NOTES


I. Introduction

One of the great surprises in the wake of the Human Genome Project\(^1\) was the discovery that human beings have a mere 30,000 genes\(^2\) rather than the projected 100,000.\(^3\) On its face, the finding implies an easier path toward understanding the molecular processes of the body. However, the reality is that genes and the proteins they encode are intimately tied together in complex pathways.\(^4\) The complexity of the pathways demands research efforts that are diverse and interconnected through shared tools and data. Yet, advances in biotechnology patent law and the trend toward commercialization of biomedical research run counter to the need for open access to research data.\(^5\) The

---

1. The Human Genome Project (HGP) represented a publicly funded, joint effort of academic scientists to completely decipher the human genetic code. A parallel effort took place within the private sector at Celera Genomics. The first draft of the human genome was released in 2000 following a ceremony with President William J. Clinton at the White House. See generally U.S. DEP’T OF ENERGY, HUMAN GENOME PROJECT, at http://www.ornl.gov/sci/techresources/Human_Genome/home.html (last visited June 30, 2004).

2. The genetic code is located within the chromosomes of each cell and is comprised of discrete units of deoxyribonucleic acid (DNA) sequence referred to as genes. STEDMAN’S MEDICAL DICTIONARY 459 (26th ed. 1995). DNA is a four-letter code of adenine, guanine, cytosine, and thymine that functions to direct the cellular machinery to produce proteins according to the code. Id. For more in-depth information, see JAMES D. WATSON ET AL., RECOMBINANT DNA 13-14 (2d ed. 1992).

3. The central dogma of molecular biology until the HGP was that one gene would code for one protein; therefore, human beings would need approximately 100,000 individual genes to account for the complexity of the species. Upon completion of the final draft of the human sequence in 2002, however, it was apparent that the dogma was incorrect and that approximately 30,000 genes were present in the human genome. See Eric S. Lander et al., Initial Sequencing and Analysis of the Human Genome, 409 NATURE 860 (2002); Craig Venter et al., The Sequence of the Human Genome, 291 SCIENCE 1434 (2002).

4. For example, one gene may code for a variety of protein derivatives with alternate functions, and proteins may function in multiple combinatorial pathways. WATSON, supra note 2, at 135.

5. A major effort is currently underway in academic science to provide for “open access” to all public domain information. The present focus of this effort is to publish peer-reviewed data in open-journal formats that are not controlled by copyright laws and major publisher
balancing of innovation and incentive in patent law has taken center stage in the battle over the experimental use of patented research tools, particularly with respect to the development of new pharmaceutical agents based on genetic information and technologies.

This note focuses on *Integra Lifesciences I, Ltd. v. Merck KGaA*, a 2003 decision that effectively extinguished the experimental use defense. This note also discusses the need for Congress to harmonize its terminology and goals, and to legislate to protect scientists’ open access to biotechnology tools. Part II of this note traces the historic roots of the experimental use defense and the development of the current de minimis interpretation. Additionally, Part II illustrates the experimental use defense in patent infringement actions, and the tension that exists between academic and commercial molecular biology. Part II further discusses the advent of the “safe harbor” provision that Congress drafted to codify a narrow version of the experimental use defense. Part III introduces *Integra*, the most recent Federal Circuit decision to speak emphatically regarding the limitations of both the experimental use exception and the safe harbor provision of the Hatch-Waxman Act. Part IV examines the majority and dissenting opinions of *Integra*, the underlying split in their rationales, and the fundamental misunderstandings that occur when complicated scientific research enters a courtroom. Part V analyzes how *Integra* affects biotechnology as a whole and the future implications of the decision. Finally, Part V proposes that Congress should extend the safe harbor provision to achieve the most efficient use of modern biotechnological advancements.

II. Historical Perspective

The U.S. Constitution specifically mandates that Congress actively participate in the advancement of science through the granting of patent rights to inventors of useful arts. This constitutional authority speaks to the importance of innovation in American society. Under U.S. patent laws, a patent owner not only has the exclusive right to prevent others from selling the

6. 331 F.3d 860 (Fed. Cir. 2003).
8. Id.
9. Specifically, Congress is authorized “[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.” U.S. CONST. art. I, § 8, cl. 8.
invention for commercial gain, but also the right to prevent unauthorized use of the invention. Patent infringement is the use of a patented invention without license from the patent owner. Unauthorized users of a patented invention are subject to civil liability. In general, the intent of the infringing party is irrelevant, and damages are automatic upon a finding of infringement. In rare circumstances, however, courts have allowed a narrow exception when the use of the patented invention falls under the guise of “experimental use.”

A. The Experimental Use Defense: A Common Law Creation

Neither the U.S. Constitution nor the Patent Act mentions an exemption for experimental use. Nevertheless, common law provides a defense to patent infringement claims where the use of a patented invention is for experimentation or research, and profit is neither a motive nor a purpose for the use. This defense originated in Justice Story’s opinion in Whittemore v. Cutter. In Whittemore, Justice Story reasoned that the constitutional framers could not have intended to allow a patent to exclude others from using the patented inventions for purposes of curiosity. He further argued that “it could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.” Because the defendant used the patented machine for the production of game cards without profiting, Justice Story noted that the jury instruction requiring
profit from the making and use of the patented technology favored a finding of noninfringement. This early articulation of the experimental use defense, largely in dicta, could hardly foreshadow the difficulty courts would face in defining “experimentation.”

