

THE CANCER IMMUNOTHERAPY PILOT PROGRAM AND CHIMERIC ANTIGEN RECEPTOR-T CELL TREATMENTS

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Abstract: The Cancer Immunotherapy Pilot Program (also known as Patents 4 Patients) provides fast-track review to patent applications describing methods of treating cancer with immunotherapy, such as chimeric antigen receptor (“CAR”)-T cell treatments. This article explores considerations for claiming CAR-T cell treatments, including court rulings and examiner guidelines on patentable subject matter in the life sciences, the Federal Circuit’s decision in *NantKwest, Inc. v. Lee* in 2017, and pending applications and current litigation over CAR-T cell treatments.

I. INTRODUCTION

Cancer immunotherapy refers to biological treatments that use the immune system to combat cancer.¹ These treatments, including monoclonal antibodies, antibody drug conjugates, cancer treatment vaccines, bacillus Calmette-Guérin therapy, gene therapy, and adoptive T-cell transfer therapy, take many approaches and have a variety of mechanisms of action.² A point of commonality, however, is that all require more complicated production schemes than those used to manufacture small molecule drugs.³ Also, because biological treatments are living organisms, such as bacteria and viruses, or substances derived from living organisms, such as antibodies of the immune system, they

¹ *Biological Therapies for Cancer*, NAT’L CANCER INST., <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet> (last visited Apr. 26, 2018).

² *Id.*; *Game Changers: How CAR-T and Cell Therapy Are Revolutionizing Cancer Immunotherapy*, FOLEY & LARDNER LLP (Dec. 7, 2017), <https://www.foley.com/game-changers-how-car-t-and-cell-therapy-are-revolutionizing-cancer-immunotherapy-12-07-2017/> [hereinafter *Game Changers*].

³ Carla Mouta-Bellum et al., *The Immunotherapy Patent Landscape: Types of patent claims for immunotherapeutic inventions*, IP WATCHDOG (Aug. 10, 2017), <http://www.ipwatchdog.com/2017/08/10/immunotherapy-patent-landscape-patent-claims-immunotherapeutic-inventions/id=86634/>.

pose challenges in terms of patentability.⁴ Though 35 U.S.C. § 101 lists broad categories of patentable subject matter, discoveries that are laws of nature, natural phenomena, or abstract ideas cannot be patented unless they also contain an inventive concept.⁵

This article reviews cancer immunotherapy, specifically chimeric antigen receptor (“CAR”)-T cell treatments, a type of adoptive T-cell transfer therapy, with respect to the current law, particularly examining patents for this technology.⁶ This article also provides an overview of recent court rulings on section 101 and an example illustrating examiner guidelines for determining subject matter eligibility.⁷ In addition, this article discusses the Federal Circuit’s decision in *NantKwest, Inc. v. Lee* in 2017 holding a method of using a particular immune cell line to treat cancer as obvious.⁸ Additionally, this article describes pending patent applications for Kymriah (tisagenlecleucel), a CAR-T cell treatment with FDA approval for use in children and young adults with B-cell precursor acute lymphoblastic leukemia.⁹ Lastly, this article discusses early court filings over Yescarta (axicabtagene ciloleucel), another CAR-T cell treatment, regarding issues likely to arise during patent litigation for this type of immunotherapy.¹⁰

⁴ See *Biological Therapies for Cancer*, *supra* note 1 (describing types of biological treatments); Mouta-Bellum, *supra* note 3 (stating the difficulty in balancing breadth and validity of claims, especially for antibody-based inventions).

⁵ *Mayo Collaborative Servs. v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 70, 72–73 (2012).

⁶ See *infra* notes 11–194 and accompanying text.

⁷ See *infra* notes 48–126 and accompanying text.

⁸ *NantKwest, Inc. v. Lee*, 686 Fed. App’x 864, 865 (Fed. Cir. 2017); see *infra* notes 143–146 and accompanying text.

⁹ See *infra* notes 147–166 and accompanying text.

¹⁰ See *infra* notes 167–194 and accompanying text.

II. CAR-T CELL TREATMENTS AND THE CANCER IMMUNOTHERAPY PILOT PROGRAM

CAR-T cell treatments are a recent advance in cancer immunotherapy, and their arrival reflects the growing personalization of medicine.¹¹ In CAR-T cell therapy, an individual patient's cells are collected, genetically modified, and returned to the patient with new cancer-fighting properties.¹² Though the United States Patent and Trademark Office ("USPTO") created the Cancer Immunotherapy Pilot Program (also known as Patents 4 Patients) with the aim of accelerating review for patent applications directed to methods of treating a cancer using the immune system, such as CAR-T cell therapies, questions remain about the patentability of these treatments given their biological subject matter.¹³

A. An Overview of the CAR-T Cell Therapy Production Process

To begin CAR-T cell therapy, a patient's white blood cells are collected through leukapheresis, and the T cells are specially frozen before being shipped to a manufacturing facility.¹⁴ At the manufacturing facility, the T cells are transfected with a viral vector containing the gene for a T cell receptor specific to an antigen found on the patient's cancer cells.¹⁵ In addition, the genetically modified T cell receptor contains intracellular domains that enhance its signaling properties and abilities to replicate and survive in the

¹¹ Martina McGrath, *Taking Personalized Medicine to a New Level: CAR-T Cell Therapy*, TRENDS IN MEDICINE (Sept. 13, 2017), <https://trends.hms.harvard.edu/2017/09/13/taking-personalized-medicine-to-a-new-level-car-t-cell-therapy/>.

¹² *Biological Therapies for Cancer*, *supra* note 1.

¹³ See *infra* notes 37–40 and accompanying text.

¹⁴ *Chimeric Antigen Receptor T Cell (CAR T) Therapy*, NOVARTIS (Aug. 2017), <https://www.novartis.com/news/media-library/car-t-cell-therapy-infographic>.

¹⁵ *Id.*

patient after infusion, termed expansion and persistence, respectively.¹⁶ Because the genetically engineered T cell receptor is composed of modular parts with distinct functions, including antigen recognition, it is called a chimeric antigen receptor, and the end product is called a chimeric antigen receptor (“CAR”)-T cell treatment.¹⁷

After the T cells have been modified to express a chimeric antigen receptor, they are expanded, checked for quality, and shipped back to the hospital.¹⁸ Prior to CAR-T infusion, the patient undergoes lymph-depleting chemotherapy to reduce the number of white blood cells.¹⁹ The treatment is given intravenously in a single dose and takes effect when CAR-T cells, now able to recognize the patient’s cancer cells, encounter the antigen and initiate cell death.²⁰

¹⁶ A “Living Drug,” NAT’L CANCER INST., <https://www.cancer.gov/about-cancer/treatment/research/car-t-cells#living-drug> (last visited Dec. 14, 2017) [hereinafter *Living Drug*].

