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Patent Infringement in Personalized Medicine: Limitations of the Existing Exemption Mechanisms

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PATENT INFRINGEMENT IN PERSONALIZED MEDICINE: LIMITATIONS OF THE EXISTING EXEMPTION MECHANISMS

INTRODUCTION

Mr. X suffers from recurrent glioblastoma, a type of deadly brain cancer. One of his physicians reads a study reporting a novel immunotherapy, which uses the chimeric antigen receptor T cell (CAR-T) technology, leading to regression of glioblastoma in a small number of patients.[1] Although the therapy has recently been approved by the U.S. Food and Drug Administration (FDA) and is now offered by two major pharmaceutical companies,[2] it is only approved for certain hematological cancers.[3] In addition, Mr. X's cancer does not express the biomarker that is necessary for the CAR-T therapy used in the published glioblastoma trial.[4] Fortunately, the physicians are aware of a research laboratory at the university associated with the medical center that has expertise on the technologies associated with the CAR-T immunotherapy as well as certain biomarkers associated with Mr. X's cancer.[5] In collaboration with the laboratory's researchers, Mr. X's physicians conduct a small clinical trial administering an experimental CAR-T therapy to Mr. X and other glioblastoma patients, for whom this clinical trial was their only remaining hope. Later, one of the pharmaceutical companies holding multiple CAR-T patents sues the physicians, researchers, and academic institution for patent infringement.

This hypothetical scenario involving the first FDA-approved gene therapy, CAR-T therapy,[6] illustrates a potential patent infringement lawsuit that might occur more frequently as we enter the new era of personalized

1. Christine E. Brown et al., *Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy*, 375 NEW ENG. J. MED. 2561 (2016).

2. *See* Press Release, FDA, FDA Approval Brings First Gene Therapy to the United States (Aug. 30, 2017), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm574058.htm [https://perma.cc/4C8Z-3DGD] [hereinafter FDA Press Release on Kymriah]; Press Release, FDA, FDA Approves CAR-T Cell Therapy to Treat Adults with Certain Types of Large B-cell Lymphoma (Oct. 18, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm [https://perma.cc/NQ8J-D9G8] [hereinafter FDA Press Release on Yescarta].

3. *Supra note* 2. While it is possible for Mr. X's physicians to use the CAR-T therapy "off-label," *see "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices–Information Sheet*, FDA, https://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm [https://perma.cc/W66S-8N2U] (last updated July 12, 2018), the CAR-T cells in the FDA-approved therapy would not target the glioblastoma cells.

4. *See* Brown et al., *supra* note 1, at 2562.

5. *See, e.g.*, David Chen & James Yang, *Development of Novel Antigen Receptors for CAR T-cell Therapy Directed Toward Solid Malignancies*, 187 TRANSLATIONAL RES. 11, 14 (2017).

6. *See supra* note 2.

and precision medicine.[7] The beauty and power of personalized medicine is that it is inherently experimental and innovative. Naturally, therapies in personalized medicine are built upon many patented technologies. Thus, underlying these novel therapies is the potential for alleged patent infringement by the physicians and researchers who experiment with and personalize the therapy in order to cure patients and save their lives.

This Note uses the CAR-T therapy as a case study to examine the unique challenges that patent law faces in the dawn of the personalized medicine era, particularly regarding patent infringement. Specifically, this Note inquires whether a use of patented medical therapy[8] related to a clinical experiment or trial by physicians, researchers, and academic institutions for the purpose of patient treatment renders them liable for patent infringement. Patent law confers exclusive rights to inventors and allows them to enforce those rights associated with a specific patent by bringing a patent infringement claim against the alleged infringer.[9] At the same time, however, patent law also permits certain unauthorized uses of patented inventions to be exempted from infringement challenges or infringement liability.[10] There are two key defenses under which an alleged infringer can be exempted: one provides exemption largely based on the *status*[11] of the alleged infringer ("medical procedure exemption")[12] and the other based on the *nature or purpose* of the alleged infringing use ("experimental use exemption").[13] This Note analyzes whether the two exemptions indeed provide effective immunity from patent infringement or infringement liability for physicians, researchers, and academic institutions involved in the use of experimental therapies in the personalized medicine era.

Analysis of the statutory text, legislative history, and case law of the medical procedure exemption reveals that the "biotechnology patents" *exception* renders the provision ineffective for infringement lawsuits involving CAR-T therapy.[14] Therefore, this Note argues that the medical procedure exemption is incompatible with the personalized medicine era.[15]

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7. In fact, the National Institute of Health (NIH) is continuing to push for precision medicine, expecting "the golden age of immunotherapies . . . ." Jeannie Baumann, *Breakthroughs Expected from NIH Precision Medicine Push*, BLOOMBERG BNA (Feb. 2, 2018), https://www.bloomberglaw.com/product/blaw/document/XBC8EMEO000000.

8. This includes both product patents and method patents regarding the therapy.

9. *See generally* 5 DONALD S. CHISUM, CHISUM ON PATENTS § 16.02 (Matthew Bender 2018).

10. *See* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1018 n.6 (1989).

11. The statutory provision, 35 U.S.C. § 287(c) (2012), also addresses the nature of the alleged infringing activity. *See infra* Part II.A.

12. 35 U.S.C. § 287(c); *see infra* Part II for further discussion.

13. Based on common law experimental use doctrine and statutory provision 35 U.S.C. § 271(e)(1); *see infra* Part III for further discussion.

14. *See infra* Parts II.A–C.

15. *See infra* Part II.D.

Meanwhile, the experimental use exemption bifurcates into a narrow common law doctrine[16] and a statutory provision that is interpreted relatively broadly when related to FDA submission.[17] However, it is ambiguous whether a clinical trial would be considered as an "experimental use" under the narrow common law experimental use doctrine and whether the statutory experimental use exemption would permit uses that might not have any realistic potential for FDA submission.[18] While many scholars have argued for a broad experimental use doctrine, the discussions have remained largely in the context of basic science.[19] This Note presents a novel argument for a broad experimental use doctrine in the context of personalized medicine and suggests that the new era of personalized medicine calls for an additional factor in the experimental use analysis—clinical trials and experiments that cure and save patients' lives.[20]

Part I provides an overview of the CAR-T immunotherapy as a model therapy representing personalized medicine and presents the issue of patent infringement. Part II examines the medical procedure exemption and analyzes its effectiveness as a defense to patent infringement liability involving CAR-T patents. Then, Part III turns to the experimental use exemption, examines its effectiveness for providing immunity from CAR-T patent infringement, and concludes by arguing for a broader experimental use doctrine for the personalized medicine era.

I. PERSONALIZED MEDICINE AND PATENT INFRINGEMENT

A. CAR-T Therapy: The First FDA-Approved Gene Therapy Heralding the Personalized Medicine Era

The new era of personalized medicine and health care is marked by the Precision Medicine Initiative[21] and the 21st Century Cures Act of 2016,[22] aiming to incorporate innovative diagnostics and therapies tailored to

16. *See infra* Part III.A.
17. *See infra* Part III.B.
18. *See infra* Part III.C.
19. *See infra* Part III.D.1.
20. *See infra* Part III.D.3.
21. The Precision Medicine Initiative is a long-term research effort to revolutionize the understanding of health and disease by investigating how an individual's genetics, environment, and lifestyle can elucidate the best approach to prevent or treat diseases. *See The Precision Medicine Initiative*, THE WHITE HOUSE, https://obamawhitehouse.archives.gov/precision-medicine [https://perma.cc/44DM-V63E]; *see also* Francis S. Collins & Harold Varmus, *A New Initiative on Precision Medicine*, 372 NEW ENG. J. MED. 793 (2015).
22. The 21st Century Cures Act (Cures Act) aims to accelerate the development of innovative medical therapies and bring those advances to patients more efficiently. Pub. L. No. 114-255, 130 Stat. 1033 (2016).