Early cases articulating the experimental use defense, and the handful of cases that applied the defense before the modern era, focused on whether the experimental use of an invention was directly or indirectly for the purpose of seeking a profit. For example, in Sawin v. Guild, Justice Story held that the making of a machine is not infringement unless it is “the making with the intent to use [the machine] for profit, and not for the mere purpose of philosophical experiment.” Courts typically held that a use or making fell outside the realm of a “philosophical experiment” when an underlying intent to profit from the experiment was established. At least one scholar has suggested that Justice Story originally conceived a broad experimental use defense that would protect any “philosophical experiment,” which most likely included “basic scientific research employing a patented invention.”

The common law origin of the experimental use defense has left the exception vulnerable to attack by evolving technology and judicial perspectives. In Roche Products v. Bolar Pharmaceutical Co., the Federal Circuit addressed the application of the experimental use defense to the infringement of a patented pharmaceutical product. The defendant, Bolar Pharmaceutical, attempted to bring a generic version of a popular Roche sleeping pill into the market on expiration of Roche’s patent. Bolar deliberately used the patented drug for premarket testing of its generic equivalent to gain quicker approval from the

22. Id.
23. See Dugan v. Lear Avia, Inc., 55 F. Supp. 223, 229 (S.D.N.Y. 1944) (declining to find infringement of a device that was clearly manufactured for experimental purposes and not offered for sale); Akro Agate Co. v. Master Marble Co., 18 F. Supp. 305, 333 (N.D. W. Va. 1937) (finding that the defendant’s use of the patented marble production apparatus was merely experimental, and further that no marbles were sold using the patented marble production, thus, infringement was excused).
24. 21 F. Cas. 554 (C.C.D. Mass. 1813) (No. 12,391).
25. Id. at 555.
26. See, e.g., Poppenhusen v. N.Y. Gutta Percha Comb Co., 19 F. Cas. 1059 (C.C.S.D.N.Y. 1858) (No. 11,283) (finding that the experimental use defense was not applicable because the use was for business purposes in that it was specifically in competition with the defendant’s product). But see Ruth v. Stearns-Roger Mfg. Co., 13 F. Supp. 697 (D. Colo. 1935) (holding that use of patented parts in flotation devices was not infringement under the experimental use defense).
27. BURCHFIELD, supra note 20, § 15.1, at 352.
28. 733 F.2d 858 (Fed. Cir. 1984).
Food and Drug Administration (FDA). To justify its patent infringement, Bolar raised the experimental use defense. Bolar conceded, however, that its use did “not fall within the traditional limits of the experimental use exception.” The court agreed and refused to extend the exception to cover such for-profit use. The court found the “experimental use exception to be truly narrow” and not applicable to infringing use for the purpose of bringing a competing product to market. In its reasoning, the court stated, “We cannot construe the experimental use rule so broadly as to allow a violation of the patent laws in the guise of ‘scientific inquiry,’ when that inquiry has definite, cognizable, and not insubstantial commercial purposes.” Accordingly, the court recognized the experimental use defense, but only as a very narrow exception applicable in the absence of commercial purposes.

Embrex, Inc. v. Service Engineering Corp. further narrowed the experimental use defense when the court held that the defendant’s infringing use of patented egg inoculation methods to test its own automated egg injection machine was outside of the narrow confines of the experimental use defense. The Embrex court reasoned that “[w]hile [defendant] tries to cloak these tests in the guise of scientific inquiry, that alone cannot immunize its acts.” Perhaps the most important aspect of the Embrex decision is the foreshadowing by concurring Judge Rader, who suggested that if the experimental use defense continued to exist, even a slight commercial interest would nullify the doctrine’s

30. Roche Prods., 733 F.2d at 860.
31. Id. at 862.
32. Id. at 863 (internal quotations omitted).
33. Id.
34. Id.
35. Bolar also made a public policy argument that such use should be allowed in the interest of bringing safe generic drug alternatives into the market on expiration of patents. Id. Essentially, if a generic drug maker was forced to wait until after the expiration of the patent to test the effectiveness of the generic against the original drug, the patent holder would receive a de facto extension of the patent term. The Federal Circuit soundly rejected this argument as something within the legislature’s realm. Id. at 863-64. Congress reacted swiftly to address this problem through the “safe harbor” provision of the Hatch-Waxman Act, which authorized the use of patented items during the patent term for the specific purpose of acquiring FDA approval. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 202, 98 Stat. 1585, 1603 (codified at 35 U.S.C. § 271(e) (2000)).
36. 216 F.3d 1343 (Fed. Cir. 2000).
37. Id. at 1349.
38. Id. (finding that the hiring of scientists to test the vaccine injection method was not to be “deemed experimental use or de minimis” for the purposes of avoiding infringement liability).
application to infringement. Judge Rader further opined that the experimental use defense garners no support in the Patent Act.

B. The Exception Nears Extinction in Madey v. Duke University

In the mid-1980s, Dr. John Madey was a research scientist in charge of a physics research program at Duke University. He owned two patents for free electron laser instrumentation, which was the core technology of the laser research facility. When Dr. Madey’s employment with Duke terminated, the laser lab continued to use the patented technology for research projects of other scientists at Duke. Consequently, Dr. Madey brought suit against Duke for patent infringement because of Duke’s continuing use of the laser facility, which he had developed with his patented laser technology.