¹⁷ *Id.* Both of the CAR-T therapies discussed in this article, Kymriah and Yescarta, express receptors for the B-lymphocyte antigen CD19; however, efforts are underway to expand the repertoire of targets for CAR-T cell treatments. *Game Changers*, *supra* note 2; *New Target Antigens for CAR T Cells*, NAT’L CANCER INST., <https://www.cancer.gov/about-cancer/treatment/research/car-t-cells#new-target> (last visited Dec. 14, 2017). The reasons for making CAR-T therapies with other antigen receptors include increasing the efficiency of immunotherapy for patients with certain types of cancers, such as CD30-positive lymphoma, or making the treatment effective for patients who did not respond or experienced recurrences following CD19 CAR-T cell therapy. *CD30 CAR-Expressing Autologous T Lymphocytes in Treating Patients with CD30-Positive Lymphomas*, NAT’L CANCER INST., <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCT03049449&r=1> (last visited Mar. 27, 2018); *New Target Antigens for CAR T Cells*, *supra*. Recurrences linked to antigen loss might be treated with another CAR-T cell therapy or prevented by targeting multiple lymphocyte antigens in one treatment. *New Target Antigens for CAR T Cells*, *supra*. So, although this article focuses on CAR-T cell treatments in which the chimeric antigen receptor is specific for CD19, the particular antigen can vary. *Id.*

¹⁸ *Chimeric Antigen Receptor T Cell (CAR T) Therapy*, *supra* note 14.

¹⁹ *Id.*

²⁰ *Id.*

B. Challenges in Producing CAR-T Cell Therapies

The production process for CAR-T cell therapies is complex, requiring a new approach to logistics, manufacturing, and administration.²¹ The resulting CAR-T cell treatments, such as Kymriah and Yescarta, are highly effective.²² These treatments, however, can have serious side effects, including death.²³ Other challenges include the high cost of producing these treatments and whether the treatments are patentable.²⁴

²¹ *Id.* Novartis, the maker of Kymriah, was the first to develop a manufacturing facility for CAR-T cell treatments with FDA approval in the United States. *Id.* It was soon followed by Gilead, which gained FDA approval in October 2017 for its manufacturing plant in El Segundo, California, where it can produce Yescarta with a 99% manufacturing success rate and a median turnaround time of 17 days. *Kite's Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA for the Treatment of Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy*, BUS. WIRE (Oct. 18 2017, 5:43 PM), <https://www.businesswire.com/news/home/20171018006639/en/> [hereinafter *Yescarta Approved*].

²² *Living Drug*, *supra* note 16. Kymriah is approved for the treatment of B-cell precursor acute lymphoblastic leukemia that is refractory or relapsed in patients up to 25 years of age. *FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm> (last visited Sept. 7, 2017) [hereinafter *FDA approves tisagenlecleucel*]. Treatment with Kymriah results in an overall remission rate of 83%, compared to a 10% five-year survival rate for this type of disease. *Game Changers*, *supra* note 2. Yescarta, approved to treat relapsed or refractory large B-cell lymphoma in patients who have failed at least two traditional treatments and who are not eligible for transplant, has a complete remission rate of 51%. *FDA approves tisagenlecleucel*, *supra*.

²³ *Living Drug*, *supra* note 16. Serious adverse reactions, including cytokine release syndrome (an immune response) and neurologic problems, occurred in 49% of patients treated with Kymriah and 52% of patients treated with Yescarta. *Game Changers*, *supra* note 2; *Yescarta Approved*, *supra* note 21. In addition, five patients died from cerebral edema (brain swelling) during a Juno Therapeutics clinical trial for another CAR-T cell therapy for acute lymphoblastic leukemia. Roni Dengler, *Cancer immunotherapy company tries to explain death in recent trial*, SCI. (Nov. 16, 2017, 5:45 PM), <http://www.sciencemag.org/news/2017/11/cancer-immunotherapy-company-tries-explain-deaths-recent-trial>. Though the exact cause of the cerebral edema leading to these patient deaths is unknown, Juno Therapeutics identified certain treatment histories that were associated with the deaths, while acknowledging that variations in the patients' white blood cells and processing also may have been responsible. *Id.*

²⁴ *See infra* notes 25–47 and accompanying text.

1. High Cost

Though CAR-T cell treatments are a new milestone in cancer immunotherapy, their customization makes them expensive to produce, raising questions about how to fund this type of treatment.²⁵ Not including the cost of infusion, the price for Kymriah is \$475,000, and Yescarta is \$373,000.²⁶ To make Kymriah more affordable, Novartis has entered into a partnership with the Centers for Medicare & Medicaid Services and elected to use a new payment arrangement, known as outcome-based pricing, in which payment is based on response.²⁷ If a patient does not respond to the treatment within one month, the fee is waived.²⁸

2. Patentability

Another issue complicating the valuation of CAR-T cell therapies, aside from the need for new reimbursement models to pay for them, is their patentability.²⁹ Obtaining a patent is often the first step in commercializing a new scientific discovery.³⁰ Because the period of market exclusivity is one of the main incentives for companies to invest in drug

²⁵ 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>.

²⁶ *With FDA Approval for Advanced Lymphoma, Second CAR T-Cell Therapy Moves to the Clinic*, NAT'L CANCER INST. (Oct. 25, 2017), <https://www.cancer.gov/news-events/cancer-currents-blog/2017/yescarta-fda-lymphoma>.

²⁷ *CMS: Innovative treatments call for innovative payment models and arrangements*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Aug. 30, 2017), <https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2017-Press-releases-items/2017-08-30-2.html>.

²⁸ *Id.*

²⁹ *Game Changers*, *supra* note 2.

³⁰ See Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 503 (2015) (describing screening practices at pharmaceutical companies in which drug candidates with weak patent protection are discarded).

development and clinical trials, the likelihood of being awarded a patent is usually a major consideration, if not a pre-requisite, for pharmaceutical companies to research a particular treatment.³¹ Thus, in a commercial context, the patentability of a potential invention heavily influences whether an idea is developed to the point that it enters the marketplace and becomes useful to society.³²

To accelerate the process of bringing cancer immunotherapy to patients, the USPTO introduced the Cancer Immunotherapy Pilot Program.³³ The Cancer Immunotherapy Pilot Program grants special status to immunotherapy patent applications meeting certain requirements.³⁴ The application must be for a method of treatment, contain three independent claims, have no more than 20 total claims, include no multiple dependent claims, and agree to a telephonic restriction without traverse if there is a restriction requirement.³⁵ The goal of the program is to reduce the examination period by half, so that a decision is issued within one year of an application being granted special status.³⁶

Though the Cancer Immunotherapy Pilot Program expedites the review period, problems remain for parties seeking to obtain patents through this program.³⁷ First, investors prefer companies that have patents for a composition, rather than a method, and

³¹ See *id.* (stating that firms with patent protection are able to delay generic competition for ten to fourteen years on average and profit from investment in R&D).

³² See *id.* (noting that the mere idea of a drug is not helpful).

³³ *Game Changers*, *supra* note 2.

