

STEMMING THE TIDE: STEM CELL INNOVATION IN THE *MYRIAD-MAYO-ROSLIN* ERA

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This year, one in three seniors will die with Alzheimer or another form of dementia.¹ In 2030, Americans will spend over 800 billion dollars on cardiovascular issues alone,² which is more than the 2013 military budgets of the United States and China combined.³ In their lifetime, 60 to 90 percent of childhood cancer survivors will suffer from health problems resulting from the aggressive cancer therapy they received.⁴ Cardiovascular diseases, cancer, and late onset neurodegenerative disorders are responsible for the highest mortality and morbidity rates in the United States.⁵ It is

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1. See Alzheimer's Ass'n, *2014 Alzheimer's Disease Facts and Figures*, 10 ALZHEIMER'S & DEMENTIA 1, 24–26 (2014).

2. See Paul A. Heidenreich et al., *American Heart Association Policy Statement: Forecasting the Future of Cardiovascular Disease in the United States*, 123 CIRCULATION 933, 934–36 (2011); see also Reuters, *Cost of Heart Disease to Triple in US by 2030; More than \$800 Billion a Year*, NEW YORK DAILY NEWS (Jan. 25, 2011, 4:00 AM), <http://www.nydailynews.com/life-style/health/cost-heart-disease-triple-2030-800-billion-year-article-1.149548>.

3. See Amanda Macias, *This Chart Shows How the Rest of the World Doesn't Even Come Close to US Military Spending*, BUS. INSIDER (Apr. 19, 2014, 8:27 PM), <http://www.businessinsider.com/us-military-spending-chart-2014-4>.

4. Nat'l Cancer Inst., *General Information About Late Effects of Treatment for Childhood Cancer*, NAT'L CANCER INST., <http://www.cancer.gov/cancertopics/pdq/treatment/lateeffects/HealthProfessional/> (last visited Jan. 20, 2015).

5. See Jerome H. Chin & Nirali Vora, *The Global Burden of Neurologic Disease*, 83 NEUROLOGY 349, 350 (2014) (reporting that neurological disorders represent 7.1 percent of the total global burden of disease); Donatus U. Ekwume et al., *Medical Costs and Productivity Losses of Cancer Survivors — United States, 2008–2011*, 63 CTRS. FOR DISEASE CONTROL & PREVENTION MORBIDITY AND MORTALITY WKLY. REP. 505, 507 (2014) (reporting that among male cancer survivors, the per capita mean annual productivity loss was \$3,719, among female survivors, the per capita mean annual productivity loss was \$4,033); Judith A. Finegold et al., *Mortality from Ischemic Heart Disease by Country, Region, and Age: Statistics from World Health Organization and United Nations*, 168 INT'L J. CARDIOLOGY 934, 938 (2013) (reporting that heart disease is the leading cause of death worldwide, causing 445,800 deaths in the United States in 2008).

only natural to ask why science does not yet offer permanent cures to these problems, despite the tremendous advancements that science has made.⁶

The core challenges faced in treating these diseases stem from their complexity. In cancer, cardiovascular disorders, or neurodegenerative disorders, the problem is not a pathogen (i.e., virus or bacteria), but rather the failure of human cells to perform their prescribed function.⁷ These diseases result from alterations of an individual's cells, and thus each patient is unique in the way in which they manifest symptoms and respond to treatment. A diagnosis needs to be fast, before the manifestation of major clinical symptoms.⁸ Optimal treatments require an understanding of how cells work and must be tailored to the individual patient.⁹ Optimal therapies would thus include cells that function in a way similar or identical to cells naturally found in the body.¹⁰

These challenges are why stem cells have sparked much hope among scientists and medical professionals in the last twenty years. Stem cells have been known and accepted for over one hundred years;¹¹ however, their application and potential in curing the major medical challenges of our time has never been more palpable.¹² Stem cells can be used to treat heart disease, neurodegenerative disorders, and cancer, among other¹³

6. Mary Carmichael, *Why Don't More Medical Discoveries Become Cures?*, NEWSWEEK (May 14, 2010, 8:00 PM), <http://www.newsweek.com/why-dont-more-medical-discoveries-become-cures-72475> (describing new needs for therapies as the complexity of disease changes).

7. *Id.*

8. See Vojtech Huser et al., *Developing Genomic Knowledge Bases and Databases to Support Clinical Management: Current Perspectives*, 7 PHARMACOGENOMICS & PERSONALIZED MED. 275, 275–76 (2014).

9. See, e.g., Anuj Garg & Nazem Akoum, *Atrial Fibrillation and Heart Failure: Beyond the Heart Rate*, 28 CURRENT OPINION CARDIOLOGY 332, 335 (2013) (explaining why patients with heart failure require a personalized approach); Paolo Pozzilli et al., *One Size Does Not Fit All Glycemic Targets for Type 2 Diabetes*, 5 J. DIABETES INVESTIGATION 134, 139–40 (2014) (explaining why individually tailored treatments are more effective in managing diabetes).

10. See Steven J. Joggerst & Antonis K. Hatzopoulos, *Stem Cell Therapy for Cardiac Repair: Benefits and Barriers*, 11 EXPERT REV. MOLECULAR MED. e20 (2009); see also Veronique L. Roger, *The Heart Failure Epidemic*, 7 INT'L J. ENVTL. RES. & PUB. HEALTH 1807, 1808–09 (2010) (explaining the increasing epidemic of heart disease and further detailing the need for autologous therapies for cardiovascular disease).

11. Miguel Ramalho-Santos & Holger Willenbring, *On the Origin of the Term "Stem Cell"*, 1 CELL STEM CELL 35, 35 (2007).

12. See Shinya Yamanaka, *The Winding Road to Pluripotency (Nobel Lecture)*, 52 ANGEWANDTE CHEMIE INT'L ED. 13900.

13. Stem cells hold the potential to treat many medical issues and diseases. For a more expansive list of their potential application, see *id.* at 13902–06.

diseases.¹⁴ Their potential lies in their ability to mimic, boost, and recreate the natural ability of cells in the body. In fact, major advantages of stem cell technology are its simplicity, reproducibility, and stem cells' ability to recapitulate the natural development.¹⁵ Academic researchers worldwide have developed promising stem cell-based therapies to all these diseases.¹⁶

However, moving a promising molecule from the bench side to a viable and safe product for the bed side is a very expensive endeavor.¹⁷ Scientists in academic research laboratories are good at discovering preliminary biomarkers for disease;¹⁸ however, academic research labs are not equipped, funded, or incentivized to do the necessary validation to push a promising molecule through to a commercially viable product.¹⁹ Private entities often do product development, relying on revenue streams generated, at least partially, as a direct result of the exclusivity that the patent system allows.²⁰ Private sector investing is necessary for medical and biotechnological innovation, and patentability plays a significant role in strategic decisions made by companies, investors, shareholders, and practitioners.²¹ Patents are thus an important element that determines which treatments make it to the clinic.

14. *Id.* at 13906 (“In Japan and other countries, researchers are conducting preclinical studies to prove the efficacy and safety of iPS cells for treating various diseases and injuries, such as Parkinson’s disease, macular degeneration, cardiac failure, spinal cord injury, and platelet deficiency.”); see also John T. Dimos et al., *Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons*, 321 SCI. 1218 (2008) (explaining how stem cells may be used to treat ALS); Daniel W. Stuckey & Khalid Shah, *Stem Cell-Based Therapies for Cancer Treatment: Separating Hope from Hype*, 14 NATURE REV. CANCER 683 (2014) (reviewing the most promising stem-cell based treatments for cancer and delineating the rationale for translating the most promising pre-clinical trials into the clinic).

15. Yamanaka, *supra* note 12, at 13906.

16. *Id.*

17. Jeffrey J. Stewart et al., *Putting a Price on Biotechnology*, BIO ENTREPRENEUR, NATURE BIOTECHNOLOGY <http://www.nature.com/bioent/2003/030101/full/nbt0901-813.html> (last visited Jan. 20, 2015).

18. See Leigh Anderson, *Candidate-Based Proteomics in the Search for Biomarkers of Cardiovascular Disease*, 563 J. PHYSIOLOGY 23, 23–24 (2005).

19. Stewart, *supra* note 17.

20. See ERNST & YOUNG, BEYOND BORDERS, GLOBAL BIOTECHNOLOGY REPORT 27, 30 (2012); Stewart, *supra* note 17; see also ROBERT P. MERGES, JUSTIFYING INTELLECTUAL PROPERTY 1–27 (2011); Michael A. Carrier, *Unraveling the Patent-Antitrust Paradox*, 150 U. PA. L. REV. 761, 762–64 (2002).

21. See GLOBAL INSIGHT & NAT’L VENTURE CAPITAL ASS’N, VENTURE IMPACT: THE ECONOMIC IMPORTANCE OF VENTURE CAPITAL-BACKED COMPANIES TO THE U.S. ECONOMY 9 (2011); ERNST & YOUNG, *supra* note 20, at 30.

Thus, it is not surprising that two recent Supreme Court cases affecting patentability in the life sciences²² have garnered interest, particularly for what some commentators have seen as scientific flaws and inconsistencies between the decisions.²³ The United States Patent and Trademark Office (“PTO”), in its recent guidelines on patent subject matter eligibility²⁴ noted that the *Myriad* and *Mayo* cases derive from a long-standing history of caselaw prohibiting the patentability of natural things.²⁵ However, despite the PTO’s assertion that the commotion that endured following the release of the guidelines is much ado about nothing,²⁶ these decisions will determine patentability of subject matter that is at the forefront of the biotechnology industry in general and specifically the stem cell industry. Furthermore, in a globalized market for innovation, driven in part by IP strength and enforcement, patent strategy depends on the international as much as the domestic patent system.

This Note will analyze the domestic patent subject matter eligibility, particularly as it applies to stem cells, and *Mayo* and *Myriad*’s effect on the stem cell industry. Part I emphasizes stem cells’ potential in treating modern medical challenges and explains the molecular characteristics that bring their patentability into question in light of recent cases.²⁷ Part II gives an overview of patentable subject matter caselaw and the evolution of the “law of nature” and “products of nature” doctrines. Part III examines patent eligibility of stem cells under the new PTO guidelines. Part IV

22. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012).

23. See Jake Gipson, *Patentable Subject Matter: A Myriad of Problems*, 65 ALA. L. REV. 815, 826–28 (2013); Ethan M. Weiner, Note, *Defining A Natural Phenomenon After Prometheus*, 28 BERKELEY TECH. L.J. 643, 659–70 (2013).

24. USPTO, *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 Fed. Reg. 74618 (Dec. 16, 2014) [hereinafter December 2014 Guidance].

25. *Id.*; see also USPTO, GUIDANCE FOR DETERMINING SUBJECT MATTER ELIGIBILITY OF CLAIMS RECITING OR INVOLVING LAWS OF NATURE, NATURAL PHENOMENA, & NATURAL PRODUCTS (Mar. 4, 2014), <http://www.uspto.gov/patent/patents-announcements/guidance-determining-subject-matter-eligibility-claims-reciting-or> (last accessed Feb. 12, 2015) [hereinafter March 2014 Guidance] (“*Myriad* relied on *Chakrabarty* as ‘central’ to the eligibility inquiry, and re-affirmed the Office’s reliance on *Chakrabarty*’s criterion for eligibility of natural products (i.e., whether the claimed product is a non-naturally occurring product of human ingenuity that is markedly different from naturally occurring products.”)).