Duke raised the experimental use defense in response to allegations that it infringed on Dr. Madey’s patents, and the district court granted Duke’s motion for summary judgment. The court referred to the “debate over the scope of the experimental use defense” and cited Embrex as allowing the defense when the use was purely for experimental, nonprofit purposes. The court found Dr. Madey’s argument that Duke was engaged in business through “obtaining grants and developing possible commercial applications for the fruits of ‘academic research’” unconvincing and instead focused on the university’s primary function as a place of education for “the expansion of knowledge.” The court concluded that Dr. Madey failed to meet his burden of proof that Duke’s use of the laser technology fell outside of the experimental use defense.

On appeal to the U.S. Court of Appeals for the Federal Circuit, Dr. Madey argued that the district court erroneously broadened the scope of the

39. Id. at 1353 (Rader, J., concurring).
40. Id.
42. Id. at 1352.
44. Madey, 307 F.3d at 1353.
45. Id.
46. Id. at 1355.
47. Id. (citing Embrex, Inc. v. Serv. Eng’g Corp., 216 F.3d 1343, 1349 (Fed. Cir. 2000)).
49. Dr. Madey also presented evidence that Duke intended to allow “for-fee” use of the laser research facility, but the court did not consider this as “for-profit” use. Id.
experimental use defense and based its decision on general propositions rather than facts.\textsuperscript{51} The appellate court agreed, concluding that “the experimental use defense persists albeit in very narrow form.”\textsuperscript{52} Furthermore, the court reasoned that the university’s use of the patented technology, even if not directly for-profit, could still be for commercial purposes.\textsuperscript{53} In an opinion that frightened academic institutions across the country,\textsuperscript{54} the Federal Circuit announced that it was possible for courts to identify commercial interests sufficient to defeat the experimental use defense where the “projects also serve . . . to increase the status of the institution and lure lucrative research grants, students and faculty.”\textsuperscript{55} The \textit{Madey} decision summarized the state of the experimental use defense as follows:

\begin{quote}
[\textit{R}egardless of whether a particular institution or entity is engaged in an endeavor for commercial gain, so long as the act is in furtherance of the alleged infringer’s legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense. Moreover, the profit or non-profit status of the user is not determinative.\textsuperscript{56}]
\end{quote}

In analyzing the legitimate business of an institution engaged in biomedical research, it appears that any use of patented tools by researchers and faculty engaged in the constant pursuit of funding, whether in the form of research grants or licensing arrangements for inventions developed at the institution, is unlikely to be experimental use.\textsuperscript{57} If commercial gain exists in a research endeavor, few, if any, institutions will meet the strict requirements necessary to escape patent infringement liability through application of the experimental use defense.\textsuperscript{58} In essence, \textit{Madey} apparently extinguished the experimental use defense.

\textsuperscript{51} \textit{Madey}, 307 F.3d at 1361.
\textsuperscript{52} \textit{Id}.
\textsuperscript{53} \textit{Id}. at 1362.
\textsuperscript{55} \textit{Madey}, 307 F.3d at 1362.
\textsuperscript{56} \textit{Id}.
\textsuperscript{57} \textit{Id}.
\textsuperscript{58} The \textit{Madey} court remanded the case to the district court with instructions to focus on whether Duke’s technology transfer policy on patent and licensing was evidence of a clear commercial interest despite supposed educational-only goals. \textit{Id}. at 1363 n.7. Technology transfer policies and offices are now a major effort in all research institutions, largely because of the Bayh-Dole Act, which authorizes the patenting of technologies developed through
defense because it is difficult to imagine any type of research that could pass the strict test articulated in *Madey*.\(^{59}\)

**C. Congress Carves Out a Limited Legislative Experimental Use Defense**

In an effort to overrule *Roche*,\(^{60}\) Congress passed a legislative “safe harbor” for the experimental use of patented pharmaceuticals as part of the Hatch-Waxman Act.\(^{61}\) The relevant provision of 35 U.S.C. § 271(e)(1) addresses a research lab’s need to test pharmaceuticals to receive FDA approval so that the lab may bring the drug, presumably a generic version, to market.\(^{62}\) Section 271(e)(1) provides that “[i]t shall not be an act of infringement to make, use or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs.”\(^{63}\) As Justice Scalia opined in *Eli Lilly & Co. v. Medtronic, Inc.*,\(^{64}\) § 271(e)(1) “allows competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval.”\(^{65}\) The parameters of the safe harbor provision continue to develop parallel with the complexities of biotechnology patenting.

---


61. Congress intended the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) to overrule the *Roche* decision. 35 U.S.C. § 271(e)(1). The purpose of the Act was to “establish that experimentation with a patented drug, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not patent infringement.” H.R. REP. 98-857, at 45 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2678.


64. 496 U.S. 661 (1990) (expanding the scope of the safe harbor provision to include medical devices).

65. Id. at 671.
D. Culture Clash: Biotechnology Versus Academic Science and the Trend Toward Open Access Science

As the Madey decision echoed in academic research labs across the country, the Federal Circuit was evidently willing to assume that all basic research had ties to commercial incentives. The appellate court, however, chose to ignore the traditional motivations of a researcher — such as scientists’ personal curiosity or desire to expand their knowledge. Yet, science had been evolving toward commerce in the modern biotech era, and it was perhaps this metamorphosis that disquieted the academic community. Undoubtedly all research labs, even those clearly for profit, are engaged in the pursuit of knowledge that will better humankind. However, the modern research lab, particularly where molecular biology takes a primary role, is an extremely expensive endeavor that requires a steady stream of grants and other financial support. Consequently, when scientists develop technology with true commercial potential, the best interest of the lab, the institute, and society are served by seeking patent and licensing rights. Whether this sort of financial support is enough to convert an academic research lab into a for-profit business lies at the core of the Madey decision.