³⁴ *Id.*

³⁵ *Id.*

³⁶ *Id.*

³⁷ Robert R. Sachs, *Will The USPTO's "Patents 4 Patients" Program Even Make It Off The "Cancer Moonshot" Launch Pad?*, BILSKI BLOG (June 30, 2016), <http://www.bilskiblog.com/blog/2016/06/will-the-usptos-patents-4-patients-program-even-make-it-off-the-launching-pad-1.html> [hereinafter "*Patents 4 Patients*" Program].

the program only allows applications describing a method.³⁸ Second, fast-track review eliminates patent term adjustment, which is highly valuable for pharmaceutical companies because the end of the patent term is usually when the highest profits are realized.³⁹ Third, the program does not change the outcome of the review, and applications still could be rejected on the basis of subject matter if the examiner determines that the method describes a law of nature, natural phenomenon, or abstract idea without an inventive concept.⁴⁰

Despite these problems, some petitioners can benefit from the program.⁴¹ Start-up companies with strong patent protection can raise more capital, so receiving an issued patent for a method within one year of being granted special status might be worth foregoing patent term adjustment for a new company.⁴² Also, in the early stages of a company's development, an issued patent protects against competition from research groups with similar technologies.⁴³

Using the Cancer Immunotherapy Pilot Program as a backdrop, this article focuses on subject matter eligibility and the types of patent claims contained in applications for CAR-T cell treatments.⁴⁴ In addition, this article explores major rulings on 35 U.S.C. § 101 and Example 29.6 from the USPTO Interim Guidance on Subject Matter Eligibility.⁴⁵ Also, this article discusses the Federal Circuit's decision in *NantKwest, Inc. v. Lee* in 2017

³⁸ *Game Changers*, *supra* note 2.

³⁹ Jing Liu & Daniel Yarbrough, *The USPTO "Patents 4 Patients" Program: What, How, and Why*, KNOBBE MARTENS (Sept. 30, 2016), <https://www.knobbe.com/news/2016/09/uspto-%E2%80%9Cpatents-4-patients%E2%80%9D-program-what-how-and-why>.

⁴⁰ *"Patents 4 Patients" Program*, *supra* note 37.

⁴¹ Liu & Yarbrough, *supra* note 39.

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *See infra* notes 48–146 and accompanying text.

⁴⁵ *See infra* notes 50–126 and accompanying text.

holding a method of treating cancer with a specific line of natural killer cells as obvious.⁴⁶ Finally, this article applies these lessons to pending applications for Kymriah and current litigation between Juno Therapeutics and Kite Pharma, a subsidiary of Gilead, over Yescarta.⁴⁷

III. THE PATENTABLE SUBJECT MATTER REQUIREMENT

Most subject matter is patentable under 35 U.S.C. § 101, unless it involves laws of nature, natural phenomena, or abstract ideas without an inventive concept.⁴⁸ These three categories of judicial exception are based on the idea that there should be a balance between promoting shared knowledge while protecting its application.⁴⁹

A. Overview

Section 101 describes broad categories of patentable subject matter.⁵⁰ It states, “Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”⁵¹ By design, the statutory language is expansive.⁵² For example, the word “any” supports a broad

⁴⁶ *NantKwest, Inc. v. Lee*, 686 Fed. App’x 864, 865 (Fed. Cir. 2017); *see infra* notes 143–146 and accompanying text.

⁴⁷ *See infra* notes 147–194 and accompanying text.

⁴⁸ *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70, 72–73 (2012).

⁴⁹ *Id.* at 70–72.

⁵⁰ *See* 35 U.S.C. § 101 (2012) (defining patentable subject matter).

⁵¹ *Id.* § 101.

⁵² *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980).

construction, and the legislative history indicates that Congress intended the statute to cover a wide array of inventions.⁵³

Although section 101 outlines categories of patentable subject matter in comprehensive terms, judicial decisions show that there are exceptions, including laws of nature, natural phenomena, and abstract ideas.⁵⁴ In 1854, in *O'Reilly v. Morse*, the United States Supreme Court held that principles of electromagnetism were not patentable, although other claims to the telegraph were patentable subject matter.⁵⁵ Similarly, in 1948, in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, the Supreme Court held that a mixture of naturally occurring strains of bacteria used to inoculate plant seeds was not patentable subject matter.⁵⁶ Though the defendant was the first to realize that a particular combination of bacterial strains could be composed without inhibiting the ability of each to assist a leguminous plant in fixing nitrogen, the product was not patentable because the bacteria already possessed these properties.⁵⁷ Consequently, the defendant did not invent a new product by combining them.⁵⁸ The Court did not address whether the methods of selecting or testing the strains were patentable, but concluded that the bacteria themselves could not be patented because they already existed in nature.⁵⁹

⁵³ *Id.* at 308–09 (citing Patent Act, ch. 11, § 1, 1 Stat. 319, (1793) (amended 1952); S. REP. NO. 82-1979 at 5 (1952); H.R. REP. NO. 82-1923 at 6 (1952)).

⁵⁴ *Id.*

⁵⁵ See *O'Reilly v. Morse*, 56 U.S. 62, 112–13 (1854) (holding that a claim directed to the use of electromagnetism to print characters over distance was too broad).

⁵⁶ *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948).

⁵⁷ *Id.* at 128–31.

⁵⁸ *Id.* at 130–31.

⁵⁹ *Id.*

The question of whether an invention is a law of nature, natural phenomenon, or abstract idea is complex.⁶⁰ In particular, merging legal and scientific concepts of what constitutes a law of nature is challenging.⁶¹ Debate continues about the existence of laws of nature and what defines them, with separate meanings given to accidental generalizations, universal truths, and law-like statements.⁶² Furthermore, disciplines such as physics and biology differ in their likelihood of meeting the conditions that might transform a law-like statement into a law of nature.⁶³ Physics concepts, such as Newton's laws of motion or Einstein's theory of relativity, are more associated with qualities that would transform a law-like statement into a law of nature, such as prediction or necessity, than biology concepts.⁶⁴ In fact, the main principles in biology, random change and evolution, run counter to some of the conditions that could support finding a law of nature.⁶⁵

Nonetheless, biology patents can be invalid for claiming natural laws; in 2012, the Court held in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* that a patent describing the relationship between thiopurine drug dosage and blood metabolite levels was invalid because it claimed a law of nature.⁶⁶ To better understand how section 101 exceptions apply to biologics, such as CAR-T cell therapies, major decisions on products

⁶⁰ Robert R. Sachs & Jennifer R. Bush, *Prometheus Unbound I: The Untethering of Laws of Nature and Patent Eligibility from Scientific Reality*, BILSKI BLOG (July 3, 2013), <http://www.bilskiblog.com/blog/2013/07/prometheus-unbound-the-untethering-of-laws-of-nature-and-patent-eligibility-from-scientific-reality.html>.

⁶¹ *Id.*

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Mayo Collaborative Servs.*, 566 U.S. at 67.

and process claims are presented below, along with a brief discussion of how these rulings affect the Cancer Immunotherapy Pilot Program.⁶⁷

B. Genetic Engineering and the Natural World: When Is Biological Subject Matter a Product of Nature?

Products of nature can be discovered, but because they are natural phenomena—that is, they exist in the world without human intervention—they cannot be patented under section 101.⁶⁸ In contrast, genetically engineered bacteria and synthetic complementary DNA are examples of biological subject matter that is patent eligible.⁶⁹

1. Human-Made Living Organisms Are Patent Eligible

In 1980, in *Diamond v. Chakrabarty*, the United States Supreme Court held that a human-made, living bacterium was patentable subject matter because it represented a “manufacture” or “composition of matter” described in section 101.⁷⁰ The defendant invented a genetically engineered bacterium with two separate pathways for breaking down crude oil that could be used to clean oil spills.⁷¹ The defendant filed a patent application claiming the method of making the bacteria, a means of applying the bacteria to water using a carrier material such as straw, and “the bacteria themselves.”⁷² The issue

⁶⁷ See *infra* notes 110–126 and accompanying text.

