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CLAIMING A CELL RESET BUTTON: INDUCED PLURIPOTENT STEM CELLS AND PREPARATION METHODS AS PATENTABLE SUBJECT MATTER

Abstract: In 2006, a team of scientists discovered a method to create pluripotent stem cells—cells that have the potential to become almost any other type of cell in the human body—by inserting specific genes into a skin cell. The resulting cells were called induced pluripotent stem cells (“iPS cells”). The ability to manufacture stem cells could eventually eliminate the need to harvest stem cells from embryos, thereby rendering the embryonic stem cell debate irrelevant. Should a patent claim directed toward an iPS cell-related technology be challenged in the future, the absence of a bright-line test for patentable subject matter could present challenges to the presiding court. This Note proposes two new standards by which courts should evaluate whether products of nature and processes in the life sciences are patentable subject matter and, applying those standards, concludes that sufficiently narrow claims directed to iPS cells and preparation methods would likely be upheld as patentable subject matter.

INTRODUCTION

The medical use of pluripotent stem cells was, for a time, one of the most contested bioethical issues in the United States.¹ Pluripotent stem cells are naturally occurring cells that have the potential to differentiate into almost any type of cell in the body.² Because of their unique differentiation capabilities, pluripotent stem cells have many different applications in medicine, including the treatment of various diseases through cell regeneration.³

¹ See President George W. Bush, Remarks on Stem Cell Research (Aug. 9, 2001), in THE PRESIDENT’S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH app. B (2004), available at https://bioethicsarchive.georgetown.edu/pcbe/reports/stemcell/appendix_b.html [<https://perma.cc/7UVZ-T8TH>] (explaining former President George W. Bush’s views against embryonic stem cell research); Mara Godoy et al., *Key Moments in the Stem Cell Debate*, NPR (Nov. 20, 2007), <http://www.npr.org/templates/story/story.php?storyId=5252449> [<http://perma.cc/6QG5-X8QN>] (outlining the scientific and political history of stem cell research); Paul Krzyzanowski, *Stem Cells: The Quiescent Issue in U.S. Elections*, SIGNALS (Sept. 20, 2012), <http://www.signalsblog.ca/stem-cells-the-quiescent-issue-in-us-elections/> [<http://perma.cc/87J3-AR8S>] (describing the stem cell debate as one of the dominant issues in pre-2012 U.S. presidential elections but “conspicuously absent” in the 2012 electoral debates).

² See Ian Murnaghan, *Multipotent Stem Cells*, EXPLORE STEM CELLS, <http://www.explorestemcells.co.uk/MultipotentStemCells.html> [<http://perma.cc/JVQ7-SRZ5>] (explaining the origin of pluripotent stem cells in the human embryo).

³ See *id.*

Under the right conditions, pluripotent stem cells can develop into specialized cells that can ultimately replace diseased cells and tissues.⁴

Prior to 2006, the only pluripotent stem cells in existence that could differentiate into nearly every type of bodily cell and that could be successfully maintained in a laboratory were embryonic stem cells (“ESCs”).⁵ Such stem cells, however, could not be harvested without destroying a human embryo.⁶ Opponents of stem cell research argue that unborn embryos should be protected and should not be sacrificed for medical purposes.⁷ Alternatively, proponents of stem cell research argue that the stem cell therapy should be explored and developed because stem cells have the potential to significantly improve the quality of life of many people with debilitating diseases.⁸ Because the harvesting and use of embryonic stem cells for medical research raises ethical questions, embryonic stem cell research has been the subject of intense political debate for nearly two decades.⁹

Since 2006, however, the debate surrounding embryonic stem cell research has been on a steady decline.¹⁰ This decline has not been fueled by

⁴ *See id.*; *What Are the Potential Uses of Human Stem Cells and the Obstacles That Must Be Overcome Before These Potential Uses Will Be Realized?*, NAT’L INSTS. OF HEALTH (Mar. 5, 2015), <http://stemcells.nih.gov/info/basics/pages/basics6.aspx> [<http://perma.cc/TJ4F-KMQ3>] [hereinafter *Potential Uses*] (outlining the conditions that can potentially be treated using pluripotent stem cells).

⁵ *See* Murnaghan, *supra* note 2. Although stem cells can also be harvested from the blood or organs of adults, ESCs have several advantages that make them better suited to scientific research. *See id.* ESCs can differentiate into almost any type of cell in the body, whereas adult stem cells can only differentiate into a limited number of cell types. *See id.* Moreover, ESCs are easily grown in a laboratory and are capable of almost unlimited division when placed in cell culture, whereas adult stem cells are not grown easily after isolation and do not multiply as readily. *See id.* Because stem cell research requires the generation of large numbers of cells, having cell lines that can grow and divide readily is critical for successful experimentation. *See id.* For this reason, ESCs are generally a better research tool than adult stem cells. *See id.*

⁶ *See* Murnaghan, *supra* note 2 (explaining how embryonic stem cells are obtained); *An Overview of Stem Cell Research*, CTR. FOR BIOETHICS & HUMAN DIGNITY, TRINITY INT’L UNIV. (Aug. 2009), <https://cbhd.org/stem-cell-research/overview> [<https://perma.cc/LH2C-GBG3>] (last updated Aug. 2009) (explaining how embryonic stem cells are obtained and the principal differences between embryonic and adult stem cells).

⁷ *See An Overview of Stem Cell Research*, *supra* note 6 (providing an overview of the ethical debate surrounding the use of embryonic stem cells for research purposes).

⁸ *See id.*

⁹ *See* John A. Robertson, *Embryo Stem Cell Research: Ten Years of Controversy*, 38 J.L., MED. & ETHICS 191, 191 (2010); *An Overview of Stem Cell Research*, *supra* note 6 (providing an overview of the ethical debate surrounding the use of embryonic stem cells for research purposes).

¹⁰ *See* Krzyzanowski, *supra* note 1 (describing the stem cell debate as one of the dominant issues in pre-2012 U.S. presidential elections but “conspicuously absent” in the 2012 electoral debates). *But see* John Farrell, *The Line Between Embryonic and Pluripotent Stem Cell Research Is Blurring*, FORBES (Sept. 28, 2012 12:35PM), <http://www.forbes.com/sites/johnfarrell/2012/09/28/the-line-between-embryonic-and-pluripotent-stem-cell-research-is-blurring/> [<http://perma.cc/P2DR-YCYE>] (arguing that iPS cells could also have the ability to create life, which would render the embryonic stem cell debate still relevant).

shifting ethical beliefs but has instead resulted from one of the most significant discoveries of the past century in the biological field.¹¹ In 2006, Dr. Shinya Yamanaka of the University of Kyoto was credited with discovering induced pluripotent stem cells (“iPS cells”).¹² Dr. Yamanaka inserted four genes into a skin cell, which essentially “reprogrammed” the skin cell to become a cell resembling a pluripotent stem cell.¹³ Because of Dr. Yamanaka’s discovery, there is a wide new range of scientific research on pluripotent stem cells that can now be carried out.¹⁴ Moreover, such research can be performed without confronting the major bioethical dilemma of destroying human embryos.¹⁵ Since Dr. Yamanaka’s discovery, the United States Patent and Trademark Office (“USPTO”) has granted patents on iPS

¹¹ See Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861, 861 (2007) [hereinafter Takahashi et al. 2007] (explaining how, using factors Oct3/4, Sox2, Klf4, and c-Myc, adult human fibroblasts were reprogrammed to become iPS cells, which resembled naturally occurring stem cells in morphology, gene expression, and proliferation, among other characteristics); Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Mouse Fibroblasts and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 663 (2006) [hereinafter Takahashi et al. 2006] (explaining that differentiated cells, such as fibroblasts, can be reprogrammed into an embryonic-like state); Paul Knoepfler, *Induced Pluripotent Stem Cells Are Similar to Cancer Cells, but Nobel Prize Still Well-Deserved*, HUFFINGTON POST (Oct. 12, 2012), http://www.huffingtonpost.com/paul-knoepfler/induced-pluripotent-stem-cells-cancer-cells_b_1926016.html [<http://perma.cc/S5PW-H5RT>] (discussing the impact of Dr. Yamanaka’s work on the field of stem cell research); Dan Vergano, *Al Gore on Board for \$20M Stem Cell Venture*, USA TODAY (Apr. 14, 2009), http://usatoday30.usatoday.com/tech/science/ethics/2009-04-14-gore-stem-cells_N.htm [<http://perma.cc/XP8H-FGCH>] (discussing the attraction of researchers and investors to emerging iPS cell technologies).

¹² See Takahashi et al. 2006, *supra* note 11, at 663; Gina Kolata, *Scientists Bypass Need for Embryo to Get Stem Cells*, N.Y. TIMES (Nov. 21, 2007), http://www.nytimes.com/2007/11/21/science/21stem.html?_r=1& [<http://perma.cc/4MGH-DBHV>] (describing iPS cells and how they were expected to impact the medical field); Alice Park, *A Breakthrough on Stem Cells*, TIME (Dec. 11, 2007), <http://content.time.com/time/health/article/0,8599,1685965,00.html> [<http://perma.cc/7XBX-VUCK>] (reporting the discovery of iPS cells).

¹³ See Takahashi et al. 2007, *supra* note 11, at 862 (observing that, two weeks following introduction of Oct3/4, Sox2, Klf4, and c-Myc into fibroblast cells, some clusters of cells appeared that did not resemble the original fibroblast cells, suggesting that the cells had been reprogrammed to a stem cell-like state); see also Takahashi et al. 2006, *supra* note 11, at 666 (observing that the same four factors used in mouse fibroblasts produced similar colonies, or clusters of cells, that did not resemble the original fibroblasts).

¹⁴ See Takahashi et al. 2007, *supra* note 11, at 862 (explaining that the reprogrammed fibroblasts resembled naturally occurring stem cells “in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes, and telomerase activity”); Kolata, *supra* note 12 (explaining that iPS cells are advantageous to researchers because they will genetically match the donor); Lori J. Schroth, *Researchers Create Embryonic Stem Cell Without Embryo*, HARV. GAZETTE (Jan. 29, 2014), <http://news.harvard.edu/gazette/story/2014/01/researchers-create-embryonic-stem-cells-without-embryo/> [<http://perma.cc/8QYV-Z3D2>] (discussing the possibility that researchers may one day be able to create stem cells from a person’s blood sample, which could allow scientists to create tissue specific to that individual).

¹⁵ See Takahashi et al. 2007, *supra* note 11, at 862; Kolata, *supra* note 12; Schroth, *supra* note 14.

cell lines, iPS cell preparation methods, and nuclear reprogramming factors.¹⁶

The U.S. Supreme Court has decided several patent cases in the past few decades relating to the patentability of life sciences inventions and methods.¹⁷ The Court has not, however, articulated a clear-cut standard as to what, in the context of life sciences products and methods, meets the patentable subject matter requirement.¹⁸ Courts have routinely found that products of nature are not patentable subject matter under 35 U.S.C. § 101.¹⁹ Despite this, in 1980 in *Diamond v. Chakrabarty*, the U.S. Supreme Court held that a bacterium with an inserted foreign gene is patentable subject matter.²⁰ An iPS cell is similar to the bacterium in *Chakrabarty* in the sense that both contain foreign genes.²¹ Unlike the bacterium, however, an iPS cell is meant to resemble an unpatentable natural product.²² Should a patent claim directed toward an iPS cell-related technology be challenged in the future on patentable subject matter grounds, such a challenge would present a unique dilemma to the presiding court.²³

This Note proposes new standards that courts should employ when considering challenges to iPS cell line patents and iPS cell preparation method patents based on the § 101 patentable subject matter requirement.²⁴ Part I provides an overview of the patentable subject matter requirement

¹⁶ See *infra* note 74 and accompanying text (explaining patents granted on iPS cell technologies).

¹⁷ See *infra* notes 95–122 and accompanying text (explaining case law addressing patentable subject matter in the context of the life sciences).

¹⁸ See *infra* notes 95–122 and accompanying text (explaining current status of standard for determining patentable subject matter in the context of the life science).

¹⁹ See 35 U.S.C. § 101 (2012) (identifying as patentable subject matter any “useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof”); *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (stating that “laws of nature, physical phenomena, and abstract ideas” are not patentable subject matter); *Parker v. Flook*, 437 U.S. 584, 598 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

²⁰ See *Chakrabarty*, 477 U.S. at 310 (stating that the patentee’s bacterium possessed “markedly different characteristics from any found in nature and one having the potential for significant utility” and that the bacterium was “not nature’s handiwork”).

²¹ See *id.* (explaining that the foreign genes the patentee inserted into the bacterium at issue enabled the bacterium to degrade hydrocarbons); Takahashi et al. 2007, *supra* note 11, at 862 (outlining the process by which the four reprogramming factors were introduced into fibroblast cells).

²² See Takahashi et al. 2007, *supra* note 11, at 861 (explaining that Oct3/4, Sox2, Klf4, and c-Myc were chosen over other reprogramming factors because fibroblasts reprogrammed with these four factors showed, over time, a high degree of similarity to naturally occurring stem cells).

²³ See *Chakrabarty*, 477 U.S. at 310 (finding a bacterium that contained foreign genes and that did not resemble any other bacterium found in nature was patentable subject matter); Takahashi et al. 2007, *supra* note 11, at 861–62 (explaining the discovery of iPS cells and how these cells contain foreign genes but do resemble other cells found in nature).

²⁴ See *infra* notes 149–207 and accompanying text.

and the invention of iPS cells.²⁵ Part II discusses the patentable subject matter requirement in the context of the life sciences.²⁶ Part III discusses the problem of patent thickets in the life sciences and how courts have handled the issue.²⁷ Part IV proposes two standards that can be used to evaluate whether patents on inventions that are derivatives of natural products and patents on biological methods are patentable subject matter.²⁸ Part V applies the two proposed standards to iPS cell technologies.²⁹ Finally, Part VI addresses the implications that a ruling upholding or invalidating claims to iPS cell technologies would have on the fields of biological research, medicine, and patent law.³⁰

I. INDUCED PLURIPOTENT STEM CELL TECHNOLOGY AND THE PATENTABLE SUBJECT MATTER REQUIREMENT: A BACKGROUND

Section A provides an overview of the patentable subject matter requirement.³¹ Section B discusses how the patentable subject matter requirement is applied to methods and processes.³² Section C discusses the development of induced pluripotent stem cells (“iPS cells”) and why the patentability of iPS cell lines and preparation methods remains unclear.³³

A. An Overview of the Patentable Subject Matter Requirement

Title 35 of the U.S. Code establishes the requirements for patentability.³⁴ In order for a technology to be patentable, the technology must be (1) useful, (2) novel, (3) nonobvious, and (4) patentable subject matter.³⁵

²⁵ See *infra* notes 34–79 and accompanying text.

