecedented, unqualified demand that researchers make demonstrable progress towards realizing the gains *or else lose the public funding*.²⁸⁴

Because of all of the risks associated with commercial clinical medical development of ambitious innovations in these three technologies, it is not surprising that venture capitalists as well as biotechnology and pharmaceutical companies have shied away from such innovations.²⁸⁵ Despite the continual waves of seemingly

CONGRESSIONAL REQUESTORS, NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS (2006) (“According to experts, several factors have hampered drug development . . . [including] limitations on the scientific understanding of how to translate research discoveries into safe and effective drugs. . .”).

283. See *supra* Section I.B.

284. Cf. Litan et al., *supra* note 278, at 17 (“More ambitiously, agencies of the federal government can condition their research grants on university demonstrations that they are experimenting with and using multiple pathways to provide competition or to advance innovations into the commercial market.”).

285. Compare PISANO, *supra* note 217, at 149 (Discussing biotechnology generally, Pisano states, “[t]here are already some signs that existing mechanisms for risk management are breaking down for the truly high-risk projects. In the post-genomics bubble period, there was a marked change in the strategies of start-ups and the preferences of venture capitalists.”) with Magnus Gittins, *A New Model for Investors*, 8 MATERIALS TODAY 54 (2005) (discussing nanotechnology, Gittins states,

[N]anotechnology is reaching a critical point in its life cycle—it must deliver on some [of its] promises or face a crisis of confidence. . . .

. . . .

Critical to ensuring that discoveries fulfill their potential is striking a balance where corporations and governments can work closely with universities to drive and

compelling promises that biotechnology start-up companies make, the vast majority of these companies have not survived to make a successful exit. Partly as a direct consequence, established biotechnology and pharmaceutical companies have become gun-shy about acquiring such start-ups, and partly as an indirect consequence, start-ups appear to have lost some of their entrepreneurial edge.²⁸⁶ Proper integration of scientific and technological knowledge in technology development is also hampered by the diverse problem set in the pertinent science and technology which the recent research at ENCODE et al. highlights, as well as the unclear patent landscape.²⁸⁷ The need for commercial success in the near future, combined with the complex biology underlying conditions of health and pathology, will thus lead commercial research designs away from ambitious, risky, long-term projects.

Extraordinarily intricate, still not well-understood, composite intracellular/extracellular pathological conditions are implicated in America's three most common killers: heart disease, cancer, and

finance product development in a low-cost, low-risk way.)

286. Cf. PISANO, *supra* note 217, at 184–85. Pisano notes, the sector appears to be retreating from its position at the radical and risky end of the R&D spectrum. It was supposed to be the entrepreneurial biotechnology firms, unshackled from tradition and bureaucracy, that would go where big pharmaceutical companies dared not. Unfortunately, the economics have not worked out, and biotechnology firms [are] mov[ing] from the frontier to less risky ventures. . . . [T]his trend should give us [some] pause. Entrepreneurial firms are expected to be at the cutting edge of research. If young biotech firms are not pursuing the high-risk strategies—if they are moving away from cutting-edge science—then who will focus on the higher-risk, long-term, and less scientifically mature projects that offer potential medical breakthroughs? Who will be on the vanguard of the biotechnology revolution in the future?

If “the economics have not worked out,” perhaps the entrepreneurial market is too precarious to rely on primarily for medical breakthroughs. Perhaps we as a public ought to demand from our federal government more prudent, well-thought-out investment in high risk, but potentially very high medical return, long-term R&D.

287. Cf. *id.* at 150–52.

IP monetization and the market for know-how[]works very well in industries like software and semiconductors. . . .

. . . .

Biotechnology is quite different . . . The pieces of the drug discovery puzzle are often not modular at all but constitute a set of independent problems. . . .

. . . .

. . . [I]n biotechnology the IP regime is more complex and murky. It is often not clear ex ante what is patentable and what is not. . . . Furthermore, the most valuable IP is often not the specific molecule, but the understanding, insight, and data about how that molecule behaves, what it can do, what its potential problems are, and how it might be developed. This type of knowledge is often much more difficult to patent, and yet it needs to be shared before and during the collaboration.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 201

cerebrovascular disease. Although there have been many improvements in diagnosis, prevention, and treatment for all three diseases, we have yet to make any breakthroughs that could be causally linked to very large reductions in incidence and prevalence rates for these diseases. This is not for a lack of funding: Over the last forty years, a massive amount of public money has been invested which can be tied directly or indirectly to the prevention and treatment of these three diseases.