individual patients into the health care practice. Under this movement, cancer immunotherapy has advanced exponentially as a prototype embodying the idea of personalized medicine.[23] At the forefront is a therapy that utilizes a cancer patient's own immune cells, genetically modifies them to recognize cancer cells, and places those modified cells back into the patient's body to attack the cancer—chimeric antigen receptor T cell (CAR-T) therapy.[24] This novel therapy has successfully treated[25] previously incurable cancers such as advanced chronic lymphoid leukemia (CLL)[26] and acute lymphoid leukemia (ALL).[27]

In addition to being in the media spotlight for its efficacy in treating cancer, the CAR-T therapy has also been at the center of patent battles between pharmaceutical companies and academic institutions.[28] The number of patents involving the CAR-T technology is already staggering and continues to grow.[29] And, on August 30, 2017, CAR-T surprised the world again when the FDA approved Novartis's CAR-T therapy—Kymriah—for the treatment of ALL in pediatric and young adult patients,[30] making it the first FDA-approved gene therapy.[31] Subsequently, the FDA approved a second CAR-T therapy—Yescarta—to Kite Pharma, Inc.[32] for

23. *See* Alice Park, *What If Your Immune System Could Be Taught to Kill Cancer?*, TIME (Mar. 24, 2016), http://time.com/4270345/what-if-your-immune-system-could-be-taught-to-kill-cancer./ [https://perma.cc/4AZ8-WPY8]; Denise Grady, *Harnessing the Immune System to Fight Cancer*, N.Y. TIMES (July 30, 2016), https://www.nytimes.com/2016/07/31/health/harnessing-the-immune-system-to-fight-cancer.html.

24. Lisa Rosenbaum, *Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy*, 377 NEW ENG. J. MED. 1313 (2017).

25. To be accurate, the patients have achieved "remission" of the disease.

26. David L. Porter et al., *Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia*, 365 NEW ENG. J. MED. 725 (2011).

27. Stephan A. Grupp et al., *Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia*, 368 NEW ENG. J. MED. 1509 (2013).

28. *See, e.g.*, Kurt Orzeck, *Novartis to Pay $12.3M, Royalties to End IP Row with Juno*, LAW 360 (Apr. 6, 2015), https://www.law360.com/articles/639776/novartis-to-pay-12-3m-royalties-to-end-ip-row-with-juno; Juno Therapeutics, Inc. v. Kite Pharma, Inc., No. 16–1243–RGA, 2017 U.S. Dist. LEXIS 90445 (D. Del. June 13, 2017); *In re* Juno Therapeutics, Inc., No. C16–1069RSM, 2017 U.S. Dist. LEXIS 91608 (W.D. Wash. June 14, 2017); Trs. of the Univ. of Pa. v. St. Jude Children's Research Hosp., No. 13–1502, 2014 U.S. Dist. LEXIS 193965 (E.D. Pa. Mar. 13, 2014).

29. Search of patents containing the terms "CAR-T" and "immunotherapy" in Westlaw yielded 322 issued patents and 1,079 patent applications. All patents and applications were checked for relevance by assessing claims (last searched on Sept. 30, 2018).

30. *See* FDA Press Release on Kymriah, *supra* note 2.

31. Denise Grady, *F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000*, N.Y. TIMES (Aug. 30, 2017), https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html. The high price of the therapy has been heavily discussed and criticized in the wake of the FDA approval. *See, e.g.*, John Lauerman & James Paton, *Novartis's $475,000 Price on Cancer Therapy Meets Resistance*, BLOOMBERG BNA (Oct. 13, 2017), https://www.bloomberglaw.com/product/blaw/document/XCDLUUG4000000.

32. Gilead Sciences Inc. now owns the FDA-approved CAR-T therapy since its acquisition of Kite Pharma Inc. Caroline Chen, *Gilead Gets FDA Approval for Kite's Novel Cancer Therapy*, BLOOMBERG BNA (Oct. 20, 2017), https://www.bloomberglaw.com/document/X31GP8R4000000.

the treatment of large B-cell lymphoma in adult patients.[33] Heralding the era of personalized medicine, FDA approval of CAR-T therapy provides promise for the field of genetic engineering and gene therapy.

However, this unconventional drug raises novel questions. Compared to a traditional drug with a fixed chemical composition, CAR-T therapy utilizes a patient's own immune cells, and, thus, there is a wide range of efficacy and toxicity.[34] Many detailed aspects of the CAR-T therapy remain unknown, requiring more clinical trials and experimentations. Also, while the therapy thus far has been successful mostly in hematological cancers, there is excitement for the application of CAR-T therapy in other solid cancers.[35] These aspects, potential for new discovery and application, can in fact be considered as characteristics of therapies in personalized medicine that are tailored to individual patients and are often based on cutting-edge biotechnology with ample possibilities for future applications. These therapies are inherently experimental and, thus, potently innovative. All this therapeutic potential, in turn, harbors potential for patent infringement: a physician, a researcher, or an academic institution using and experimenting with the CAR-T therapy to treat more patients and cure more diseases could become liable for patent infringement.

B. Patent Infringement and Exemption from Infringement

United States patent laws confer an exclusive right to make, use, or sell an invention for twenty years[36] to achieve the constitutional prerogative "[t]o promote the Progress of Science and useful Arts."[37] The patentee has "the right to exclude others from making, using, offering for sale, or selling the invention,"[38] regardless of the alleged infringer's intention or access to the invention.[39] Despite the seemingly unqualified rights of the patentee, patent statutes allow certain unauthorized uses of a patented invention by providing exemption from patent infringement or liability.[40] Conceptually, these statutes can be categorized as providing an exemption based on either the alleged infringer's special *status* or the special *nature or purpose* of the infringing act. Indeed, for physicians, researchers, and academic institutions

33. *See* FDA Press Release on Yescarta, *supra* note 2.
34. *See* Sattva S. Neelapu et al., *Chimeric Antigen Receptor T-cell Therapy—Assessment and Management of Toxicities*, 15 NATURE REVS. CLINICAL ONCOLOGY 47 (2018).
35. *See* Babak Moghimi & David Barrett, *CAR T Cells for Solid Tumors*, 3 CURRENT STEM CELL REPS. 269 (2017).
36. 35 U.S.C. § 154(a) (2012).
37. U.S. CONST. art. I, § 8, cl. 8.
38. 35 U.S.C. § 154(a)(1).
39. 35 U.S.C. § 271(a).
40. *See* 35 U.S.C. §§ 271(e)(1), 273, 287(c).

that become liable for patent infringement from using a patented medical therapy, such as CAR-T, patent law provides two sources of potential exemptions: [41] exemption from infringement liability for a medical practitioner's medical activity [42] and exemption from infringement for experimental use of the invention.[43]

II. 35 U.S.C. § 287(C): MEDICAL PROCEDURE EXEMPTION FROM PATENT INFRINGEMENT LIABILITY

This Part provides a brief legislative history of 35 U.S.C. § 287(c),[44] the so-called "medical procedure exemption" provision, and reviews the case law interpreting the statute. It proceeds to an analysis of whether a physician, researcher, or academic institution using the CAR-T therapy will qualify under § 287(c) for immunity from infringement liability and concludes by arguing that the provision is incompatible with the personalized medicine era.

A. Legislative History and Text of 35 U.S.C. § 287(c)

35 U.S.C. § 287(c) was enacted to exempt medical professionals from patent infringement liability when performing a medical or surgical procedure involving the patent in dispute.[45] The instigating case, *Pallin v. Singer*,[46] involved a dispute over a patent claiming a new process of making sutureless incisions in cataract surgery.[47] Dr. Samuel Pallin, a surgeon, sued several other surgeons, including Dr. Jack Singer, for infringement of his patent on the new technique. [48] The defendants moved for summary judgment, alleging that the patent was invalid.[49] The district court denied summary judgment[50] but ultimately entered a consent order stating that four

41. Another potential source of exemption, "defense to infringement based on prior commercial use," codified at 35 U.S.C. § 273, does not apply to the question posed in this Note and, therefore, is beyond the scope of this Note.