²⁶ See *infra* notes 80–122 and accompanying text.

²⁷ See *infra* notes 123–148 and accompanying text.

²⁸ See *infra* notes 149–207 and accompanying text.

²⁹ See *infra* notes 208–233 and accompanying text.

³⁰ See *infra* notes 234–242 and accompanying text.

³¹ See *infra* notes 34–47 and accompanying text.

³² See *infra* notes 48–53 and accompanying text.

³³ See *infra* notes 54–79 and accompanying text.

³⁴ See 35 U.S.C. § 101 (setting forth patentability requirements).

³⁵ *Id.* The utility requirement for obtaining a patent is stated in 35 U.S.C. § 101. See *id.* An invention is “useful” if it provides some identifiable benefit and is capable of use. See *Brenner v. Manson*, 383 U.S. 519, 528–29 (1966) (holding that a novel process for synthesizing a steroid was not useful because the steroid served no known function); Utility Examination Guidelines, 66 Fed. Reg. 1092, 1092 (Jan. 5, 2001) (providing that a patent application must express a specific, credible, and substantial utility in order for the inventor to be awarded a patent). Because iPS cells show significant promise as a research tool and possible source of medical treatments, plaintiffs would not be likely to challenge iPS cell patents on utility grounds. See Takahashi et al. 2007, *supra* note 11, at 861; Monya Baker, *Adult Cells Reprogrammed to Pluripotency, Without Tumors*, NATURE REPORTS: STEM CELLS (Dec. 6, 2007), <http://www.nature.com/stemcells/2007/0712/071206/full/stemcells.2007.124.html> [<http://perma.cc/P5MJ-AMTZ>]. The novelty requirement provides that an invention is not patentable if it was known to the public prior to the patent’s

The patentable subject matter requirement dictates that only inventions that fall into one of four categories—processes, machines, manufactures, and compositions of matter—are eligible to be patented.³⁶ The purpose of the patentable subject matter requirement is to prevent a patent monopoly on certain tools that are necessary for inventors to create new and useful inventions.³⁷ The limits of these four categories are not perfectly clear, as Congress has left the courts with the task of defining what should be included under this statute.³⁸

Courts have historically construed the boundaries of patentable subject matter rather broadly.³⁹ Courts have created three categories of judicial exclusions to patentable subject matter: laws of nature, physical phenomena, and abstract ideas.⁴⁰ A claim directed toward an invention that falls within one of these three judicial exclusions is not patentable under § 101.⁴¹ In creating these judicial exclusions, courts sought to keep this subject matter in

priority date. 35 U.S.C. §§ 101–102 (2012). A patent, a patent application, or an invention that was known of or in use in the United States prior to the applicant priority date will render an invention non-novel. 35 U.S.C. §§ 101–102; *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966)) (explaining that proof of conception alone does not qualify as prior art). Additionally, an invention must be nonobvious, or “sufficiently inventive,” in order to be patented. 35 U.S.C. § 103.

³⁶ 35 U.S.C. § 101; *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2350 (2014) (explaining that the “buildin[g] block[s] of human ingenuity” are not patentable, whereas inventions “that integrate the building blocks into something more” may be patentable) (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1303 (2012) (finding invalid a patent claiming the correlation between concentrations of metabolites in the blood and the effectiveness of a drug)).

³⁷ *Alice*, 134 S. Ct. at 2350; see *Brenner*, 383 U.S. at 535 (explaining that the USPTO may not grant patent applications that are so broad they “engross” a field); Dmitry Karshtedt, *The Completeness Requirement in Patent Law*, 56 B.C. L. REV. 949, 953 (2015) (describing how the doctrines of utility, written description, and patentable subject matter are used to deem potentially problematic classes of inventions unpatentable).

³⁸ Anu R. Sawkar, *Are Storylines Patentable? Testing the Boundaries of Patentable Subject Matter*, 76 FORDHAM L. REV. 3001, 3009–12 (2008) (discussing the statutory framework of the patentable subject matter requirement); Brandon Smith, *The Patentability of Human Embryonic Stem Cells in Light of Myriad*, 96 J. PAT. & TRADEMARK OFF. SOC’Y 112, 117 (2014) (discussing how the lack of clarity surrounding the patentable subject matter requirement has left uncertain whether certain life sciences inventions are patentable).

³⁹ 35 U.S.C. § 101; see *Chakrabarty*, 447 U.S. at 309 (“Congress intended statutory subject matter to ‘include anything under the sun that is made by man.’” (quoting S. REP. NO. 82-1979, at 5 (1952))).

⁴⁰ See *Chakrabarty*, 447 U.S. at 309 (articulating three judicial exclusions to patentable subject matter); *Parker v. Flook*, 437 U.S. 584, 598 (1978) (offering a method of calculating alarm limit values to be not patentable subject matter); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) (establishing a mathematical formula used in connection with a computer to be an unpatentable process); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (determining claims directed to inoculants containing several species of nitrogen-fixing bacteria to be invalid).

⁴¹ See *Chakrabarty*, 447 U.S. at 309 (stating that laws of nature, natural phenomena, and abstract ideas cannot be patented); *Parker*, 437 U.S. at 598; *Gottschalk*, 409 U.S. at 67; *Funk Bros. Seed Co.*, 333 U.S. at 130.

the public domain and free from monopoly.⁴² Courts have not, however, articulated a bright-line standard beyond these three judicial exclusions.⁴³

The patentable subject matter requirement has been enmeshed in uncertainty in recent years.⁴⁴ In the field of biotechnology, inventions are often composed of or resemble products of nature.⁴⁵ In these cases, it is often unclear whether the invention falls within a judicial exception.⁴⁶ Because courts have not clearly defined the judicial exceptions to patentable subject matter, it is often difficult to determine whether a product or method patent in the biotechnology sphere is in fact patent-eligible subject matter.⁴⁷

B. The Patentable Subject Matter Requirement as Applied to Processes and Methods

Just as a patent can be obtained on an invention that is a physical product, inventors can also obtain patents on methods or processes, including the method or process by which a physical product is created or transformed.⁴⁸ Although courts have not developed a clear-cut test to assess whether meth-

⁴² See generally David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 1021 (2005) (arguing that limiting access to tools that are widely used to carry out various scientific research methods through granting patents on those tools will hinder innovation and technological process).

⁴³ See *Chakrabarty*, 447 U.S. at 309 (articulating the three judicial exclusions to patentable subject matter); *Parker*, 437 U.S. at 598 (“The line between a patentable ‘process’ and an unpatentable ‘principle’ is not always clear. Both are ‘conception[s] of the mind, seen only by [their] effects when being executed or performed.’” (quoting *Le Roy v. Tatham*, 55 U.S. 156, 175 (1852))); *Gottschalk*, 409 U.S. at 67 (explaining that although a law of nature cannot be patented, an invention may be patentable if it applies a law of nature “to a new and useful end” (quoting *Funk Bros. Seed Co.*, 333 U.S. at 130)).

⁴⁴ See 35 U.S.C. § 101; e.g., *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2119 (2013) (finding cDNA to be patentable subject matter despite containing naturally occurring nucleotide sequences); *Chakrabarty*, 447 U.S. at 310 (finding a bacterium with exogenous genes encoding hydrogen degradation pathway components to be patentable subject matter); see also *Parke-Davis & Co. v. H.K. Mulford* 196 F. 496, 500 (2d Cir. 1912) (finding isolated adrenaline to be patentable subject matter).

⁴⁵ See *Myriad*, 133 S. Ct. at 2119 (challenging patent claim directed to cDNA); U.S. Patent No. 7,514,258 (filed Apr. 7, 2009) (mammalian cultured inner cell mass cell culture using a quiescent cell as nuclear); U.S. Patent Application No. 09/255,233 (filed Feb. 22, 1999) (quiescent cell populations for nuclear transfer).

⁴⁶ 35 U.S.C. § 101; see *Myriad*, 133 S. Ct. at 2119 (finding cDNA to be patentable subject matter in spite of the fact that cDNA is composed of nucleotides, which are naturally occurring phenomena excluded from patentable subject matter); *Funk Bros. Seed Co.*, 333 U.S. at 130 (articulating three judicial patentable subject matter exclusions).

⁴⁷ 35 U.S.C. § 101; see *Myriad*, 133 S. Ct. at 2119 (finding cDNA, a sequence of naturally occurring nucleotides, not to be a natural phenomenon); *Funk Bros. Seed Co.*, 333 U.S. at 130 (outlining the three judicial exclusions without further elaborating on how to apply these exclusions).

⁴⁸ 35 U.S.C. § 101. One of the four categories of patentable subject matter under § 101 is processes. *Id.*

ods patents are patentable subject matter, several previous decisions provide guidance on this issue.⁴⁹ In 2008, in *In re Bilski*, the United States Court of Appeals for the Federal Circuit articulated a standard to determine whether a method is patentable subject matter, known as the machine-or-transformation test.⁵⁰ According to this standard, an invention is patentable subject matter if the invention is (1) tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.⁵¹

In 2010, in *Bilski v. Kappos*, the U.S. Supreme Court diluted the Federal Circuit machine-or-transformation test, changing it from a test to an investigative tool.⁵² The outcome of the machine or transformation test, according to the Court, correlates with, but does not indicate, the presence of patentable subject matter.⁵³

C. The Invention of iPS Cells

Pluripotent stem cells are cells that can differentiate into nearly any type of bodily, or somatic, cell.⁵⁴ These cells arise in the human embryo at a very early stage of development, only a few days following the fertilization of an egg cell.⁵⁵ Scientific researches have used the innate differentiating

⁴⁹ See *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008) (en banc) (establishing the machine-or-transformation test to determine patentability of methods), *aff'd*, *Bilski v. Kappos*, 561 U.S. 593 (2010) (rejecting machine-or-transformation test as the sole test for determining patentability of methods); see also *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336, 1349 (Fed. Cir. 2009) (applying the machine-or-transformation test to upheld a patent on a method for administering a drug), *vacated*, 561 U.S. 1040 (2010).

⁵⁰ *In re Bilski*, 545 F.3d at 954 (holding claim directed to hedging risk to be invalid); see Matthew Moore, *In re Bilski and the "Machine-or-Transformation" Test: Receding Boundaries for Patent-Eligible Subject Matter*, DUKE L. & TECH. REV. 005, at ¶¶ 8–12 (2010) (summarizing the Federal Circuit's explanation of the machine-or-transformation test and explaining the types of transformations that would be considered sufficient to satisfy the patentable subject matter requirement).

⁵¹ *In re Bilski*, 545 F.3d at 954. In 2009, the Federal Circuit decided *Prometheus Laboratories, Inc. v. Mayo Collaborative Services* and utilized the machine-or-transformation test set out in *Bilski*. See *Prometheus Laboratories*, 581 F.3d at 1349; *In re Bilski*, 545 F.3d at 954. In *Prometheus Laboratories*, the defendant held a patent on a method for administering a drug. See 628 F.3d 1347, 1349–50 (on remand from 561 U.S. 1040). The method involved measuring the level of metabolites of the drug in the bloodstream and increasing or decreasing the administered dose of the drug accordingly. See *id.* The Federal Circuit loosely applied the machine-or-transformation test set forth in *In re Bilski* and upheld the patent, stating that because the method involved a physical transformation, it therefore constituted patentable subject matter. See *id.* at 1355.

⁵² See *Bilski*, 561 U.S. at 604; Mark A. Lemley et al, *Life After Bilski*, 63 STAN. L. REV. 1315, 1315 (2011) (describing the machine-or-transformation test as a "presumptive starting point that threatens to effectively become mandatory"). The U.S. Supreme Court, however, upheld the invalidity of the patents at issue. See *Bilski*, 561 U.S. at 604.

⁵³ See *Bilski*, 561 U.S. at 604; Takahashi et al. 2007, *supra* note 11, at 861.

⁵⁴ See Murnaghan, *supra* note 2.

⁵⁵ See *id.* In order to understand the origin of embryonic stem cells, it is essential to consider the first steps of embryonic development. See *id.* After an egg is fertilized by a sperm, a single cell re-

ability of pluripotent stem cells to develop treatments for certain degenerative diseases.⁵⁶ When exposed to the right conditions, pluripotent stem cells can develop into healthy specialized cells that replace diseased cells and tissues.⁵⁷ In addition, as an alternative to testing drugs on animals, human pluripotent stem cells can be used in initial drug testing.⁵⁸ Drugs that are well tolerated by the cells can then progress to testing in animals and humans.⁵⁹

Prior to the invention of iPS cells, embryonic stem cells (“ESCs”) were arguably better suited for laboratory work than adult stem cells due to their ability to survive for longer durations in a laboratory and to differentiate into more different types of cells.⁶⁰ Despite the many applications and enormous potential benefits of stem cells in scientific research and medicine, embryonic stem cells have been at the center of political and ethical debate for over two decades.⁶¹ The ESCs used for laboratory research are harvested from embryos originally created for reproductive purposes through in vitro fertilization.⁶² In order to harvest stem cells, scientists must extract cells from the blastocyst, thereby destroying the embryo.⁶³ Because

sults. *See id.* This cell is totipotent, meaning it has the potential to differentiate into any type of cell. *See Stem Cell Classification*, BROWN UNIV., http://biomed.brown.edu/Courses/BI108/BI108_2002_Groups/pancstems/stemcell/stemcellclassversatility.htm [<http://perma.cc/NZ26-TJYQ>]. The original cell then divides several times into totipotent cells that are exact copies of the original. *See id.* Three to five days after fertilization, the totipotent cells begin to form a blastocyst, a cluster of cells that will eventually form most organs and tissues. *See Murnaghan, supra* note 2. It is these blastocyst cells that are pluripotent. *See id.*

⁵⁶ *See Murnaghan, supra* note 2; *Stem Cell Classification, supra* note 55.

⁵⁷ *See Stem Cell Classification, supra* note 55. Potential beneficiaries of stem cell regenerative treatment include individuals with severe burns, heart disease, spinal cord injuries, diabetes, Alzheimer’s, or Parkinson’s disease. *See id.*; *Potential Uses, supra* note 4.

⁵⁸ *See Murnaghan, supra* note 2.

⁵⁹ *See id.* Until 2006, scientists primarily worked with two types of stem cells: embryonic stem cells and adult stem cells. *See What Are the Similarities and Differences Between Embryonic and Adult Stem Cells?*, NAT’L INSTS. OF HEALTH (Mar. 3, 2015), <http://stemcells.nih.gov/info/basics/pages/basics5.aspx> [<http://perma.cc/ZYE7-6ESQ>].