26. See Donald Zuhn, *USPTO Provides Update on Status of Revised Myriad-Mayo Guidance*, PATENT DOCS (Nov. 12, 2014), <http://www.patentdocs.org/2014/11/uspto-provides-update-on-status-of-revised-myriad-mayo-guidance.html>.

27. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012).

analyzes the possible effects of the legal regimes on the development of stem cell technologies, and Part V concludes.

I. THE SCIENCE OF STEM CELLS

Not unlike subject matter eligibility, defining and understanding stem cells is complex and confusing, even for those who deal with them on a daily basis. This Part will explain some characteristics of stem cell molecular biology and physiology that are particularly important when analyzing their current patentability. More specifically, Section I.A will delineate the different types of stem cells and their therapeutic applicability for different diseases. Section I.B will provide important background on the molecular biology of stem cells and explain the scientific flaw of using DNA sequence identity to determine whether two products are “markedly different”²⁸ from one another.

A. STEM CELLS: THE TYPES, THE GENETICS, AND THE POTENTIAL

Stem cells are many different types of cells sharing two functional characteristics: the ability to self-renew, and the ability to give rise to a variety of differentiated and specialized cells in the body.²⁹ Stem cells are most commonly categorized into different types based on their potency: a stem cell can be totipotent, multipotent, or pluripotent.³⁰

A totipotent stem cell is able to differentiate into any adult human tissue or any extra-embryonic tissue, such as the placenta.³¹ The zygote (the first cell post-fertilization) is the best example of a totipotent cell. Shortly after the nuclei of the sperm and the egg fuse to form the zygote, multiple molecular mechanisms activate, resulting in rapidly changing and highly synchronized patterns of gene expression.³² These rapid cell divisions and gene expression ultimately results in the formation of inner cell mass (“ICM”), which is the group of cells that turns into the fetus, at which point none of the cells are truly totipotent anymore.³³

28. *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

29. Nat'l Insts. of Health, Stem Cell Basics, NAT'L INSTS. OF HEALTH <http://stemcells.nih.gov/info/basics/pages/basics3.aspx> (last visited Dec. 17, 2014) [hereinafter Stem Cell Basics].

30. *Id.*

31. *Id.*

32. SCOTT F. GILBERT, DEVELOPMENTAL BIOLOGY 300 (2013) (discussing mechanisms of compaction and the formation of the inner cell mass).

33. *Id.*

What most people picture when referring to stem cells is a pluripotent cell. A pluripotent stem cell can give rise to any adult tissue, but cannot differentiate into extra-embryonic tissue.³⁴ Embryonic stem (“ES”) cells are the best example of a pluripotent cell.³⁵ During embryonic development, by day four post-fertilization, cells have arranged into an outer layer called the trophoblast.³⁶ The trophoblast and ICM are distinct structures with different functions.³⁷ The trophoblast gives rise to all extra-embryonic supportive tissue, and the ICM differentiates into the embryo and ultimately the fetus.³⁸ ES cells are isolated from the ICM at around day four post-fertilization, which is why they are only able to differentiate into embryonic tissue.³⁹ Since ES cells are isolated at such an early stage of development, they still retain the ability to differentiate and divide indefinitely into any adult tissue, and these are the key characteristics for their potential therapeutic uses.⁴⁰

For over a decade, scientists believed that ES cells were the only isolated human cells to be pluripotent and that all other mammalian cells followed linear differentiation patterns—meaning that once a cell differentiated, it could not go back to a pluripotent state.⁴¹ However, in

34. *Id.*

35. Stem Cell Basics, *supra* note 29.

36. GILBERT, *supra* note 32 (discussing mechanisms of compaction and the formation of the inner cell mass).

37. *Id.*

38. *Id.*

39. James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCI. 1145, 1145 (1998).

40. *Id.*

41. C.H. Waddington, the father of epigenetics and a key player in the development of systems biology) coined the famous Waddington Epigenetic Landscape, where the differentiating fate of cells is compared to marbles rolling down a hill. As the marble rolls, it chooses a specific path until it comes to a stop, at which point it cannot roll upwards anymore. Another way to explain the Waddington landscape is to imagine skiing downhill, and how at each bifurcation a skier makes a decision of where to go. Once at the bottom of the hill, it is very difficult to go back uphill and choose a different path, unless the skier uses a ski-lift or chair. Similarly as cells differentiate, the gene expression pattern dictates which path the cells take and with each decision, going back to a previous state becomes very difficult. As cells differentiate they reach a critical point of no return, that is, they commit to a specific lineage or cell type. For example, with cardiomyocytes, once a specific transcription factor is turned on (Nkx2.5), the cell will either become a cardiomyocyte or die; there is no more turning back. Scientists believed this to be true until, more than half a century after the Waddington landscape was first published, Yamanaka discovered the “ski-lift” that cells could use to go back to the top of the hill. For further explanation of the Waddington landscape, see Aaron D. Goldberg et al., *Epigenetics: A Landscape Takes Shape*, 128 CELL 635, 635 (2007).

2006 Shinya Yamanaka's lab in Kyoto, Japan showed that a differentiated mouse cell could be reprogrammed back to a pluripotent state by overexpressing (through transgenes⁴²) four key pluripotency genes in the cell.⁴³ The Yamanaka team called these cells induced pluripotent stem cells ("iPS cells").⁴⁴ A year later, James Thomson's lab in Madison, Wisconsin showed that a similar procedure could be followed to reprogram differentiated human cells into iPS cells.⁴⁵ Yamanaka received the Nobel Prize for his work on induced pluripotent stem cells in 2012, as by this time, it was apparent that iPS cells held the potential to revolutionize regenerative medicine.⁴⁶

Subsequent research on iPS cells led to methods giving improved cellular derivation and differentiation.⁴⁷ Initially the four genes required for reprogramming were overexpressed in the differentiated cell through the integration of genetic cassettes (pre-determined sequences of DNA).⁴⁸ Retroviruses integrated these cassettes into the host genome.⁴⁹ This technique proved problematic, however. During differentiation, a cell silences pluripotency genes and activates organ-specific genes.⁵⁰ Failure to fully silence pluripotency genes during differentiation can result in cancer.⁵¹ Thus, in order for iPS cells to be useful therapeutically, reprogramming cassettes had to be removed from iPS cells shortly after

42. A transgene is a "gene that is taken from the genome of one organism and introduced into the genome of another organism by artificial techniques." Merriam-Webster Online Dictionary, <http://www.merriam-webster.com/dictionary/transgene> (last visited Mar. 12, 2015).

43. Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006).

44. *Id.*

45. Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCI. 1917 (2007).

46. Nobel Prize in Physiology or Medicine, 2012 Press Release, http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html (last visited Feb. 12, 2015).

47. See Vimal Selvaraj et al., *Switching Cell Fate: the Remarkable Rise of iPS Cells and Lineage Reprogramming Technologies*, 28 TRENDS IN BIOTECHNOLOGY 214, 214 (2012).

48. *Id.*

49. Takahashi & Yamanaka, *supra* note 43, at 664–65.

50. Eneida Hoxha and Raj Kishore, *Induced Pluripotent Cells in Cardiovascular Biology: Epigenetics, Promises, and Challenges*, in 111 PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE: GENETICS OF STEM CELLS 1–25, 5 (Y. Tang ed., 2012).

51. *Id.*

reprogramming.⁵² Scientists can now create patient-specific iPS cells from small amounts of peripheral blood. The pluripotency genetic cassettes used during reprogramming are removed shortly after de-differentiation is complete.⁵³ After the transgene is removed from the iPS cell, only a few residual DNA base pairs remain at the site of integration within the host DNA.⁵⁴

Like ES cells, iPS cells are pluripotent and have the ability to differentiate into any tissue type.⁵⁵ They are, however, superior to ES cells for use in regenerative therapy.⁵⁶ Patient-specific iPS cells share the same DNA identity with all other cells in the patient and are not prone to tissue rejection.⁵⁷ Furthermore, the use of iPS cells does not have the same type of ethical issues that the use of ES cells does, since no embryos are destroyed in the process of making iPS cells.⁵⁸

Unlike ES and iPS cells, multipotent stem cells have a much narrower differentiating potential.⁵⁹ Often referred to as adult stem cells, multipotent cells are partially differentiated cells that can only give rise to limited types of cells.⁶⁰ Hematopoietic stem cells, which give rise to different types of blood cells, are an example of a multipotent type of cell.⁶¹

B. DNA IDENTITY AND STEM CELLS

The central dogma of molecular biology is that DNA codes for mRNA that in turn codes for proteins.⁶² While this explanation of how DNA works is well accepted, in reality, biology is far more complex. Adult mammals contain hundreds of cell types distributed among their organs, each with identical DNA content. Studies suggest that much of the molecular basis of tissue-specific gene expression is rooted in the details of chromatin structure.⁶³ In addition to DNA, chromatin comprises proteins

52. Keisuke Okita et al., *Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors*, 322 SCI. 949, 949 (2008).

53. See Selvaraj, *supra* note 47, at 217–19.

54. *Id.*

55. *Id.* at 216.

56. *Id.*

57. *Id.*

58. *Id.*

59. See Stem Cell Basics, *supra* note 29.

60. *Id.*

61. *Id.*

62. Francis Crick, *Central Dogma of Molecular Biology*, 227 NATURE 561 (1970).

63. See S. Eden et al., *DNA Methylation Models Histone Acetylation*, 394 NATURE 842 (1998); Patrick Trojer & Danny Reinberg, *Histone Lysine Demethylases and their Impact on Epigenetics*, 125 CELL 213 (2006).

that help the DNA retain its structural integrity while tightly packed within a cell's nucleus.⁶⁴

DNA has a very long length relative to the size of the nucleus in which it is located, and thus requires a complex packing mechanism.⁶⁵ Histone proteins provide a scaffold to guide and maintain the structural integrity of DNA, allowing it to fold and condense into chromatin.⁶⁶ In order for DNA to function, it needs to be accessible to other proteins within the cell. Thus, how tightly or loosely the DNA is folded within the histone scaffold directly determines how accessible it is to other proteins within the cell. Thus, functionally the chromatin status and the DNA sequence are critical to DNA expression. Conversely, epigenetic changes are chemical modifications of DNA or chromatin that do not involve DNA sequence alteration or deletion.⁶⁷

The epigenetics of pluripotent cells, including ES and iPS cells, are extremely complex. During differentiation, the epigenetic structure of the cell changes as genes are continuously silenced and activated. When a fully differentiated cell is reprogrammed back to pluripotency, it retains some epigenetic memory.⁶⁸ Thus, even though both ES and iPS cells are pluripotent, they possess distinct epigenetic structures. Furthermore, the epigenetic state of both of these types of cells is distinct from fully differentiated cells in the human body.