In addition to the Madey decision, the influx of biotechnology patents into academic research also creates problems surrounding a scientist’s ability to openly communicate and verify scientific data. Rather than bring their findings to light at the earliest possible time either through presentations at scientific meetings or publications in peer-reviewed journals, scientists now remain silent about their findings until a patent attorney or business partner approves the information for release to the public.66 More significantly, the sharing of data and research tools has become nearly impossible in an era of patents and royalties, though only ten years earlier, scientists commonly shared plasmids, peptides, or antibodies with other scientists working in the same field.67 Such sharing now requires a careful analysis of whether applicable licensing and competitive issues are at stake, which includes the drafting of time-consuming and complex material transfer agreements. The commercial success of

67. Plasmids are nonnuclear segments of DNA genetically engineered to contain a gene of interest for expression in bacterial, mammalian, or other host systems. STEDMAN’S MEDICAL DICTIONARY 1377 (26th ed. 1995). Peptides are segments of proteins often used for eliciting cellular responses or for blocking the binding of natural proteins to the cellular surface. Id. at 1323.

Antibodies are the proteins produced by the immune system in response to a variety of extracellular pathogens and environmental triggers. Id. at 99-100. Antibodies have a wide variety of uses in research labs, both as reagents and as end-product therapeutics. Id.
biotechnology has the unfortunate side effect of hampering the progress of science in academic labs; it also creates problematic conflicts of interest with other researchers, participants in research studies, and society at large.  

III. Statement of the Case: Integra Lifesciences I, Ltd. v. Merck KGaA

Given the near-death experience of the experimental use defense, the confusion surrounding exactly how to apply the Hatch-Waxman “safe harbor” provision, and the tensions existing within academic labs in a biotechnology age, it was inevitable that a case would develop that allowed the Federal Circuit to tackle all of these issues. Integra became that case.

A. Factual Basis: Peptides, Patents, and Participants in a Research Endeavor

The patents at issue in Integra were directed toward short segments of fibronectin, an extremely important protein for the communication and adhesion between neighboring cells of human tissues. Fibronectin promotes cellular growth and attachment through interaction with cell surface receptors, which send biochemical signals to the intracellular machinery indicating that either more or less growth activity is warranted in a given cellular neighborhood. The active site of the fibronectin protein where it contacts the receptor is a short sequence of three amino acids, arginine-glycine-aspartic acid (RGD).
Integra’s patents involved recombinantly produced RGD peptides and associated technical uses for the peptides. The patents covered the production of pharmaceuticals to promote wound healing and blood vessel growth through infusion of RGD peptides, which stimulate cell growth and adhesion. The patents also covered the potential use of the peptides in common laboratory practices associated with growing cells in tissue culture.

During the time Integra was obtaining its patents, Dr. David Cheresh, a pioneering academic scientist in the field of cellular adhesion and signal transduction, was working independently at Scripps Research Institute on research involving the molecular mechanisms of integrins, the receptors for fibronectin. Dr. Cheresh’s research revealed that blocking the receptors inhibited the process of blood vessel development — a method that would potentially stop tumor growth by starving tumor cells. Dr. Cheresh blocked integrin binding and cell activation with antibodies engineered to bind to the active site of the integrin molecule that would normally be bound by the RGD peptide. Further, Dr. Cheresh discovered the cyclical RGD peptide’s use in blocking integrin activation. Consequently, Merck, a leading pharmaceutical

research lab, or as a potential therapeutic. RGD peptides are classic research tools used by a wide variety of research labs studying diverse areas of interest, such as gene therapy vector development (one family of which is based on Adenovirus, which binds to $\alpha v \beta 3$ integrins), signal transduction research, which attempts to decipher the downstream pathways, and cell adhesion research. In essence, fibronectin protein is the “key” that unlocks a cell’s growth potential. The RGD peptide represents a short piece of the whole protein, similar to the grooves of a key that allow the lock to recognize the key.

74. As an example, the ‘237 patent owned by Integra covers a method for the “use of peptides in control of cell attachment and detachment.” U.S. Patent No. 4,879,237 (issued Nov. 7, 1989).
75. Id.
76. See, e.g., U.S. Patent No. 4,988,621 (issued Jan. 29, 1991) (describing the industrial application of the invention for the “production of cell lines for research” and the production of end-product therapeutics).
77. Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 863 (Fed. Cir. 2003). As previously noted supra note 73, integrin molecules are the “locks” opened by the fibronectin/RGD “key.”
78. Dr. Cheresh has published extensively on all aspects of integrin function and characterization. See, e.g., P.C. Brook et al., Anti-Integrin $\alpha v \beta 3$ Blocks Human Breast Cancer Growth and Angiogenesis in Human Skin, 96 J. CLIN. INVEST. 1815 (1995) (describing the results of research conducted with antibodies that block the activation of integrin receptors leading to a reversal of breast cancer cell growth).
79. Robert A. Orlando & David A. Cheresh, Arginine-Glycine-Aspartic Acid Binding Leading to Molecular Stabilization Between Integrin $\alpha v \beta 3$ and Its Ligand, 266 J. BIOL. CHEM. 19,543 (1991) (describing research that revealed the manner of RGD peptide binding to integrins).
company, became interested in collaborating with Dr. Cheresh on a project to (1) develop potential cancer therapeutics, and (2) perform the necessary testing for approval to proceed with clinical trials.\textsuperscript{80} The Merck-Scripps research focused on a variety of Merck-synthesized cyclical RGD peptides, each tested for efficacy against antibody blocking and traditional RGD peptides in growth inhibition studies.\textsuperscript{81}