⁶⁰ *See Murnaghan, supra* note 2.

⁶¹ *See Robertson, supra* note 9, at 191.

⁶² *What Are Embryonic Stem Cells?*, NAT’L INSTS. OF HEALTH (Mar. 4, 2015), <http://stemcells.nih.gov/info/basics/pages/basics3.aspx> [<http://perma.cc/9SZV-ZUQ4>]. When a couple that has pursued in vitro fertilization decides that they have completed their family and the remaining embryos are no longer needed for their original purpose, the donor has the option to donate the embryos for research. *Myths and Misconceptions About Stem Cell Research*, CAL. INST. FOR REGENERATIVE MED., <http://www.cirm.ca.gov/our-progress/myths-and-misconceptions-about-stem-cell-research> [<http://perma.cc/WTB6-MM4Z>] [hereinafter *Myths and Misconceptions*]. Individuals who have elected to pursue in vitro fertilization have several options regarding what to do with the remaining embryos once they have elected not to have more children. *Id.* One such option is to elect to store the embryos indefinitely at the couple’s own expense. *Id.* The cost of storing embryos, however, is very high. *Id.* The embryos can also be given to another infertile couple. *Id.* The two remaining options are to discard the excess embryos or to donate them for cell research. *Id.* Both of these options entail destroying the embryo. *See id.*

⁶³ *See Myths and Misconceptions, supra* note 62.

the destruction of any embryo raises ethical questions, the use of ESCs in order to better understand and treat certain diseases has been the subject of intense debate.⁶⁴ Consequentially, the level of federal funding devoted to stem cell research since 1998 has been sporadic, which has slowed progress in developing stem cell-based treatments.⁶⁵

Recently, scientists at the University of Kyoto developed a new technology called induced pluripotent stem cells (“iPS cells”), which could eventually render the embryonic stem cell debate irrelevant by eliminating the need to harvest stem cells from embryos.⁶⁶ In 2007, Dr. Shinya Yamanaka of the University of Kyoto developed a method to genetically reprogram human adult somatic cells to return them to a stem cell-like state.⁶⁷ Essentially, Dr. Yamanaka found a way to create stem cells, which he called iPS cells, from skin cells.⁶⁸ He did this by identifying four genes called

⁶⁴ See Robertson, *supra* note 9, at 191; *An Overview of Stem Cell Research*, *supra* note 6 (“We must not sacrifice one class of human beings (the embryonic) to benefit another (those suffering from serious illness).”); *Myths and Misconceptions*, *supra* note 62; *Obama Overturns Bush Policy on Stem Cells*, CNN (Mar. 9, 2009), <http://www.cnn.com/2009/POLITICS/03/09/obama.stem.cells/index.html> [<http://perma.cc/UX9R-JJPN>] (discussing President Obama’s stance on embryonic stem cell research, including his statement that “we have been given the capacity and will to pursue this research—and the humanity and conscience to do so responsibly”).

⁶⁵ See Robertson, *supra* note 9, at 191.

⁶⁶ See Takahashi et al. 2007, *supra* note 11, at 861.

⁶⁷ See *id.* In 2006, prior to developing human iPS cells, Dr. Yamanaka published a method for reprogramming skin cells, or fibroblasts, from mice to return them to a stem cell-like state. See Takahashi et al. 2006, *supra* note 11, at 663. To do so, Dr. Yamanaka identified 24 genes in mice known to be important for cellular development. See *id.* He then forced fibroblasts to express different combinations of these 24 genes. See *id.* at 664–65. This was done by engineering retroviruses to insert various combinations of these 24 genes into the mouse genome. See *id.* He found that when 4 genes called Oct3/4, Sox2, Klf4, and c-Myc were introduced in combination, the fibroblast was reprogrammed to resemble an embryonic cell. See *id.* at 666. The forced expression of those 4 genes essentially caused a skin cell to become a cell resembling a stem cell. See *id.*

⁶⁸ See Takahashi et al. 2007, *supra* note 11, at 861. Before examining how iPS cells were developed, it is important to understand how stem cells differ genetically from other types of bodily cells. See *id.*; *Gene Expression*, NATURE EDUC., <http://www.nature.com/scitable/topicpage/gene-expression-14121669> [<http://perma.cc/UY32-56YB>]. Each cell in the human body generally has the same genetic content. See Barry Starr, *DNA Basics*, STANFORD AT THE TECH: UNDERSTANDING GENETICS, <http://genetics.thetech.org/ask/ask4> [<http://perma.cc/694U-8UER>]. Skin cells, heart muscle cells, and liver cells, for example, have the same DNA. See *id.* What makes these cells different is that different genes are “turned on,” or expressed, in each cell type. See *id.* When a gene is expressed, a certain protein is in turn produced, which allows the cell to perform its function. See *id.* Genes encoding the protein hemoglobin, for example, need to be expressed in red blood cells, as hemoglobin is involved in carrying oxygen to cells. See *id.* In contrast, these same genes encoding hemoglobin are “turned off,” or silenced, in cells in the eye because oxygen transport is not a function of eye cells. See *id.* The combination of genes that are turned on and off is referred to as a cell’s gene expression pattern. See John P.T. Higgins, et al., *Gene Expression Patterns in Renal Cell Carcinoma Assessed by Complementary DNA Microarray*, 162 AM. J. PATHOLOGY 925, 925 (2003). Just as muscle cells and liver cells possess certain characteristics based on their gene expression pattern, the ability of a pluripotent stem cell to differentiate into a somatic cell is also attributed to its gene expression pattern. See Starr, *supra*. That is, the genes

Oct3/4, Sox2, Klf4, and c-Myc that are important for maintaining the properties of a stem cell.⁶⁹ These genes were subsequently inserted into a skin cell, or fibroblast, using a genetically engineered virus.⁷⁰ The resulting iPS cells demonstrated an ability to differentiate into many types of somatic cells.⁷¹ Because of their stem cell-like character, iPS cells could effectively end the embryonic stem cell debate, as scientists would no longer need to harvest embryonic cells in order to develop stem cell therapies.⁷²

that are expressed in a stem cell enable the stem cell to become almost any cell in the body under the right circumstances. *See id.* Dr. Yamanaka's goal was to determine what combination of expressed genes enables the stem cell to maintain its pluripotent state. *See generally* Baker, *supra* note 35 (explaining the techniques by which teams led by Dr. Yamanaka and Dr. James Thomson reprogrammed fibroblast cells). In other words, he sought to determine which genes need to be "turned on" in order for a cell to be a stem cell. *See* Takahashi et al. 2007, *supra* note 11, at 861; Takahashi et al. 2006, *supra* note 11, at 663. According to Dr. Yamanaka's logic, if a skin cell, for example, could be forced to express the genes that stem cells typically express, the skin cell would then become a stem cell. *See* Takahashi et al. 2007, *supra* note 11, at 861; Takahashi et al. 2006, *supra* note 11, at 663. This process of forcing cells to express certain genes is called cellular reprogramming. *See* Takahashi et al. 2007, *supra* note 11, at 861; Takahashi et al. 2006, *supra* note 11, at 673.

⁶⁹ *See* Takahashi et al. 2007, *supra* note 11, at 861.

⁷⁰ *See id.* at 863. A virus is essentially a piece of DNA encapsulated in a protein shell. *How Are Genes Engineered?*, PHYSICIANS AND SCIENTISTS FOR RESPONSIBLE APPLICATION OF SCI. AND TECH., <http://www.psrast.org/whisge.htm> [<http://perma.cc/QL6U-89VC>]. Viruses have the capability of injecting their genetic material into cells. *See* J. Stern Carter, *Viruses*, UNIV. OF CINCINNATI AT CLERMONT DEP'T OF BIOLOGY (Jan. 16, 2014), <http://biology.clc.uc.edu/courses/bio106/viruses.htm> [<http://perma.cc/DJK3-QSF5>]. The cells then produce the proteins that the viral genes encode. *See id.* In the method described in Dr. Takahashi and colleagues' 2006 publication, the harmful retroviral genes were removed from the viral protein shell, and Oct3/4, Sox2, Klf4, and c-Myc were inserted into the virus. *See* Takahashi et al. 2006, *supra* note 11, at 664–65; A.G. Uren et al., *Retroviral Insertional Mutagenesis: Past, Present, and Future*, 24 ONCOGENE 7656, 7656 (2005). This process is called retroviral gene therapy. *See* Donald S. Anson, *The Use of Retroviral Vectors—What Are the Risks? A Review of Retroviral Pathogenesis and Its Relevance to Retroviral Vector-Mediated Gene Delivery*, 2:9 GENETIC VACCINES & THERAPY (2004), <http://www.gvt-journal.com/content/pdf/1479-0556-2-9.pdf> [<http://perma.cc/XEQ9-HW4N>].

⁷¹ *See* Takahashi et al. 2007, *supra* note 11, at 863–65. The cells were left to grow in culture for eight days, and it was observed that the cells began to show similar gene expression patterns as other types of somatic cells, including heart muscle cells and neurons. *See id.* This result suggested that Dr. Yamanaka's iPS cells had the potential to differentiate into various types of somatic cells and had thereby acquired stem cell character. *See id.*

⁷² *See id.* at 861. In 2012, Dr. Yamanaka won the Nobel Prize in Physiology or Medicine for the development of human iPS cells. *Shinya Yamanaka—Facts*, THE NOBEL MUSEUM, http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/yamanaka-facts.html [<http://perma.cc/QX23-8JCN>]. Nearly concurrently in 2007, Dr. James Thomson and his colleagues at the University of Wisconsin published a similar method for developing iPS cells. *See* Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCI. 1917, 1917 (2007). Instead of inducing the expression of Klf4 and c-Myc in fibroblasts, Dr. Thomson induced the expression of the Nanog and Lin28 genes along with Oct3/4 and Sox2. *Id.* Like the cells developed by Dr. Yamanaka, the cells developed by Dr. Thomson also behaved like ESCs in cell culture and exhibited gene expression patterns of different somatic cell types, which suggested that Dr. Thomson's iPS cells were pluripotent. *Id.* Thomson's findings that cells could be reprogrammed without the insertion of c-Myc and Klf4 was significant because c-Myc and Klf4 are

In the past eight years since Dr. Yamanaka's discovery, the United States Patent and Trademark Office ("USPTO") has issued over 100 patents related to iPS cell technologies.⁷³ The subject matter claimed in these patents is directed toward several categories of technology related to iPS cells, including methods to develop human iPS cells from somatic cells, products comprising iPS cells, including iPS cells produced by various claimed methods, and nuclear reprogramming factors.⁷⁴ The term "nuclear reprogramming factor" in the context of existing patents refers to a virus containing a certain combination of genes that are inserted into the cell and thereafter expressed, which ultimately results in somatic cell reprogramming.⁷⁵

As more scientists begin to use iPS cells as a research tool and develop medical treatments based on this patented technology, it is very possible that the validity of many of these patents will eventually be challenged.⁷⁶ The current statutes and case law governing the patentability requirements make unclear whether iPS cell technologies would be patentable.⁷⁷ Although it can be argued that iPS cells are a natural phenomenon because they resemble naturally occurring pluripotent stem cells, they

oncogenes, meaning that their insertion into the cellular genome can cause cancer. See Baker, *supra* note 35; C.E. Pasi et al., *Genomic Instability in Induced Stem Cells*, 18(5) CELL DEATH AND DIFFERENTIATION 745, 745 (2011).

⁷³ U.S. Patent Full-Text and Image Database, U.S. PATENT & TRADEMARK OFFICE, <http://patft.uspto.gov/netahtml/PTO/search-bool.html> (enter text "induced pluripotent stem cell" with quotations in Term 1 field, press "search").

⁷⁴ U.S. Patent No. 8,048,999 (issued Nov. 1, 2011); Bilyana P. Georgieva & Jane M. Love, *Human Induced Pluripotent Stem Cells: A Review of the U.S. Patent Landscape*, 5 REGENERATIVE MED. 581, 581 (2010). See generally K. Triller Vrtovec & B. Vrtovec, *Patent Eligibility of Induced Pluripotent Stem Cell Theranostics*, 93 CLINICAL PHARMACOLOGY & THERAPEUTICS 318, 319 (2013) (listing patents granted on iPS cell technologies in the United States). Dr. Yamanaka filed three patent applications in the United States on December 13, 2005, claiming: nuclear reprogramming factors comprising different combinations of the genes Oct3/4, Sox2, Klf4, and c-Myc; methods of preparing iPS cells through nuclear reprogramming; and a method of inducing differentiation of iPS cells. Brenda Simon et al., *Pluripotent Patents Make Prime Time: An Analysis of the Emerging Landscape*, 28 NATURE BIOTECHNOLOGY 557, 559 (2010). Seven U.S. patents relating to iPS cell technologies were granted to Kyoto University in 2011 and 2012. Vrtovec & Vrtovec, *supra*, at 319. Dr. James Thomson was granted a U.S. patent in March of 2012, which claims a method of creating a population of primate pluripotent neural stem cells from iPS cells. U.S. Patent No. 8,133,731 (issued Mar. 13, 2012); Simon et al., *supra*, at 559. In March of 2010, a patent was granted to Rudolf Jaenisch claiming a somatic cell comprising in its genome a pluripotency gene, wherein the pluripotency gene is a gene that is expressed in a pluripotent embryonic cell, is required for the pluripotency of the embryonic stem cell, and is down-regulated as the embryonic stem cell differentiates. U.S. Patent No. 7,682,828 (issued Mar. 23, 2010).

⁷⁵ '999 Patent.

⁷⁶ See Paul Knoepfler, *Putting the IP in iPS Cells: A Patent War Looming?*, KNOEPFLER LAB STEM CELL BLOG (May 13, 2013), <http://www.ipscell.com/2013/05/putting-the-ip-in-ips-cells-patent-war-looming/> [<http://perma.cc/7WRS-4DMT>] (discussing a filed complaint challenging patent claims related to iPS cell technologies).