⁶⁸ See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 596 U.S. 576, 580 (2013) (holding that a naturally occurring gene segment is a patent ineligible product of nature); *Funk Bros. Seed Co.*, 333 U.S. at 130–31 (stating that a patent ineligible product claim is a work of nature, existing independent of the inventor’s activity).

⁶⁹ *Ass’n for Molecular Pathology*, 596 U.S. at 595; *Chakrabarty*, 447 U.S. at 305–10.

⁷⁰ *Chakrabarty*, 447 U.S. at 305, 309–10.

⁷¹ *Id.* at 305.

⁷² *Id.*

was whether the bacterium, as a living thing, could be a “manufacture” or “composition of matter” under section 101.⁷³

The Court reasoned that, by the ordinary meanings of “manufacture” and “composition of matter,” the defendant’s genetically engineered bacteria were within the scope of the statute.⁷⁴ Oil-cleaning bacteria do not ordinarily occur in nature, so the defendant’s work in bringing them about is why they were a “manufacture” or “composition of matter.”⁷⁵ In addition, the genetically modified bacteria were “markedly different” from naturally occurring bacteria.⁷⁶ By comparison, the product in *Funk Bros. Seed Co.* was a composition of six naturally occurring bacteria that took on no new properties or uses when assembled, so it was not patentable.⁷⁷

Furthermore, the only relevant issue was whether the bacteria were a “manufacture” or “composition of matter,” so the plaintiff’s argument that living things were intended to be patent ineligible under section 101 was unconvincing to the Court.⁷⁸ Citing the 1930 Plant Patent Act and the 1970 Plant Variety Protection Act, the plaintiff contended that living things were not patentable subject matter; otherwise, there would be no need for the Acts.⁷⁹ In addition, the plaintiff argued that a letter from Secretary of Agriculture Hyde to the Chairmen of the House and Senate Committees, in which he stated that patent law was understood to apply only to inanimate objects, indicated congressional agreement that living things were outside the scope of section 101 prior to

⁷³ *Id.* at 307.

⁷⁴ *Id.* at 309.

⁷⁵ *Id.* at 309–10.

⁷⁶ *Id.* at 315.

⁷⁷ *Id.* at 310.

⁷⁸ *Id.* at 313–14.

⁷⁹ *Id.* at 310–11.

the passage of the 1930 Plant Patent Act.⁸⁰ The Court considered contrary evidence, such as the motivating reasons behind the 1930 Plant Patent Act and the House and Senate Committee Reports.⁸¹ In the Reports, the House and Senate Committee distinguished between cultivated plant varieties and naturally occurring minerals, with the former being an example of something Congress wished to make patent eligible and the latter not.⁸² The Court held that this language in the House and Senate Committee Reports reflected an understanding that “the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions.”⁸³ Thus, in order for a natural or living product to be patent eligible, it must occur as a result of human endeavor.⁸⁴

In addition, the Court dismissed the plaintiff’s argument that genetically engineered bacteria cannot be patentable subject matter without express congressional authorization.⁸⁵ While recognizing that there may be reasons why Congress would want to regulate products of genetic engineering, the Court maintained that its role was to interpret section 101 as written, finding that the oil-cleaning bacteria constituted a “manufacture” or “composition of matter” under the statute.⁸⁶

⁸⁰ *Id.* at 312–13.

⁸¹ *Id.* at 310–13.

⁸² *Id.* at 313.

⁸³ *Id.*

⁸⁴ *See id.* at 309–10 (describing the difference between a patent ineligible composition of naturally occurring bacteria and patent eligible genetically engineered bacteria in terms of production, and stating that “[h]is discovery is not nature’s handiwork, but his own; accordingly it is patentable subject matter under § 101”).

⁸⁵ *Id.* at 314–18.

⁸⁶ *Id.*

2. Isolated Genes Are Patent Ineligible Products of Nature, but Complementary DNA Is Patent Eligible

Similarly, in 2013, the United States Supreme Court held in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* that naturally occurring, isolated gene sequences are not patentable subject matter, but complementary DNA (“cDNA”) is patentable subject matter because it is synthetically created.⁸⁷ The difference between the isolated genes and the cDNA was not the research effort, which the Court recognized was extensive in discovering the location of the BRCA1 and BRCA2 gene sequences, but the creation of something new.⁸⁸ Though the isolated genes were an important and useful discovery, they already existed in nature, so they were not patentable subject matter under section 101.⁸⁹ The cDNA, on the other hand, was not a product of nature.⁹⁰ Because removing the non-coding sequences was necessary to produce the cDNA, the Court held that it was patentable subject matter.⁹¹

The Court observed that Myriad did not file methods claims because the process of locating and sequencing the DNA was commonly used.⁹² In addition, there were no application claims stemming from the discovery of the gene sequences.⁹³ Finally, the Court noted that it was not considering how it would decide the case if the gene sequence was altered from what is found in nature.⁹⁴

⁸⁷ *Ass'n for Molecular Pathology*, 596 U.S. at 580.

⁸⁸ *Id.* at 591–93.

⁸⁹ *Id.* at 591.

⁹⁰ *Id.* at 595.

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Id.* at 595–96.

⁹⁴ *Id.* at 596.

C. *The Mayo/Alice Test: When Are Biological Relationships Natural Laws?*

Whereas the ruling in *Myriad Genetics* focused on products of nature as patentable subject matter, the following cases discuss methods claims involving natural laws and abstract ideas.⁹⁵ Together, these decisions form the *Mayo/Alice* test for determining subject matter eligibility.⁹⁶ The *Mayo/Alice* test requires asking if any of the claims involve patent ineligible subject matter and then examining the remaining claims for an inventive concept.⁹⁷

1. Overview of the *Mayo/Alice* Test

In 2012, in *Mayo Collaborative Services*, the United States Supreme Court held that a method of adjusting thiopurine drug dosage based on blood metabolite levels was patent ineligible.⁹⁸ The method involved administering thiopurine drugs to treat autoimmune disease, and then measuring blood metabolite levels to see if the body was breaking down the drug too readily, in which case it would be ineffective, or too slowly, in which case it would be harmful.⁹⁹ Because the optimal range of blood metabolites levels indicating a proper dosage of thiopurine drugs was already known, and taking these measurements and adjusting accordingly was common practice, the Court held that the

⁹⁵ See *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2349 (2014) (holding that generic computer implementation of standard business concepts is a patent ineligible abstract idea); *Ass'n for Molecular Pathology*, 596 U.S. at 596 (holding that isolated DNA is a patent ineligible product of nature); *Mayo Collaborative Servs.*, 566 U.S. at 66–67 (holding that a method of adjusting drug dosage based on blood metabolite levels is a patent ineligible law of nature).

⁹⁶ See *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355 (describing the two-part test for subject matter eligibility).

⁹⁷ See *id.* (describing the two-part test for subject matter eligibility).

⁹⁸ *Mayo Collaborative Servs.*, 566 U.S. at 66–67.