42. 35 U.S.C. § 287(c).

43. Whittemore v. Cutter, 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600); 35 U.S.C. § 271(e)(1).

44. Pub. L. No. 104-208, § 616, 110 Stat. 3009, 67–68 (1996).

45. *See generally* Chris J. Katopis, *Patients v. Patents?: Policy Implications of Recent Patent Legislation*, 71 ST. JOHN'S L. REV. 329, 331–37 (1997); Weldon E. Havins, *Immunizing the Medical Practitioner "Process" Infringer: Greasing the Squeaky Wheel, Good Public Policy, or What?*, 77 U. DET. MERCY L. REV. 51, 63–68 (1999); Leisa Talbert Peschel, Note, *Revisiting the Compromise of 35 U.S.C. §287(c)*, 16 TEX. INTELL. PROP. L.J. 299, 306–09 (2008).

46. 36 U.S.P.Q.2d 1050 (D. Vt. 1995).

47. Method of Making Self-Sealing Episcleral Incision, U.S. Patent No. 5,080,111 (filed June 28, 1990) (issued Jan. 14, 1992).

48. *Pallin*, 36 U.S.P.Q.2d at 1051–52.

49. *Id.* at 1051.

50. *Id.* at 1053–54.

claims of the patent in controversy were invalid, and Pallin agreed not to enforce the other claims.[51]

Although the case itself did not develop into further legal disputes, it fueled a debate on the patentability of medical and surgical procedures.[52] In response,[53] several bills[54] proposing either a prohibition of medical procedure patents or a patent infringement liability exemption for physicians were introduced in both the House and the Senate, with the support of the medical community.[55] Despite continued attempts, however, these bills failed to pass in the Senate.[56] After the failure of Senate Bill 2105, interestingly, the core part of this bill was incorporated into House Bill 3610[57] and fast-tracked to passage as a part of the Omnibus Consolidated Appropriation Act of 1997 without any formal debates.[58] On September 30, 1996, the President signed the bill containing an amendment to 35 U.S.C. § 287(c).[59]

Subsection (1) of the medical procedure exemption provision provides that a "medical practitioner" or "related health care entity" is exempt from patent infringement liability in regards to performance of a "medical activity."[60] Subsection (2) provides definitions of the key terms including

51. Pallin v. Singer, Civ. A. No. 2:93–CV–202, 1996 WL 274407 (D. Vt. Mar. 28, 1996).

52. For other controversial patents contributing to the debate, see Peschel, *supra* note 45, at 305.

53. In fact, the bills were introduced during the litigation of the *Pallin* case. *See id.* at 304; Havins, *supra* note 45, at 54.

54. The following bills were introduced: H.R. 1127, 104th Cong. (1995) (to prohibit issuance of medical or surgical procedure patents); H.R. 3814, 104th Cong. § 619 (1996) (to restrict funds for medical and surgical procedure patents and explicitly define medical and surgical procedures while adding "biological process" exception in response to criticism from the biotechnology industry); S. 1334, 104th Cong. (1995) (to provide patent infringement exemption to physicians); S. 2105, 104th Cong. (1996) (similar to Senate Bill 1334).

55. The American Medical Association (AMA) House of Delegates condemned medical and surgical procedure patents, and the American Academy of Ophthalmology urged enactment of legislation to exempt those patents. William D. Noonan, *Patenting Medical and Surgical Procedures*, 77 J. PAT. & TRADEMARK OFF. SOC'Y 651, 651–52 (1995).

56. One of the strongest sources of opposition was the biotechnology industry, as they rely on the patent system for innovation and development. The industry expressed strong concern regarding H.R. 1127. *See Medical Procedures Innovation and Affordability Act and Inventor Protection Act of 1995: Hearing Before the Subcomm. on Courts & Intellectual Prop. of the Comm. on the Judiciary*, 104th Cong. 92–100 (1995) (statement of Dr. Frank Baldino, Jr., President and CEO, Cephalon, Inc.).

57. H.R. 3610, 104th Cong. (1996).

58. This was an unusual legislative process for a significant provision. *See* 142 CONG. REC. 26,639 (1996) (statement of Sen. Hatch) ("This measure was added notwithstanding the fact that there were no Senate hearings, and over the objections of myself, the chairman of the Finance Committee and the U.S. Trade Representative. It is an unprecedented change to our patent code . . . .").

59. Pub. L. No. 104-208, § 616, 110 Stat. 3009, 3009–67 (codified at 35 U.S.C. § 287(c)).

60. "With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity." 35 U.S.C. § 287(c)(1) (2012).

"medical practitioner"[61] and "related health care entity."[62] The definition of "medical activity" is provided in subsection (A) as "the performance of a medical or surgical procedure on a body,"[63] which also lists three *exceptions* to the protected medical activity:

> (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent,
> (ii) the practice of a patented use of a composition of matter[64] in violation of such patent, or
> (iii) the practice of a process in violation of a biotechnology patent.[65]

The exception of biotechnology patents was a response to the opposition of the biotechnology industry, which voiced concerns regarding the potential negative impact of differential treatment of medical procedure patents.[66] However, despite the inclusion of this exception, the provision does not provide a definition for the term "biotechnology patent."

Subsection (3) further limits the scope of immunity by stating that the provision:

> does not apply to the activities of any person, or employee or agent of such person . . . , who is engaged in the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or *clinical laboratory services* . . . .[67]

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61. "[A]ny natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity." 35 U.S.C. § 287(c)(2)(B).

62. "[A]n entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic." 35 U.S.C. § 287(c)(2)(C).

63. The definition of "body" is provided in § 287(c)(2)(E) as "a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans." 35 U.S.C. § 287(c)(2)(E).

64. [T]he term 'patented use of a composition of matter' does not include a claim for a method of performing a medical or surgical procedure on a body that recites the use of a composition of matter where the use of that composition of matter does not directly contribute to achievement of the objective of the claimed method.

35 U.S.C. § 287(c)(2)(F).

65. 35 U.S.C. § 287(c)(2)(A).

66. *See supra* note 56.

67. 35 U.S.C. § 287(c)(3) (emphasis added). The subsection further defines the covered activities as:

> (A) directly related to the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition or matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), and
> (B) regulated under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act,

Therefore, researchers are not exempt from patent infringement liability under this provision.

B. Case Law Interpreting 35 U.S.C. § 287(c)

Albeit enacted in 1996, 35 U.S.C. § 287(c) has only been cited in five cases to date.[68] Among those cases, only *Emtel, Inc. v. LipidLabs, Inc.*,[69] *Viveve, Inc. v. Thermigen, LLC*,[70] and *Lamson v. United States*[71] have interpreted parts of the statute.[72] In *Emtel*, the patent holder of a "telemedicine" method patent "using videoconferencing to allow a physician to communicate with a medical caregiver and patient in a remote healthcare facility"[73] sued telemedicine support providers for patent infringement when physicians under contract with the providers diagnosed medical conditions and provided treatment instructions to medical caregivers at remote locations. The defendants moved for summary judgment claiming immunity under § 287(c).[74] The district court determined that the alleged infringing activity, which was remote diagnosis and treatment instructions, qualified as "performance of a medical or surgical procedure on a body" under § 287(c)[75] and the defendants qualified as "related health care entities" because the contract between the defendants and physicians governed the medical service.[76] However, the court ultimately held that the medical activity did not infringe the patent claims.[77]

In *Viveve*, the issue was whether a physician's alleged infringing acts fell under the § 287(c)(3) "commercial development" or "sale" exception when

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or the Clinical Laboratories Improvement Act.

Id.

68. Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 548 U.S. 124 (2006) (per curiam); Emtel, Inc. v. LipidLabs, Inc., 583 F. Supp. 2d 811 (S.D. Tex. 2008); Lamson v. United States, 117 Fed. Cl. 755 (2014); Viveve, Inc. v. Thermigen, LLC, No. 2:16–CV–1189–JRG, 2017 U.S. Dist. LEXIS 60477 (E.D. Tex. Apr. 20, 2017); Johns Hopkins Univ. v. Alcon Labs., Inc., No. 15-525-SLR-SRF, 2018 U.S. Dist. LEXIS 70403 (D. Del. Mar. 1, 2018).

69. 583 F. Supp. 2d at 811.

70. 2017 U.S. Dist. LEXIS 60477.

71. 117 Fed. Cl. at 755.

72. *Lab. Corp. of Am. Holdings* does not concern § 287(c) but rather simply cites the statute in dissent as an example of limiting the liability of medical profession. 548 U.S. at 138 (Breyer, J., dissenting). In *Johns Hopkins Univ.*, the judgment refers to § 287(c) when addressing the defendant's motion for summary judgment alleging that there was no direct infringement under § 271 and the doctors are immune under § 287(c). 2018 U.S. Dist. LEXIS 70403, at *36–37. The court decided that, as there was no direct infringement, § 287(c) does not apply "because they are not being sued in the first instance." *Id.* at *40.

73. 583 F. Supp. 2d at 814.

74. *Id.*

75. *Id.* at 823–24.

76. *Id.* at 824–25.

77. *Id.* at 825–26.

he appeared on a television show and performed the method claimed by the allegedly infringed patent and marketed the device and procedure.[78] The court held that the medical activity did qualify as "directly related to the commercial development" or "sale,"[79] and therefore, the physician did not qualify for exemption from infringement liability.[80] And, in *Lamson*, it was determined that the United States could be protected from patent infringement liability by § 287(c) immunity[81] under 28 U.S.C. § 1498.[82] There are no cases, however, that address the interpretation of the term "biotechnology patent."[83]

C. Exemption from CAR-T Patent Infringement Liability Under 35 U.S.C. § 287(c)

Would a physician, researcher, or academic institution using the CAR-T therapy in a small-scale clinical trial be exempt from infringement liability under 35 U.S.C. § 287(c)? The researchers involved in the clinical trial would not qualify for exemption under § 287(c) because of the § 287(c)(3) exception.[84] However, would the physician or academic institution still qualify for the exemption? First, they clearly satisfy the status requirement under §287(c)(2)(B) and §287(c)(2)(C) as "medical practitioner"[85] and "related health care entity,"[86] respectively.[87] Then, the issue is whether their alleged infringing act is "medical activity" under § 287(c)(2)(A) without being disqualified as one (or more) of the three exceptions.[88] Given the large number of CAR-T patents,[89] the analysis will focus on the patents involved in the two FDA approved CAR-T therapies.[90]

There are two early patents behind Novartis's CAR-T therapy, one of which Novartis licensed from the University of Pennsylvania (Penn) in August 2012[91]—U.S. Patent No. 7,638,325 ('325 patent)[92]—and the other which Novartis eventually licensed from Juno Therapeutics Inc. in 2015

78. Viveve, Inc. v. Thermigen, LLC, No. 2:16–CV–1189–JRG, 2017 U.S. Dist. LEXIS 60477, at *6–8 (E.D. Tex. Apr. 20, 2017).
79. *See* 35 U.S.C. § 287(c)(3)(A).
80. 2017 U.S. Dist. LEXIS 60477, at *10–14.
81. Lamson v. United States, 117 Fed. Cl. 755, 761–63 (2014).
82. "In the absence of statutory restriction, any defense available to a private party is equally available to the United States." 28 U.S.C. § 1498 note (2012) (1948 Act).
83. 35 U.S.C. § 287(c)(2)(A)(iii) (2012).
84. *See supra* text accompanying note 67.
85. 35 U.S.C. § 287(c)(2)(B).
86. 35 U.S.C. § 287(c)(2)(C).
87. *See supra* notes 61–62.
88. *See supra* text accompanying notes 63–65.
89. *See supra* note 29.
90. *See supra* Part I.A.
91. Kurt Orzeck, *supra* note 28.
92. (filed Jan. 3, 2003) (issued Dec. 29, 2009).

after a settlement following a patent dispute[93]—U.S. Patent No. 8,399,645 ('645 patent).[94] The '325 patent claims an engineered T cell for long-term expansion and activation,[95] and the '645 patent describes the genetic sequence of a chimeric receptor containing a specific signaling domain[96] as well as the related vector[97] and host cell.[98] Based on the claim language, these two patents are composition of matter patents[99] and would fall under the exception to the protected medical activity exemption under 35 U.S.C. § 287(c)(2)(A)(i) "use of . . . composition of matter." Therefore, § 287(c) would not provide immunity for alleged patent infringement related to either the '325 or '645 patent.

Given the exclusive licensing agreement between Novartis and Penn,[100] several key patents owned by Penn and/or Novartis are also noteworthy, as they claim both composition and method.[101] U.S. Patent No. 9,499,629 ('629 patent) is representative of such patents, and the relevant claims are:

> 1. A method for stimulating a T cell-mediated immune response to a target cell population or tissue in a human, the method comprising administering to the human an effective amount of a cell genetically modified to express a CAR . . . , wherein the cell is from a human having cancer.

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93. Ashley Jean Yeager, *Patent Disputes Bring Immunotherapy Technology and Patent Review Process into Focus*, GEN (Sept. 11, 2017), https://www.genengnews.com/gen-exclusives/car-t-in-the-courts/77900974 [https://perma.cc/6N7G-JJR9].

94. (filed July 12, 2012) (issued Mar. 19, 2013).

95. The pertinent claim provides:

> 1. A K562 cell engineered to induce long term expansion of T cells, wherein said engineered K562 cell comprises on its surface: an anti-CD3 antibody loaded onto a human Fcγ receptor, . . . and wherein said K562 cell is further genetically modified to express the co-stimulatory molecule, 4-1BBL.

'325 Patent col. 52 ll. 20–32.

96. The pertinent claim provides:

> 1. A polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

'645 Patent col. 45 ll. 13–18.

97. '645 Patent col. 45 ll. 19–27.

98. '645 Patent col. 45 ll. 28–36.

99. The United States Supreme Court has defined "composition of matter" as including "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980) (quoting Shell Dev. Co. v. Watson, 149 F. Supp. 279, 280 (D.D.C. 1957)).

100. *University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients*, PENN MED. (Aug. 6, 2012), https://www.pennmedicine.org/news/news-releases/2012/august/university-of-pennsylvania-and [https://perma.cc/AD63-Z27R].

101. U.S. Patent No. 9,499,629; U.S. Patent No. 9,446,105; U.S. Patent No. 9,394,368; U.S. Patent No. 9,328,156.

> 2. A method of providing an anti-tumor immunity in a human, the method comprising administering to the human an effective amount of a cell genetically modified to express a CAR . . . , wherein the cell is from a human having cancer.
>
> . . .
>
> 5. A method of treating a human with chronic lymphocytic leukemia or acute lymphocytic leukemia, the method comprising administering to the human a T cell genetically engineered to express a CAR . . . , wherein the T cell is from a human having cancer.[102]

While the '629 patent is not a composition of matter patent, the question remains as to whether it can be considered as a biotechnology patent which would render the alleged infringement of the patent disqualified for liability immunity under § 287(c).

As stated above, the statute does not explicitly define the term "biotechnology patent."[103] In *Bilski v. Kappos*, the Supreme Court provided that "[i]n patent law, as in all statutory construction, '[u]nless otherwise defined, "words will be interpreted as taking their ordinary, contemporary, common meaning."'"[104] In dictionaries, "biotechnology" is defined as "the manipulation (as through genetic engineering) of living organisms or their components to produce useful usually commercial products"[105] or "[t]he exploitation of biological processes for industrial and other purposes, especially the genetic manipulation of microorganisms for the production of antibiotics, hormones, etc."[106] Therefore, it appears that a patent involving genetic engineering technology will likely be considered a "biotechnology patent."