⁷⁷ See *infra* notes 80–122 and accompanying text.

are also a synthetic creation made in a laboratory.⁷⁸ Because iPS cell lines do not fit neatly within a judicial exclusion to patentable subject matter, a challenge to an iPS cell patent would present a particularly unique challenge to courts.⁷⁹

II. APPLICATION OF THE PATENTABLE SUBJECT MATTER REQUIREMENT IN LIFE SCIENCES

Although no bright-line standard has been developed to assess whether an invention in the life sciences field is patentable subject matter, the Federal Circuit and the U.S. Supreme Court have issued a few crucial decisions that provide guidance as to when an invention that is derived from a naturally occurring product is considered patentable subject matter.⁸⁰ Section A will discuss the early applications of patentable subject matter in life sciences.⁸¹ Section B will discuss how the U.S. Supreme Court applied the patentable subject matter requirement to DNA claims in *Association for Molecular Pathology v. Myriad Genetics, Inc.*⁸² Section C will discuss the Interim Guidance on Patent Subject Matter Eligibility issued by the United States Patent and Trademark Office (“USPTO”) in December, 2014.⁸³

A. Applications of Patentable Subject Matter in Life Sciences Pre-Myriad

In 1911 in *Parke-Davis & Co. v. H.K. Mulford Co.*, the United States District Court for the Southern District of New York decided one of the first major cases relating to biotechnology as patentable subject matter.⁸⁴ Judge Learned Hand upheld the validity of a patent on a purified and isolated form of adrenaline based upon certain structural differences between the purified and naturally occurring forms of adrenaline.⁸⁵ The notion that a structural distinction between an original product and a purified product is sufficient

⁷⁸ See Takahashi et al. 2007, *supra* note 11, at 862 (explaining that iPS cells are composed of a human fibroblast and four reprogramming factors).

⁷⁹ See 35 U.S.C. § 101; *Funk Bros. Seed Co.*, 333 U.S. at 130 (articulating the three judicial exclusions to patentable subject matter); Takahashi et al. 2007, *supra* note 11, at 862 (explaining the method by which iPS cells were created by Dr. Yamanaka’s laboratory).

⁸⁰ See *infra* notes 84–122 and accompanying text.

⁸¹ See *infra* notes 84–94 and accompanying text.

⁸² See *infra* notes 95–103 and accompanying text.

⁸³ See *infra* notes 104–122 and accompanying text.

⁸⁴ *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911), *aff’d in part, rev’d in part*, 196 F. 496 (2d Cir. 1912) (addressing novelty, not patentable subject matter).

⁸⁵ *Id.* The court concluded that the patented purified extract was not, in fact, different from the prior art “only for a degree of purity,” but rather was a different chemical substance from that found in the prior art. *Id.* at 114–15 (discussing how no one had ever isolated a substance produced by the adrenal glands that was not in salt form and that the claimed base form of adrenaline was an original production of the patentee).

to uphold a patent was reinforced in 1938 by the United States Court of Customs and Patent Appeals, in *In re Merz*, wherein the Court of Customs and Patent Appeals ruled that if the purified product differs from the original not only in degree but in kind, it may be patentable.⁸⁶

Nearly seventy years later in 1980, in *Diamond v. Chakrabarty*, the U.S. Supreme Court held that a bacterium with an inserted plasmid containing genes that are not naturally occurring in the plasmid is patentable subject matter.⁸⁷ Prior to *Chakrabarty*, it was generally understood that living things were not patentable subject matter.⁸⁸ Here, the Court emphasized that because the bacterium contained inserted genetic material that was not native to the bacterium, it was a non-natural manufacture or composition of matter and a product of human ingenuity.⁸⁹

In *Chakrabarty*, the patent examiner initially rejected the petitioner's claims to the bacterium, stating that the bacterium did not constitute patentable subject matter on two grounds: 1) that bacteria are products of nature, and 2) that bacteria are living things.⁹⁰ The U.S. Supreme Court rejected both of these grounds and found the bacterium to be patentable subject matter, reasoning that the petitioner's new bacterium had markedly different characteristics from any organism found in nature, and the invented bacterium, according to the Court, had the potential for significant practical utility.⁹¹

The broad language that the Court used in *Chakrabarty* has made its logic difficult to apply to other life sciences inventions.⁹² The Court stated

⁸⁶ *In re Merz*, 97 F.2d 599, 601 (C.C.P.A. 1938) (finding a purified substance with a greater degree of purity than any product previously produced to be patentable subject matter).

⁸⁷ *Diamond v. Chakrabarty*, 447 U.S. 303, 309–10 (1980); Anna Lumelsky, *Diamond v. Chakrabarty: Gauging Congress's Response to Dynamic Statutory Interpretation by the Supreme Court*, 39 U.S.F. L. REV. 641, 643–48 (2005) (discussing the Supreme Court's interpretation of 35 U.S.C. § 101 in *Chakrabarty*). Plasmids are units of genetic material physically separate from the bacterium's chromosomes. *Chakrabarty*, 447 U.S. at 310 n.1. The patentee discovered a process by which four plasmids could be transferred to a *Pseudomonas* bacterium. *Id.* The resulting bacterium possessed the ability to degrade oil. *Id.*

⁸⁸ *Chakrabarty*, 447 U.S. at 309–10; Smith, *supra* note 38, at 117.

⁸⁹ *Chakrabarty*, 447 U.S. at 309–10. In his dissent, Justice Brennan stated that § 101 does not include living organisms. *Id.* at 320 (Brennan, J., dissenting); see also 35 U.S.C. § 101 (2012). He reasoned that because Congress created separate statutes to render agricultural inventions patentable, the lack of legislation governing the patentability of bacteria is indicative of Congress's intent to exclude bacteria from patentable subject matter. *Chakrabarty*, 447 U.S. at 320 (Brennan, J., dissenting).

⁹⁰ See *Chakrabarty*, 447 U.S. at 306.

⁹¹ See *id.* at 310 (explaining that because the patentee's bacterium possessed "markedly different characteristics" than any found in nature, it is patentable subject matter).

⁹² See *id.*; Brent J. Jensen, *Live, Human-Made Bacteria as Patentable Subject Matter Under 35 U.S.C. § 101*; *Diamond v. Chakrabarty*, 1980 BYU L. REV. 705, 712 (arguing that developing the markedly different characteristics test was unnecessary because *Chakrabarty's* bacterium, which, according to the author, was more practically useful than the unmodified bacterium, fit into

that the bacterium at issue in *Chakrabarty* did not share characteristics with any bacterium found in nature.⁹³ The Court did not clarify, however, whether the bacterium at issue would have been patentable subject matter had it *only* possessed characteristics that were markedly different from the bacterium from which it was derived, and not from all bacteria found in nature.⁹⁴

B. The Patentable Subject Matter Requirement as Applied to DNA in Association for Molecular Pathology v. Myriad

In 2013, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court was faced with the question of whether a purified and isolated substance constitutes patentable subject matter.⁹⁵ In *Myriad*, the defendant offered diagnostic tests for mutations in the BRCA1 and BRCA2 genes.⁹⁶ Such mutations put women at an exceptionally high risk for breast and ovarian cancer.⁹⁷ Myriad held patents claiming 1) the sequence of the BRCA1 and BRCA2 genes, and 2) the complementary DNA (“cDNA”) of the BRCA1 and BRCA2 genes.⁹⁸

the definition of “manufacture” set out in 35 U.S.C. § 101); Smith, *supra* note 38 (explaining that *Chakrabarty* does not make clear whether iPS cell technologies would be patentable).

⁹³ *Chakrabarty*, 447 U.S. at 310.

⁹⁴ *See id.*

⁹⁵ *See* *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2113 (2013); Tup Ingram, *Association for Molecular Pathology v. Myriad Genetics, Inc.: The Product of Nature Doctrine, Revisited*, 29 BERKELEY TECH. L.J. 385, 387 (2014) (describing the potential implications of the *Myriad* ruling).

⁹⁶ *See Myriad*, 133 S. Ct. at 2112; Sarah Elizabeth Hagan, *DNA Real Estate: The Myriad Genetics Case and the Implications of Granting Patent Eligibility to Complementary DNA*, 35 N. ILL. U. L. REV. 205, 221 (2014) (stating the concern that patents on genetic testing could increase the cost of such tests, which would harm both the public and the scientific community).

⁹⁷ *See Myriad*, 133 S. Ct. at 2112–13.

⁹⁸ *See id.* at 2113. Two steps must occur in order for a protein to be created from DNA: transcription and translation. *See Ribosomes, Transcription and Translation*, NATURE EDUC., <http://www.nature.com/scitable/topicpage/ribosomes-transcription-and-translation-14120660> [<http://perma.cc/AX7X-6WXX>]. DNA is a double-stranded molecule containing the nucleotides adenine, guanine, thymine, and cytosine. *See id.* An adenine molecule on one strand of DNA will always bind to thymine on the opposite strand of DNA, and cytosine will always bind with guanine. *See id.* During transcription, the two strands of DNA are “unzipped,” and a complementary strand of RNA forms opposite each strand of DNA. *See id.* This complementary strand is called messenger RNA, or mRNA. *See id.* Once the mRNA is transcribed, it is processed. *See id.* Certain segments of the DNA are removed from the sequence, and the remaining segments, called exons, are spliced together. *See Ribosomes, Transcription and Translation, supra.* The cDNA, which was claimed in the defendant’s patent, is the DNA complement of processed mRNA. *See Myriad*, 133 S. Ct. at 2111; *cDNA Production*, DAVIDSON COLL. DEP’T OF BIOLOGY (2002), <http://www.bio.davidson.edu/genomics/method/cDNAproduction.html> [<http://perma.cc/VDQ9-KC8S>]. Although the genes contained in cDNA exist in nature, cDNA itself does not exist in nature and is a synthetic creation by scientists. *See Myriad*, 133 S. Ct. at 2119; DAVIDSON COLL. DEP’T OF BIOLOGY, *supra*. In *Myriad*, the Court reasoned that the BRCA genes contained in the form of cDNA can be patented because cDNA does not exist in nature. *See* 133 S. Ct. at 2119.

The Court held that the sequence of the BRCA genes was a naturally occurring segment and was not merely patent-eligible through isolation.⁹⁹ Justice Thomas explained that although Myriad had discovered the locus of the BRCA genes, Myriad did not do anything further to alter the genes.¹⁰⁰ The Court did, however, find that cDNA was patent eligible because it was a synthetic creation that did not occur in nature.¹⁰¹ To the Court, the principal difference between the cDNA and the naturally occurring gene, aside from cDNA not occurring in nature, was that only DNA contained introns, or “junk” regions of DNA that do not encode proteins and are eventually removed from the genetic transcript by the cell.¹⁰² Although cDNA contains the same functional genetic material as DNA, encodes the same proteins, and thereby essentially performs the same function, only cDNA, according to the Court, was patentable subject matter.¹⁰³

C. Interim Guidance by the USPTO

On December 16, 2014, the USPTO released interim guidance on patent subject matter eligibility (“Guidance”).¹⁰⁴ In the Guidance, the USPTO sets forth a three-step test for determining whether a product or process is patentable subject matter under § 101.¹⁰⁵

The first step requires an examiner to determine whether the claim is directed to a process, machine, manufacture, or composition of matter.¹⁰⁶ If the claim is not so directed, the claim is not eligible subject matter under

⁹⁹ See *Myriad*, 133 S. Ct. at 2118.

¹⁰⁰ See *id.* at 2116 (explaining that § 101 prevents the tools of innovation from being “tie[d] up”); *id.* at 2118 (noting how Myriad’s claims only listed the steps it took to discover gene sequences and did not “rely in any way on the chemical changes that result from the isolation of a particular section of DNA”).

¹⁰¹ See *id.* at 2119.

¹⁰² *Id.*; Reply Brief for Petitioners at 9–10, *Myriad*, 133 S. Ct. 2107 (No. 12-398), 2013 WL 1850746, at *9 (explaining the difference between DNA and cDNA).

¹⁰³ See *Myriad*, 113 S. Ct. at 2119; Reply Brief for Petitioners, *supra* note 102, at 9–10.

¹⁰⁴ Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74, 618 (Dec. 16, 2014) (to be codified at 37 C.F.R. 1). This guidance became effective on December 16, 2014, and applies to all applications filed before, on, or after December 16, 2014. *Id.* The Guidance was prepared for use by USPTO personnel in determining subject matter eligibility under § 101 and was intended to supplement the guidance on preliminary examinations issued by the USPTO in June 2014. *Id.*; ANDREW H. HIRSCHFIELD, U.S. PATENT & TRADEMARK OFFICE, PRELIMINARY EXAMINATION INSTRUCTIONS IN VIEW OF THE SUPREME COURT DECISION IN *ALICE CORPORATION PTY. LTD. V. CLS BANK INTERNATIONAL, ET AL.* (June 25, 2014), http://www.uspto.gov/sites/default/files/patents/announce/alice_pec_25jun2014.pdf [<http://perma.cc/V47L-TRW2>]. This test does not constitute statutory law or binding precedent. Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

¹⁰⁵ Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 622.

¹⁰⁶ *Id.* Claims directed to these categories are patentable under 35 U.S.C. § 101. See *id.*

§ 101.¹⁰⁷ The second step requires a determination as to whether the claim is directed to a law of nature, a natural phenomenon, or an abstract idea.¹⁰⁸ If the claim is not directed to one of these categories, the claim is eligible subject matter.¹⁰⁹ If the claim is directed to one of these categories, the examiner should carry out the third step of the test, which requires the examiner to determine whether the claim recites additional elements that amount to significantly more than the judicial exception.¹¹⁰ “Judicial exception” in the context of the third step refers to each of the three categories listed in the second step.¹¹¹

The Guidance sets out examples of considerations identified by the U.S. Supreme Court for determining whether a claim amounts to “significantly more” than the judicial exception.¹¹² Examples of limitations that qualify as “significantly more” include improvements to another technology or technical field, applying the judicial exception with a particular machine, effecting a transformation or reduction of a particular article to a different state or thing, and adding a specific limitation other than what is conventional in the field.¹¹³

Although the Guidance attempts to create a bright-line test for determining patentable subject matter, the test set out by the Guidelines does not clarify the uncertainty that has surrounded the patentable subject matter requirement since the *Myriad* decision.¹¹⁴ For example, the Guidance seem-

¹⁰⁷ 35 U.S.C. § 101 (defining patent eligible subject matter); Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 622.

¹⁰⁸ Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 622 (explaining that courts are careful when deciding if a claim falls under a judicial exception “because at some level all inventions embody, use, reflect, rest upon, or apply a law of nature, natural phenomenon, or abstract idea”).

¹⁰⁹ 35 U.S.C. § 101 (defining patent eligible subject matter); Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

¹¹⁰ Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 622–23 (outlining the “markedly different characteristics analysis,” which “compares the nature-based product limitation to its naturally occurring counterpart in its natural state,” unless there is no naturally occurring counterpart, in which case “the comparison should be made to the closest naturally occurring counterpart”).