Upon learning of the Merck-Scripps agreement, Integra offered to license its patented RGD technology to Merck; however, Merck declined.\textsuperscript{82} Although Integra had never actually developed pharmaceuticals with its patented technology, it brought an infringement action against Dr. Cheresh, Scripps Research Institute, and Merck for their allegedly infringing study of angiogenesis and RGD peptides.\textsuperscript{83}

\textbf{B. Procedural History}

Integra sought monetary damages for Merck’s infringement and declaratory judgment against Dr. Cheresh and Scripps.\textsuperscript{84} Without explanation, the district court granted a motion to dismiss the declaratory judgment action against Dr. Cheresh and Scripps.\textsuperscript{85} The court, however, held Merck liable for infringing on four RGD patents, despite Merck’s argument that its activities fell under the safe harbor provision of § 271(e)(1).\textsuperscript{86} The court also denied Merck’s motion for judgment as a matter of law, in which Merck asserted that the experiments were exempt from infringement.\textsuperscript{87} Merck appealed to the Federal Circuit, where Merck again raised the § 271(e)(1) defense. Integra also appealed the denial of its motion for declaratory judgment against Dr. Cheresh and Scripps.\textsuperscript{88}

\textsuperscript{80} \textit{Integra Lifesciences}, 331 F.3d at 863.
\textsuperscript{81} Dr. Cheresh listed the purposes of the Merck-Scripps agreement as follows: “(1) [A]ssess the potential efficacy of the peptides as therapeutic agents; (2) discover the mechanism of action of the peptides; and (3) shed light on histopathology, toxicology, circulation, diffusion, and half life of the peptides in the bloodstream.” \textit{Id.} at 874 (Newman, J., dissenting) (quoting Appellant’s Brief at 15).
\textsuperscript{82} \textit{Id.}
\textsuperscript{83} \textit{Id.}
\textsuperscript{84} \textit{Id.} at 863.
\textsuperscript{85} \textit{Id.} at 874. This leads to speculation that, at least as far as individual academic scientists and their institutes are concerned, there may be a viable experimental use defense at work.
\textsuperscript{86} \textit{Id.} at 864.
\textsuperscript{87} \textit{Id.}
\textsuperscript{88} \textit{Id.}
C. Issue: If the Experimental Use Defense Does Not Survive Madey v. Duke, Does § 271(e)(1) Create an Exemption from Infringement for Pre-Clinical Research?

The precise question presented in Integra was “whether the pre-clinical research conducted under the Scripps-Merck agreement [was] exempt from liability for infringement of Integra’s patents under Section 271(e)(1).” The majority and dissenting opinions differed sharply regarding whether the traditional experimental use defense was raised as an issue in this case. While the dissent would apply the experimental use defense, the majority focused intently on the application of the safe harbor provision and addressed whether the provision “reach[e]d back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval.”

Section 271(e)(1) immunity requires that the activities be “reasonably related to the development and submission of information” to the FDA. Merck argued that it was developing its own FDA-compliant pharmaceutical drug directed toward cancer therapy and that the use of the patented RGD peptide technology comprised part of the testing process. Thus, the question before the Federal Circuit was whether such use was reasonably related, as required by § 271(e)(1).

D. Holding: Neither the Experimental Use Defense Nor Statutory Construction of the Safe Harbor Provision Are Consistent with the Scripps-Merck Research Use of RGD Peptides

Writing for the majority, Judge Rader found that Merck’s research in developing its own novel drug using RGD peptide technology constituted activity that was too far removed from the intent of the safe harbor provision to enjoy its protection. The court reasoned that, instead of providing a means to develop novel drugs, the express objective of the provision was to allow for

89. Id. at 865.
90. See infra Part V, which discusses the tension between Judge Rader and Judge Newman in Integra.
91. Integra Lifesciences, 331 F.3d at 865-66.
93. Integra Lifesciences, 331 F.3d at 865-66.
94. Recall that Judge Rader previously expressed strong feelings that experimental use should not exist as a defense to infringement. See Embrex, Inc. v. Serv. Eng’g Corp., 216 F.3d 1343, 1353 (Fed. Cir. 2002).
95. Integra Lifesciences, 331 F.3d at 867.
rapid development and marketing of generic versions of pioneer drugs as they
began to lose patent protection. Judge Rader opined that to find that Merck’s
research fell within the exception would require “exaggerating Section 271(e)(1)
out of context [which] would swallow the whole benefit of the Patent Act for
some categories of biotechnological inventions.” Accordingly, the court
upheld the lower court’s infringement finding against Merck and carved out
a damages calculation based on Merck’s use of the RGD peptides as research
tools.

IV. The Three Judge Panel of the Federal Circuit Splits Sharply in
Analyzing Application of the Experimental Use Defense and the § 271(e)(1)
“Safe Harbor” Provision

Judge Newman’s dissenting opinion takes a different look at the facts and
issues of the case. For Judge Newman, “The question [was] whether, and to
what extent, the patentee’s permission [was] required in order to study that
which is patented.” In her opinion, the majority erroneously found that the
research was beyond the scope of the experimental use defense or statutory
immunity of § 271(e)(1). From her perspective, the research fell squarely
within either the experimental use defense or § 271(e)(1) and, as such, Merck’s
“activities were either exempt from or immune from infringement.”