As explained here, gene expression is more complex than pure reliance on DNA sequence. Thus genetic identity and DNA sequence identity are distinct concepts. Reliance on DNA sequence identity alone as a test for determining the patentability of inventions is a gross oversimplification and an inaccurate interpretation of molecular biology. As interpretation of scientific elements is a key aspect of patent law, how the underlying science is defined by courts has important implications on how patent subject matter eligibility is determined. The following section highlights

64. Steven Henikoff and M. Mitchell Smith, *Histone Variants and Epigenetics*, 7 COLD SPRING HARBOR PERSPECTIVES IN BIOLOGY 1 (2015).

65. *Id.*

66. Karolin Luger et al., *Crystal Structure of the Nucleosome Core Particle at 2.8 Å Resolution*, 389 NATURE 251, 251 (1997).

67. Myriam Hemberger et al., *Epigenetic Dynamics of Stem Cells and Cell Lineage Commitment: Digging Waddington's Canal*, 10 NATURE REV. MOLECULAR CELL BIOLOGY 526, 526 (2009); Robert J. Klose & Adrian P. Bird, *Genomic DNA Methylation: the Mark and its Mediators*, 31 TRENDS IN BIOCHEMICAL SCIS. 89, 89 (2006).

68. K. Kim et al., *Epigenetic Memory in Induced Pluripotent Stem Cells*, 467 NATURE 285 (2010).

the evolution of subject matter eligibility in U.S. patent law and the Court's reliance on scientific interpretation to determine what constitutes patentable subject matter.

II. U.S. PATENT LAW AND THE EVOLUTION OF SUBJECT MATTER PATENT ELIGIBILITY

The statutory language of 35 U.S.C. § 101⁶⁹ has remained largely unchanged since the Patent Act of 1952.⁷⁰ In the 1952 Act, Congress intended § 101 to be interpreted broadly and inclusively⁷¹ and fifty years later chose not to change § 101 when the America Invents Act was enacted.⁷² Historically, the courts have largely defined the boundaries of patentable subject matter.⁷³

The current patentability restrictions affecting biotechnology—lack of patentability for “products of nature” or processes that fall under “laws of nature”—date back to the Supreme Court's 1853 decision *Le Roy v. Tatham*, which established that a scientific principle cannot be patented.⁷⁴ The Court in *Le Roy*, however, introduced an exception to this rule, reiterated a year later in *O'Reilly v. Morse*,⁷⁵ that while scientific principles are not patentable, practical applications of such principles are.⁷⁶ Three Patent Acts⁷⁷ and 160 years have passed since these two decisions, science

69. 35 U.S.C. § 101 (2012) (“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”).

70. Compare to the statutory language of *id.* (“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”).

71. *Diamond v. Chakrabarty*, 447 U.S. 303, 315–16 (1980).

72. See Joe Matal, *A Guide to the Legislative History of the America Invents Act: Part I of II*, 21 FED. CIR. B.J. 435, 443–47 (2012) (reviewing the America Invents Act's passage through Congress).

73. See, e.g., *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

74. 55 U.S. 156, 174–75 (1853).

75. See *O'Reilly v. Morse*, 56 U.S. 62, 117 (1853) (reasoning that the patentee was entitled to a patent on a specific application of electromagnetism, but that electromagnetic current itself was not patentable subject matter).

76. *Le Roy*, 55 U.S. at 175.

77. Patent Act of 1922, 42 Stat. 392 (1922); Patent Act of 1952, 66 Stat. 797 (1952); and the Leahy-Smith America Invents Act, 125 Stat. 284 (2011). The obviousness requirement (now 35 U.S.C. § 103 (2012)) was not codified until the Patent Act of 1952. Cases preceding the 1952 Act do not always clearly distinguish between subject matter analysis and the obviousness test.

and medicine have changed dramatically, but the rules stated in *Le Roy* and *Morse* continue to guide the determination of patentability in the twenty-first century.

A. THE EVOLUTION OF THE “LAWS OF NATURE” DOCTRINE

Before *Mayo*, the “laws of nature” doctrine was shaped through cases concerning algorithms (including computer-implemented algorithms), and business-method patents. In *Gottschalk v. Benson*, the Court concluded that an algorithm for converting binary-coded decimal numbers into pure binary numbers was not patentable subject matter.⁷⁸ The *Benson* Court concluded that the algorithm was an abstract idea⁷⁹ and that mere implementation of the algorithm on a digital computer was not enough to make it a patentable invention.⁸⁰ A few years later in *Parker v. Flook*, the Court decided that another computer implementation of an algorithm was not patentable, since once the algorithm was assumed to be in the prior art, the rest of the system was anticipated.⁸¹

As the world of technology rapidly evolved in the late 1970s and early 1980s, so did the Court’s attitude toward patents generally, and software patents specifically. Only three years after *Flook*, the Court used the same analysis in *Flook* to hold that the algorithm claimed in *Diamond v. Diehr* was patentable subject matter.⁸² Following *Diehr*, and the expansion of technology and its applications in all sectors of life, there was a drastic increase in business and other algorithm-based patents.⁸³ The Federal Circuit addressed algorithm-based patents again in *In re Bilski*, when it introduced the machine-or-transformation test.⁸⁴ Under this test, an abstract idea was patentable only if it (i) was tied to a particular machine; or (ii) resulted in transformation of an article from one state to another.⁸⁵ The Federal Circuit concluded that the claims in *Bilski* did not fall under either category and rejected them.⁸⁶ The Supreme Court affirmed the Federal

78. 409 U.S. 63, 71–73 (1972).

79. *Id.*

80. *Id.*

81. 437 U.S. 584, 590 (1978).

82. 450 U.S. 175, 188–92 (1981).

83. *See, e.g., State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1093 (1999).

84. *In re Bilski*, 545 F.3d 943, 964 (Fed. Cir. 2008).

85. *Id.*

86. *Id.*

Circuit's decision, but rejected the analytical analysis under the machine-or-transformation test used by the Federal Circuit.⁸⁷

In over 150 years since *Le Roy* and *Morse*, the Supreme Court had built a judicial exception to patentability by relying on the definition of algorithms and mathematical formulas as “laws of nature.” That exception changed in 2012 when the Court expanded its definition of “laws of nature” by applying the test to a method patent on therapeutic medical treatments, in *Mayo v. Prometheus*.⁸⁸ The challenged patents in *Mayo*⁸⁹ claimed methods for optimizing therapeutic efficacy for the treatment of a specific disorder, by

- (i) administering a drug;
- (ii) measuring the internal blood levels of the drug standardized by concentration divided by the number of red blood cells;
- and (iii) adjusting the dose of the drug based on the individual patient's blood drug concentration as measured in (ii).⁹⁰

The Supreme Court rejected these claims based on the premise that “laws of nature” are not patentable subject matter.⁹¹ The Court stated that the method claimed merely set forth laws of nature⁹² without adding any significant additional step.⁹³ According to the Court, each step, taken separately, referred to either a routine practice in the medical profession, or simply reminded medical personnel to consider relevant “natural laws” when treating a patient.⁹⁴ The court then added that even when taken together, the claimed steps do nothing more than tell doctors to gather data from which they may draw an inference in light of correlations that exist purely because of laws of nature.⁹⁵

87. *Bilski v. Kappos*, 561 U.S. 593, 603–04 (2010). For an analysis and explanation of the machine-or-transformation-test, see Stefania Fusco, *Is In re Bilski a Déjà Vu?*, 2009 STAN. TECH. L. REV. P1 (2009).

88. See Rebecca S. Eisenberg, *Prometheus Rebound: Diagnostics, Nature, and Mathematical Algorithms*, 122 YALE L.J. ONLINE 341, 342–43 (2013).

89. U.S. Patent No. 6,355,623 (filed Apr. 8, 1999); U.S. Patent No. 6,680,302 (filed Dec. 27, 2001).

90. Claim 1 of US 6,355,623 is representative of this treatment process.

91. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1305 (2012).

92. *Id.* at 1297.

93. *Id.* at 1297–98.

94. *Id.* at 1297.

95. See *id.*

B. THE EVOLUTION OF THE “PRODUCTS OF NATURE” DOCTRINE

The “products of nature” doctrine has evolved through the Supreme Court’s struggle to incentivize innovation without monopolizing nature.⁹⁶ Some believe that products of nature are a common heritage of all humans, so no one should have exclusive rights to them. In *American Wood-Paper v. The Fibre Disintegrating Co.*, the Court stated that a pulp mixture for use in papermaking was not patentable subject matter.⁹⁷ Similarly in *Cochrane v. Badische Anilin & Soda Fabrik*, the Court concluded that a dye isolated from an herb was not patentable subject matter.⁹⁸ The “product of nature” doctrine first appears in *Ex Parte Latimer*.⁹⁹ In *Latimer* the patent in question was a fibrous material isolated from pine needles.¹⁰⁰ The patent was rejected because the fiber and its characteristics derived from the plant itself (*Pinus australis*) and were thus a product of nature.¹⁰¹

The upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations. To put the matter more succinctly, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. For these reasons we believe that the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities.

Id. at 1297–99.

96. *See* *The Am. Wood-Paper Co. v. The Fibre Disintegrating Co.*, 90 U.S. 566, 596 (1874) (determining patentability of paper-pulp obtained from various vegetables); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884) (determining patentability of alizarine of madder, which was similar to that found in nature, but was made artificially for the first time). It is important to note that in both cases the patents were rejected on questions of novelty. Neither of the two early cases references a “product of nature” as unpatentable subject matter.

97. 90 U.S. at 596.

98. 111 U.S. at 311–13.

99. *Ex parte Latimer*, 1889 Dec. Comm’r Pat. 123 (1889).

100. *Id.* at 124–25.

101. *See id.* at 125–26:

Nature made them so and not the process by which they are taken from the leaf or the needle. It cannot be said that the applicant in this case has made any discovery, or is entitled to patent the idea, or fact, rather, that fiber can be found in the needle of the *Pinus australis* . . . that grow in the forest and the construction of the woody fiber and tissue of which they are composed is not a patentable invention, recognized by the statute, any more than to find a new gem or jewel in the earth

Judge Learned Hand, in one of the most referenced district court patent cases ever published, used a more flexible approach in determining whether isolated and concentrated adrenaline could be patented.¹⁰² The court in *Parke-Davis* decided that a product, isolated and concentrated from what was found in nature, was patentable subject matter.¹⁰³ Despite the decision in *Latimer*, the court concluded that there are no rules against patenting a product that is new both commercially and therapeutically.¹⁰⁴ The *Parke-Davis* decision has become common knowledge among patent law scholars, and it is frequently cited¹⁰⁵ and relied upon,¹⁰⁶ despite its friction with several other contemporary and subsequent decisions.

The “natural product” doctrine was fully endorsed by the Supreme Court in *Funk Brothers Seed v. Kalo Inoculant Co.*¹⁰⁷ The patent claimed a mixture of nitrogen-fixing bacteria that could be used to fertilize a wide

would entitle the discoverer to patent all gems which should be subsequently found. . . . Otherwise it would be possible for an element or a principle to be secured by patent, and the patentee would obtain the right, to the exclusion of all other men...the fiber which nature has produced and which nature has intended to be equally for the use of all men.