¹¹¹ *Id.* Laws of nature, abstract ideas, and natural phenomenon are the three categories defined by courts to be unpatentable subject matter. See *supra* note 40 and accompanying text (outlining the three categories of judicial exclusions).

¹¹² Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 624.

¹¹³ *Id.* Examples of limitations that were found not to qualify as “significantly more” include mere instructions to implement an abstract idea on a computer, appending well-understood activities previously known to the industry, adding insignificant activity to the judicial exception, and generally linking the use of the judicial exception to a particular technological environment or field of use. *Id.*

¹¹⁴ *Myriad*, 133 S. Ct. at 2119 (finding cDNA to be patentable subject matter despite containing naturally occurring nucleotide sequences); Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

ingly conflicts with *Myriad* with regard to whether the “markedly different characteristics” analysis should be applied.¹¹⁵ The Guidance indicates that nature-based products are subject to the markedly different characteristics analysis used to identify exceptions to the judicial exclusions.¹¹⁶ According to the markedly different characteristics test, a claim directed to a nature-based product that does not exhibit markedly different characteristics from its naturally occurring counterpart falls into a judicial exclusion category and is not patentable subject matter unless it recites elements that amount to “significantly more” than the judicial exception.¹¹⁷

The presence of the markedly different characteristics test in the Guidance is seemingly inconsistent with prior case law.¹¹⁸ The markedly different characteristics test was mentioned in *Chakrabarty* as dictum, but it was not used to determine whether the bacterium at issue constituted patentable subject matter.¹¹⁹ Furthermore, this test was not used or mentioned in *Myriad*.¹²⁰ If this test had been utilized, the court would have likely reached the opposite result with regard to the cDNA claims.¹²¹ Due to this inconsistency between the Guidance and prior precedent, the Guidance does not provide much clarity as to how the patentable subject matter requirement should be applied to inventions in the life sciences.¹²²

¹¹⁵ *Myriad*, 133 S. Ct. at 2119 (reasoning that because cDNA is a man-made construct, it is patentable subject matter in spite of the fact that it encodes the same proteins as naturally occurring DNA sequences); Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

¹¹⁶ Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

¹¹⁷ *Id.*

¹¹⁸ *Id.*; see also *Myriad*, 133 S. Ct. at 2119 (finding a patent claim directed to cDNA is patentable subject matter without assessing whether such cDNA contained “markedly different characteristics” to DNA found in nature); *Chakrabarty*, 447 U.S. at 309–10 (mentioning in dictum that the defendant’s bacterium, which was found to be patent eligible subject matter, possessed markedly different characteristics from bacteria found in nature).

¹¹⁹ *Chakrabarty*, 447 U.S. at 310 (holding the bacterium at issue to be “not nature’s handiwork” and therefore to be patentable subject matter).

¹²⁰ *Myriad*, 133 S. Ct. at 2119 (explaining that “the lab technician unquestionably creates something new when cDNA is made” in response to petitioner’s argument that a cDNA nucleotide sequence is dictated by nature).

¹²¹ *Id.* Because there is very little difference between the function and properties of DNA and cDNA, the Court could have found that the cDNA contained no “markedly different” characteristics from DNA, which is found in nature. *Id.* Following such logic, cDNA would be unpatentable under the test set out by the USPTO’s Guidance. *Id.*; Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

¹²² Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 74, 618.

III. THE PROBLEM OF PATENT THICKETS IN LIFE SCIENCES

Courts have, in the past, considered arguments concerning patent thickets in cases concerning patent invalidity.¹²³ Patent thickets present a major problem in the life sciences field.¹²⁴ A patent thicket is an overlapping set of intellectual property rights that requires an inventor to seek a license in order to commercialize an invention.¹²⁵ Cumulative innovation, or innovations which grow off existing innovations, is an economic asset.¹²⁶ Patent thickets are viewed negatively because they make commercializing cumulative innovation difficult, which discourages inventors from improving upon the innovations of others.¹²⁷ Section A discusses the Federal Circuit's treatment of patent thickets in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*¹²⁸ Section B discusses the U.S. Supreme Court's more recent consideration of the issue in *Association for Molecular Pathology v. Myriad Genetics, Inc.*¹²⁹

A. The Federal Circuit's Consideration of Patent Thickets in *Ariad*

The U.S. Court of Appeals for the Federal Circuit's 2010 decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* marked one of the first cases in which the Federal Circuit considered arguments concerning the creation of patent thickets surrounding biochemical pathways.¹³⁰ Although patentable subject matter was not at issue in *Ariad*, arguments made by the plaintiff concerning the dangers of patent thickets could also be relevant in a case in which iPS cell preparation methods are at issue.¹³¹

¹²³ See *infra* notes 130–148 and accompanying text (discussing how the U.S. Supreme Court and the Federal Circuit have considered patent thickets when evaluating whether an invention is patentable subject matter).

¹²⁴ CARL SHAPIRO, INNOVATION POLICY AND THE ECONOMY 120 (Adam B. Jaffe et al. eds., 2001), available at <http://www.nber.org/chapters/c10778.pdf> [<http://perma.cc/J42L-XDZJ>].

¹²⁵ *Id.* (defining a patent thicket as “a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology”).

¹²⁶ *Id.*

¹²⁷ *Id.* at 121 (arguing that the large number of patents in the United States hinders the commercialization of new technologies because it requires innovators to pay patent-holders in order to utilize certain products, processes, and methods).

¹²⁸ See *infra* notes 130–138 and accompanying text.

¹²⁹ See *infra* notes 139–148 and accompanying text.

¹³⁰ See *Ariad Pharm., Inc. v. Eli Lilly & Co. (Ariad II)*, 598 F.3d 1336, 1340 (Fed. Cir. 2010); Defendant Eli Lilly and Company's Opposition Claim Construction Brief at 15, *Ariad Pharm., Inc. v. Eli Lilly & Co. (Ariad I)*, 529 F. Supp. 2d 106, 117 (D. Mass. 2007), *aff'd in part, rev'd in part*, 598 F.3d 1336 (Fed. Cir. 2010) (No. 02 CV 11280 RWZ), 2003 WL 24337596 (stating that *Ariad* had claimed in its patent all compounds that function to inhibit NF-κB).

¹³¹ See Opposition Claim Construction Brief, *supra* note 130, at 15 (explaining that the patent claims at issue were not limited to any particular compound containing any particular structure); Takahashi et al. 2007, *supra* note 11, at 862.

In *Ariad*, the defendant, Ariad, had created a molecule that reduced binding of the transcription factor NF- κ B, which in turn reduces cytokine production.¹³² Ariad had claimed use of all substances that achieve the result of reducing binding of NF- κ B to NF- κ B recognition sites.¹³³ At the district court level, plaintiff Eli Lilly had argued that the cytokine production pathway in which NF- κ B is involved is a natural phenomenon.¹³⁴ Eli Lilly asserted that Ariad's claim to all means of reducing NF- κ B binding without naming the specific molecule that inhibits binding created a patent thicket surrounding the cytokine production pathway.¹³⁵

Judge Rader responded to Eli Lilly's argument in his dissent.¹³⁶ Judge Rader stated that Congress, and not the courts, is ultimately responsible for balancing upstream and downstream innovation.¹³⁷ Although the court ultimately did not find Eli Lilly's argument to be persuasive, *Ariad* was one of the first cases to bring attention to the potentially problematic effects that patent thickets surrounding biochemical pathways or processes could have on technological advancement in the biological sciences.¹³⁸

B. The Supreme Court's Consideration of Patent Thickets in Myriad

The U.S. Supreme Court has also considered the issue of patent thickets.¹³⁹ In 2013, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court heard arguments regarding the need to prevent the creation of patent thickets so as not to hinder biological research.¹⁴⁰ Pe-

¹³² See *Ariad II*, 598 F.3d at 1340 (finding the claim at issue that was directed to all embodiments of NF- κ B inhibitors to be patent ineligible).

¹³³ See *id.*

¹³⁴ Opposition Claim Construction Brief, *supra* note 130, at 15.

¹³⁵ See *id.* That is, if a court were to find Ariad's claims to be valid, there would be little room for innovation because virtually all methods of reducing NF- κ B binding have already been claimed. See *id.*; Ken Garber, *Patently Absurd?*, 24 NATURE BIOTECHNOLOGY 737, 738 (2006) (explaining that a broad patent similar to Ariad's patent that covers "upstream" research tools could lead to patent thickets). But see Jonathan E. Barbee, *Innovation on the Cutting Edge of Ariad: Reinventing the Written Description Requirement*, 86 N.Y.U. L. REV. 1895, 1929 (2011) (arguing that scholars should not be as concerned about patent thickets and noting that Ariad's patent "was one of nearly one hundred" patents related to NF- κ B).

¹³⁶ See *Ariad II*, 598 F.3d at 1361 (Rader, J., dissenting in part).

¹³⁷ See *id.* (explaining that § 101 already balances upstream and downstream innovation by setting forth the written description requirement, which requires patent applicants to provide "a written description of the invention") (citing 35 U.S.C. § 112 (2012)).

¹³⁸ See *id.*

¹³⁹ See *Ariad I*, 529 F. Supp. 2d at 117; see also *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013) ("[W]ithout [§ 101], there would be considerable danger that the grant of patents would 'tie up' the use of such tools and thereby 'inhibit future innovation premised upon them.'") (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012)).

¹⁴⁰ See *Myriad*, 133 S. Ct. at 2116.

tioners argued that Myriad's claim of DNA containing the BRCA1 and BRCA2 genes should be invalid because DNA is a naturally occurring product.¹⁴¹ The Court held the claim to be invalid, explaining that although Myriad had discovered the locus of the BRCA genes, Myriad did not do anything further to alter the genes.¹⁴² Accordingly, the BRCA genes were found not to be patentable subject matter.¹⁴³ Justice Thomas emphasized in his opinion that the very purpose of patents is to promote creation, and by "tying up" natural phenomena, which are the basic tools of scientific research, the patent system would inhibit future innovation premised upon such phenomena.¹⁴⁴

Although *Myriad* and *Ariad* differ in that only in *Myriad* was patentable subject matter at issue, both cases represent two contrasting ways in which courts have grappled with the issue of patent thickets in the life sciences field.¹⁴⁵ The fact that *Myriad* was decided recently in 2013 could suggest that courts are more willing than they were five years ago to consider the effect of a validating decision on patent thickets in the biological field.¹⁴⁶ The *Myriad* decision could also suggest that the Court's view of what constitutes patentable subject matter is evolving to become more restrictive.¹⁴⁷ Contrastingly, the *Myriad* decision could simply be an outlier, and future decisions could more closely resemble the approach taken in *Ar-*

¹⁴¹ See *id.*; Reply Brief for Petitioners, *supra* note 102, at 9–10 (explaining that Myriad's proposed standard for § 101 would be "whether the composition is a result of 'human intervention'").

¹⁴² See *Myriad*, 133 S. Ct. at 2118 ("Many of Myriad's patent descriptions simply detail the iterative process of discovery by which Myriad narrowed the possible locations for the gene sequences that it sought . . . [Myriad's claims do not] rely in any way on the chemical changes that result from the isolation of a particular section of DNA.").

¹⁴³ See *id.*

¹⁴⁴ See *id.* at 2116 (explaining § 101's purpose as a preventative measure against patent thickets). Although the Court's ruling arguably prevents patent thickets surrounding DNA, another concern is whether such a ruling will discourage genetic research. See Editorial, *After DNA Patent Ruling, Congress Must Encourage Genetic Research*, WASH. POST (June 13, 2013), https://www.washingtonpost.com/opinions/after-dna-patent-ruling-congress-must-encourage-genetic-research/2013/06/13/c7a86d98-d458-11e2-b05f-3ea3f0e7bb5a_story.html [<https://perma.cc/47NT-DZVV>] [hereinafter *Congress Must Encourage Genetic Research*] (arguing that Congress must develop a better scheme by which the patent system can foster genetic research but still protect upstream research tools); *Intellectual Property and Genomics*, NAT'L INSTS. OF HEALTH (Oct. 30, 2014), <http://www.genome.gov/19016590> [<http://perma.cc/7K8D-6RKN>] (stating that the National Institutes of Health and the National Human Genome Research Institute were "very pleased" with the ruling in *Ariad* and believe that *Ariad* will promote progress in the field of genomic medicine).

¹⁴⁵ See *Myriad*, 133 S. Ct. at 2116 (discussing the goal of keeping scientific research tools in the public domain); *Ariad I*, 529 F. Supp. 2d at 117 (explaining that the courts are not responsible for balancing upstream and downstream innovation).

¹⁴⁶ See *Myriad*, 133 S. Ct. at 2116; *Ariad I*, 529 F. Supp. 2d at 117.

¹⁴⁷ See *Myriad*, 133 S. Ct. at 2116 (disallowing patents on DNA sequences, despite their potential to help scientists detect mutations).

iad, which seems to consider less carefully the possibility that a validating decision would create a patent thicket.¹⁴⁸

IV. NEW STANDARDS WITH WHICH TO EVALUATE PATENTABLE SUBJECT MATTER IN THE CONTEXT OF LIFE SCIENCES INVENTIONS AND METHODS

Recent decisions related to the patentability of purified products, living organisms, and methods evidence the ongoing struggle of the courts to identify the boundaries of patentable subject matter, especially in the field of biotechnology.¹⁴⁹ The lack of clear boundaries in this area leaves unclear whether induced pluripotent stem cells (“iPS cells”) and methods for preparing iPS cells are in fact patentable.¹⁵⁰ iPS cells are only one example of an invention within the life sciences that neither clearly meets the patentable subject matter requirement nor explicitly falls under the definition of “product of nature” in the context of 35 U.S.C. § 101.¹⁵¹ Many inventions in the life sciences field, like iPS cells, are derived from a product of nature, and researchers in this field have no clear way to anticipate whether such inventions will be patentable.¹⁵²

Developing a clearer standard with which to evaluate patentable subject matter in the context of the life sciences would not only assist inventors in anticipating whether their creations are patentable, but it would also assist judges, who often have a limited scientific background, in assessing whether complex inventions fit under the broad categories of patentable

¹⁴⁸ See *Myriad*, 133 S. Ct. at 2116; *Ariad I*, 529 F. Supp. 2d at 117.

¹⁴⁹ See *supra* notes 84–122 and accompanying text (explaining how courts have previously applied the patentable subject matter requirement to life sciences innovations); see also *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2360 (2014). In 2014, in *Alice Corp. Pty. Ltd. v. CLS Bank International*, the U.S. Supreme Court once again confronted the issue of determining what constitutes patentable subject matter and again fell short of articulating a clear standard. See 134 S. Ct. at 2360. Although the Court emphasized that the machine-or-transformation test is still useful, the holding in *Alice* suggests that patent holders will need to show something beyond tying a law of nature, abstract idea, or physical phenomenon to a machine. See *id.* at 2357.