Another canon of statutory interpretation instructs that "[a] term appearing in several places in a statutory text is generally read the same way each time it appears."[107] Prior to the Leahy-Smith America Invents Act (AIA), 35 U.S.C. § 103(b) contained the term "biotechnological process"

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102. '629 Patent col. 91 ll. 19–29, 51–59.

103. *See supra* text accompanying note 67.

104. 561 U.S. 593, 603 (2010) (alterations in original) (quoting Diamond v. Diehr, 450 U.S. 175, 182 (1981)).

105. *Biotechnology*, DICTIONARY BY MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/biotechnology [https://perma.cc/D6HG-AT8Q].

106. *Biotechnology*, OXFORD ENGLISH DICTIONARY, https://en.oxforddictionaries.com/definition/biotechnology [https://perma.cc/JMB9-LYYF].

107. Ratzlaf v. United States, 510 U.S. 135, 143 (1994). However, this is not a strong presumption and can be overridden based on statutory context and legislative history. *See, e.g.*, Robinson v. Shell Oil Co., 519 U.S. 337, 342–43 (1997) (term "employees" means "current employees" only in some sections of Title VII of Civil Rights Act, but includes "former employees" in other sections); Gen. Dynamics Land Sys., Inc. v. Cline, 540 U.S. 581, 596–97 (2004) (in the Age Discrimination in Employment Act, the word "age" means "old age" in the term "age discrimination," while it is used in the primary sense elsewhere in the act).

which was defined to include genetic engineering.[108] In addition, the legislative history, another key source for statutory interpretation, pointed to the pre-AIA § 103(b) provision and also provided that "biotechnology patents" "include[] a patent on a process of making or using biological materials, including treatment using those materials, where those materials have been manipulated *ex vivo* at the cellular or molecular level."[109]

The claims of the '629 patent include a process of genetic engineering or modification. They also describe "a process of making or using biological material,"[110] which is the creation of genetically modified T cells expressing a CAR and their use for treatment of cancer; "treatment using those materials,"[111] which is the treatment of types of cancers such as CLL or ALL; and the "materials [that are] manipulated *ex vivo* at the cellular or molecular level,"[112] as T cells from cancer patients are engineered *ex vivo* to express the CAR. Therefore, the CAR-T method patents[113] appear to fall under the "biotechnology patent" exception. In consequence, § 287(c) does not provide exemption from liability of alleged infringement of such patents.

Meanwhile, the key patent behind Kite's CAR-T therapy is U.S. Patent No. 7,741,465 ('465 patent).[114] The patent covers a DNA sequence of a chimeric T cell receptor,[115] an expression vector comprising the chimeric DNA,[116] and isolated lymphocyte transformed with the expression vector or chimeric DNA.[117] Like the '325 and '645 patents, the '465 patent is also a

108. [T]he term "biotechnological process" means—

(A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to—

(i) express an exogenous nucleotide sequence,

(ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or

(iii) express a specific physiological characteristic not naturally associated with said organism;

(B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and

(C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).

35 U.S.C. § 103(b)(2) (2006) (amended 2011).

109. 142 CONG. REC. 26,173 (1996).

110. *Id.*

111. *Id.*

112. *Id.*

113. Similar analysis can be done for the other patents in *supra* note 101.

114. (filed July 2, 1993) (issued June 22, 2010). *See* Press Release, Kite Pharma, Inc., U.S. Patent Office to Confirm Kite's Seminal Eshhar CAR-T Patent (June 28, 2017), https://www.gilead.com/news/press-releases/2017/6/us-patent-office-to-confirm-kites-seminal-eshhar-cart-patent [https://perma.cc/H74E-7L8E].

115. '465 Patent col. 35–38 (claims 1–16).

116. '465 Patent col. 38 l. 20–21 (claim 17).

117. '465 Patent col. 38 l. 22–33 (claims 18–20).

composition of matter patent and, therefore, there will be no liability exemption from infringing said patent under 35 U.S.C. § 287(c) as well.

D. 35 U.S.C. § 287(c) Is Incompatible with the Personalized Medicine Era

Providing no shield of immunity for physicians, researchers, or academic institutions that might become liable for patent infringement from using CAR-T therapy for novel treatments,[118] the medical procedure exemption is incompatible with the personalized medicine era. This incompatibility is accentuated when compared to international practices. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs),[119] to which the United States is a signatory, creates a minimum international standard for intellectual property protection. 35 U.S.C. § 287(c) is considered an attempt at TRIPs compliance, where the pertinent TRIPs provision provides that "[m]embers may also exclude from patentability . . . diagnostic, therapeutic and surgical methods for the treatment of humans or animals."[120] Prior commentaries have criticized § 287(c) for being over-inclusive for TRIPs compliance.[121] This Note, however, argues that § 287(c) is under-inclusive when viewed in light of the CAR-T therapy. In fact, under Article 53 of the European Patent Convention (EPC), "methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body"[122] are not patentable, keeping in line with the true intention of TRIPs Article 27. In fact, so far, there are no method patents on the medical procedure of the CAR-T therapy granted by the European Patent Office (EPO).[123] Due to the discrepancy, while European patients will be able to benefit from innovative usages of the CAR-T therapy and related personalized medicine therapies, U.S. patients might have less opportunity for experimental CAR-T therapy or other innovative therapies given the providers' potential patent infringement liability due to the inadequate protection of § 287(c).

In line with the argument that 35 U.S.C. § 287(c) is under-inclusive, academic commentary has proposed to revise the provision to allow

118. *See supra* Part II.C.

119. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299.

120. *Id.* art. 27.

121. *See, e.g.*, Cynthia M. Ho, *Patent, Patients, and Public Policy: An Incomplete Intersection at 35 U.S.C. § 287(c)*, 33 U.C. DAVIS L. REV. 601 (2000); Fariba Sirjani & Dariush Keyhani, *35 U.S.C. § 287(c): Language Slightly Beyond Intent*, 3 BUFF. INTELL. PROP. L.J. 13 (2005).

122. Convention on the Grant of European Patents (European Patent Convention) art. 53, Oct. 5, 1973 (amended Nov. 29, 2000), https://www.epo.org/law-practice/legal-texts/html/epc/2016/e/ar53.html [https://perma.cc/YQ6K-UPMP].

123. There is one EPO patent on the modified T cell, which is a composition of matter patent. European Patent No. 2 649 086 (issued July 19, 2017).

"genetic diagnostics" as an exempted medical activity.[124] However, such piecemeal modification of a statute has a potential to distort its legislative purpose and operation. Therefore, unless the biotechnology patent exception is excluded, the medical procedure exemption provision does not have a role in the personalized medicine era.[125]

III. EXPERIMENTAL USE EXEMPTION TO PATENT INFRINGEMENT

An alternative defense that a physician, researcher, or academic institution providing the CAR-T immunotherapy could use against an alleged patent infringement lawsuit regarding CAR-T patents is the experimental use exemption. This Part starts with an overview of the two branches of the exemption: the common law experimental use doctrine and the statutory experimental use exemption codified in 35 U.S.C. § 271(e)(1). It proceeds to the analysis of whether either type of the exemption would provide immunity to patent infringement from the use of CAR-T therapy and concludes by arguing for a broad experimental use doctrine for the personalized medicine era.

A. Common Law Experimental Use Doctrine

The experimental use exemption to patent infringement can find its roots in *Whittemore v. Cutter*.[126] Though the case itself did not involve a claim of experimental use,[127] Justice Story stated that patent infringement did not intend to punish an alleged infringer who conducted "merely . . . philosophical experiments."[128] Early cases applying the experimental use exemption focused on financial motive as the determining factor. In *Sawin v. Guild*, citing *Whittemore*, Justice Story held that the alleged patent infringers were not liable because they did not have "an intent to use for profit" but rather had "the mere purpose of philosophical experiment[] or to ascertain the verity and exactness of the specification."[129] And, in 1861, the

124. *See* Sherizaan Minwalla, *A Modest Proposal to Amend the Patent Code 35 U.S.C. § 287(c) to Allow Health Care Providers to Examine Their Patients' DNA*, 26 S. ILL. U. L.J. 471, 503 (2002).