Id.

102. *Parke-Davis & Co v. H.K. Mulford Co.*, 189 F. 95, 97 (C.C.S.D.N.Y. 1911).

103. *Id.* at 103:

[E]ven if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine [the inventor] was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.

Id.

104. *Id.*

105. The *Parke-Davis* decision is included in several casebooks, hornbooks and treatises. See, e.g., ROBERT P. MERGES & JOHN F. DUFFY, *PATENT LAW AND POLICY: CASES AND MATERIALS* 158 (2013); ROBERT P. MERGES, PETER S. MENELL & MARK A. LEMLEY, *INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE* 139, 142 (2012). The decision even made it into the guidelines issued by the PTO on patentable subject matter. See *Utility Examination Guidelines*, 66 FED. REG. 1092, 1093 (2001) (“Patenting compositions or compounds isolated from nature follows well-established principles, and is not a new practice.”).

106. See *In re Merz*, 97 F.2d 599, 601 (C.C.P.A. 1938) (expanding on *Parke-Davis* by stating that the isolated product must be different “in kind,” not just in “degree,” from the substance that occurs in nature); see also *In re King*, 107 F.2d 618, 620 (C.C.P.A. 1939).

107. 333 U.S. 127 (1948).

array of plants.¹⁰⁸ The Court rejected the patent on the grounds that it claimed a property of natural phenomena.¹⁰⁹ The Court reasoned that both the nitrogen fixing abilities of the bacteria and the non-inhibitory effects against other nitrogen-fixing bacteria existed in nature.¹¹⁰ The Court reasoned that such abilities were “part of the storehouse of knowledge . . . free to all men and reserved exclusively to none.”¹¹¹ The Court in *Funk Brothers* was sensitive to patents that would preclude innovation and purely exploit inherent laws of nature.¹¹²

However, in *Chakrabarty*,¹¹³ the Court stated that a transgenic organism “had markedly different characteristics from any found in nature” and was a product of human ingenuity.¹¹⁴ The “markedly different characteristics from any found in nature” language has been adopted by the PTO in the Manual of Patent Examining Procedure (“MPEP”) guidelines and remains a staple in § 101 patentability analysis today.¹¹⁵

The Supreme Court revisited what it means to have “markedly different characteristics” thirty years after *Chakrabarty* in *Association for Molecular Pathology v. Myriad*.¹¹⁶ In *Myriad*, the Court stated that isolated DNA was not patentable.¹¹⁷ The bacterium in *Chakrabarty* was non-naturally occurring and a product of human ingenuity.¹¹⁸ *Myriad*, on the other hand, the Court stated, had not made anything by merely isolating

108. *Id.* at 128. The mixture was an important advancement in agricultural biology and commercially successful since it was the first time that scientists had succeeded in creating a mixture of oxygen fixing bacteria that did not inhibit each other’s growth.

109. *Id.* at 130.

110. *Id.*

111. *Id.* at 130.

112. It is important to note that *Le Roy*, *Morse* and *Funk Brothers* were adjudicated before Congress included a non-obviousness provision in the Patent Act of 1952. The “synergy test” derived from *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152 (1950), required that patents claiming a combination of known elements must have unusual characteristics whereby the whole exceeds the sum of its parts. Subject matter patentability and non-obviousness are separate requirements of patentability encoded in separate sections of the America Invents Act. That was not the case when the *Funk Brothers* decision was made.

113. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

114. *Id.*

115. *See* MPEP § 2106.01 (9th ed., Mar. 2014) (“Composition of matter—all compositions of two or more substances and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids, for example. *Chakrabarty*, 447 U.S. at 308.”).

116. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

117. *Id.* at 2111.

118. 447 U.S. at 309.

the DNA.¹¹⁹ However, the Court found cDNA to be patentable subject matter as it was different from the native DNA found in nature.¹²⁰ *Myriad* makes clear (and possibly silently overturns *Parke-Davis*)¹²¹ that mere isolation is not enough to render a composition of matter patent eligible.¹²² The Court in *Myriad* relied on chemical differences between native DNA and cDNA to allow for the patentability of cDNA.¹²³

As anticipated, *Myriad* was quickly applied outside the field of nucleic acid sequences. The Federal Circuit, in a recent ruling, denied a patent to the Roslin Research Institute for Dolly, the first mammal to be cloned through nuclear transfer.¹²⁴

C. *IN RE ROSLIN INSTITUTE*

1. *Procedural History*

Dr. Keith H.S. Campbell and Sir Ian Wilmut were the first scientists to clone a mammal, Dolly the sheep, from an adult somatic cell.¹²⁵ In doing so, they proved that a fully differentiated nucleus could be reprogrammed,¹²⁶ and influenced research that gave rise to the first induced pluripotent stem cells a decade later.¹²⁷ As explained earlier, almost all cells in the human body share the same DNA sequence.¹²⁸ Different portions of the DNA are expressed and silenced in different cells, which results in different cells having different identities.¹²⁹ The process to create Dolly involved three main steps: (i) inserting a nucleus of a quiescent differentiated cell into an oocyte, (ii) culturing the reconstructed embryo, and (iii) isolating and culturing the inner cell mass cells obtained from the culture in step (ii).¹³⁰ Because of this process, Dolly shared the same nuclear DNA with her somatic cell donor and the same mitochondrial DNA with her oocyte donor.

119. 133 S. Ct. at 2111.

120. *Id.* at 2119–2120.

121. *United States v. Parke, Davis & Co.*, 362 U.S. 29 (1960).

122. 133 S. Ct. at 2111.

123. *Id.* at 2119–20.

124. *In re Roslin Inst.*, 750 F.3d 1333, 1336 (Fed. Cir. 2014).

125. K. H. Campbell et al., *Sheep Cloned by Nuclear Transfer from a Cultured Cell Line*, 380 NATURE 64 (1996).

126. K. Takahashi et al., *Induction of Pluripotent Stem Cells From Adult Human Fibroblasts by Defined Factors*, 131 CELL 861, 861 (2007).

127. *Id.* at 869–71.

128. *See supra* Part I.

129. *Id.*

130. U.S. Patent No. 7,514,258 Claim 1 (filed Nov. 3, 2005).

The Roslin Institute filed for patents on both the cloning method used to create Dolly, and the cloned animal itself,¹³¹ which the Examiner rejected¹³² as non-patentable subject matter under 35 U.S.C. § 101, and as anticipated and obvious under §§ 102 and 103.¹³³ The Roslin Institute filed an appeal brief before the Board of Patent Appeals and Interferences (“BPAI”) in September 2009.¹³⁴ The Board affirmed the Examiner’s rejections determining that the claims in question were not patentable subject matter as delineated by § 101.¹³⁵ The Board further affirmed the Examiner’s rejections under §§ 102 and 103, stating that the claims were anticipated and obvious from prior art clones produced from embryonic mammals.¹³⁶ Following the rejection by the Board, the Roslin Institute appealed the decision to the Federal Circuit.

2. Federal Circuit Decision

The Federal Circuit affirmed the Board’s decision, stating that the claims in question in the patent application are not patentable subject matter.¹³⁷ In affirming the decision the court explained that even before the Supreme Court’s decision in *Myriad*,¹³⁸ the Court’s opinions in *Chakrabarty*¹³⁹ and *Funk Brothers*¹⁴⁰ made clear that naturally occurring

131. A patent for the invention was first filed in Great Britain in August 1995. G.B. Patent No. 9517780.4 (Aug. 31, 1995). Less than a year later PCT/GB96/02099 was filed, that claimed priority to the 80.4 patent. G.B. Patent No. 96/02099 (Aug. 30, 1996). A continuation on PCT/GB96/02099, application 08/802,282, was first filed in the U.S. in 1997 (“the `282 patent application”). U.S. Patent Application No. 08/802,282 (Feb. 19, 1997). The `282 patent application contained both method and composition claims. *Id.* Application 09/225,233 (1999) was filed as divisional application of 08/802,282 with compositions claims. U.S. Patent Application No. 09/225,233 (Jan. 4, 1999). The method claims describing the nuclear transfer process were granted by the PTO and are not in dispute. U.S. Patent No. 6147276A.

132. Notice of Non-Final Rejection, Nov. 10, 2008. More specifically, the claims rejected are 155–159 and 164, of which claims 155 and 164 are representative:

155. A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats.

164. The clone of any of claims 155–159, wherein the donor mammal is non-foetal.

133. *Id.* at 6, 13, 18.

134. *In re Roslin Inst.*, 750 F.3d 1333, 1333 (Fed. Cir. 2014).

135. *Ex parte Roslin Inst.*, No. 2010-006828, 20 (B.P.A.I. Feb. 7, 2013).

136. *Id.* at 22–23.

137. *Roslin*, 750 F.3d at 1334.

138. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

139. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

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

organisms are not patentable.¹⁴¹ The Federal Circuit relied substantially on all three opinions in rejecting the claims at issue as ineligible patentable subject matter.

On appeal, the Roslin Institute argued that unlike other sheep, Dolly is eligible for protection as it is a product of human ingenuity and not nature's handiwork.¹⁴² The court rejected this proposition under *Chakrabarty*, as "Dolly herself is an exact genetic replica of another sheep and does not possess 'markedly different characteristics from any [farm animals] found in nature."¹⁴³ Relying on *Myriad*, the court further noted that the Roslin Institute did not create or alter the genetic structure used to make the clones, and that such a copy of the genetic material is not eligible for patent protection.¹⁴⁴ However, the court also stated that "having the same nuclear DNA as the donor mammal may not necessarily result in patent ineligibility in every case. Here, however, the claims do not describe clones that have markedly different characteristics from the donor animals of which they are copies."¹⁴⁵

Roslin further argued that the clones were patent eligible because they were distinguishable from the donor mammals in at least two ways: (i) environmental factors led to phenotypic differences between the animals, and (ii) the nuclear DNA belonged to the donor somatic cell but the mitochondrial DNA belonged to the oocyte, leading to differences in DNA between the clone and the somatic cell donor.¹⁴⁶ The Federal Circuit rejected both these arguments, noting that neither the phenotypic differences nor the mitochondrial DNA differences were claimed in the '233 patent application.¹⁴⁷ The court further noted that any phenotypic differences between the cloned animal and the donor are the result of environmental factors and came about independently of the invention.¹⁴⁸ Relying on *Funk Brothers* and *Chakrabarty*, the court elaborated that "any phenotypic differences came about or were produced 'quite independently of any effort of the patentee."¹⁴⁹ The court reasoned that when "qualities

141. *Roslin*, 750 F.3d 1333, 1336 (Fed. Cir. 2014).

142. *Id.* at 1337.

143. *Id.* (quoting *Chakrabarty*, 447 U.S. at 310).

144. *Id.*

145. *Id.* at 1339.

146. *Id.* at 1338.