¹⁵⁰ See *Alice*, 134 S. Ct. at 2357; *Bilski v. Kappos*, 561 U.S. 593, 603 (2010).

¹⁵¹ See 35 U.S.C. § 101 (2012); Josephine Johnston, *Intellectual Property and Biomedicine, in FROM BIRTH TO DEATH AND BENCH TO CLINIC: THE HASTINGS CENTER BIOETHICS BRIEFING BOOK FOR JOURNALISTS, POLICYMAKERS, AND CAMPAIGNS 93, 93* (Mary Crowley ed., 2008), available at http://www.thehastingscenter.org/uploadedFiles/Publications/Briefing_Book/intellectual%20property%20chapter.pdf [<http://perma.cc/M6GQ-FMSE>] (discussing the rising number of patents related to “biomedical materials and processes, such as cell lines, and methods of replicating them, such as cloning”); *What Will Happen to Biotech’s Patent Thickets After Myriad?*, MICH. TELECOMMUNICATIONS & TECH. L. REV. BLOG (Oct. 21, 2014), <http://mtlr.org/2014/10/21/what-will-happen-to-biotechs-patent-thickets-after-myrriad-and-prometheus/> [<http://perma.cc/EXS4-D9DC>] (explaining that the patentability of iPS cells is uncertain following *Association for Molecular Pathology v. Myriad Genetics, Inc.*).

¹⁵² See *supra* notes 84–122 and accompanying text (explaining why there is no clear standard with which to determine whether an invention derived from a product of nature is patentable).

subject matter set out in § 101.¹⁵³ Section A articulates a standard with which patentable subject matter can be evaluated in the context of life sciences inventions.¹⁵⁴ Section B articulates a standard with which methods patents can be evaluated.¹⁵⁵

A. Evaluating Patentable Subject Matter in the Context of the Life Sciences Using a Modified Chakrabarty Standard

The U.S. Supreme Court's 1980 decision in *Diamond v. Chakrabarty* provides the best starting point for determining how much an invention derived from a product of nature must be altered in order to be considered a man-made invention for purposes of § 101.¹⁵⁶ In *Chakrabarty*, the Court indicated in its analysis that the bacterium had characteristics that were "markedly different" from any existing bacterium.¹⁵⁷ The Court also noted that the bacterium had the potential for significant utility.¹⁵⁸ Although this language in *Chakrabarty* provides some direction as to what might constitute a product of nature, courts have not employed this language as a strict standard for evaluating patentable subject matter.¹⁵⁹ To promote clarity in this important area of the law, courts should adopt a more clear-cut standard to evaluate when inventions derived from products of nature are patentable under § 101.¹⁶⁰

¹⁵³ See 35 U.S.C. § 101; Johnston, *supra* note 151, at 93 (acknowledging that Congress can develop new laws and courts can adopt practices that will both encourage innovation and prevent the patent system from hindering access to medical treatments).

¹⁵⁴ See *infra* notes 156–196 and accompanying text.

¹⁵⁵ See *infra* notes 197–207 and accompanying text.

¹⁵⁶ *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980); Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1173–83 (2002) (describing how courts have applied patent law to biotechnology in pre-2002 cases).

¹⁵⁷ *Chakrabarty*, 447 U.S. at 310 (“[T]he patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature’s handiwork, but his own; accordingly it is patentable subject matter under § 101.”).

¹⁵⁸ See *id.* at 309–10 (noting that the claim at issue was “a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity ‘having a distinctive name, character [and] use’” and therefore should be patentable) (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

¹⁵⁹ See *id.* at 310. Although Justice Thomas quoted this language in *Myriad*, the Court in *Myriad* did not treat the possession of markedly different characteristics and the potential for significant utility as distinct criteria that must be met in order for an invention to be considered patentable subject matter. See Association for Molecular Pathology v. *Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013); *Chakrabarty*, 447 U.S. at 310. The Court also did not articulate a separate standard that must be met in order for an invention derived from a natural product to be considered patentable subject matter. *Myriad*, 133 S. Ct. at 2117; *Chakrabarty*, 447 U.S. at 310.

¹⁶⁰ 35 U.S.C. § 101; see *supra* notes 79–121 and accompanying text (describing the confusion surrounding the patentable subject matter requirement in the context of life sciences).

In order to assess whether a biological invention derived from a product of nature is patentable subject matter, courts should assess: (1) whether the invention at issue possesses “markedly different characteristics” from the natural product from which it was derived; and (2) whether the invention possesses a practical utility, or combination of practical utilities, that does not exist in any product occurring in nature.¹⁶¹ Because this standard draws on the language used in *Chakrabarty*, it is referred to in this Note as the “modified *Chakrabarty* standard.”¹⁶²

It is important to note two key differences between the modified *Chakrabarty* standard and the language used in *Chakrabarty*.¹⁶³ First, the Court in *Chakrabarty* indicated that the bacterium at issue possesses characteristics that were “markedly different” than any bacterium found in nature, whereas according to the modified *Chakrabarty* standard, an invention must possess markedly different characteristics from the product of nature from which the invention is derived.¹⁶⁴ Second, the Court in *Chakrabarty* indicated that the bacterium at issue possessed the potential for significant utility.¹⁶⁵ The modified *Chakrabarty* standard not only requires the invention to possess practical utility, but it also requires that the invention’s practical utility, or combination of practical utilities, not exist in another known product of nature.¹⁶⁶ This criterion would be separate from the § 101 utility requirement.¹⁶⁷

Accordingly, section 1 addresses the rationale behind requiring that an invention possess a markedly different characteristic from the natural product from which it was derived.¹⁶⁸ Section 2 addresses why, under the modified *Chakrabarty* standard, an invention must possess a practical utility or

¹⁶¹ See *Chakrabarty*, 447 U.S. at 310. The goal of this standard is not only to elucidate which inventions in the biotechnology field are patent-eligible, but also to prevent widely-used research tools from being the subject of a patent monopoly. See generally David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 1021 (2005) (arguing that limiting access to scientific research tools through patent protection can hinder technological innovation).

¹⁶² See *Chakrabarty*, 447 U.S. at 310 (finding a bacterium with characteristics “markedly different” from any found in nature to be patentable).

¹⁶³ See *id.*

¹⁶⁴ See *id.*

¹⁶⁵ See *id.* It is unclear whether the Court intended to convey that merely meeting the utility requirement was evidence in support of an invention being patentable subject matter. See 35 U.S.C. § 101; *Chakrabarty*, 447 U.S. at 310.

¹⁶⁶ See *Chakrabarty*, 447 U.S. at 310.

¹⁶⁷ See 35 U.S.C. § 101; *Chakrabarty*, 447 U.S. at 310; David B. Resnik, *A Biotechnology Patent Pool: An Idea Whose Time Has Come?*, J. PHIL., SCI. & L., vol. 3 (2003), <http://jpsl.org/archives/biotechnology-patent-pool-idea-whose-time-has-come/> [<http://perma.cc/8UMR-2WY8>] (discussing various approaches that have been proposed by scholars to prevent the formation of patent thickets in biotechnology).

¹⁶⁸ See *infra* notes 170–186 and accompanying text.

combination of practical utilities that does not exist in any known product of nature.¹⁶⁹

1. An Invention Must Possess a “Markedly Different” Characteristic from the Natural Product from Which It Was Derived

The modified *Chakrabarty* standard compares the invention to only the natural product from which it was derived for three principal reasons.¹⁷⁰ First, requiring that an invention possess a markedly different characteristic from all products of nature could prompt researchers to tailor their inventions to comply with this requirement, which could compromise the effectiveness of certain medical treatments or other biological inventions.¹⁷¹ The synthetic creation of products that resemble products found in nature is becoming increasingly common.¹⁷² In the case of iPS cells and of most cell lines maintained in laboratories, certain minor differences do exist between the laboratory cells and cells found in nature.¹⁷³ Generally, however, the more similar a cell line maintained in a laboratory is to a cell line found in nature, the more useful that cell line is for scientific research.¹⁷⁴ In the case of an iPS cell, for example, the more similar an iPS cell is to a naturally occurring embryonic stem cell, the more likely it will be able to differentiate into nearly every type of human cell.¹⁷⁵

If a court were to set out a standard that a cell created in a laboratory must contain a certain degree of dissimilarity to all naturally occurring cells, scientists might purposefully try to create iPS cells that possess that degree of dissimilarity instead of trying to create cells that are as similar as possible to naturally occurring cells.¹⁷⁶ Doing so would likely compromise the effective-

¹⁶⁹ See *infra* notes 187–196 and accompanying text.

¹⁷⁰ See *infra* notes 171–186 and accompanying text.

¹⁷¹ See *Chakrabarty*, 447 U.S. at 307 (noting that patent laws promote economic development by creating incentives for ingenuity through the use of exclusive rights).

¹⁷² See Johnston, *supra* note 151, at 93 (discussing the rise in the number of patents granted on biomedical materials and processes).

¹⁷³ See Barbara S. Mallon et al., *Comparison of the Molecular Profiles of Human Embryonic and Induced Pluripotent Stem Cells of Isogenic Origin*, 12 STEM CELL RES. 376, 376 (2014) (discussing the results of a study that found embryonic stem cells and iPS cells possessed a similar methylation pattern and genetic expression pattern, which suggested that the two types of cells have a high degree of similarity); Takahashi et al. 2007, *supra* note 11, at 861. *But see* Kazim H. Narsinh et al., *Comparison of Human Induced Pluripotent and Embryonic Stem Cells: Fraternal or Identical Twins?*, 19 MOLECULAR THERAPY 635, 635 (2010) (explaining that iPS cells have varying differentiation propensities and do not always develop into the desired cell type).

¹⁷⁴ See Robin Feldman & Deborah Furth, *The Intellectual Property Landscape for iPS Cells*, 3 STAN. J.L. SCI. & POL'Y 16, 24 (2010) (explaining that improper reprogramming can hinder an iPS cell's ability to differentiate into different types of cells and can result in teratoma formation).

¹⁷⁵ See *id.*

¹⁷⁶ *Chakrabarty*, 447 U.S. at 307 (explaining how scientists have an economic motivation to create patentable inventions). The goal and purpose of patent law, as articulated in *Chakrabarty*, is

ness of any medical treatments or diagnostic methods for which the iPS cells would be used.¹⁷⁷ Cells that are intentionally created to be dissimilar to a certain degree to naturally occurring stem cells might not differentiate into other types of cells as readily or consistently, which could render medical treatments or diagnostic tools derived from these cells less effective.¹⁷⁸

Second, the modified *Chakrabarty* standard assesses whether a markedly different characteristic exists only between the invention and the product from which it was derived because society should incentivize scientists to create inventions that mimic naturally-occurring biological products, for such inventions have substantial utility.¹⁷⁹ Isolated insulin, for example, is essential to the management of Type I diabetes.¹⁸⁰ Isolated adrenaline is critical in the treatment of cardiac arrest or anaphylaxis.¹⁸¹ Although insulin and adrenaline used therapeutically possess certain structural differences from naturally-occurring insulin and adrenaline, it is not always the case that a natural product created or isolated in a laboratory will be markedly

to drive inventiveness and research efforts. *See id.* If such laws will only protect inventiveness and research efforts that result in iPS cells that are similar to, but not as similar as possible to ESCs, such laws will drive research efforts to create iPS cells that are patent eligible subject matter but not necessarily optimal for use as a diagnostic tool and medical treatment. *See id.*; Feldman & Furth, *supra* note 174, at 24 (explaining the consequences of improper iPS cell reprogramming).

¹⁷⁷ *See* Feldman & Furth, *supra* note 174, at 24.

¹⁷⁸ *See id.*; Narsinh et al., *supra* note 173, at 635 (finding significant variation in the differentiation propensities of iPS cells and ESCs). *But see* Mallon et al., *supra* note 173, at 376 (finding no gene probe with expression that altered significantly between human iPS cells and ESCs). Regardless of policy interests in favor of or against a finding that iPS cells do contain markedly different characteristics from naturally occurring ESCs, a court would have difficulty examining the molecular differences between iPS cells and ESCs because it is still very much under debate whether significant molecular difference exist between the two types of cells. *See* Narsinh et al., *supra* note 173, at 635. *But see* Mallon et al., *supra* note 173, at 376 (finding that iPS cells and ESCs have highly similar genetic expression and methylation patterns). Because of the lack of definitive research on the topic, a court would be likely to approach the issue of whether marked differences exist between iPS cells and ESCs by looking at the non-molecular differences between the cells, such as the fact that iPS cells can be obtained without harming human embryos. *See Chakrabarty*, 447 U.S. at 310; Narsinh et al., *supra* note 173, at 635. *But see* Mallon et al., *supra* note 173, at 376 (finding that iPS cells and ESCs possess a high degree of similarity).

¹⁷⁹ *See Chakrabarty*, 447 U.S. at 307 (explaining the purpose of the patent system as an incentive for innovation); Paul Cole, *USPTO Patent Eligibility Guidelines: A Topsy-Turvy Approach for Natural Products*, IPWATCHDOG (Mar. 10, 2014), <http://www.ipwatchdog.com/2014/03/10/uspto-patent-eligibility-guidelines-natural-products/id=48451/> [<http://perma.cc/D3NV-AASQ>] (arguing that the *Myriad* decision creates uncertainty surrounding patents on biotechnology, which could, in turn, harm the economy).

¹⁸⁰ *See The Discovery of Insulin*, NOBELPRIZE.ORG (Feb. 2009), <http://www.nobelprize.org/educational/medicine/insulin/discovery-insulin.html> [<http://perma.cc/SNV3-T9QB>] (explaining the discovery and medical uses of insulin).