125. It is also worth emphasizing that 35 U.S.C. § 287(c) provides exemption from infringement *liability* but not the infringement claim itself. "With respect to a medical practitioner's performance of a medical activity *that constitutes an infringement under section 271(a) or (b)*, the provisions of sections 281, 283, 284, and 285 shall not apply . . . ." 35 U.S.C. § 287(c)(1) (emphasis added). Therefore, it is a weak mechanism of immunity overall.

126. 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600).

127. It involved an alleged infringement of a patent for a playing cards-manufacturing machine. *Id.* at 1123.

128. *Id.* at 1121.

129. Sawin v. Guild, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391). This is in line with the spirit of patent law allowing patents on "any new and useful *improvement*," 35 U.S.C. § 101

court in *Poppenhusen v. Falke* clarified the doctrine by providing that "an experiment with a patented article for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement, is not an infringement of the rights of the patentee,"[130] which became the current test for the experimental use exemption. Prior to 1984,[131] the scope of experimental use doctrine was unclear, and the court exempted inventors who experimented on patented technology to invent patentable improvements.[132]

As the Court of Appeals for the Federal Circuit (Federal Circuit) gradually narrowed the scope of the experimental use doctrine based on commercial motives,[133] it also started to emphasize the *business interest* of the alleged infringer in determining whether the experimental use exemption applied. In a 1984 case, *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, involving a pharmaceutical drug company, the Federal Circuit held that the experimental use exception is "truly narrow."[134] In *Roche*, a drug company imported and began running tests on a patented drug to obtain FDA approval for production and marketing of the drug in the U.S. market.[135] The court held that "[e]xperimental use is not a defense"[136] to alleged infringement "for the purpose of furthering the legitimate business interests of the infringer."[137] It emphasized that the infringer's activities were "solely for business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry,"[138] and could not be

(emphasis added), thus authorizing patentable experiments to improve existing inventions. *See also In re* Hogan, 559 F.2d 595, 606 (C.C.P.A. 1977) ("[E]ncouragement of improvements on prior inventions is a major contribution of the patent system and the vast majority of patents are issued on improvements."). In contrast, copyright law allows only the *original* copyright holder to obtain copyrights on subsequent works or improvements based on original work. 17 U.S.C. § 106(2); *see* Pickett v. Prince, 207 F.3d 402, 405 (7th Cir. 2000).

130. Poppenhusen v. Falke, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y. 1861) (No. 11,279).

131. This is the year when *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), *superseded by statute*, Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, *as recognized in* Eli Lilly & Co. v. Medtronic, Inc., 872 F.2d 402 (Fed. Cir. 1989), was decided. *See infra* text accompanying notes 134–139.

132. *See, e.g.*, Chesterfield v. United States, 159 F. Supp. 371, 375 (Ct. Cl. 1958) (uses "for testing and for experimental purposes" are not infringement); Standard Measuring Mach. Co. v. Teague, 15 F. 390, 393 (C.C.D. Mass. 1883) (making a machine to illustrate an improvement did not infringe the pioneering patent).

133. *See, e.g.*, Dugan v. Lear Avia, Inc., 55 F. Supp. 223, 229 (S.D.N.Y. 1944), *aff'd*, 156 F.2d 29 (2d Cir. 1946) (experimental use is not infringement because the defendant had not "sold any" of the experimental product); Akro Agate Co. v. Master Marble Co., 18 F. Supp. 305, 333 (N.D. W. Va. 1937) (experimental use of a patented marble-making machine is not infringement because "marbles were not commercially sold").

134. *Roche*, 733 F.2d at 863.

135. *Id.* at 860.

136. *Id.* at 863 (alteration in original) (quoting Pitcairn v. United States, 547 F.2d 1106 (Ct. Cl. 1976)).

137. *Id.*

138. *Id.*

considered experimental use when they had "definite, cognizable, and not insubstantial commercial purposes."[139]

More recently, the Federal Circuit affirmed that the experimental use exemption is indeed "very narrow and strictly limited."[140] In *Madey v. Duke University*, a patent infringement suit involving a university and one of its former professors,[141] the court used this language and provided that "so long as the [alleged infringing] 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,"[142] the experimental use exemption does not apply. Emphasizing that the "non-profit, educational status"[143] of the alleged infringer, Duke University,[144] was not determinative, the Federal Circuit rejected the district court's "broad conception of . . . experimental use"[145] which included uses for research, academic, experimental, or non-profit purposes.[146] Instead, it emphasized that "major research universities, such as Duke, often sanction and fund research projects with arguably no commercial application"[147] and that "these projects unmistakably further the institution's *legitimate business objectives*, including educating and enlightening students and faculty participating in these projects"[148] and "increase the status of the institution and lure lucrative research grants, students and faculty."[149]

B. 35 U.S.C. § 271(e)(1): Statutory Experimental Use Exemption

While the scope of the common law experimental use exemption has been extremely limited by the Federal Circuit's practice, the statutory exemption provided in 35 U.S.C. § 271(e)(1) has been interpreted relatively broadly.[150] Six months after the Federal Circuit's *Roche* decision,[151] Congress overturned it by enacting the Drug Price Competition and Patent

139. *Id.*
140. Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002).
141. *Id.* at 1352–53.
142. *Id.* at 1362.
143. *Id.*
144. *Id.*
145. *Id.* at 1361.
146. *Id.*
147. *Id.* at 1362.
148. *Id* (emphasis added).
149. *Id.*
150. *See generally* Gregory N. Pate, Note, *Analysis of the Experimental Use Exception*, 3 N.C. J.L. & TECH. 253, 269–70 (2002). It is worth noting that the Supreme Court has not ruled on the scope of the common law experimental use exemption.
151. Roche Prods., Co. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 1984).

Term Restoration Act of 1984, known as the Hatch-Waxman Act.[152] Codifying the experimental use exemption,[153] § 271(e)(1) provides immunity to patent infringement "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."[154] Six years later, in 1990, the Supreme Court held that § 271(e)(1) provided immunity for tests on not only drugs but also medical devices when tests were performed to generate information for FDA regulations.[155]

The Court interpreted the statutory experimental use exemption even more broadly in *Merck KGaA v. Integra Lifesciences I, Ltd*.[156] In *Merck*, the Supreme Court held that § 271(e)(1) immunity can include "either (1) experimentation on drugs that are not ultimately the subject of an FDA submission or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA."[157] It recognized that drug development is a "process of trial and error"[158] and that there is no way of knowing whether a drug candidate will ultimately be successful or whether an experiment or finding will be submitted to the FDA.[159] While emphasizing that Congress did not intend to limit § 271(e)(1) immunity solely to the development of information for submission to the FDA, the Court concluded that the "reasonably related"[160] requirement should be read broadly.[161]

152. Pub. L. No. 98-417, § 202, 98 Stat. 1585, 1603 (1984) (codified as amended at 35 U.S.C. § 271(e)(1)). For academic commentary, see Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 25 (2001); Elizabeth A. Rowe, *The Experimental Use Exception to Patent Infringement: Do Universities Deserve Special Treatment?*, 57 HASTINGS L.J. 921, 932–33 (2006).

153. The statutory provision is also referred to as the "safe harbor provision." Alicia A. Russo & Jason Johnson, *Research Use Exemptions to Patent Infringement for Drug Discovery and Development in the United States*, 5 COLD SPRING HARBOR PERSP. MED., Feb. 2015, at 4–5, http://perspectivesinmedicine.cshlp.org/content/5/2/a020933.

154. 35 U.S.C. §271(e)(1) (2012) (emphasis added). The full text of the provision provides:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) 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 or veterinary biological products.

Id.

155. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 668–69 (1990).

156. 545 U.S. 193 (2005).

157. *Id.* at 206.