147. *Id.*

148. *Id.*

149. *Id.* (quoting *Funk Bros.*, 333 U.S. at 131).

are the work of nature . . . [t]hose qualities are of course not patentable.”¹⁵⁰ The court further rejected Roslin’s arguments regarding differences resulting from mitochondrial DNA,¹⁵¹ as such differences were not initially claimed, and the patentee did not initially explain how the mitochondrial DNA could influence the characteristics of the cloned mammal.¹⁵²

In regard to Roslin’s argument that the clones are patent eligible because they are time-delayed versions of their donor mammals, the court stated that such a distinction cannot confer patentability.¹⁵³ Any copy of an original is a time-delayed version of the original.¹⁵⁴ Because the court rejected all pending claims on subject matter ineligibility, it did not evaluate the novelty or obviousness rejections issued by the Board.

3. *The Scientific and Legal Inconsistencies in Roslin*

Roslin did not just apply *Myriad*; it took the reasoning much further by using identity to DNA as a test to measure whether a claimed product falls under the “product of nature” eligibility exemption.¹⁵⁵ By using this test, the *Roslin* court determined that a product—a cloned animal—that would not exist if not for human intervention was a product of nature. Besides the logical inconsistency of determining that something that could never exist in nature—such as a cloned mammal—is a product of nature, the *Roslin* decision contains multiple scientific flaws. As explained in Part II of this Note,¹⁵⁶ DNA sequence is only one component of genetic identity. By using DNA sequence identity as a test to measure identity between a product found in nature and one created in the lab, the Federal Circuit grossly simplified the molecular biology at hand and failed to recognize the elements in Dolly that are a direct result of human intervention. These elements were as much a product of human ingenuity in 1996 as the transgene used in *Chakrabarty* was in 1980. Furthermore, even if we consider DNA sequence identity as the proper test, Dolly differed from its nuclear donor as it included a different sequence of mitochondrial DNA. Similarly to the transgene in *Chakrabarty*, the mitochondrial DNA was present in Dolly as a direct result of human intervention through cloning.

150. *Id.* (quoting *Diamond v Chakrabarty*, 447 U.S. 303, 310 (1980)).

151. *Id.*

152. *Id.*

153. *Id.* at 1339.

154. *Id.* (citing *Ex parte Roslin Inst.*, No. 2010-006828, 20 (B.P.A.I. Feb. 7, 2013)).

155. *See id.* at 1338–39.

156. *See supra* Part II.

Scientists have known about the presence of DNA in mitochondria for more than half a century,¹⁵⁷ and the presence of mitochondrial DNA in Dolly, distinct from that of its nuclear donor, would have been obvious to a person of ordinary skill in the art. The Federal Circuit rejected the presence of mitochondrial DNA as a characteristic that made Dolly distinct from a product of nature, because such a difference was not claimed.

The Federal Circuit rejected arguments that highlighted the differences between a cloned animal and an animal found in the wild, by noting that the genetic and phenotypic differences were not claimed in the patent application.¹⁵⁸ This is a rather interesting argument, since it is not within the purpose of the claim as traditionally interpreted by the courts, to define differences between elements of the claim outside of what is required during prosecution.¹⁵⁹ Courts interpret the claim as written, and assume that “[t]he patentee seeks the broadest claim he can get.”¹⁶⁰ So it is the claim that defines the boundaries, and the written description cannot broaden the reach of what is claimed.¹⁶¹ Thus the claim as written would determine the broadest possible reach of the claim, including the method limitation. Elements of the claim cannot be broadened by the specifications. A product claim is still valid and infringed if the same product or composition is made through a different method. It is a long-standing interpretation of United States courts that claims define the boundaries of an invention, not describe it.¹⁶² “Claims define and circumscribe,” whereas the “written description discloses and teaches.”¹⁶³ In *Ariad*, the court stated that the principal function of a claim is to “provide notice of the boundaries of the right to exclude and to define

157. Mitochondrial DNA was first described in 1963, less than ten years after the structure of DNA had been published. Margit M. K. Nass & Sylvan Nass, *Intramitochondrial fibers with DNA characteristics*, 19 J. CELL BIOLOGY 593 (1963).

158. *Roslin*, 750 F.3d at 1338.

159. See *Ex parte Sinai-Zingde*, No. 94-0377, 1995 WL 1747988 (B.P.A.I. July 31, 1995), (stating that “it is not the purpose of the claims to include every detail of an applicant's invention. That function is left to the specification.”). But see *In re Johnson*, 558 F.2d 1008 (C.C.P.A. 1977) (stating that “[c]laim language must be read in light of the specification as it would be interpreted by one of ordinary skill in the art”).

160. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1054 (Fed. Cir. 1988).

161. See *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996); see also *McClain v. Ortmyer*, 141 U.S. 419, 424 (1891) (“The claim is the measure of his right to relief, and, while the specification may be referred to limit the claim, it can never be made available to expand it.”).

162. See, e.g., *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010).

163. *Id.* at 1334.

limits; it is not to describe the invention.”¹⁶⁴ Support for a composition claim does not need to provide any additional methods of making the composition. The Federal Circuit has stated that a “patentee need only describe the invention as claimed, and need not describe an unclaimed method of making the claimed product;” thus, a court “cannot invalidate a patent for failure to describe a method of producing the claimed compositions that is not itself claimed.”¹⁶⁵ In fact, in *Amgen*, the court determined that a composition claim for an erythropoietin (“EPO”) was valid and infringed, regardless of differences in the method used to produce the infringing EPO.¹⁶⁶ The general interpretation by the courts is that an old product is not patentable even if made by a new method.

Thus, by rejecting epigenetic, genetic, and phenotypic differences that made Dolly distinct from the sheep that served as the nuclear donor, the Federal Circuit rejected well-established scientific principles of molecular biology, and legal principles of the degree of information required to be claimed in a patent.

D. NEW PTO GUIDELINES POST-*ROSLIN*

On December 16, 2014, the PTO announced its interim guidance on subject matter eligibility.¹⁶⁷ The December guidelines included more detail and expanded guidance on examination procedures after the decision in *Alice Corp. v. CLS Bank*.¹⁶⁸ In addition, the guidelines addressed and clarified several issues based on some of the concerns that practitioners had expressed over the *Myriad–Mayo* guidelines released in March.¹⁶⁹ Specifically, the PTO noted that the analysis outlined in the interim guidance differed from the *Myriad–Mayo* guidance in several ways.¹⁷⁰ The

164. *Id.*

165. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003).

166. *Id.* at 1358.

167. USPTO DECEMBER 2014 GUIDANCE, *supra* note 24.

168. The USPTO released preliminary examination instructions regarding *Alice Corp. v. CLS Bank International* in June 2014. USPTO, 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/patent/patents-announcements/preliminary-examination-instructions-determining-subject-matter> (last accessed Feb. 12, 2015).

169. USPTO MARCH 2014 GUIDANCE, *supra* note 25.

170. The PTO stated that the December 2014 interim guidance differed from the *Myriad/Mayo* March 2014 guidelines in several ways. Note, for example, the test for determining whether a claim is directed to a “product of nature” exception is separated from the analysis of whether the claim includes significantly more than the exception.

office also notes that the interim guide “offers a comprehensive view of subject matter eligibility in line with *Alice Corp, Myriad, Mayo*, and the related body of case law,” and “promotes examination efficiency and consistency across all technologies.”¹⁷¹

According to the interim guidance, examiners will use a two-step analysis to determine subject matter eligibility.¹⁷² The first step is determining whether the claimed invention falls within the statutory requirements for subject matter patentability (i.e., process, machine, manufacture or composition of matter).¹⁷³ The second step involves determining whether the claim is directed at a judicially determined exception to patentability¹⁷⁴ (i.e., laws of nature, products of nature) and whether “any element, or combination of elements, in the claim is sufficient to ensure that the claim amounts to significantly more than the judicial exception.”¹⁷⁵ However, the December guidelines also note that they differ from the prior *Myriad–Mayo* guidelines because “changes in functional characteristics and other non-structural properties can evidence markedly different characteristics, whereas in the [*Myriad–Mayo* guidance] only structural changes were sufficient to show a marked difference.”¹⁷⁶ The guidelines further note that “[m]arkedly different characteristics can be expressed as the product’s structure, function, and/or other properties,” noting that “even a small change can result in markedly different characteristics from the product’s naturally occurring counterpart.”¹⁷⁷ Thus, based on the new guidelines,¹⁷⁸ if a claim includes a nature-based

Also, the application of the overall analysis is based on claims directed to judicial exceptions (defined as claims reciting the exception, i.e., set forth or described), rather than claims merely “involving” an exception. For instance, process claims that merely use a nature-based product are not necessarily subject to an analysis for markedly different characteristics. Additionally, the markedly different analysis focuses on characteristics that can include a product’s structure, function, and/or other properties as compared to its naturally occurring counterpart in its natural state. *See generally* USPTO DECEMBER 2014 GUIDANCE, *supra* note 24.

171. *Id.* at 74619–20.

172. *Id.* at 74621–22; *see also* MPEP § 2106 (9th ed., Mar. 2014).

173. *Id.* at 74622.

174. The guidelines clarify that “[l]aws of nature and natural phenomena, as identified by the courts include naturally occurring principles/substances and substances that do not have markedly different characteristics compared to what occurs in nature.” *Id.* at 74622.

175. *Id.* at 74624.

176. *Id.* at 74623, n.27.

177. *Id.* at 74623.

178. *See id.*

product that has markedly different characteristics, the claim would be eligible for patentability. In giving examples of what the courts have determined to constitute markedly different characteristics, the guidelines explain that biological, pharmacological, physical, genetic, and chemical differences in structure, form or function could be construed as providing markedly different characteristics.¹⁷⁹ However, the guidelines point out that differences that resulted independently of any effort or influence by the applicant cannot be construed as markedly different.¹⁸⁰

The new guidelines on their face seem more clear and lenient to the patentability of products of nature than the March guidelines. However, interpreting what construes a marked difference is still very challenging, especially after *Roslin*, which indicates that the differences that resulted independently of the effort or influence by the applicant cannot be patented. Showing that differences resulted directly because of the effort of the applicant, requires that the scientists not only know the end result they are trying to achieve, but also the molecular and genetic details that result in the process, at the time of patent application. In a field where the cost of research and development is already very high, it is unclear how much additional claiming and “scientifically unnecessary experimentation” inventors need to do in order to show “markedly different” characteristics so as to procure a patent.

In accordance with this analysis, a product that is purified or isolated, for example, will be eligible when there is a resultant change in characteristics sufficient to show a marked difference from the product's naturally occurring counterpart. If the claim recites a nature-based product limitation that does not exhibit markedly different characteristics, the claim is directed to a “product of nature” exception (a law of nature or naturally occurring phenomenon), and the claim will require further analysis to determine eligibility based on whether additional elements add significantly more to the exception.

Id.

179. *See id.* at 74623 (enumerating examples of what constitutes a markedly different characteristic: biological or pharmacological functions or activities (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, *Diamond v. Chakrabarty*, *In re King*, and *Myriad*); chemical and physical properties (citing *Parke-Davis & Co. v. H.K. Mulford Co.* and *Funk Bros.*); phenotype, including functional and structural characteristics (citing *In re Roslin Inst.*); and structure and form, whether chemical, genetic or physical (citing *Chakrabarty*, *Parke-Davis*, and *Myriad*)). For examples of the analysis on nature-based products, see USPTO, NATURE-BASED PRODUCTS, http://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf (last visited Dec. 18, 2014).