⁹⁹ *Id.*

defendant's method claimed natural laws.¹⁰⁰ Furthermore, describing the steps of using a natural law was not a patentable application of those laws, but rather a claim to the laws themselves.¹⁰¹ In addition, the ordered combination of the three steps did not change the steps when considered separately, which still lacked an inventive concept that added "significantly more" to the natural laws.¹⁰²

Similarly, the United States Supreme Court held in 2014 in *Alice Corp. Proprietary Ltd. v. CLS Bank International* that computer software applying standard business concepts was patent ineligible because it claimed abstract ideas already present in the industry.¹⁰³ The plaintiff developed a generic computer process for reducing settlement risk by using a third-party intermediary.¹⁰⁴ Intermediated settlement and the use of third-party intermediaries were already familiar concepts in the field, so the Court found that they were abstract ideas, and generic computer implementation of these abstract ideas could not be patented without something more.¹⁰⁵

In addition, the Court formally created a two-part test to determine patentable subject matter in cases involving possible section 101 exceptions, clarifying its earlier ruling in *Mayo Collaborative Services*.¹⁰⁶ In the first step, claims must be examined for a patent ineligible concept, such as a law of nature, natural phenomenon, or abstract idea.¹⁰⁷ In the second step, the remaining claims must be examined for an inventive concept.¹⁰⁸

¹⁰⁰ *Id.* at 67.

¹⁰¹ *Id.*

¹⁰² *Id.* at 72–73.

¹⁰³ *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2349.

¹⁰⁴ *Id.*

¹⁰⁵ *Id.* at 2349–50.

¹⁰⁶ *Id.* at 2350.

¹⁰⁷ *Id.* at 2355.

¹⁰⁸ *Id.*

The “search for an inventive concept” involves answering whether the remaining elements of the claim, either individually or in combination, transform the patent ineligible subject matter into a patentable invention.¹⁰⁹

2. Impact of the *Mayo/Alice* Test on the Cancer Immunotherapy Pilot Program

By requiring a two-step inquiry to determine patentable subject matter, the *Mayo/Alice* test shifts away from the idea that “claims must be considered as a whole” and turns towards an approach favoring preemption.¹¹⁰ As a result, the *Mayo Collaborative Services* and *Alice Corp. Proprietary Ltd.* decisions raises questions about how method patents filed through the Cancer Immunotherapy Pilot Program will be treated.¹¹¹

Some believe the Court’s interpretation of “natural laws” in *Mayo Collaborative Services* will predispose examiners and judiciaries to hold cancer immunotherapy claims invalid.¹¹² For example, using the *Mayo Collaborative Services* definition, the body’s response to treatment with immunotherapy could be seen as a natural relationship.¹¹³ Also, since the claims in *Mayo Collaborative Services* sought to increase “therapeutic

¹⁰⁹ *Id.*

¹¹⁰ Joyce C. Li, Note, *Preemption, Diagnostics, and the Machine-or-Transformation Test: Federal Circuit Refinement of Biotech Method Eligibility*, 32 BERKELEY TECH. L.J. 379, 384 (2017); see *Diamond v. Diehr*, 450 U.S. 175, 188 (1981) (holding that use of a mathematical formula, computer program, or digital computer does not invalidate a process that is otherwise patentable subject matter).

¹¹¹ John T. Aquino, *Attorneys Debate Risk of Cancer ‘Moonshot’ Patent Claims Facing Rejection*, BLOOMBERG LAW (Aug. 31, 2017), <https://www.bna.com/attorneys-debate-risk-n73014447075/>.

¹¹² *Id.*

¹¹³ *Id.*

efficacy,” the decision could apply to treatment methods, such as those allowed through the Cancer Immunotherapy Pilot Program.¹¹⁴

Those who are more optimistic about the validity of cancer immunotherapy claims point out that the Court in *Mayo Collaborative Services* ruled on a diagnostic test, and since applications submitted through the Cancer Immunotherapy Pilot Program must be for treatment methods, there is a low chance that they will be rejected based on the understanding of natural relationships set out in that case.¹¹⁵ Moreover, the goal of making new treatments available through the Cancer Immunotherapy Pilot Programs is compatible with the Court’s stated policy objective of facilitating innovation by reserving natural phenomena, laws of nature, and abstract ideas as shared tools for science and medicine.¹¹⁶

Furthermore, regardless of whether *Mayo Collaborative Services* applies to diagnostic or therapeutic methods, the key issue is whether the claims contain “significantly more” than a natural relationship or abstract idea.¹¹⁷ In May 2016, the USPTO issued supplementary guidelines to examiners for determining subject matter eligibility in life sciences, particularly illustrating in Example 29.6 how “significantly more” is identified in diagnostic and treatment claims.¹¹⁸

As stated in the guidelines, claims involving a law of nature or abstract idea are patent eligible if they “recite specific and unconventional reagents and/or treatments that

¹¹⁴ *Id.*

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ *Id.*

amount to significantly more than the exception.”¹¹⁹ These are distinguished from patent ineligible claims that lack a meaningful limitation on the use of the exception.¹²⁰ Typically, patent ineligible claims describe a well-understood, routine, or conventional technique at a high level of generality, so that the claims function simply as a way of using the natural correlation.¹²¹ In contrast, claims containing a step using a natural correlation, as well as steps directed to well-understood, routine, or conventional activity, can be patent eligible if the steps as a combination have a meaningful limit on the use of the exception.¹²² For instance, a claim reciting a process of obtaining a plasma sample, detecting the presence of a protein in the plasma, diagnosing a condition if the protein is present, and treating the condition in a particular way is patent eligible, as shown in Example 29.6.¹²³

The *Mayo/Alice* criteria redirect the focus of the inquiry for determining patentable subject matter, but this does not necessarily pose a problem for the Cancer Immunotherapy Pilot Program.¹²⁴ Though there is debate about whether the holding in *Mayo Collaborative Services* can be limited to diagnostic methods, or whether it applies to diagnostic and treatment methods, the key issue for determining patent eligibility for inventions involving biological processes is whether the claims contain “significantly more” than a natural correlation.¹²⁵ Ideally, USPTO examiners will differentiate between claims that merely recite laws of nature or abstract ideas and make use of them, and grant

¹¹⁹ *Subject Matter Eligibility Examples: Life Sciences*, U.S. PAT. & TRADEMARK OFF. 1, 9 (May 2016), <https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf>.

¹²⁰ *Id.* at 12.

¹²¹ *Id.*

¹²² *Id.* at 15.

¹²³ *Id.*

¹²⁴ Aquino, *supra* note 111.

¹²⁵ *Id.*

patent applications seeking to fight cancer with immunotherapy, such as CAR-T cell treatments.¹²⁶

IV. RECENT CASES INVOLVING IMMUNOTHERAPY AND SIMILAR TECHNOLOGY

In 2016, in *Bristol-Myers Squibb Co. v. Merck & Co.*, the United States District Court for the District of Delaware ruled that a method of treating cancer using a monoclonal antibody was patent ineligible at step one of the *Mayo/Alice* analysis, but delayed deciding whether the claims amounted to significantly more until after discovery could be completed.¹²⁷ In addition, the United States District Court for the District of Massachusetts held in 2017 in *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.* that radiolabeling a protein for a method of diagnosing Myasthenia Gravis was not enough to transform a claim directed to a patent ineligible law of nature.¹²⁸ Lastly, in 2017, in *NantKwest, Inc. v. Lee*, the United States Court of Appeals for the Federal Circuit held that claims directed to a method of treating cancer using a line of natural killer cells were invalid based on prior art.¹²⁹

A. T Cell Activation is a Natural Phenomenon Satisfying Step 1 of the Mayo/Alice Test

In 2016, in *Bristol-Myers Squibb*, the United States District Court for the District of Delaware denied a motion to dismiss in a patent infringement suit involving cancer

¹²⁶ *Id.*

¹²⁷ *Bristol-Myers Squibb Co. v. Merck & Co.*, No. CV 15-572-GMS, 2016 WL 1698385, at *1 (D. Del. Mar. 29, 2016).