¹⁸¹ *See Epinephrine*, UNIV. OF DEL., <http://www.udel.edu/chem/C465/senior/fall00/Performance1/epinephrine.htm.html> [<http://perma.cc/UM5N-QXPD>] (explaining the medical uses of epinephrine).

different than that which exists in nature.¹⁸² If there were a strict ban on patenting inventions that do not markedly differ from products of nature, there would not be as much incentive for scientists to isolate or create a compound or cell that could be of enormous benefit to the public.¹⁸³

Finally, scientists' capacity to identify genes and their function has vastly expanded since the 1980s and the Court's decision in *Chakrabarty*.¹⁸⁴ Due to the technological progress that has been made, plaintiffs can more easily identify naturally occurring organisms that share characteristics with the invention at issue.¹⁸⁵ Therefore, requiring that an invention possess markedly different characteristics than any organism found in nature presents a greater challenge to patentability today than it did when *Chakrabarty* was decided.¹⁸⁶

2. The Invention Must Possess a Practical Utility or Combination of Practical Utilities That Does Not Exist in Any Known Product of Nature

In order to safeguard against patent thickets on natural products, the modified *Chakrabarty* standard also requires that the invention possess a practical utility or combination of practical utilities that does not exist in any product of nature.¹⁸⁷ If the invention possessed only as much practical utility as an existing natural product, there would be little or no public benefit rendered by granting a patent on such an invention.¹⁸⁸ There could, how-

¹⁸² See Narsinh et al., *supra* note 173, at 635 (finding significant variation in the differentiation propensities of iPS cells and ESCs). *But see* Mallon et al., *supra* note 173, at 376 (finding no gene probe with expression that altered significantly between human iPS cells and ESCs). In the case of iPS cells or in the case of many types of cell lines maintained in a laboratory, there is often no markedly different characteristic, aside from differences in molecular markers, between the cells maintained in a lab and the cells as they exist in nature. *See* Narsinh et al., *supra* note 173, at 635. *But see* Mallon et al., *supra* note 173, at 376.

¹⁸³ See Johnston, *supra* note 151, at 85 (explaining the importance of patents and listing how patents “[a]ct as an incentive for biomedical research,” “[s]ecure funds to turn early discoveries into medical products,” “[e]nsure that knowledge is disclosed to the public,” and “[i]ncrease the chance that people will have access to . . . medical products they need”); *Congress Must Encourage Genetic Research*, *supra* note 144 (arguing that because the *Myriad* decision could discourage genetic research by denying scientists patents on genes used for diagnostic purposes, Congress should reexamine other sources of economic motivation for scientists to conduct such research).

¹⁸⁴ See *Chakrabarty*, 447 U.S. at 307; P.C.Y. Woo et al., *Then and Now: Use of 16S rDNA Sequencing for Bacterial Identification and Discovery of Novel Bacteria in Clinical Microbiology Laboratories*, 14 CLINICAL MICROBIOLOGY & INFECTION 908, 908 (2008) (explaining how, since the 1990s, scientists' ability to sequence DNA and identify genes has led to the discovery of novel bacteria).

¹⁸⁵ See *Chakrabarty*, 447 U.S. at 307; Woo et al., *supra* note 184, at 908.

¹⁸⁶ See *Chakrabarty*, 447 U.S. at 307; Woo et al., *supra* note 184, at 908.

¹⁸⁷ See *infra* notes 188–196 and accompanying text (explaining how the modified *Chakrabarty* standard protects against patent thickets, or patent monopolies on technologies within a given field).

¹⁸⁸ See Johnston, *supra* note 151, at 85 (explaining how the patent system incentivizes scientific research and enables scientists to obtain the financial backing to further develop discoveries); William Hubbard, *The Competitive Advantage of Weak Patents*, 54 B.C. L. REV. 1909, 1910

ever, be consequences from granting a monopoly on a man-made product that is a derivative of a natural product.¹⁸⁹ If a scientist, for example, sought a patent on a complementary DNA (“cDNA”) sequence and, unlike the BRCA cDNA in the 2013 U.S. Supreme Court case *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the cDNA sequence at issue had no practical utility as a diagnostic tool, the granting of a patent on such an invention would render little public benefit.¹⁹⁰ The patent could, however, force scientists to obtain licensing agreements to utilize certain cDNA sequences in the course of their research.¹⁹¹ By this logic, granting patents on certain inventions derived from natural products could slow the pace of scientific research within certain fields.¹⁹²

Although the modified *Chakrabarty* standard would make clearer to scientists when natural-product-derived inventions are and are not patentable, the standard is still sufficiently flexible to allow judges to interpret and apply the law as they see fit.¹⁹³ The term “markedly different characteristic,” for example, in the context of the modified *Chakrabarty* standard, is not defined.¹⁹⁴ The standard also does not articulate the degree to which the practical utility of the invention must differ from the practical utility of an existing natural product.¹⁹⁵ Each court may construe these terms as broadly or as narrowly as it deems appropriate given the circumstances of each case.¹⁹⁶

B. Evaluating Patentable Subject Matter in the Context of Life Sciences Methods Using the Transformation-or-Thicket Guidelines

Just as the modified *Chakrabarty* standard would elucidate the patentable subject matter requirement as applied to life sciences products, the transformation-or-thicket standard would clarify which processes in meth-

(2013) (explaining how the U.S. patent system enables American patent-holders to compete with international rivals); Gideon Parchomovsky & R. Polk Wagner, *Patent Portfolios*, 154 U. PENN. L. REV. 1, 12 (2005) (arguing that the patent system leads to more efficient production).

¹⁸⁹ See Johnston, *supra* note 151, at 85 (explaining that patents can hinder public access to medical treatments through the creation of monopolies, and patents on research tools can increase the cost of scientific research); Hubbard, *supra* note 188, at 1910 (stating that policymakers try to “balance the incentive effect of U.S. patents against the competitive costs”); Parchomovsky & Wagner, *supra* note 188, at 14 (stating that most U.S. patents are not commercialized and thereby “pass their lives in complete idleness, gathering dust rather than revenues”).

¹⁹⁰ See *Myriad*, 133 S. Ct. at 2119; Johnston, *supra* note 151, at 85.

¹⁹¹ See Steven J. Hultquist, *Reach Through Royalties: The Scope of Research Tool Patents*, 86 J. PAT. & TRADEMARK OFF. SOC’Y 285, 286 (2004) (explaining the consequences of granting patents on research tools).

¹⁹² See Johnston, *supra* note 151, at 85; Hultquist, *supra* note 191, at 286.

¹⁹³ See *supra* notes 170–192 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

¹⁹⁴ See *supra* notes 170–192 and accompanying text.

¹⁹⁵ See *supra* notes 170–192 and accompanying text.

¹⁹⁶ See *supra* notes 170–192 and accompanying text.

ods in the life sciences context are patentable subject matter.¹⁹⁷ A source of confusion surrounding process patents is the degree to which the machine-or-transformation test established by the Federal Circuit in 2008 in *In re Bilski* should be given weight when determining if a process is patentable subject matter.¹⁹⁸ Under the transformation-or-thicket standard, courts should continue to consider the machine-or-transformation test as an investigative tool when evaluating whether life sciences research methods that involve altering a product of nature constitute patentable subject matter.¹⁹⁹ Courts should additionally consider whether finding that the invention at issue is patentable subject matter would lead to the creation of patent thickets.²⁰⁰ If courts do not consider the issue of patent thicket creation, crucial research tools could become tied up, which would require scientists to seek licensing agreements in order to conduct certain research.²⁰¹

A court should not uphold a patent on a method if the party challenging the patent has proven by clear and convincing evidence that the patent (1) could lead to the creation of a patent thicket over a certain category of research tools, and (2) such a category of research tools possesses a practical utility that differs from existing accessible research tools.²⁰² Because this standard requires courts to consider both the machine-or-transformation test and the aforementioned thicket criteria to evaluate patentable subject matter, this Note refers to this standard as the “transformation-or-thicket standard.”²⁰³

Similar to the modified *Chakrabarty* standard, the transformation-or-thicket standard provides some degree of notice to scientists as to whether their methods inventions will be patentable; the standard, however, is still somewhat flexible and allows courts to define the terms within the standard

¹⁹⁷ See *infra* notes 198–207 and accompanying text.

¹⁹⁸ See *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc), *aff'd*, *Bilski v. Kappos*, 561 U.S. 593, 604 (2010). The Federal Circuit explained the machine-or-transformation test by stating that a claimed process is patent eligible under § 101 if the process is tied to a machine or apparatus or if it transforms something into a different state or thing. 35 U.S.C. § 101; *In re Bilski*, 545 F.3d at 954. The U.S. Supreme Court established that the machine-or-transformation test is not the sole test for deciding when an invention is a patent eligible process, but it is instead a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101. 35 U.S.C. § 101; *Bilski*, 561 U.S. at 604.

¹⁹⁹ See *In re Bilski*, 545 F.3d at 954; Moore, *supra* note 50, at ¶¶ 8–12 (2010) (summarizing the Federal Circuit’s explanation of the machine-or-transformation test and explaining the types of transformations that would be considered sufficient to satisfy the patentable subject matter requirement).

²⁰⁰ See Johnston, *supra* note 151, at 85 (explaining that patents limit access to materials or methods that might lead to the discovery of other important products).

²⁰¹ See Johnston, *supra* note 151, at 85; Hultquist, *supra* note 191, at 286.

²⁰² See *infra* notes 204–222 and accompanying text (articulating the requirements for patentable subject matter under the transformation-or-thicket standard).

²⁰³ See *infra* notes 204–222 and accompanying text.

as they see fit.²⁰⁴ The goal of the transformation-or-thicket standard is not to establish a bright-line test, but to encourage greater scrutiny of inventions that could be considered important or basic tools of research.²⁰⁵ Adopting such a standard would also encourage parties to rely on experts to testify as to why an invention would or would not create a patent thicket.²⁰⁶ The involvement of more individuals with relevant scientific knowledge would allow judges and juries, who often have little scientific background, to better understand the effect of upholding the patent at issue on the relevant scientific field as a whole.²⁰⁷

V. APPLYING THE NEW STANDARDS TO PATENTS ON IPS CELL TECHNOLOGIES

Section A of this Part explains how the modified standard of the U.S. Supreme Court's 1980 decision in *Diamond v. Chakrabarty* would be applied to patent claims directed to induced pluripotent stem ("iPS") cell lines.²⁰⁸ Section B explains how the transformation-or-thicket standard would be applied to patent claims directed to methods of creating iPS cells.²⁰⁹

A. Under the Modified Chakrabarty Standard, iPS Cell Lines Are Likely to Be Considered Patentable Subject Matter

Under the modified *Chakrabarty* standard, iPS cells would be found to be patentable subject matter.²¹⁰ Because iPS cells are pluripotent, or can differentiate into many types of cells, a court would be likely to find that iPS cells possess a "markedly different characteristic" from the skin cells

²⁰⁴ See *Chakrabarty*, 447 U.S. at 310; Johnston, *supra* note 151, at 85. The patent system provides an incentive for scientists to pursue certain areas of research. Johnston, *supra* note 151, at 85. In order for this incentive to be in place, scientists must know the boundaries and limitations of the patent system. See *id.* If scientists are unaware of whether their invention is patentable or not, such incentive might be diminished. See *id.*

²⁰⁵ See Hultquist, *supra* note 191, at 286 (explaining the consequences of granting patents on critical research tools); Karshedt, *supra* note 37, at 949 (proposing that "completeness" be a separate requirement of patentability to improve access to research tools).

²⁰⁶ See Karshedt, *supra* note 37, at 988 n.300 (recognizing that expert testimony can help courts to identify broad claims to research tools); *Cutting Through the Patent Thicket*, BLOOMBERG BUS. (Dec. 19, 2005), <http://www.bloomberg.com/bw/stories/2005-12-19/cutting-through-the-patent-thicket> [<http://perma.cc/2EJX-SRP2>] (suggesting that the scientific community should be able to comment on patent filings so that the United States Patent and Trademark Office ("USPTO") is informed as to what inventions are truly new).

²⁰⁷ See Karshedt, *supra* note 37, at 998 n.300; *Cutting Through the Patent Thicket*, *supra* note 206.

²⁰⁸ See *infra* notes 210–222 and accompanying text.

²⁰⁹ See *infra* notes 223–233 and accompanying text.

²¹⁰ See *infra* notes 211–212 and accompanying text.

from which they are derived.²¹¹ Furthermore, the court would be likely to find that iPS cells possess a combination of practical utilities that no product of nature possesses, that combination being: (1) iPS cells are pluripotent, and (2) iPS cells can be obtained without destroying a human embryo.²¹²

One potential shortcoming of the modified *Chakrabarty* standard is that the term “practical utility” in the context of the second step of the analysis is left to the courts to interpret and define.²¹³ “Practical utility” should be construed narrowly enough such that research tools and other basic necessities for invention are not tied up by patents.²¹⁴ At the same time, “practical utility” should be construed broadly enough such that patents can be obtained on biotechnologies without substantial difficulty such that there is still incentive to innovate.²¹⁵

In the context of iPS cells, a court could find that the ease at which iPS cells are obtained as compared to embryonic stem cells (“ESCs”) does not warrant a practical utility.²¹⁶ Such an interpretation, however, would compromise the incentive to develop better and more efficient methods of creating pluripotent stem cells.²¹⁷ Because the creation of easily obtainable stem

²¹¹ See *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980) (finding a bacterium with characteristics “markedly different” from any found in nature to be patentable); Narsinh et al., *supra* note 173, at 635 (finding significant variation in the differentiation propensities of iPS cells and ESCs); Takahashi et al. 2007, *supra* note 11, at 861. *But see* Mallon et al., *supra* note 173, at 376 (finding no gene probe with expression that altered significantly between human iPS cells and ESCs).

²¹² See Takahashi et al. 2007, *supra* note 11, at 861. Adult stem cells are another type of naturally occurring stem cell available to scientists; embryonic stem cells and iPS cells, however, have the ability to differentiate into more different types of cells than adult stem cells. See Murnaghan, *supra* note 2. Furthermore, embryonic stem cells and iPS cells can both be maintained in a laboratory more easily than adult stem cells. See *id.* For these reasons, iPS cells would possess a combination of practical utilities (i.e., a differentiation potential equivalent to that of an embryonic stem cell and an ability to be obtained without destroying an embryo) that is not present in any product of nature or existing research tool. See *id.*; Takahashi et al. 2007, *supra* note 11, at 861.

²¹³ See *Chakrabarty*, 447 U.S. at 310 (finding a bacterium with characteristics “markedly different” from any found in nature to be patentable); *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²¹⁴ See SHAPIRO, *supra* note 124, at 120 (describing the problem of patent thickets); Ed Levy et al., *Patent Pools and Genomics: Navigating a Course to Open Science?* 16 B.U. SCI. & TECH L. REV. 1, 3 (2010) (explaining that critics of gene patents believe that such patents would disrupt scientific research by creating patent thickets).

²¹⁵ See SHAPIRO, *supra* note 124, at 120 (describing the consequences of granting overly broad patents).