V. Analysis: Integra Highlights the Debate Over the Use of Research Tools
and the Limitations of the Experimental Use Defense

At times, the Integra opinion looks more like an academic debate than a
judicial opinion, reflecting the larger controversy concerning the appropriate
way to manage patents that result from biomedical research advances. The
intensity of the opinion not only draws attention to the court’s split over the

96. Id. at 866-67.
97. Id. at 867.
98. The majority found Integra’s arguments, which sought reversal of the dismissal of the
declaratory judgment motions against Scripps and Cheresh, unpersuasive. Id. at 872.
99. Id. at 870-73 (instructing the lower court to implement the damages calculation upon
remand).
100. Id. at 872 (Newman, J., dissenting) (stating that contrary to the majority’s findings,
“This case raises a question of the nature and application of the common law research
exemption.”).
101. Id. at 872-73.
102. Id. at 873.
103. Id. at 878.
issue, but also illustrates that the court lacks guidance for interpreting experimental use.

A. A Need for Clearer Understanding of What It Means to Be a “Research Tool”

A modern research lab depends on a variety of research tools. In 1998, the National Institutes of Health (NIH) focused on the twin problems of defining and sharing research tools and highlighted the issue as a matter of perspective.\textsuperscript{104} To a scientist, research tools are essential to growing cell lines, testing antibodies, and sequencing DNA samples.\textsuperscript{105} Research tools are the reagents, machines, and techniques that make science function. However, as demonstrated by \textit{Integra}, the legal meaning of research tools appears imprecise at best.

1. Exactly What Is in the Research Toolbox?

Despite NIH’s attempt to define research tools as those things “that scientists use,”\textsuperscript{106} the precise definition of research tool remains difficult to decipher in the research lab context. RGD peptides, however, are widely recognized as “research tools” in diverse areas of investigation and are readily available in laboratory freezers across the country.

The five patents at issue in \textit{Integra} were all directed toward technology associated with RGD peptides. The patents described ways in which the peptides could be used to make cell line maintenance easier or to discover novel receptors. The inventions claimed in the Integra patents could easily be categorized as either technology or research tools. However, “[O]ne institution’s research tool may be another institution’s end product.”\textsuperscript{107}

2. The Majority Creates a Solution Based on the Hypothetical Cash Value of Tools in the Toolbox

Part of the majority’s rationale for restricting the reach of § 271(e)(1) immunity was that the provision would detrimentally affect biotechnology.\textsuperscript{108}

\begin{footnotesize}
\begin{enumerate}
\item \textsuperscript{105} NIH has formally defined research tools as those things “that scientists use in the laboratory, . . . [including] cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines.” \textit{Id}.
\item \textsuperscript{106} \textit{Id}.
\item \textsuperscript{107} \textit{Id}.
\item \textsuperscript{108} \textit{Integra Lifesciences}, 331 F.3d at 867.
\end{enumerate}
\end{footnotesize}
Allowing Merck to use Integra’s patented peptide technology to develop its own cancer therapeutic “would effectively vitiate the exclusive right of patentees owning biotechnology tool patents. After all, patented tools facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs.”\(^{109}\) By viewing the Integra technology as a research tool, the majority sought to prevent the loss of incentive to develop technical innovations that facilitate research by refusing to allow the safe harbor provision to “swallow the whole benefit of the Patent Act for some categories of biotechnological inventions.”\(^{110}\)

Arguably, this shortsighted perspective fails to acknowledge the work of academic scientists who develop research tools without any intent to patent the innovation. The vast majority of biomedical researchers work with an eye toward solving intellectual questions regarding how things work; thus, they care little if financial profits are involved. The researcher works for the incentive of publication, tenure, and recognition in their field, not for maximum patent protection. When a particular tool is necessary for a researcher’s experimentation, researchers usually contact colleagues, who are willing to share. However, under a license-requiring patented tool scheme that collects royalties and places restrictions on publication, the effectiveness of research decreases, and the general expansion of common knowledge is hindered. Ultimately, valuable vaccines, treatments, and cures are lost because the research becomes cost prohibitive.

While refusing to acknowledge that use of a research tool could be an act of noninfringement under the common law defense or the statutory safe harbor provision, the majority found that the use could be de minimis, and if so, should be a limiting factor in the calculation of damages.\(^{111}\) The proper value to assign for calculating damages from the infringement of a research tool is a difficult analysis.\(^{112}\) As the majority correctly noted, “The value to a licensee of research tools lies, in part, in the point at which those tools are employed in the drug development continuum.”\(^{113}\) Thus, a royalty on a tool that is used early

\(^{109}\) Id.

\(^{110}\) Id.

\(^{111}\) Id. at 869-73 (remanding the case to the lower court for factual analysis of the financial value of the RGD peptides to Merck’s research).


\(^{113}\) Integra Lifesciences, 331 F.3d at 871.
in the process would be less valuable than a key reagent that confirms or provides proof of the entire concept.

A major problem with a royalty-based system is that it increases the overall cost of research by stacking licensing fees for any given experimental approach. This creates a significant dilemma for modern research labs reliant on an ever-increasing number of patented research tools. Because research labs survive on a fixed budget of research grants, increasing royalty costs can determine the scientific route that a particular investigator may be forced to pursue. Such restraints on academic freedom and biomedical advancement run counter to the core value of the patent system and are an unfortunate side effect of the current research tool scheme.

The Integra opinion comes close to judicially creating a reasonable royalty system for the unlicensed use of patented research tools. Such a solution has previously been proposed and seems to have garnered moderate support; however, this system favors those who are commercially driven at the expense of academia.