Publicly funded biomedical research has consistently failed to deliver on its greatest promises. In the 1960s, cures for all types of cancer were promised; we are still waiting for a cure for just one type. The laboratory researchers announce breakthrough after breakthrough, but where is the real medical breakthrough? We expect far too little for our health-related research money. The government granting system has not produced a truly major breakthrough in heart disease, cancer, or cerebrovascular disease, in part because of a lack of sufficient incentives for the most ambitious research. But this could and should change. Given the stakes—our lives—we need extremely prudent public financing of these endeavors, based on thorough analyses from a large and varied group of relatively disinterested experts.

Perhaps no one can be relied on to be absolutely disinterested in the sense of not having career-based or other particular professional motives that could possibly lead to the advocacy or pursuit of research of suboptimal long-term value to the public. The basic science and technology research culture may not have, even in the Bayh-Dole era, a comparably strong demand for near-term commercialization which is virtually ubiquitous in private R&D. Nonetheless, the federal government agency as grant-provider is itself a seller in a market niche where political forces such as patient advocacy groups may have particular short-term interests that are not consistent with the general long-term public welfare. These groups often include family members of victims of lethal diseases. Many of these family members, desperate to hear of cures just around the corner, will be averse to skepticism. Sympathy for their plight should not lead to a waste of billions of tax dollars, especially when such waste will probably just perpetuate the prevalence of many diseases for future generations.

George Miklos and Phillip Baird's scathing criticism of apparently grossly misfocused and overhyped research at The Cancer Genome Atlas (TCGA), notwithstanding the probability that the criticism is only

202 *MARQUETTE INTELLECTUAL PROPERTY LAW REVIEW* [Vol. 13:1

partly justified,²⁸⁸ underscores the point that publicly funded and ambitious research is not all that we need. The promise from a former National Cancer Institute Director of a cure from such research coming by 2015 leads to serious worries that the culture of the institute may be driven by desires to show swift progress to get coveted congressionally earmarked funding. Part of the problem may be the careerist motives that lead to distorted reports; when this happens in a research setting, money can be wasted, but when it happens in an experimental clinical setting, lives can be lost.²⁸⁹

The ultimate source of this problem is us—the public—for being too impatient, for perpetuating our ignorance as to the complexities of human pathologies such as cancer, for demanding swift change in the near-term rather than more certain change in the long-term.²⁹⁰ Although this Article still maintains that the balance of public commons-to-private patent-protected research is skewed somewhat towards the latter,²⁹¹ increasing the commons will only be beneficial if

288. Miklos & Baird, *supra* note 236.

289. Perhaps the most notorious example of distorted information reporting occurred, according to the Justice Department, prior to the death of eighteen-year-old Jesse Gelsinger. His death was the result of gene therapy that he received in 2000 as part of an experimental clinical trial at the University of Pennsylvania and Children's National Medical Center. The Justice Department, which investigated the incident and activities that preceded it, settled the case in 2005, reportedly alleging that human toxic reactions should have halted the trial, but lead investigators misrepresented clinical findings to both the NIH and the FDA which oversaw the trial. One of the investigators accused of this deception also reportedly had "a financial interest in a company that stood to profit if the trial was successful." Jennifer Couzin & Jocelyn Kaiser, *As Gelsinger Case Ends, Gene Therapy Suffers Another Blow*, 307 *SCIENCE* 1028 (2005). Of course, it is easy to make too much of this high-profile tragedy, but one must nonetheless wonder about critical conflicts of interest. Certainly, having a principal investigator with an outside financial interest in a successful trial is something an experimental trial for a new complicated procedure with many obstacles, both anticipated and unanticipated, does not need. There may inevitably be incentives to downplay, if not conceal, problems to successful implementation if one's reputation as a scientist may be affected by whether the trial proceeds at all and if one has cognitive biases oneself that tend to skew risk negatively. Possible commercial conflicts of interest could easily provide additional incentives.

290. *Cf.* PISANO, *supra* note 217, at 8–9. Pisano argues,

In the context of biotechnology, the challenges of high risk and primary uncertainty are further amplified by the long time horizons over which these risks and uncertainties are resolved. . . . In science . . . the uncertainty and risks may linger for years, sometimes decades. Cancer continues to prove a devilishly difficult disease to understand and treat despite several decades of massive investment in basic research. And even when one finds a "solution," it does not necessarily have clear implications for commercial R&D; rather, it may instead trigger a new round of basic research.