180. USPTO DECEMBER 2014 GUIDANCE, *supra* note 24, at 74623–24.

III. DETERMINING THE CURRENT STATE OF PATENTABILITY OF STEM CELLS

Subject matter patentability is the first hurdle to obtain a patent. As such, any test for patentable subject matter should be viewed as an act of promoting the progress of science¹⁸¹ by balancing the need to incentivize innovation on the one hand, and retain an open reservoir of ideas and scientific tools that other scientists can benefit from on the other hand. While fears that patents will slow down research are common,¹⁸² patent holders rarely enforce their patents against academic research labs.¹⁸³

As noted in Part I, the biggest challenges faced in modern medicine require fast and personalized diagnostics, treatments, and therapies that mimic natural processes or cells in the human body. Following *Mayo* and *Myriad*, patenting these processes and compositions will be more difficult, and these patents will be more challenging to defend.

A. COMPOUND/COMPOSITION CLAIMS

1. *Embryonic Stem Cells and Adult Stem Cells*

Despite their utility and scientific importance, embryonic stem cell patents have been scrutinized since their early years. In 1998, James Thomson became the first scientist to successfully isolate and maintain human embryonic stem cells (“hESCs”).¹⁸⁴ The invention encompassed three key features: (i) the process for isolating embryonic stem cells, (ii) the embryonic stem cells isolated, and (iii) the process of maintaining these pluripotent cells.¹⁸⁵ The key features of this invention¹⁸⁶ were covered in three foundational U.S. patents for his work (the “WARF patents”) assigned to the Wisconsin Alumni Research Foundation (“WARF”) and its subsidiary WiCell Research Institute (“WiCell”).¹⁸⁷ Some of these

181. U.S. CONST. art. I, § 8, cl. 8.

182. Dan L. Burk, *The Problem of Process in Biotechnology*, 43 HOUS. L. REV. 561, 564–565 (2006).

183. For example, despite its aggressive assertion of patent rights in the market place, Myriad did not assert any of its patents against academic labs, as evidenced by over 10,000 publications on PubMed on research using isolated BRCA DNA. See Christopher M. Holman, *Trends in Human Gene Patent Litigation*, 322 SCI. 198 (2008).

184. James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCI. 1145 (1998).

185. *Id.*

186. *Id.*

187. U.S. Patent No. 5,843,780 (filed Jan. 18, 1996); U.S. Patent No. 6,200,806 (filed June 26, 1998); U.S. Patent No. 7,029,913 (filed Oct. 18, 2001).

patents are currently licensed to Cellular Dynamics International.¹⁸⁸ The WARF patents have gone through exceptional scrutiny at the PTO, and have received several re-examination requests.¹⁸⁹ Many of the initial claims have been invalidated as anticipated or obvious.¹⁹⁰ However, some of the original claims still stand.¹⁹¹ Following the *Myriad* decision, Consumers Watchdog filed an appeal to the Patent Board's decision, in which it asked the court to invalidate the remaining WARF patents on hESCs.¹⁹² Consumer Watchdog claims that hESCs are products of nature since they are "not markedly different from naturally occurring hESCs."¹⁹³ However, other scholars have argued that isolated stem cells are different from those naturally found in a day four embryo due to the process and human directed environment in which they are maintained.¹⁹⁴ Thus, several

188. Cellular Dynamics International ("CDI") is the leading biotechnology company in the development of cells and tissue through stem cell technologies. CDI's current products have revolutionized how drugs are tested. CDI is currently collaborating with CERM to produce and market patient-specific stem cells. *See Cellular Dynamics: Cells to Order*, LIFE SCIS. INTELLECTUAL PROP. REV. (Jan. 13, 2014), <http://www.lifesciencespreview.com/article/cells-to-order>; *see also* Cellular Dynamics International, Inc. Patent Applications, PATENTDOCS (Nov. 27, 2014), <http://www.faqs.org/patents/assignee/cellular-dynamics-international-inc/>; *Cellular Dynamics International In-Licenses Key Patent Portfolio for Using Stem Cell-Derived Cells in Drug Testing*, CELLULAR DYNAMICS INT'L (July 15, 2009), http://www.cellulardynamics.com/news/pr/2009_07_15.html. In March 2015 it was announced that Fujifilm Holdings will acquire CDI via an all-cash tender offer to be followed by a second-step merger. *See Fujifilm Holdings to Acquire Cellular Dynamics International, Inc.*, CELLULAR DYNAMICS INT'L (Mar. 30, 2015), <http://investors.cellulardynamics.com/releasedetail.cfm?ReleaseID=903900>; (PMZN) *Fujifilm Holdings to Acquire Cellular Dynamics International, Inc.*, WALL STREET JOURNAL (Mar. 30, 2015), <http://www.wsj.com/articles/PR-CO-20150330-903128>.

189. *See* John M. Golden, *WARF stem cell patents and tensions between public and private sector approaches to research*, 38 J.L. MED. & ETHICS 314, 315-16 (2010).

190. *See* Action Closing Prosecution from *Inter Partes*, Reexamination No. 95/000,154; *Ex Parte* Reexamination, Reexamination No. 90/008,139; *Ex Parte* Reexamination, Reexamination No. 90/008,102; *Found. for Taxpayer & Consumer Rights v. Wisconsin Alumni Research Found.*, No. 2010-001854, 2010 Pat. App. LEXIS 15017 (B.P.A.I. Apr. 28, 2010).

191. *See, e.g.*, U.S. Patent No. 5,843,780 Claim 1 (filed Jan. 18, 1996).

192. *Consumer Watchdog v. Wisconsin Alumni Research Found.*, 753 F.3d 1258 (Fed. Cir. 2013).

193. Ari Haque, *Human Embryonic Stem Cell Patent Challenged*, CONSUMER WATCHDOG (July 8, 2013), <http://www.consumerwatchdog.org/story/human-embryonic-stem-cell-patent-challenged>.

194. Due to their nature, stem cells have an inherent tendency to differentiate rather than remain pluripotent. Differentiation and tissue development occur as a cascade of events that is very hard to curtail and control, since it is not fully understood. Thus, the factors used in stem cell culture result isolated ESCs with slightly different epigenetic

arguments could be made that these cells are different from native embryonic stem cells, despite *Myriad's* holding. Their expressed protein profile is slightly different, their epigenetic status is different and ultimately, their functionality is different. These characteristics would have allowed patentability under *Parke-Davis*¹⁹⁵ and are a product of human ingenuity.¹⁹⁶ It is not clear if the “human ingenuity” involved in isolating stem cells is the same type the court in *Chakrabarty* found to be a key step toward patentability.¹⁹⁷

However, none of these arguments are persuasive in light of *Roslin*. In *Roslin* the Federal Circuit stated that since the DNA identity between Dolly and its parental nuclear donor were the same; Dolly was a product of nature.¹⁹⁸ Isolated ES cells also share the same DNA identity with their parental donor. Furthermore, unlike Dolly, isolated embryonic stem cells share both the nuclear and mitochondrial DNA with their donor embryo. The Federal Circuit also rejected the argument that non-DNA differences could be enough to confer patentability.¹⁹⁹ However, the decision to dismiss epigenetic differences relied on such differences not being claimed in the original patent.²⁰⁰ Such differences are also not claimed in the WARF patents either,²⁰¹ and would thus be rejected under *Roslin*. Furthermore, any arguments that rely on the premise that ESCs are time-delayed versions of the original embryo they were derived from, would be unpersuasive, since the Federal Circuit considered and rejected the same

imprint and protein expression profiles than cells at day four of embryonic development have. ROBERT LANZA & ANTHONY ATALA, *ESSENTIALS OF STEM CELL BIOLOGY* 537 (2013).

195. *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911):

[E]ven if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine [the inventor] was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.

Id.

196. The isolation of human embryonic stem cells is considered a landmark in cell biology and is recognized by the scientific community as a highlight in modern cell and molecular biology. Frederic Golden, *Cellular Biology: Stem Winder*, *TIME* (Aug. 20, 2001), <http://content.time.com/time/magazine/article/0,9171,1000598,00.html>.

197. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

198. *In re Roslin Inst.*, 750 F.3d 1333, 1337 (Fed. Cir. 2014).

199. *Id.*

200. *Id.* at 1338.

201. *See, e.g.*, U.S. Patent No. 5,843,780.

argument in *Roslin*.²⁰² Thus, if the Federal Circuit follows the *Roslin* analysis to evaluate the remaining composition claims of the WARF patents, such claims would likely be found invalid as products of nature.

On the other end of the spectrum are adult derived stem cells. These cells would also be difficult to patent under *Myriad/Roslin*. Hematopoietic stem cells, ePS cells and other multipotent cells are isolated and purified from blood or tissue by using a distinct receptor.²⁰³ These cells share the same DNA with other cells found in the body. Differences in protein expression profiles or the epigenome between the isolated and native cells, are likely not to be persuasive in light of *Roslin* for the same reasons explained above.

2. Induced Pluripotent Stem Cells

Induced pluripotent stem cells (“iPSCs”) differ in one key aspect when it comes to patentability from ESCs and other adult derived stem cells. iPSCs are generated through transgenic expression of two to four key pluripotency genes. Thus, under *Chakrabarty*, claims to iPSCs should be valid.²⁰⁴

However, there is one important caveat to this analysis. Expression of these pluripotency genes is one of the major problems and limitations of iPSC therapy.²⁰⁵ The ability to differentiate into any cell type and divide indefinitely is both the blessing and the curse of iPSC therapy, because indefinite cell division and differentiation also result in cancer.²⁰⁶ Thus, it is important that the exogenous genetic cassettes are fully silenced or ideally fully excised from the resulting iPSCs genome, before they are transplanted into a patient.²⁰⁷ Labs (both academic and industrial) use methods that excise exogenous genetic cassettes from iPSCs after the cells have been de-differentiated into a pluripotent state. Thus, these cells do not pose a transgene post-differentiation and share the same sequence

202. *Roslin*, 750 F.3d at 1339.

203. Hematopoietic cells are isolated by using CD34/CD31 receptors. *See, e.g.,* Reema Jain and Daniel H.D. Gray, *UNIT 3.26 Isolation of Thymic Epithelial Cells and Analysis by Flow Cytometry*, 107 CURRENT PROTOCOLS IN IMMUNOLOGY 3.26 (2014); Masahiro Yoa et al., *Fucci-Guided Purification of Hematopoietic Stem Cells with High Repopulating Activity*, 457 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUN. 7 (2015).

204. *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) (supporting a broad interpretation of the term “composition of matter”).

205. Hoxha & Kishore, *supra* note 50, at 5.

206. *Id.*

207. *Id.*

identity with the rest of the cells found in the patient they were derived from, with the exception (if any) of a very short sequence flanking the insertion site. For iPS cells that retain the short flanking sequence, it is unclear whether such a short sequence is enough to distinguish these cells from nature products.²⁰⁸ That is, it is unclear whether such an invention is more like that in *Chakrabarty* or *Roslin*. Furthermore, if scientists are able to fully excise the exogenous gene expression cassette, leaving a cell that shares complete DNA identity with other cells native to the patient, that cell then, under *Roslin*, would not be patentable. The question then becomes: Should a dozen base-pairs with obsolete functionality in the fully reprogrammed cell determine the fate of its patentability?