158. *Id.*

159. *Id.*

160. 35 U.S.C. § 271(e)(1) (2012).

161. *Merck*, 545 U.S. at 207.

C. Exemption from CAR-T Patent Infringement as Experimental Use

Whether a physician, researcher, or academic institution could be exempted from alleged infringement of CAR-T patent(s) under the experimental use doctrine would depend on the court's analysis of the nature and purpose of the alleged infringing use. Under the current common law experimental use doctrine, the use of CAR-T therapy might not satisfy its narrow conception.[162] First, the use is clearly not "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry"[163] and, therefore, does not satisfy the Federal Circuit's narrow experimental use test.[164] Secondly, while it can be reasonably argued that the use of CAR-T therapy is not solely for profit,[165] the courts might interpret it as serving a "legitimate business interest" in light of *Madey v. Duke University*.[166] CAR-T therapies, especially experimental therapies that would be liable for patent infringement challenges, are mostly (and will likely continue to be) performed at academic medical centers, and these alleged infringers[167] could be considered as (or part of) an academic institution similar to Duke in *Madey*. It is possible that the courts could view performing an experimental therapy as part of a legitimate business interest of an academic medical center, which includes increasing the status of the institution.[168] Indeed, it has been commented that the *Madey* ruling effectively prevents academic institutions from using the experimental use exemption as a defense for patent infringement.[169] However, while *Madey* involved the use of laser technology of which the primary purpose is research,[170] the use of CAR-T therapy has the primary purpose of saving patient lives. And this is a factor that has never been considered by the court in its analysis of the common law experimental use doctrine.[171]

Meanwhile, under the broad interpretation of 35 U.S.C. § 271(e)(1)—the statutory experimental use exemption—the experimental CAR-T therapy, particularly in the form of a clinical trial, can be considered to have a "reasonable relation" to FDA submission even though the CAR-T therapy

162. *See supra* Part III.A.
163. Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002).
164. *Id.*
165. Sawin v. Guild, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391).
166. *Madey*, 307 F.3d at 1362.
167. This would include the physicians, researchers, and academic institution involved in the clinical trial.
168. *Madey*, 307 F.3d at 1362.
169. Rebecca S. Eisenberg, *Patent Swords and Shields*, 299 SCIENCE 1018, 1019 (2003).
170. *Madey*, 307 F.3d at 1361–63.
171. *See infra* Part III.D. for further analysis and arguments.

might not ultimately be successful or submitted to the FDA.[172] In *Merck*, the Supreme Court seemingly allowed preclinical experiments to fall under the § 271(e)(1) exemption by stating:

> At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information under . . . Federal law."[173]

Yet, even though the Supreme Court provided a *broad* interpretation of § 271(e)(1), it did not allow a *loose* interpretation. It stated,

> Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not "reasonably related to the development and submission of information" to the FDA.[174]

The problem is, however, that the line between basic science and preclinical research is not entirely bright.[175] This is particularly the case in research during the development of many gene therapies and personalized medical therapies. Interestingly, in *Merck*, the Supreme Court explicitly refused to rule on whether "research tools" would be exempt from infringement under § 271(e)(1).[176] While no case has explicitly addressed the exemption of research tools under § 271(e)(1), in *Proveris Scientific Corp. v. Innovasystems, Inc.*,[177] the Federal Circuit ruled that the § 271(e)(1) exemption did not apply to a newly developed spray apparatus, which was alleged to infringe on an existing patented spray apparatus.[178] The court explained that although the allegedly infringing apparatus was used in several FDA submissions as a delivery device for drug products, the device itself was not subject to FDA approval and, thus, not protected under § 271(e)(1).[179] Therefore, while the alleged infringing acts in CAR-T clinical trials might be considered exempt from patent infringement under § 271(e)(1), the use and experiments of "research tools" related to the

172. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 206 (2005).
173. *Id.* at 207 (quoting § 271(e)(1)).
174. *Id.* at 205–06.
175. *See* Russo & Johnson, *supra* note 154, at 7.
176. *Merck*, 545 U.S. at 205 n.7.
177. 536 F.3d 1256 (Fed. Cir. 2008).
178. *Id.* at 1258.
179. *Id.* at 1259, 1265–66.

development of the novel CAR-T therapy might not qualify for exemption under § 271(e)(1) because those uses could be deemed too remote from FDA submission or review.[180]

D. Argument for a Broad Experimental Use Doctrine for the Personalized Medicine Era

1. Support for Broad Experimental Use Doctrine

Many academic commentaries have supported a broader experimental use exemption doctrine.[181] In particular, Professor Rebecca Eisenberg pointed out the blurring line between "basic and applied research"[182] in biotechnology as a core basis for a broader experimental use exemption. This rationale can be translated to patented technologies, which are forming the core of personalized medicine, where it is becoming even harder to demarcate the line between basic science research, translational research, preclinical research, and clinical research and practice. In fact, most major foreign jurisdictions have explicitly adopted broad experimental use exemptions to infringement,[183] which are codified in statutory provisions.[184]

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180. In fact, the issue of the treatment of "research tools" by the experimental use exemption has been the subject of a number of academic commentaries. *See, e.g.*, Mueller, *supra* note 152, at 54–65; David C. Hoffman, Note, *A Modest Proposal: Toward Improved Access to Biotechnology Research Tools by Implementing a Broad Experimental Use Exception*, 89 CORNELL. L. REV. 993 (2004).

181. *See, e.g.*, Eisenberg, *supra* note 10; Eyal H. Barash, Comment, *Experimental Uses, Patents, and Scientific Progress*, 91 NW. U. L. REV. 667 (1997); Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 ARIZ. L. REV. 457 (2004); Ted Hagelin, *The Experimental Use Exemption to Patent Infringement: Information on Ice, Competition on Hold*, 58 FLA. L. REV. 483 (2006); Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 BAYLOR L. REV. 917 (2004); Hoffman, *supra* note 180.

182. Eisenberg, *supra* note 10, at 1018.

183. *See, e.g.*, INTELLECTUAL PROP. OFFICE, MANUAL OF PATENT PRACTICE § 60.24 (2017) (U.K.), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/646801/Mopp-Oct-2017.pdf [http://perma.cc/6S9P-3VDU] (noting that experimental use exception extends to commercial experiments and "[t]rials carried out in order to discover something unknown or to test a hypothesis or even in order to find out whether something which is known to work in specific conditions will work in different conditions"); Micro Chems. Ltd. v. Smith Kline & French Inter-American Corp. (1971), [1972] S.C.R. 506, 519 (Can.) (Canadian Supreme Court confirming a broad experimental use exemption by holding that "[p]atent rights were never granted to prevent persons of ingenuity exercising their talents in a fair way"); Yusuke Hiraki, *Patents: Infringement—Experimental Use Exempted for Clinical Trials*, 21 EUR. INTELL. PROP. REV. N140 (1999) (Japan) (explaining the broad interpretation of experimental used exemption by Japanese Supreme Court).

184. *See, e.g.*, Patent Act 1977, c. 37, § 60(5)(b), *reprinted in* INTELLECTUAL PROP. OFFICE, *supra* note 183 (providing defense to patent infringement for actions "done for experimental purposes relating to the subject-matter of the invention"); Patentgesetz [PatG] [Patent Act], Dec. 16, 1980, Bundesgesetzblatt [BGBL] I at § 11.2, last amended by Gesetz [G], Act of Oct. 19, 2013 BGBL I at 3830, art. 1 (Ger.), https://www.wipo.int/wipolex/en/text.jsp?file_id=401424 [http://perma.cc/YDZ5-6RFB] ("The effect of a patent shall not extend to . . . acts done for experimental purposes relating to the subject-

2. Arguments Against Broad Experimental Use Doctrine

Of course, there is support for preserving the status quo of the Federal Circuit's narrow experimental use doctrine.[185] Among the traditional arguments against a broad experimental use exemption,[186] the key concern is reducing incentives for innovation.[187] While protecting the patentee's right and maintaining the economic incentive for innovation are crucial functions of the patent system, these features are important mainly for industries that largely depend on patent protection for innovation.[188] On the other hand, there are alternative incentives for innovation which include the prospect of prestige, prizes for invention, and academic rewards in the form of tenure or promotion.[189] Perhaps more importantly, inventors can be motivated by the desire to do good, such as saving lives or curing diseases, and can also be supported ex ante through government grants or university funding.[190] These latter sets of incentives are prominently influential in the fields of medicine and biotechnology.[191] Therefore, in considering patents related to medical therapies, broadening the experimental use exemption would not have an enormously detrimental effect on innovation in the field.