¹²⁸ *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, 275 F. Supp. 3d 306, 310, 312, (2017).

¹²⁹ *NantKwest, Inc. v. Lee*, 686 Fed. App'x 864, 865 (Fed. Cir. 2017).

immunotherapy, but concluded that there were grounds for challenging the technology based on 35 U.S.C. § 101 exceptions.¹³⁰ The claims involved a method of treating metastatic melanoma using a monoclonal anti-PD1 antibody.¹³¹ By binding PD1 and blockings its ligands, the treatment interrupts an immune suppression pathway and allows T cells to function more effectively in targeting cancer cells.¹³² Because the treatment works by increasing T cell activation, the court held that it “touch[ed] upon” a natural phenomenon, triggering the first step of the *Mayo/Alice* analysis.¹³³ The court ruled that the second step of the *Mayo/Alice* test, determining whether the claims amount to “significantly more” than the section 101 exception, was a fact-intensive inquiry that would be better addressed after discovery.¹³⁴

B. Using a Radiolabel Does Not Transform Subject Matter Under the Mayo/Alice Test

In 2017, in *Athena Diagnostics*, the United States District Court for the District of Massachusetts held that a method of diagnosing Myasthenia Gravis with a radiolabeled protein was patent ineligible because the claims were directed to a law of nature and employed routine or conventional techniques.¹³⁵ The method was based on the discovery that 20% of Myasthenia Gravis patients have autoantibodies for muscle specific tyrosine kinase (“MuSK”) rather than acetylcholine.¹³⁶ Using this knowledge, the method called

¹³⁰ *Bristol-Myers Squibb Co.*, 2016 WL 1698385, at *1.

¹³¹ *Id.*

¹³² *Id.*

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ *Athena Diagnostics, Inc.*, 275 F. Supp. 3d at 310, 312.

¹³⁶ *Id.* at 307.

for diagnosing Myasthenia Gravis with a radiolabeled-MuSK fragment to detect MuSK autoantibodies.¹³⁷

The court reasoned that this interaction was a natural process, even though a man-made substance was used to observe it.¹³⁸ Furthermore, the court concluded that the useful discovery was the presence of MuSK autoantibodies in samples from Myasthenia Gravis patients, not the detection method.¹³⁹ In addition, unlike a method of preserving hepatocyte cells that went beyond the cells' ability to survive multiple freeze-thaw cycles by allowing for multiple-donor pools, the radiolabeled-MuSK did not provide new research tools or produce something useful aside from the diagnosis.¹⁴⁰ Therefore, the court found that the claims were directed to a patent ineligible law of nature, meeting the requirements of step one of the *Mayo/Alice* test.¹⁴¹ Also, the court held the claims patent ineligible at step two of the *Mayo/Alice* analysis because they specified "standard techniques in the art" to produce radiolabeled-MuSK.¹⁴²

C. Cancer Immunotherapy and the Nonobviousness Requirement

Although this article focuses on subject matter exceptions, it is worth mentioning a recent decision regarding cancer immunotherapy and nonobviousness.¹⁴³ In 2017, in *NantKwest, Inc. v. Lee*, the United States Court of Appeals for the Federal Circuit held

¹³⁷ *Id.* at 308.

¹³⁸ *Id.* at 310.

¹³⁹ *Id.* at 311 (citing *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1372 (Fed. Cir. 2015)).

¹⁴⁰ *Id.* at 311 (citing *Rapid Litig. Mgmt., Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048–49 (Fed. Cir. 2016)).

¹⁴¹ *Id.* at 312.

¹⁴² *Id.* at 312–13.

¹⁴³ *NantKwest, Inc.*, 686 Fed. App'x at 865.

that a method of using a type of innate immune cells known as natural killer cells to treat cancer was an obvious combination of prior art and therefore was patent ineligible.¹⁴⁴ The claims were for the use of a specific line of NK cells, NK-92, and called for administering the cells intravenously with a cytokine to promote NK cell expansion.¹⁴⁵ Due to two prior art references and the level of knowledge in the field at the time the patent applications were filed in 1997, the court held these claims invalid.¹⁴⁶

V. PENDING AND APPROVED PATENT APPLICATIONS FOR CAR-T CELL TREATMENTS

Several patent applications related to Kymriah are currently under review.¹⁴⁷ In addition, the USPTO has approved patents for chimeric T-cell receptors, including one that is the subject of ongoing litigation between Juno Therapeutics and Kite Pharma over Kite Pharma's lead product, Yescarta.¹⁴⁸

¹⁴⁴ *Id.*

¹⁴⁵ *Id.* at 866.

¹⁴⁶ *Id.* at 865–67.

¹⁴⁷ U.S. Patent App. No. 2017/0306416 (filed Oct. 26, 2017); U.S. Patent App. No. 2017/0296659 (filed Oct. 19, 2017); U.S. Patent App. No. 2017/0209492 (filed July 27, 2017); U.S. Patent App. No. 2017/0137783 (filed May 18, 2017); U.S. Patent App. No. 2016/0185861 (filed June 30, 2016); U.S. Patent App. No. 2016/0362472 (filed Dec. 15, 2016).

¹⁴⁸ U.S. Patent No. 7,446,190 (issued Nov. 4, 2008).

A. Pending Patent Applications for Kymriah

Though Kymriah already has FDA approval, its patent applications are still pending at the USPTO.¹⁴⁹ These include applications for compositions, methods, and combination therapies, as listed in the table below:¹⁵⁰

Publication Number	Publication Date	Title
US 2017/0209492 A1	07/27/2017	SUBSET-OPTIMIZED CHIMERIC ANTIGEN RECEPTOR-CONTAINING T-CELLS
US 2017/0306416 A1	10/26/2017	BIOMARKERS PREDICTIVE OF THERAPEUTIC RESPONSIVENESS TO CHIMERIC ANTIGEN RECEPTOR THERAPY AND USES THEREOF
US 2016/0185861 A1	06/30/2016	METHODS OF MAKING CHIMERIC ANTIGEN RECEPTOR -EXPRESSING CELLS
US 2017/0137783 A1	05/18/2017	METHODS FOR IMPROVING THE EFFICACY AND EXPANSION OF IMMUNE CELLS
US 2016/0362472 A1	12/15/2016	CD20 THERAPIES, CD22 THERAPIES, AND COMBINATION THERAPIES WITH A CD19 CHIMERIC ANTIGEN RECEPTOR (CAR)- EXPRESSING CELL
US 2017/0296659 A1	10/19/2017	COMBINATION THERAPIES

The claim for subset-optimized chimeric antigen receptor containing T-cells has a good chance of meeting the requirements for patentable subject matter.¹⁵¹ The T-cells likely will not be held patent ineligible solely for being “living organisms,” as the ruling in

¹⁴⁹ Bristol-Myers Squibb Co. v. Merck & Co., No. CV 15–572–GMS, 2016 WL 1698385, at *1 (D. Del. Mar. 29, 2016).