On the other hand, epigenetic differences between iPS cells and ESCs, or fully differentiated cells, are well accepted in the scientific community.²⁰⁹ Epigenetic differences were not discussed in *Myriad* and they were rejected in *Roslin* because they were not claimed in the original patent.²¹⁰ The question then remains whether epigenetic differences if claimed, would allow the patent to pass the subject matter eligibility hurdle. That in turn creates a lot of uncertainty of how much and what epigenetic changes need to be claimed, which would frustrate invention disclosure and prosecution practices.

B. METHOD CLAIMS UNDER *MAYO*

Stem cells used in diagnosis and therapies are a great example through which personalized medicine can help with the complex medical challenges described in Part I. The goal of personalized medicine is to optimize diagnosis and treatment by combining a person's genetic data with information about personal lifestyle, and correlating it to pre-determined expression outcomes.²¹¹ The utility of personalized medicine starts with prenatal genomics and continues through fetal development and throughout a person's life.²¹² The field relies largely on the expression of individual genes, biomarkers, and metabolites to determine diagnosis

208. See *In re Roslin Inst.*, 750 F.3d 1333, 1336 (Fed. Cir. 2014).

209. See, e.g., Kim et al., *supra* note 68 (describing epigenetic memory in iPS cells when compared to ES cells).

210. *Roslin*, 750 F.3d at 1337.

211. Diana W. Bianchi, *From Prenatal Genomic Diagnosis to Fetal Personalized Medicine: Progress and Challenges*, 18 NATURE MED. 1041, 1041 (2012); see also Muin J. Khoury et al., *The Scientific Foundation for Personal Genomics: Recommendations from a National Institutes of Health-Centers for Disease Control and Prevention Multidisciplinary Workshop*, 11 GENETIC MED. 559, 560-61 (2009).

212. Bianchi, *supra* note 211, at 1041.

and treatment regimens.²¹³ These correlations exist because the principles of molecular biology apply—the laws of nature.²¹⁴ Under *Mayo*, a claim to a diagnostic method that derives from rigorous scientific inquisition, but ultimately relies in the understanding and application of such laws of nature, will be more challenging to patent.²¹⁵ Similarly, claims to methods of adjusting treatment protocols by analyzing gene expression profiles will be challenged²¹⁶ during prosecution and litigation.

With the development of next generation sequencing and improvement of isolation and amplification protocols,²¹⁷ scientists and medical personnel can diagnose and treat a patient from information gathered from a very small amount of peripheral blood.²¹⁸ Medical professionals can diagnose problems by classifying patients based on the genetic expression imprint at any given point. That is, scientists can measure and classify expression levels of genes and diagnose a patient, even before the patient has shown any clinical signs or problems. Even though under *Myriad* cDNA can be patented,²¹⁹ it is unclear that under *Mayo*, methods that compare a patient's gene expression profile to a pre-determined dataset to diagnose disease would be patentable. The laws of nature control how and when genes are expressed. However, decoding such genes and recognizing patterns in expression profiles so as to best “apply” nature to cure disease, requires the same type of human ingenuity that the Court found sufficient to distinguish between “products of nature” and patentable subject matter in *Chakrabarty*.²²⁰

While *Mayo* will be challenging for method patents, *Myriad* will not be as challenging to overcome for composition claims. Despite the magnitude of concern that *Myriad* generated, the Supreme Court decision

213. *Id.*

214. Khoury, *supra* note 211.

215. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1297–98 (2012).

216. *See id.* at 1297 (“The relation is a consequence of the ways in which [drug] compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law.”).

217. *See, e.g.*, Michael L. Metzker, *Sequencing Technologies—The Next Generation*, 11 NATURE REV. GENETICS 31 (2010).

218. *See, e.g.*, James S. Ware et al., *Next Generation Sequencing for Clinical Diagnostics and Personalised Medicine: Implications for the Next Generation Cardiologist*, 98 HEART 276 (2012) (explaining how genomics can aid in the diagnosis and treatment of patients with cardiovascular disease).

219. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2119 (2013).

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

had minimal effects on the BRCA1/2 test itself.²²¹ Furthermore, next-generation sequencing techniques use universal primers,²²² which do not rely on any specific DNA sequence, and are thus unlikely to be affected by the decision. Additionally, the sequence of the human genome is largely available online, and thus part of prior art, which would likely trigger rejections on novelty for any future patents on a DNA sequence. What *Myriad* does not bar are applications of the knowledge derived from correlating a mutation to a disease. Such claims were not challenged during the *Myriad* litigation.²²³ It is *Mayo* that poses a significant challenge to such uses of genetic information.

IV. PATENTS, INNOVATION AND THE BIOTECHNOLOGY INDUSTRY

A. THE COST OF STEM CELLS AND PATENT PROTECTION

Developing a promising biotechnological or medical breakthrough into a viable clinically useful product is an expensive and long journey, subject to multiple regulatory hurdles.²²⁴ It is estimated that commercializing a biotechnological innovation (up to the point of bringing it to the market) costs over \$1.2 billion and requires about ten to fifteen years for pre-market validation and approval.²²⁵ In industries developing biological products such as cells, besides funding necessary for product development, additional costs include recruiting and maintaining a highly skilled workforce in a competitive market concentrated in three small geographic regions.²²⁶

221. *Ambry Genetics Countersues Myriad Genetics in BRCA Testing Fight*, THE PATHOLOGY BLAWG (Aug. 12, 2013), <http://pathologyblawg.com/pathology-news/pathology-vendors/myriad-genetics/ambry-genetics-countersues-myriad-genetics-brca-testing-fight/> (last accessed Feb. 13, 2015); Kevin E. Noonan, *Myriad Throws the Towel*, PATENT DOCS (Jan. 27, 2015), <http://www.patentdocs.org/2015/01/myriad-throws-in-the-towel.html> (last accessed Mar. 12, 2015).

222. See Metzker, *supra* note 217, at 32–33.

223. *Myriad*, 133 S. Ct. at 2120 (quoting Ass’n for Molecular Pathology v. USPTO, 689 F.3d 1303, 1349 (Fed. Cir. 2012)).

224. BIOTECHNOLOGY INDUSTRY ORGANIZATION, GUIDE TO BIOTECHNOLOGY 38–42, 77 (Roxanna Guilford-Blake & Debbie Strickland eds., 2008) [hereinafter BIO GUIDE].

225. Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 482 (2008); see also BIO GUIDE, *supra* note 224, at 38 (“It typically takes 10 to 15 years and an average of more than \$800 million (including the cost of failures) to develop a new therapy.”).

226. See YALI FRIEDMAN, BUILDING BIOTECHNOLOGY 3–9 (3d ed. 2014).

The cost of stem cell technologies comes from five sources: (i) research and development; (ii) process engineering; (iii) production and scaling, including licensing fees; (iv) efficiency and safety testing; and, (v) marketing, technology support, and management.²²⁷ It is important to note that the process engineering and production steps in stem cell technologies require skilled workers with at least a bachelor's degree and experience in cell culture and other laboratory techniques. This monetary cost is different from most drugs, which cost very little to produce once the Research & Development phase has concluded.²²⁸ Furthermore, the mode of operation and revenue stream in biotechnology companies is such that for these companies, patent protection is critical to attract the necessary capital to fund such high-risk investment.²²⁹ Heart attacks and the underlying health problems that precede and follow a heart attack are a great example illustrating the need for stem cell therapies and the cost to develop such therapies.

B. DEVELOPING STEM CELL THERAPY FOR CARDIOVASCULAR DISEASE: GETTING TO THE HEART OF THE MATTER

Generally, cardiovascular diseases, and specifically ischemic heart disease, are the leading cause of death worldwide.²³⁰ About one in three deaths in the US is a result of cardiovascular disease.²³¹ In fact more than twice as many women die from a heart attack, or myocardial infarction ("MI"), than from all other cancers combined.²³² Recent medical advancements have resulted in approximately 90–95% of patients surviving their first MI.²³³ The high first heart attack survival rate has contributed to the current epidemic of heart failure, placing an enormous burden on the healthcare system.²³⁴ After an MI, local cardiac mechanisms are activated

227. *Id.* at 163–74, 209–223.

228. Grabowski, *supra* note 225.

229. See FTC, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY, A REPORT BY THE FEDERAL TRADE COMMISSION, ch.3, 1, 17–18 (2003) ("Biotech representatives emphasized that patent protection is critical to attract the capital necessary to fund this high-risk investment.").

230. Alan S. Go et al., *Heart Disease and Stroke Statistics—2014 Update: A Report from the American Heart Association*, 129 CIRCULATION e28, e30 (2014).

231. *Id.*

232. *Id.* at 116.

233. See Wayne D. Rosamond et al., *Twenty-two Year Trends in Incidence of Myocardial Infarction, Coronary Heart Disease Mortality, and Case Fatality in Four US Communities, 1987 to 2008*, 125 CIRCULATION 1848 (2012).

234. Veronique L. Roger et al., *Heart Disease and Stroke Statistics—2011 Update: A Report from the American Heart Association*, 123 CIRCULATION e18, e20 (2011).

that result in a vicious cycle of metabolic insufficiency and tissue death.²³⁵ After a patient survives the first heart attack, there are no therapies that are able to reverse the tissue loss and the inevitable decline in cardiac function, which puts the patient at increased risk for a second heart attack.²³⁶ Typically, the first heart attack does not kill a patient; the second does.²³⁷ Since the underlying trigger of this process is the loss of cardiomyocytes and microvasculature in the infarcted wall, it is important that new cardiomyocytes replace the ones lost after the attack. One way to replenish the lost cardiomyocytes in the heart is through implantation of stem cells or their derivatives directly into the heart.²³⁸ Ideally, the cardiomyocytes would be derived from an autologous source and share the same DNA identity with the other natural resident heart cells.

As explained in Part II, scientists are able to isolate peripheral blood cells from a patient and reprogram them into iPS cells. Assume that a scientist has found a way to differentiate these patient derived iPS cells into cardiomyocytes, which can be used to treat and regenerate lost tissue after a heart attack.²³⁹ Before the treatment can be available to a patient several milestones need to be achieved. The scientist has shown that a standard iPS cell line can be differentiated into cardiomyocytes. However, because different patients have accumulated different mutations in their lifetime, their iPS cells behave differently in the re-differentiation process. Thus, multiple experiments are required to show that functional cardiomyocytes can be derived from the patient that suffered from the heart attack. After the applicability of such an invention has been tested, a

235. See, e.g., Stein Orn et al., *Effect of Left Ventricular Scar Size, Location, and Transmurality on Left Ventricular Remodeling with Healed Myocardial Infarction*, 99 AM. J. CARDIOLOGY 1109 (2007).

236. See Patrick T. O'Gara et al., *2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*, 127 CIRCULATION e362, e392 (2013) (describing that roughly twenty percent of patients that suffered from a heart attack and survived, die within the year).