3. The Dissent’s Perspective Empties the Toolbox and Focuses on Whether Research Concerns the Patented Technology

Judge Newman’s dissent relied on the presumption that Integra’s patented peptides were not research tools, but instead were, in themselves, patented technology. A close reading of the patents, however, suggests that the technology is equally used as a research tool or as a means to its own end. As defined by the dissent, a “research tool is a product or method whose purpose is use in the conduct of research.” For Judge Newman, the ultimate distinction was that the “[u]se of an existing tool in one’s research is quite different from study of the tool itself.” Nevertheless, it remains unclear where the line between research tools and patented technology should be drawn.

Based on the knowledge Dr. Cheresh and his colleagues had contributed to the field of cell adhesion interactions, the work performed under the Scripps-Merck agreement was directed toward the development of cancer therapeutics.

114. An alternate solution would be to make the acquisition of a patent on pure research tools even more stringent through heightened, nonobviousness, and written description requirements.
115. See, e.g., Mueller, supra note 112.
116. Integra Lifesciences, 331 F.3d at 877-78 (Newman, J., dissenting).
117. For example, the ‘621 patent states that “[t]his invention finds application in the production of cell lines for research, in diagnosis and therapy, and the industrial production of cell biological products.” U.S. Patent No. 4,988,621 (issued Jan. 29, 1991).
118. Integra Lifesciences, 331 F.3d at 878 (Newman, J., dissenting).
119. Id.
Thus, the same biological phenomenon underlies both the Integra patents and the Scripps-Merck agreement. In essence, a researcher’s early discovery in one area of scientific research is capable, if patented, to tie up future research in tangential matters. Such bioprospecting remains particularly troublesome when genes and proteins are involved in highly complex networks of action.

**B. The Footnote Battle — A Death Blow Through Dicta to the Experimental Use Defense**

Opposing footnotes in *Integra* reveal two distinct variations of the experimental use defense after *Madey*. Although the majority opinion clearly leans toward abandonment of the defense, confusion remains about its application. Apparently, the majority did not abandon the defense, but instead, changed the defense into a calculation of damages where truly minimal, noncommercial use is exempted because it creates no harm. Therefore, under the majority’s reasoning, experimental use that does not result in profit will fail to produce an actionable infringement. However, it is nearly impossible to calculate profit from the use of a poorly defined research tool because of the variety of ways it could affect the research being conducted.

1. **Footnote Two Reiterates the Holding of Madey**

As a consequence of *Madey*, *Integra*’s footnote two draws attention to the lingering issue of when and how to apply the experimental use defense.\(^\text{120}\) Although the debate was seemingly over after *Madey*, *Integra* ensures the end of the experimental use defense to patent infringement. Arguably, Judge Rader and others in the patent law field doubted its existence in the first place.\(^\text{121}\) *Integra*’s majority firmly indicates that the experimental use defense exists only to the extent that it provides for de minimis infringement and calculation of limited damages. However, the court suggests that any use could result in damages, no matter how slight.\(^\text{122}\) Thus, the focus is placed on the court’s proposed royalty calculation to provide relief when an infringer, even an experimental researcher, uses the patented technology. By eliminating lawyers’ hair-splitting distinctions between research tools and technology, the majority’s holding has the potential to clarify the state of the law by focusing on whether profit resulted from a tool’s use. Unfortunately, academic scientists remain in the precarious position of either electing upfront licenses, which entails multiple

\(^{120}\) *Id.* at 863-64 n.2.

\(^{121}\) *Id.* Merck never contended that the defense was applicable, even when given an opportunity to do so at oral argument. Apparently, they abandoned the defense in light of the *Madey* decision. *Id.*

\(^{122}\) *Id.* (paraphrasing Embrex, Inc. v. Serv. Eng’g Corp., 216 F.3d 1343 (Fed. Cir. 2002)).
legal constraints, or risking legal action at a later date. A better system would provide immunity to academic researchers to facilitate research freedom and increase the chance for innovation.

2. “Research on” Versus “Research with” Amounts to a Distinction Without Difference

Judge Newman sharply fired back with her own footnote, stating that Madey was nothing more than “sweeping dictum” that failed to “distinguish between investigation into patented things, as have always been permitted, and investigation using patented things, as have never been permitted.”

Regardless of whether Judge Newman is correct, the problem of knowing where the differences lie in the complexity of postgenomic research remains. In Judge Newman’s opinion, the court “disapprove[d] and essentially eliminate[d] the common law research exemption . . . a change of law ill-suited to today’s research-founded, technology-based economy.”

Judge Newman highlighted a laundry list of research protocols performed under the Scripps-Merck arrangement and drew the conclusion that the use of the peptides in any of these assays was tantamount to research on the technology of the peptides. A counter argument could be made, equally compatible with the science involved, that the assays listed, and use of the peptides, were not intended to study the peptides at all. Under this alternate explanation, the Scripps-Merck research used the peptides to determine events downstream of receptor binding, such as changes in intracellular biochemical activity. In other words, the peptides were reagents to study the ultimate goal of manipulating receptor functions and altering disease progression. The significance of this choice of perspective between the second innovator and the patent owner highlights that the topic is fraught with line-drawing. Ultimately, what one may consider “research on,” another may consider “research with,” and significant consequences flow from making such a determination.