¹⁵⁰ *Id.*

¹⁵¹ See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 596 U.S. 576, 580 (2013) (stating that cDNA is patent eligible); *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (stating that genetically engineered bacteria are patent eligible).

Diamond v. Chakrabarty indicates, and the fact that they are a product of genetic engineering may support a conclusion that they are a “manufacture” or “composition of matter” under 35 U.S.C. § 101.¹⁵² In addition, the decision in *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.* also suggests a strong likelihood that the claim will be valid.¹⁵³ Similar to cDNA that was synthetically created in a lab, the subset-optimized chimeric antigen receptor containing T-cells are not a product of nature, and therefore would be patentable subject matter.¹⁵⁴

Additionally, although the use of a radiolabeled protein in a diagnostic method was patent ineligible in *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, that decision was based on the claim being directed to a law of nature and using conventional or routine techniques.¹⁵⁵ In contrast, the claim for subset-optimized chimeric antigen receptor containing T-cells is directed to a composition produced through genetic engineering, more along the lines of the bacteria in *Chakrabarty*, and using a new approach to manufacturing.¹⁵⁶ As a result, the *Athena Diagnostics, Inc.* reasoning is unlikely to apply to the claim for subset-optimized chimeric antigen receptor containing T-cells.¹⁵⁷

¹⁵² See *Chakrabarty*, 447 U.S. at 309–10 (holding that genetically engineered bacteria is a manufacture or composition of matter), 313 (highlighting the difference between products of nature and human-made inventions, not living things and inanimate objects, as important for determining subject matter eligibility).

¹⁵³ See *Ass’n for Molecular Pathology*, 596 U.S. at 580 (holding that cDNA is patentable subject matter).

¹⁵⁴ See *id.* at 595 (stating that DNA, a product of nature, becomes patent eligible when the noncoding sequences are removed to produce cDNA).

¹⁵⁵ *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, 275 F. Supp. 3d 306, 310, 312, (2017).

¹⁵⁶ See *Chakrabarty*, 447 U.S. at 309–10 (holding that genetically engineered bacteria is a manufacture or composition of matter).

¹⁵⁷ See *Athena Diagnostics, Inc.*, 275 F. Supp. 3d at 310 (concluding that using a radiolabeled protein does not transform a patent ineligible claim).

There is a strong possibility that many of the methods claims will be patentable subject matter as well, but it is less clear in light of the Supreme Court's interpretation of natural laws in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*¹⁵⁸ If the body's immune response is a law of nature, then the remaining aspects of the claim must be examined for an inventive concept.¹⁵⁹ Nonetheless, many of the remaining claims are still likely to be viewed as sufficiently inventive because CAR T-cell therapy is the first method to involve harvesting, modifying, and infusing T-cells in the treatment of cancer, and these steps do more than simply apply natural laws or abstract ideas.¹⁶⁰ Furthermore, the opinion in *Bristol-Myers Squibb Co. v. Merck & Co.* shows that even when T cell activation is found to satisfy step one of the *Mayo/Alice* test, determining whether cancer immunotherapy claims relying on T cell activation add "significantly more" to the concept is a complicated question, likely to be decided on a case-by-case basis.¹⁶¹

Lastly, Novartis's patent applications for Kymriah include claims to compositions containing a primary intracellular domain, CD3 ζ , and a secondary costimulatory signaling domain, CD28.¹⁶² These claims likely infringe on U.S. Patent 7,446,190 (the '190 patent),

¹⁵⁸ See *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 67 (2012) (holding that a method of adjusting drug dosage based on metabolite levels was patent ineligible because it claimed a law of nature).

¹⁵⁹ See *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (describing the second step of determining patent eligibility when a claim is directed to a judicial exception to section 101).

¹⁶⁰ See *Subject Matter Eligibility Examples: Life Sciences*, *supra* note 119, at 1, 9 (illustrating how diagnostic or treatment methods involving a section 101 exception can be patent eligible if limited by specific and unconventional reagents).

¹⁶¹ *Bristol-Myers Squibb Co.*, 2016 WL 1698385, at *1.

¹⁶² U.S. Patent App. No. 2017/0209492 (filed July 27, 2017).

“Nucleic Acids Encoding Chimeric T Cell Receptors,” granted to Memorial Sloan Kettering Cancer Center in 2003.¹⁶³ The ‘190 patent contains one independent claim for:

A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising:

- (a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain
- (b) a costimulatory signaling region, and
- (c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.¹⁶⁴

The ‘190 patent is licensed exclusively to Juno Therapeutics, Inc., and is the subject of current litigation between Juno Therapeutics and Kite Pharma, the manufacturer of Yescarta.¹⁶⁵ Approved patents for CAR-T cell therapies belonging to Juno Therapeutics and Kite Pharma, as well as litigation over the ‘190 patent, are discussed below.¹⁶⁶

B. Approved Patents for Chimeric T-Cell Receptors and Early Litigation Between Juno Therapeutics and Kite Pharma

The USPTO has granted several patents for chimeric T-cell receptors. Some examples include U.S. Patent 6,319,494, “Chimeric Chains for Receptor-Associated Signal Transduction Pathways” (the ‘494 patent), and U.S. Patent 7,741,465, “Chimeric

¹⁶³ See Juno Therapeutics, Inc. v. Kite Pharma, Inc., No. CV 17–07639 SJO (RAOx), 2018 WL 1470594, at *1 (C.D. Cal. Mar. 8, 2018) (describing the claim in the ‘190 patent).

¹⁶⁴ *Id.*

¹⁶⁵ *Id.*

¹⁶⁶ See *infra* notes 167–194 and accompanying text.

Receptor Genes and Cells Transformed Therewith” (the ‘465 patent), as well as the ‘190 patent, “Nucleic Acids Encoding Chimeric T Cell Receptors.”¹⁶⁷

Kite Pharma owns the ‘494 and ‘465 patents and challenged the ‘190 patent before the USPTO, filing a petition for *inter partes* review in August 2015.¹⁶⁸ The USPTO granted the petition, but upheld the validity of the ‘190 patent in a decision issued on December 16, 2016.¹⁶⁹ In response, Juno Therapeutics filed for declaratory judgment against Kite Pharma on December 19, 2016 in the United States District Court for the District of Delaware.¹⁷⁰ Juno Therapeutics contended that Kite Pharma’s lead product, Yescarta, infringed or would infringe on the ‘190 patent.¹⁷¹ The court dismissed the motion for declaratory judgment, not only on the grounds that the claim failed to meet the immediacy requirement necessary for subject matter jurisdiction, but also because it would allow Juno Therapeutics to circumvent the Safe Harbor Provision of the Patent Act.¹⁷²

Declaratory judgment is meant “to prevent avoidable damages from being incurred by a person uncertain of his rights and threatened with damage by delayed adjudication.”¹⁷³ In order to win declaratory judgment, the plaintiff must show the future

¹⁶⁷ U.S. Patent No. 7,741,465 (issued June 22, 2010); U.S. Patent No. 7,446,190 (issued Nov. 4, 2008); U.S. Patent No. 6,319,494 (issued Nov. 20, 2001).