291. *Cf.* Bruce H. Littman et al., *What's Next in Translational Medicine?*, *CLINICAL*

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 203

that commons is broadly conceived and maintained. We must always think of the health of future generations. Their health will benefit most from prudent investment in both rigorously defensive research—i.e., the thorough study of all potential scientific and technological barriers to revolutionary medical advances—and rigorously offensive research that aims to make these advances. Patient advocacy groups may not want to hear the sobering news that rigorously defensive research has already provided and will continue to provide about formidable obstacles that need to be overcome before success can be achieved, but not to pursue such research is to perpetuate the obstacles. If, for instance, we want more than just extensions of chemotherapy, radiation, and surgery for cancer treatment in the long-term, we had better face up to the near-term obstacles.²⁹²

This is not to say that patent portfolio-enabled commercial R&D should not be pursued for accumulated incremental gains, just that it must be better complemented by prudently planned R&D into associated basic science and technology. There is simply far too much unknown about short-term and long-term efficacy and safety effects of pertinent inventions considered individually and as a totality. More importantly, there is even less known about whether the more ambitious medical promises associated with NB/BN, synthetic biology, and RNAi will ever be efficacious and safe. Countless research articles have identified obstacles for NB/BN and RNAi-enabled targeted drug delivery and ways to surmount the obstacles, while also emphasizing that there are probably additional, yet-to-be-identified obstacles.²⁹³

A point rarely made in the literature comparing innovation in semiconductors and the rapid growth of information technology with the comparative slow growth of medical biotechnology is that the intracellular and extracellular dynamics of human pathological processes such as those associated with different types of cancer are many times more complex than the complicated circuitry involved in electrical engineering. Much research on the comparative lack of progress in biotechnology has rightly focused on economic factors that foster suboptimal incentives for innovation. However, it is very possible that ignorance in basic science and technology—masked by hype—is an

SCI., 217, 219 (2007) (noting that, in 2003, over 60% of total R&D spending on biomedical research was private).

292. Cf. PISANO, *supra* note 217.

293. See *supra* Part I.B.

even greater barrier.²⁹⁴

Despite high levels of scientific and technological knowledge and skill in NB/BN, synthetic biology, and RNAi, we need to push ourselves to much higher levels to reap the major rewards in medical breakthroughs that very carefully constructed interventions in these technologies could provide twenty years hence.²⁹⁵ Evolution appears to have created extraordinarily intricate, metabolically interdependent, and seemingly ultimately phenotype-controlled, cellular, intercellular, and molecular dynamics. This complexity, combined with the emergent nature of the technologies, will demand much greater knowledge and skill in all three technologies²⁹⁶ for us to realize the promises of high-tech, highly personalized medicine.

CONCLUSION

NB/BN, synthetic biology, and RNAi all hold great medical promises but, despite hype suggesting the contrary, the greatest medical promises will not be fulfilled in the near future. In the near-term, the patent landscapes must be effectively uncluttered and patent prosecutors must work with patent examiners to produce thorough and precise patents that would increase confidence in patent quality. Patent

294. Cf. PISANO, *supra* note 217, at 8.

In science-based business, R&D confronts fundamental questions about technical feasibility. Is it possible to express a protein in a bacterial cell? Is it possible to culture mammalian cells in vitro? What genes are involved in depression? Which biochemical pathways are involved in inflammation? What role do kinases play in certain diseases? Why are some people more likely than others to be stricken with Alzheimer's Disease? These are the types of questions with which science-based businesses in biotechnology have had to grapple.

Not only are such questions difficult to answer, but the attempt to answer them leads, in all likelihood, to more questions—or to unexpected results.

295. Regarding NB/BN, compare Chih-Ming Ho, Dean Ho, and Dan Garcia, *Bio-Nano-Information Fusion*, 209, 220, in LYNN FOSTER, *NANOTECHNOLOGY: SCIENCE, INNOVATION, AND OPPORTUNITY* (2006).

Although the nanotechnology industry is in a nascent stage, rapid advancements and a streamlined road map of progress ensure that the future is quite promising. . . .

However, to reach this point in the roadmap, we must address in depth several key areas. . . . Through the use of emerging technologies and methodologies for discovery . . . we will achieve an unprecedented, more complex level of control of biological molecules. This, in turn, will give us a deeper understanding of how . . . biomolecules and their respective activities contribute to global functionality (such as the systemic performance of the human body) to create an emergent behavior in nature. In this way, nanotechnology will then be poised to reproduce this behavior to combat disease. . . .

296. As well as in other related “anticipated” (that is, likely to emerge) technologies.

2009] *NANOBIOTECHNOLOGY, SYNTHETIC BIOLOGY, AND RNAi* 205

portfolio construction and management must also be an integral part of multidimensional modifiable roadmaps to commercialization. The roadmaps should include initial patent portfolio-guided R&D path construction and maintenance to generate and improve prospects for exclusive licensing, financing, and acquisition.

Patent portfolio-enabled short-term commercialization nonetheless needs to be complemented by scientific and technological commons. Commons are needed to create valid and reliable building block standards and to facilitate very high risk, but potentially revolutionary, long-term biomedical R&D in these technologies. More prudent government funding of long-term research would allow for both a greatly increased understanding of the basic science and technology and the capacity twenty years hence to translate that understanding into revolutionary advances in clinical medicine.