3. Research Tool “Fair Use”: Solution or Same Old Confusion?

Recognizing the difficulties in identifying the boundaries of the experimental use defense, Judge Newman suggested that an analogy to “fair use” in the

123. Id. at 878 n.10 (Newman, J., dissenting).
124. Id. at 873 (Newman, J., dissenting).
125. Id. at 874 (Newman, J., dissenting).
126. Id. at 876 (Newman, J., dissenting) (recognizing that the “distinction between ‘research’ and ‘development,’ as a matter of scale, creativity, resource allocation, and often the level of scientific/engineering skill needed for the project,” may be a useful route for drawing the boundary of uses under experimental use).
area of copyrights may be a better solution. The suggestion that legitimate fair use of patented technology exists implies that researchers will recognize fair use of a patent when they see it. This solution, however, seems to be nothing more than giving a new name to an old problem.

Congress may have considered a fair use scheme in drafting § 271(e), as evidenced by House Report comments highlighting the Subcommittee on the Courts, the Internet and Intellectual Property’s desire to “balance the need to stimulate innovation against the goal of furthering the public interest.” To achieve this balance, Congress acknowledged that “[j]ust as [it had] recognized the doctrine of fair use in copyright, it was appropriate to create a similar mechanism in the patent law.” However, the clear limitation of the safe harbor provision in § 271(e) to the unique situation of generic drug and device approval suggests that Congress did not intend to broadly define a fair use test in patents. Integra drew the line at discovery-based research, which leaves vast amounts of research still vulnerable to liability for patent infringement without an experimental use defense.

C. A Biomedical Research Tool “Safe Harbor” Provision Could Alleviate Tension

Given the demise of the experimental use defense subsequent to Madey and Integra, the failure of the § 271(e)(1) safe harbor provision to reach down to the level of experimental use, and the general lack of clarity on the subject, Congress should take action to provide adequate protection for researchers. This is particularly important at a time when the cost of research and development of pharmaceuticals remains in the spotlight for health care reform.

1. Going “Down the Chain of Experimentation”

The majority and dissenting opinions agree that, as originally intended, § 271(e)(1) does not reach far enough “down the chain of experimentation” to

127. The fair use defense in copyright law provides that limited copying of protected material for purposes such as education, scholarship, or criticism will not be an act of infringement. 17 U.S.C. § 107 (2000).
129. Id.
130. For an example of the scholarly argument in favor of a fair use exemption for genetic sequence data to ensure equal access, see Donna M. Glitter, International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair Use Exemption, 76 N.Y.U. L. Rev. 1623 (2001). There is little reason to exclude other forms of biomedical information and discovery from such an exemption.
protect unlicensed use of the RGD peptides. Rather, Congress clearly articulated that it envisioned the provision to protect only the limited use of patented drugs for bioequivalency studies to produce generic drugs ready for competition with name-brand drugs at the end of the patented drug’s term of protection. However, Judge Newman contended that the safe harbor provision had been judicially extended to create a much broader protection providing immunity for research, such as the Scripps-Merck collaboration. Clearly, Congress never intended the provision to be a codification of whatever remained of the common law experimental use defense after Roche.

2. The Next Logical Step in the Metamorphosis of Biomedical Research

Patent law already alters the landscape, or at least the perception, of biomedical research. Biomedical research is no longer viewed as purely an intellectual pursuit with results ultimately benefitting the common goal of longer, healthier lives. Instead, if Madey is correct, biomedical research constitutes a commercial endeavor geared toward fast track drug development. This cynical approach undercuts those researchers who strive to expand knowledge for the sake of knowing. The economic nature of the Madey decision, however, reflects a modern reality that must be dealt with to ensure continued progress.

As long as the patent office remains content to grant patents for biomedical research tools far upstream of end-product innovations, scientists would be foolish not to pursue such rewards for their efforts. Thus, a system must be created to ensure that those patents do not stifle progress and defeat the entire endeavor. Given the state of confusion in the courts, Congress should act by codifying an experimental use defense, which would begin to alleviate the confusion.

3. A Codified Experimental Use Defense Would Protect the Public Interest in Efficient Biomedical Research and Innovation

A significant need exists to protect access to innovations and research tools as postgenomic medicine and interconnected biological processes become more apparent. The human genome is now known and scientists are turning their attention to uncovering the sequence and function of all human proteins. The

131. Integra Lifesciences, 331 F.3d at 877 (Newman, J., concurring in part). “The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical trials.” Id. at 867.
133. Integra Lifesciences, 331 F.3d at 877.
134. “The term ‘proteome’ is often used to describe the total set of proteins expressed
vast array of available knowledge cannot be locked up in patents at the expense of future drug developments or advancements in knowledge. The current system blocks access by threatening infringement litigation whenever scientists’ research takes them into the path of another scientist’s patented tool.

Public policy, and indeed the fundamental principles underlying the patent system, place a premium on effective and efficient technological progress, particularly when taxpayer-derived grants pay for much of the new innovation at the early stages of discovery. Accordingly, Congress has the motive and authority to step in and clarify the ownership and ability to use patents. What is necessary is a definitive statement that experimental use of research tools, particularly in an academic environment, must be exempt from infringement liability when it is one piece of an intricate advancement in science. A safe harbor for the use of research tools, along with clearer guidelines to prevent the overpatenting of biological processes and products, would allow scientists to focus more on research and less on legal hurdles.

VI. Conclusion

Recent Federal Circuit decisions reveal that the experimental use defense has at least one foot in the grave, and may in fact be entirely sealed in a coffin. Consequently, researchers are faced with the difficult choice of pursuing their intellectual curiosity or giving it up because the needed tools are beyond their reach. This sort of cost-benefit analysis has no place in academic science, and Congress should create a safe harbor provision in the patent laws that truly protects the experimental use of technology and the tools required to solve the riddles of molecular medicine.

Melissa J. Alcorn, Ph.D.