¹⁶⁸ *Kite Pharma Announces Successful Defense of Roberts Patent and Intent to Appeal U.S. Patent and Trademark Office Decision on a Narrow Patent Focused on Select CD28 CAR-T Products*, BUS. WIRE (Dec. 19, 2016, 8:30 AM), <https://www.businesswire.com/news/home/20161219005607/en/Kite-Pharma-Announces-Successful-Defense-Roberts-Patent>.

¹⁶⁹ *Juno Therapeutics, Inc.*, 2017 WL 2559735, at *1.

¹⁷⁰ *Id.*

¹⁷¹ *Id.*

¹⁷² *Id.* at *3.

¹⁷³ *Id.* at *1 (quoting *Minnesota Min. & Mfg. Co. v. Norton Co.*, 929 F.2d 670, 673 (Fed. Cir. 1991)).

dispute has immediacy and reality based on the facts of the case.¹⁷⁴ Immediacy requires that the potential infringer has taken steps to manufacture or use the product; however, the case is less immediate the longer the time between when the motion was submitted and when infringement will occur.¹⁷⁵ Courts have found periods of nine and twelve months too long to meet the immediacy requirement.¹⁷⁶

In this case, the court concluded that there was a lack of immediacy to Kite Pharma's potential infringement of the '190 patent, despite Kite Pharma's having filed a Biologics License Application ("BLA") with the FDA.¹⁷⁷ Though an earlier decision found that a drug company filing an Abbreviated New Drug Application ("ANDA") with the FDA showed immediacy, the court ruled that the likelihood and timing of the FDA awarding a BLA was more speculative.¹⁷⁸ Whereas an ANDA allows for making and selling a generic version of an FDA-approved drug, a BLA would be the first instance of the drug getting FDA approval.¹⁷⁹ As a result, the timing and outcome of a BLA were not as certain, and the possibility of infringement was less immediate.¹⁸⁰ Also, six months had already passed since Juno Therapeutics filed suit, with no indication that the FDA would issue a decision on Kite Pharma's BLA in the immediate future.¹⁸¹

¹⁷⁴ *Id.* at *1.

¹⁷⁵ *Id.* at *2.

¹⁷⁶ *Id.*

¹⁷⁷ *Id.* at *3.

¹⁷⁸ *Id.* at *2 (citing *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1564 (Fed. Cir. 1997)).

¹⁷⁹ *Id.* at *3.

¹⁸⁰ *Id.*

¹⁸¹ *Id.*

In addition, the court held that granting Juno Therapeutics' motion for declaratory judgment would defeat the purpose of the Safe Harbor Provision of the Patent Act.¹⁸² The goal of the Safe Harbor Provision is to protect drug companies seeking FDA approval from litigation, so allowing a declaratory judgment action would run counter to that objective.¹⁸³

Four months after the court denied declaratory judgment to Juno Therapeutics, and ten months after the action was filed, Kite Pharma received FDA approval for Yescarta, making it the second CAR-T cell therapy approved in the United States.¹⁸⁴ On October 18, 2017, the FDA approved Yescarta for the treatment of certain types of large B-cell lymphomas in adult patients who have not responded or have relapsed after at least two other kinds of treatment.¹⁸⁵ As part of the approval, the FDA required a risk evaluation and mitigation strategy, including elements to assure safe use, and a post-marketing observational study for patients treated with Yescarta.¹⁸⁶ In addition, the FDA granted Priority Review, Breakthrough Therapy, and Orphan Drug designations to Yescarta.¹⁸⁷ Also, shortly before the FDA reached its decision, Gilead acquired Kite Pharma for \$11.9 billion.¹⁸⁸

¹⁸² *Id.*

¹⁸³ *Id.*

¹⁸⁴ *FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm> (last visited Oct. 18, 2017).

¹⁸⁵ *Id.*

¹⁸⁶ *Id.*

¹⁸⁷ *Id.*

¹⁸⁸ *Gilead Sciences Completes Acquisition of Kite Pharma, Inc.*, BUS. WIRE (Oct. 3, 2017, 8:45 AM), <https://www.businesswire.com/news/home/20171003005880/en/Gilead-Sciences-Completes-Acquisition-Kite-Pharma>.

Litigation between Juno Therapeutics and Kite Pharma continues.¹⁸⁹ The United States District Court for the Central District of California granted Juno Therapeutics' Motion to Dismiss Counterclaims and Strike Affirmative Defenses and denied Kite Pharma's Motion to Stay Proceedings in March 2018.¹⁹⁰

Though prior art was the sole theory that Kite Pharma used to challenge the validity of the '190 patent before the USPTO, it is possible that the company will bring up patentable subject matter as an invalidity defense in Juno Therapeutics' infringement suit.¹⁹¹ Kite Pharma appealed the outcome of the USPTO's *inter partes* review to the Federal Circuit, where oral arguments are expected to take place in Spring of 2018, with a decision following in the Fall.¹⁹² If the validity of the '190 patent is upheld, then Juno Therapeutics' infringement suit will continue, with Kite Pharma already having indicated that it would claim invalidity on any basis, including patentable subject matter.¹⁹³ Also, as litigation continues, it is possible that Novartis could join the infringement suit, given that Kymriah uses similar technology to that covered by the '190 patent.¹⁹⁴

¹⁸⁹ *Juno Therapeutics, Inc.*, 2018 WL 1470594, at *1–*2.

¹⁹⁰ *Id.* at *1.

¹⁹¹ *See id.* at *2, *4 (describing prior art as the basis for *inter partes* review before the USPTO and listing a number of patentability requirements in the invalidity counterclaim, including section 101).

¹⁹² *Id.* at *2.

¹⁹³ *Id.* at *4.

¹⁹⁴ *See* U.S. Patent No. 7,446,190 (issued Nov. 4, 2008); U.S. Patent App. No. 2017/0296659 (filed Oct. 19, 2017); U.S. Patent App. No. 2017/0209492 (filed July 27, 2017); U.S. Patent App. No. 2017/0137783 (filed May 18, 2017); U.S. Patent App. No. 2016/0362472 (filed Dec. 15, 2016); U.S. Patent App. No. 2016/0185861 (filed June 30, 2016).

CONCLUSION

The Cancer Immunotherapy Pilot Program allows fast-track review for methods of treating cancer using the immune system, such as CAR-T cell therapies. Applications filed through this program are subject to the same standards of review, so methods patents must meet the requirements of the *Mayo/Alice* test in order to be valid. In addition to the patentable subject matter issue, cancer immunotherapy patents also need to be nonobvious, as shown by the Federal Circuit's decision in *NantKwest, Inc. v. Lee* in 2017. Lastly, ongoing litigation between Juno Therapeutics and Kite Pharma suggests that claims to these technologies will be contested as CAR-T cell treatments move into the commercial mainstream.

From a policy point of view, if the goal of 35 U.S.C. § 101 is to encourage innovation through private investment, CAR-T cell therapies should be patentable. Even then, the expense of producing CAR-T cell treatments might incentivize companies to pursue private-public partnerships, such as the one between Novartis and the Centers for Medicaid & Medicare Resources, or updated funding models that can meet the challenges of bringing these treatments to patients.