²¹⁶ See *Chakrabarty*, 447 U.S. at 310; *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²¹⁷ See SHAPIRO, *supra* note 124, at 121. The availability of patent protection for iPS cells, however, would incentivize iPS cell research. See Hubbard, *supra* note 188, at 1910 (explaining that the patent system encourages innovation and allows American inventors to be internationally competitive in commercializing their products); Parchomovsky & Wagner, *supra* note 188, at 12 (arguing that the U.S. patent system leads to more efficient production).

cells is highly economically beneficial, the term “practical utility” should be construed to incentivize this activity.²¹⁸

Because the modified *Chakrabarty* standard can be easily applied to inventions that are derivatives of natural products, the adoption of the modified *Chakrabarty* standard would give iPS cell researchers and other biologists a better indication of whether their work products are patentable subject matter.²¹⁹ This would, in turn, allow them to focus their efforts on technologies, such as iPS cells, that would be likely to be patent-eligible under this standard.²²⁰

Although the modified *Chakrabarty* standard is fairly easily applied to iPS cells, courts might have difficulty applying this standard to inventions that are derived from more than one natural product.²²¹ While courts should have the discretion to choose what natural product should be used for purposes of the modified *Chakrabarty* analysis, courts should base their analyses on the one or more natural products that make up the invention in largest part.²²²

B. Under the Transformation-or-Thicket Standard, Method Patents Related to iPS Cells Would Likely Be Upheld as Valid

Under the transformation-or-thicket standard, a court would be likely to uphold only certain iPS cell preparation methods claims.²²³ With regard to the first element of the test, iPS cells clearly undergo a transition when transfect-

²¹⁸ See SHAPIRO, *supra* note 124, at 121 (describing the patent system as a “spur” to innovation).

²¹⁹ See *Chakrabarty*, 447 U.S. at 310; *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²²⁰ See Takahashi et al. 2007, *supra* note 11, at 861 (explaining the characteristics and composition of iPS cells and how they compare to naturally occurring stem cells); *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²²¹ See Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74, 618 (Dec. 16, 2014) (to be codified at 37 C.F.R. 1) (recognizing that some nature-based inventions do not have a “naturally occurring counterpart”); *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²²² See Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. at 622–23 (explaining that when a product does not have a “naturally occurring counterpart,” the patent examiner should compare the product to the “closest naturally occurring counterpart”); *supra* notes 156–196 and accompanying text (articulating requirements for patentable subject matter under modified *Chakrabarty* standard).

²²³ See *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013) (recognizing that, without 35 U.S.C. § 101, patents could be granted on crucial research tools, creating patent thickets and thereby hindering scientific research and progress); *Ariad Pharm., Inc. v. Eli Lilly & Co. (Ariad II)*, 598 F.3d 1336, 1361 (Fed. Cir. 2010) (explaining how the Patent Act balances encouraging innovation and protecting research tools through the requirement that patent applicants include a written description of the invention); *supra* notes 197–207 and accompanying text (describing the application of the transformation-or-thicket standard to iPS cell preparation methods).

ed with pluripotency genes.²²⁴ A fibroblast, upon transfection, clearly “transforms” into another cell type with different characteristics and capabilities.²²⁵ Therefore, a claim directed to iPS cell preparation methods would clearly meet the first element of the transformation-or-thicket analysis.²²⁶

Whether an iPS cell preparation method claim meets the second element, however, would depend on the scope of the claim.²²⁷ For example, a claim teaching a method of iPS cell preparation using a combination of specific genes, such as Oct3/4, Sox2, c-Myc, and Klf4, would be upheld as patentable subject matter.²²⁸ Since the genes utilized are specifically enumerated, such a claim would be unlikely to create a patent thicket on a broader category of research tools.²²⁹ A claim teaching a method of iPS cell preparation using “a combination of pluripotency genes” would be less likely to be upheld under the transformation-or-thicket standard, even if the patent holder had enabled the creation of iPS cells using many combinations of pluripotency genes.²³⁰

Likewise, a claim teaching a method of iPS cell preparation using one specifically named gene in combination with other pluripotency genes (e.g., using Oct3/4 in combination with one or more pluripotency genes) would also be unlikely to be upheld under this standard.²³¹ This is because certain

²²⁴ See Takahashi et al. 2007, *supra* note 11 at 862 (comparing the gene expression profile of differentiated iPS cells with those of various somatic cell types).

²²⁵ See Mallon et al., *supra* note 173, at 376 (observing a high degree of similarity in the gene expression patterns and methylation patterns of iPS cells and ESCs); Takahashi et al. 2007, *supra* note 11, at 861 (observing a high degree of similarity between iPS cells and naturally occurring stem cells with regard to morphology, surface antigens, and gene expression, among other characteristics). *But see* Narsinh et al., *supra* note 173, at 635 (observing variation in the differentiation propensities of iPS cells, which could pose an obstacle to researchers seeking to use iPS cells as an alternative to ESCs).

²²⁶ See Mallon et al., *supra* note 173, at 376 (observing a high degree of similarity between iPS cells and ESCs); Takahashi et al. 2007, *supra* note 11, at 861 (observing a high degree of similarity between iPS cells and naturally occurring stem cells with regard to morphology, surface antigens, and gene expression, among other characteristics). *But see* Narsinh et al., *supra* note 173, at 635 (observing variation in the differentiation propensities of iPS cells).

²²⁷ See Baker, *supra* note 35 (explaining the techniques by which doctors created iPS cells, both using Oct3/4 and Sox2 reprogramming factors); Takahashi et al. 2007, *supra* note 11, at 861 (utilizing reprogramming factors Lin28, Nanog, Oct3/4, and Sox2 to create iPS cells).

²²⁸ See Baker, *supra* note 35 (describing using Oct3/4, Sox2, Klf4, and c-Myc to create iPS cells); *supra* notes 124–127 and accompanying text (describing the concern surrounding overly broad patents in the stem cell field).

²²⁹ See Hultquist, *supra* note 191, at 286 (describing how if there were patents on research tools, royalties paid on such research tools would be disproportionate to the value realized by the user of the research tool).

²³⁰ See *supra* notes 197–207 and accompanying text (explaining the requirements for upholding a patent under the transformation-or-thicket standard).

²³¹ See Takahashi et al. 2007, *supra* note 11, at 862 (utilizing Oct3/4 and Sox2 to create iPS cells); *supra* notes 124–127 and accompanying text (describing the concern surrounding overly

genes—namely Oct3/4 and Sox2—are utilized in many known iPS cell preparation protocols, which suggests that using one or both of these genes could be crucial to iPS cell preparation.²³² If the other genes used are not specifically enumerated, such a claim could create a patent thicket over all methods of cellular reprogramming using Oct3/4 or Sox2, which would pose a significant hindrance to scientists in their quests to develop medical treatments from iPS cells.²³³

VI. WHERE WOULD A VALIDATING OR INVALIDATING DECISION LEAVE THE FIELDS OF STEM CELL TECHNOLOGY AND PATENT LAW?

In addition to articulating a clearer standard by which patentable subject matter should be evaluated, a court hearing a challenge to an iPS cell line or iPS cell preparation patent should pay close attention to the practical effects of an invalidating or validating decision on the fields of biological research and patent law.²³⁴

Should a patent on any type of iPS cell technology be upheld in an invalidity challenge, such a result could impact the availability of what are now considered to be basic research tools in the life sciences.²³⁵ Increasingly, labs across the United States are preparing and manipulating iPS cell lines, developing medical treatments and diagnostic methods derived from iPS cell lines, and engineering nuclear reprogramming factors.²³⁶ Regardless of the purpose for which iPS cell labs are using patented iPS cell technology, it is possible that labs across the country are infringing on existing patent rights by using iPS cell lines, preparation methods, or nuclear repro-

broad patents in the stem cell field and the broader policy considerations that the transformation-or-thicket standard takes into account).

²³² See, e.g., U.S. Patent No. 7,682,828 (issued Mar. 23, 2010) (claiming an iPS cell preparation method using Oct3/4 and Sox2); Takahashi et al. 2007, *supra* note 11, at 861 (utilizing Oct3/4 and Sox2 to create iPS cells); Yu et al., *supra* note 72, at 1917 (utilizing Oct3/4 and Sox2 to create iPS cells).

²³³ See Hultquist, *supra* note 191 at 286; e.g., '828 Patent; Takahashi et al. 2007, *supra* note 11, at 861; Yu et al., *supra* note 72, at 1917.

²³⁴ See *infra* notes 236–242 and accompanying text.

²³⁵ See *infra* notes 236–242 and accompanying text.

²³⁶ *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)*, NAT'L INSTS. OF HEALTH (Feb. 5, 2015), http://report.nih.gov/categorical_spending.aspx [<http://perma.cc/V83S-5KB3>] [hereinafter *Estimates of Funding*]. In 2011, 2012, and 2013, the amount given by the National Institutes of Health (“NIH”) in grant money toward non-embryonic stem cell research was \$1.015 billion, \$1.157 billion, and \$1.044 billion, respectively. *Id.* In the same years, the amount given by the NIH in grant money toward embryonic stem cell research was \$288 million, \$310 million, and \$300 million, respectively. *Id.* As of March 2014, the amount that the NIH anticipated to spend on non-embryonic stem cell research in the years 2014 and 2015 was \$1.072 billion in each year. *Id.* As of March 2014, the NIH anticipated to spend \$307 million in 2014 and in 2015 on embryonic stem cell research. *Id.*

gramming factors in the labs' experimentation.²³⁷ If a holder of patent rights over a certain iPS cell technology were to start suing labs for infringement, iPS cell research could come to a temporary halt until the infringing labs are able to obtain licensing agreements or develop an alternative method to prepare iPS cells without infringing on existing patents.²³⁸

Alternatively, should an iPS cell technology patent be held invalid, such a ruling could raise concerns that the court is construing patentability requirements too narrowly or ruling in light of hindsight bias.²³⁹ Additionally, a finding of invalidity could decrease incentive for scientists to develop medical treatments derived from iPS cell technology.²⁴⁰ Until scientists perfect a method by which iPS cells can be produced at a relatively high yield, scientists will continue to rely in part on embryonic stem cells to conduct

²³⁷ See *Estimates of Funding*, *supra* note 236. This report indicated that over \$1 billion each year since the year 2010 has been spent by the NIH alone to fund non-embryonic stem cell research, excluding umbilical cord blood research, which in turn indicates the vast number of laboratories across the United States conducting such research. See *id.*; Dustin Siggins, *Funding of Embryonic Stem Cell Research Down Dramatically*, *Report Notes*, LIFE SITE NEWS (Dec. 5, 2013), <https://www.lifesitenews.com/news/funding-of-embryonic-stem-cell-research-down-dramatically-report-notes> [<https://perma.cc/GB8Q-53HE>] (observing that the California Institute for Regenerative Medicine and the state government of Maryland "are funding far more adult stem cell research projects, while embryonic stem cell research has decreased nearly to nothing").

²³⁸ See *Estimates of Funding*, *supra* note 236. This scenario assumes that the holder of an iPS cell technology patent would act in a similar manner as the patent-holder in *Association for Molecular Pathology v. Myriad Genetics, Inc.* See 133 S. Ct. 2107, 2119 (2013); Derek So et al., *Commercial Opportunities and Ethical Pitfalls in Personalized Medicine: A Myriad of Reasons to Revisit the Myriad Genetics Saga*, 11 CURRENT PHARMACOGENETICS & PERSONALIZED MED. 98, 99–100 (2013). In this case, although Myriad permitted laboratories to use the patented cDNA and DNA to conduct experimentation relating to the BRCA genes, Myriad would not permit laboratories to reveal the results of BRCA mutation tests to test subjects. See So et al., *supra*, at 99. An iPS patent-holder could, however, neglect to enforce his or her patent rights and permit laboratories to use the patented technology. See *id.* Permitting further research on one's patented product could actually be in the best interests of the patent-holder, as discovering new applications of the patented product would presumably increase its value, in turn increasing profit to the patent-holder. See Charles W. Adams, *Blocking Patents and the Scope of Claims* (unpublished manuscript), <https://web.stanford.edu/dept/law/ipsc/pdf/adams-charles.pdf> [<https://perma.cc/Q6J4-HT3M>].

²³⁹ See 35 U.S.C. § 103 (2012) ("A patent . . . may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole *would have been obvious before the effective filing date* . . . to a person having ordinary skill in the art to which the claimed invention pertains." (emphasis added)). Since the filing date of the invention is likely to be several years or decades before the dispute, a fact-finder is likely to have hindsight bias, or to be predisposed to thinking that an invention is obvious because technology has advanced since the time of invention. See *id.* Such bias has the potential to distort the outcome of patent suits in which nonobviousness is at issue. See *id.*

²⁴⁰ See Johnston, *supra* note 151, at 85 (explaining that the patent system incentivizes innovation, furthering technological progress); Hubbard, *supra* note 188, at 1910 (explaining how the U.S. patent system provides incentives to scientists and enables American patent-holders to be internationally competitive); Parchomovsky & Wagner, *supra* note 188, at 12 (arguing that the patent system leads to more efficient production).

stem cell research.²⁴¹ Slowing the rate of iPS cell research will only prolong scientists' dependency on embryonic stem cells and, in turn, will prolong the embryonic stem cell debate.²⁴²

CONCLUSION

Given that induced pluripotent stem cell ("iPS cell") technology is a rapidly burgeoning area of biological research that has attracted hundreds of scientists across the United States over the past decade, it is likely that claims directed toward iPS cell technologies will be challenged in coming years. The lack of clarity surrounding the patentable subject matter requirement as it applies to life sciences renders unclear whether iPS cell technologies would be invalidated if challenged. In order to encourage research and innovation in the stem cell field, courts should establish clearer standards to evaluate patentable subject matter in the context of life sciences products and methods. The modified *Chakrabarty* standard and the transformation-or-thicket standard would encourage innovation by providing clarity in this area. Courts and patent examiners would be given much needed guidance with which to determine the patentability of future impactful biological inventions. Accordingly, courts and examiners would be able to better balance the patent system's goal of incentivizing innovation while keeping essential research tools in the public domain.

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²⁴¹ See Monya Baker, *Stem Cells Made with Near-Perfect Efficiency*, NATURE NEWS (Sept. 18, 2013), <http://www.nature.com/news/stem-cells-made-with-near-perfect-efficiency-1.13775> [<http://perma.cc/L5ZU-3S7M>] (explaining how low cell-conversion rates have hindered iPS cell research); David Cyranoski, *Stem Cells: The Black Box of Reprogramming*, NATURE NEWS (Dec. 10, 2014), <http://www.nature.com/news/stem-cells-the-black-box-of-reprogramming-1.16525> [<http://perma.cc/69XG-VLR3>] (proposing reasons for the low cell-conversion rates).

²⁴² See Baker, *supra* note 241.