Additionally, it could also be argued that the realistic possibility of a CAR-T patent infringement lawsuit against physicians and academic institutions is low, as the patent owner might be reluctant to bring a lawsuit against physicians who are saving patients' lives. However, academic

matter of the patented invention."); JAPAN PATENT OFFICE ASIA-PAC. INDUS. PROP. CTR., PATENT INFRINGEMENT LITIGATION IN JAPAN 13 (2016), https://www.jpo.go.jp/torikumi_e/kokusai_e/training/textbook/pdf/Patent_Infringement_Litigation_in_Japan(2016).pdf [http://perma.cc/U6W8-Q8ZX] (explaining Article 69(1), the experimental use exemption, of the Japanese Patent Act).

185. *See, e.g.*, Jordan P. Karp, Note, *Experimental Use as Patent Infringement: The Impropriety of a Broad Exception*, 100 YALE. L.J. 2169 (1991); Rowe, *supra* note 152; Alan Devlin, *Restricting Experimental Use*, 32 HARV. J.L. & PUB. POL'Y 599 (2009).

186. For a detailed analysis of arguments against a broad experimental use exemption and corresponding responses to each argument, see Mueller, *supra* note 152, at 41–54 (addressing the arguments of incentive function of exclusivity, transformative versus commercial purpose, research tool patentability and claim scope, constitutional implications, and conventional U.S. norms of patent exclusivity).

187. *See* Karp, *supra* note 185, at 2181–82; Mueller, *supra* note 152, at 41–42.

188. *See* Karp, *supra* note 185, at 2181.

189. *See* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1586 (2003).

190. *See id.* at 1586–87.

191. *See id.* at 1587 n.30.

institutions are frequently sued,[192] and as long as there is a patent owner, the threat of a patent infringement suit exists.

3. Personalized Medicine Presents a Novel Case for a Broad Experimental Use Doctrine

In addition to the traditional factors of "amusement, . . . idle curiosity, . . . philosophical inquiry"[193] and "profit" or "legitimate business objectives,"[194] this Note proposes another factor for experimental use exemption analysis in the personalized medicine era—clinical experiments to find new cures.

Indeed, other countries have already allowed broader experimental use exemptions, particularly concerning clinical trials.[195] The Federal Supreme Court of Germany interpreted the statutory experimental use exemption provision in German patent law[196] to cover allegedly infringing activity of clinical trials of a patented drug, where the trials were conducted to find new applications for the drug.[197] Furthermore, the court also added that the experimental use exemption would apply even if the alleged infringing activity would lead to a new patent application by the alleged infringer.[198]

Conceptually, Professor Maureen O'Rourke's argument for adopting copyright law's *fair use* exemption[199] into patent law[200] can be considered in line with adding the "clinical experiment" factor to broaden the experimental use doctrine. Professor O'Rouke's proposal has been interpreted as a version of broad experimental use exemption, accepting alleged infringing uses as experimental uses when they are in the context of research or other socially valuable activities.[201] Following this argument, as

192. *See, e.g.*, Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002); Trs. of the Univ. of Pa. v. St. Jude Children's Research Hosp., No. 13–1502, 2014 U.S. Dist. LEXIS 193965 (E.D. Pa. Mar. 13, 2014).

193. *Madey*, 307 F.3d at 1362.

194. *Id.*

195. *See generally* Hans-Rainer Jaenichen & Johann Pitz, *Research Exemption/Experimental Use in the European Union: Patents Do Not Block the Progress of Science*, 5 COLD SPRING HARBOR PERSP. MED., Feb. 2015, http://perspectivesinmedicine.cshlp.org/content/5/2/a020941.

196. "The effects of the patent shall not extend to acts performed for experimental purposes relating to the subject-matter of the patented invention." Wolfgang von Meibom & Johann Pitz, *Experimental Use and Compulsory Licence Under German Patent Law*, PAT. WORLD, June–July 1997, at 27 (quoting Section 11, No. 2 of German Patent Act of 1981).

197. *Id.* at 29.

198. *Id.*

199. Act of Oct. 19, 1976, Pub. L. No. 94-553, § 107, 90 Stat. 2541, 2546 (codified as amended at 17 U.S.C. § 107 (2012)).

200. Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177 (2000).

201. Rowe, *supra* note 152, at 950. The author, however, subsequently criticizes the proposal based on the legal ambiguities of the fair use doctrine in copyright law itself. *Id.* at 951.

clinical trials leading to novel therapies and saved lives are undisputedly socially valuable activities, they should be considered an experimental use.

It has also been previously argued that the experimental use exemption should be broadened to include patented biomedical research tools, as the increased transaction costs would jeopardize the development of new therapeutic drugs or devices crucial for health.[202] An even stronger case can be made for research tools related to clinical experiments (or trials) which are in closer proximity to health care. Therefore, the inherently experimental nature of personalized medicine treatments, such as the CAR-T therapy, strongly calls for a broader experimental use doctrine.

CONCLUSION

Due to its fundamentally dynamic nature being intertwined with innovation and "adapt[ing] flexibly to both old and new technologies,"[203] patent law has often been discussed in conjunction with "paradigm shifts"[204] in the progress of science.[205] Regardless of whether patents do indeed induce paradigm shifts, patent law should not ignore a paradigm shift that is patently in progress. The era of personalized medicine is revolutionizing the way we conceptualize medicine and science, marking a true paradigm shift. While a radical change in patent law might be unrealistic and even unnecessary, the patent system of the new era should at least ensure adequate protection or defense for those whose innocent and well-intended use of a patented technology renders them vulnerable to potential patent infringement lawsuits.

As evident from this analysis using CAR-T therapy as a case study, the current patent regime leaves the inherently experimental personalized medical therapies vulnerable to patent infringement claims and liabilities. Among the two available sources of immunity from patent infringement or infringement liability, the medical procedure exemption provision, 35 U.S.C. § 287(c), is incompatible with personalized medicine due to its excepting biotechnology patents from exemption.[206] Regarding the two types of the experimental use exemption, the Federal Circuit has applied the common law doctrine in a narrow manner, and while the statutory experimental use exemption, 35 U.S.C. § 271(e)(1), has been applied

202. *See* Mueller, *supra* note 152, at 66.

203. Burk & Lemley, *supra* note 189, at 1576.

204. *See generally* THOMAS KUHN, THE STRUCTURE OF SCIENTIFIC REVOLUTIONS (Otto Neurath et al. eds., 2d ed. 1970).

205. *See* Eisenberg, *supra* note 10, at 1051–55; Peter Lee, Note, *Patents, Paradigm Shifts, and Progress in Biomedical Science*, 114 YALE L.J. 659, 686–94 (2004).

206. 35 U.S.C. § 287(c)(2)(A)(iii) (2012).

broadly,[207] the extent of its reach is unclear.[208] Thus, the new paradigm of personalized medicine provides additional support to the long-standing arguments for broadening the experimental use doctrine.[209] The traditional conception of the experimental use analysis confined to "philosophical inquiry"[210] and "legitimate business objectives"[211] is no longer viable. The personalized medicine era calls for a broader experimental use exemption that considers the true nature of clinical experiments and trials and their social value.

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207. *See* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 668–69 (1990); Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 206 (2005).

208. *See supra* text accompanying notes 174-180.

209. *See supra* note 181.

210. Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002).

211. *Id.*

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