237. Go et al., *supra* note 230, at e30.

238. See Michael A. Laflamme & Charles E. Murry, *Heart Regeneration*, 473 NATURE 326, 326 (2011); Doris A. Taylor, *From Stem Cells and Cadaveric Matrix to Engineered Organs*, 20 CURRENT OPINION BIOTECHNOLOGY 598, 598 (2009).

239. This example is to illustrate the path to redifferentiating patient-specific cells to be used in regenerative therapy following a heart attack. Scientists have already developed ways to re-differentiate patient-specific cells into cardiomyocytes. See *Cellular Dynamics International Launches iCell Cardiomyocytes*, NEWS MED. (Dec. 16, 2009, 3:21 AM). <http://www.news-medical.net/news/20091216/Cellular-Dynamics-International-launches-iCell-Cardiomyocytes.aspx>.

process must be engineered through which cells from different patients can be differentiated into heart cells.²⁴⁰ After a process has been engineered, the protocol is passed on to the production team that must consistently and safely differentiate different patient cells. The next step is then to obtain necessary FDA approval through rigorous clinical testing.²⁴¹ The last step of the process is to optimize and tweak cell differentiation to each patient based on the feedback from the transplanted cells. Each step is costly. In fact, leading companies in the field, such as Cellular Dynamics International and NeoStem, still operate at a deficit despite launching very successful and innovative products over six years ago.²⁴² Thus, in order to commercialize the innovation described above, scientists need a large amount of funding for each step.

C. THE IMPORTANCE OF PATENTS

The value of patents on scientific innovation has been widely debated.²⁴³ Essentially, the patent system operates under the assumption that “market knows best” and incentivizes entities to both innovate and share information by providing temporary exclusivity.²⁴⁴ These incentives are particularly important in the biotechnology and pharmaceutical industries, where the cost of R&D is high, but the barrier of entry for an established working product is low.²⁴⁵ Stem cell technologies, however, have both high R&D costs and high production costs, making it harder for new competitors to enter the market. So the question then becomes,

240. It would be prohibitively expensive and long if a different process had to be engineered for each patient.

241. For the cost and financial demands of FDA approval in the stem cell field, see Heidi Ledford, *Stem Cell Company in Crisis: Financial Woes Threatened Advanced Cell Technology*, NATURE NEWS (Jan. 25, 2014), <http://www.nature.com/news/stem-cell-company-in-crisis-1.14591>.

242. CDI brings in over twelve million dollars in revenue each year, and spends over forty-four million, most of which are in R&D, production and marketing costs. See Cellular Dynamics Int'l, Inc., Quarterly Report (Form 10-Q) (Aug. 29, 2013); Cellular Dynamics Int'l, Inc., Quarterly Report (Form 10-Q) (Nov. 12, 2013); Cellular Dynamics Int'l, Inc., Quarterly Report (Form 10-Q) (May 5, 2014); Cellular Dynamics Int'l, Inc., Quarterly Report (Form 10-Q) (Aug. 11, 2014).

243. See, e.g., Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHIC. L. REV. 129 (2004).

244. See *id.*

245. For most synthetic chemicals, the cost of production is actually very low, and thus the barrier of entry for a competitor easy to overcome. On the other hand, in a technology where significant infrastructure is necessary, the barrier of entry would be high, offsetting the need for a patent. See Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y, L. & ETHICS 717, 725–27 (2005).

how much exclusivity is needed to allow for the necessary investment to push stem cell innovation through the commercialization process? The answer to this depends on several factors, which include company size, venture capital reliance, and investor sophistication.

1. *IP Protection and Company Size*

The biggest innovators in stem cell technologies are small companies,²⁴⁶ for which venture capital investment is particularly important.²⁴⁷ Arora and Merges²⁴⁸ formulate a game between two identities that are working on a contract where one identity, which holds intellectual property, would provide highly customized products to another identity. In the vast majority of cases, it is shown that independence creates higher net surplus, and furthermore, the stronger the intellectual portfolio, the larger the difference between the surplus created by independent integration versus vertical integration.²⁴⁹ And thus, a conclusion that one can form is that when firms hold strong intellectual properties, they tend to stay independent.²⁵⁰

Following this logic, strong IP rights within the stem cell industry would result in a higher number of smaller companies, more collaboration between large and small companies, and less vertical integration. Since this is the current state of the stem cell space,²⁵¹ this theory seems to apply.

246. Karl Bergman & Gregory D. Graff, *The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development*, 25 NATURE BIOTECHNOLOGY 419, 421 (2007).

247. See NAT'L VENTURE CAPITAL ASS'N, PATIENT CAPITAL: HOW VENTURE CAPITAL INVESTMENT DRIVES REVOLUTIONARY MEDICAL INNOVATION, 3, 7 (2007) (emphasizing that the biotechnology industry would not exist without venture capital financing and stating that "[b]ecause their capital needs are so large and their path to market is so long and risky, it is difficult for life sciences startups to access bank financing or other more traditional sources of capital").

248. See Ashish Arora & Robert P. Merges, *Specialized Supply Firms, Property Rights and Firm Boundaries*, 13 INDUS. & CORP. CHANGE 451, 461–62 (2004).

249. *Id.* at 468–70.

250. *Id.* at 471–72.

251. Bergman & Graff, *supra* note 246:

No single company, even after accounting for mergers and acquisitions, held more than 3 percent of US granted stem cell patents. The top eight companies together owned just 13 percent of the total. Interestingly, the top eight public sector institutions likewise owned 13 percent, and half of these were located in California. The strong showing of large biotech and pharmaceutical companies was somewhat surprising. Amgen, Novartis, Pfizer and GlaxoSmithKline are rarely mentioned by market analysts as prominent players in stem cell

However, weaker IP rights stemming from recent court decisions might lead to more vertical integration that could in turn lead to less innovation and higher R&D costs. Due to their size, stem cell companies rely on venture capital investment. As IP rights weaken, and venture capital funding gets sparser, stem cell innovation would shift to bigger companies, which—considering the way that biotechnology currently operates—is not optimal.²⁵²

As explained above, investment in small biotechnology companies is tied closely to the strength of its patents.²⁵³ However, investors evaluate different factors when considering investment.²⁵⁴ Investment is tied to company valuation,²⁵⁵ and company valuation depends on many factors,

research. Instead, it is the smaller companies with a specific focus on stem cells, such as Geron, that are more frequently cited.

Id. at 421.

252. See Avik Roy, *How Big Pharma Undermined Medical Innovation for Financial Gain*, FORBES: PHARMA AND HEALTHCARE (Feb. 15, 2012, 7:22 PM) <http://www.forbes.com/sites/aroy/2012/02/15/how-big-pharma-undermined-medical-innovation-for-financial-gain/> (explaining how big pharma opposed FDA reforms that would bring innovative medicines to market more quickly); see also Mike Wokasch, *Biotech: A Source for Big Pharma Innovative New Products*, PHARMA REFORM (May 11, 2010), <http://www.pharmareform.com/2010/05/11/biotech-a-source-for-big-pharma-innovative-new-products/> (“Big Pharma has never been renowned for innovation. Rather, large pharmaceutical companies have traditionally focused on developing and testing conventional therapeutics, such as small molecule drugs and monoclonal antibodies, building and investing in the substantial infrastructure required to support these efforts.”).

253. See Dan L. Burk & Mark A. Lemley, *Biotechnology’s Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 724–26 (2004); see also PRESIDENT’S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, PRIORITIES FOR PERSONALIZED MEDICINE 21 (2008) (“The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products”).

254. For a detailed analysis on economic theories of investments and patents, see ROBERT P. MERGES & JOHN F. DUFFY, PATENT LAW AND POLICY 727–28 (6th ed. 2013) (discussing the different effects that §§ 101, 102, and 103 have on determining which innovations to pursue and which to commercialize); Mark A. Lemley, *Reconceiving Patents in the Age of Venture Capital*, 4 J. SMALL & EMERGING BUS. L. 137 (2000).

255. Jerry X. Cao & Po-Hsuan Hsu, *The Informational Role of Patents in Venture Capital Financing*, 1–2 (June 8, 2011) (unpublished manuscript), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1678809; see also Carolin Häussler et al., *To Be Financed or Not . . . —The Role of Patents for Venture Capital-Financing*, 32–33 (Feb. 28, 2008) (unpublished manuscript), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1393725.

including venture capital (“VC”) sophistication,²⁵⁶ or how much VCs value patent strength.²⁵⁷ Patent strength relies not only on the patents the company has, but rather on the patents owned, compared to those owned by others. Furthermore, while the decision of whether to invest or not is based on possession of key patents that cover the technology, how much to invest depends on the strength of such patents against other patents. Generally there is a strong positive correlation on patent applications, patents, and VC financing.²⁵⁸ In stem cell technologies, most investors are specialized in such technologies. Thus, it is more likely that patent strength plays an important role in the valuation of the company as a whole.

2. *Other Effects of Weaker Patent Protection*

Stem cell companies can protect their intellectual property in two ways: trade secrets or patents. Several scholars have argued that a decrease in patent rights could lead to increased secrecy in research and decreased collaboration²⁵⁹ Myriad, for example, created an extensive database of

256. For a detailed analysis on economic theories of investments and patents, see ROBERT P. MERGES AND JOHN F. DUFFY, *PATENT LAW AND POLICY* 727–28 (6th ed. 2013) (discussing the different effects that §§ 101, 102, and 103 have on determining which innovations to pursue and which to commercialize); Mark A. Lemley, *Reconceiving Patents in the Age of Venture Capital*, 4 J. SMALL & EMERGING BUS. L. 137 (2000).

257. See Dan L. Burk & Mark A. Lemley, *Biotechnology’s Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 724–26 (2004); President’s Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* 21 (2008) (“The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products”).

258. See Brownlynn H. Hall et al., *Market Value and Patent Citations*, 36 RAND J. ECON. 16 (2005); Sebastian Hoenena et al., *The diminishing signaling value of patents between early rounds of venture capital financing*, 43 RESEARCH POLY 956, 956–57, 986–87 (stating that “a handful of empirical studies has documented that patents attract prominent VCFs, prompt VCFs to invest faster and generally increase the amounts invested in firms that own them” and finding a particularly strong correlation for early investment.).

259. See Robert Cook-Deegan et al., *The next controversy in genetic testing: clinical data as trade secrets?*, 21 EUR. J HUM. GENET. 585–88 (2013), Chris Palmer, *The Myriad Decision: A move towards trade secrets?*, 22 NIH CATALYST 2:1, 8–10 (stating that “Without genomic DNA being patentable, it may throw into question protection for important technology that’s critical to improving public health. The decision may even backfire on its proponents, leading to increased secrecy in research and reduced collaboration.”).

genetic variants, which it made public.²⁶⁰ Some fear that such databases, which are very important to third party researchers, would not exist if a company did not enjoy patent protection.²⁶¹ Similarly, stem cell companies often publish relevant data on cell culture techniques and optimal differentiation.²⁶² This data is particularly valuable, since academic labs do not possess the resources to test cell culture protocols across multiple lines at the same rate that a commercial company does. An inability to patent a technology might lead these companies to greater trade secret protection, reduced workforce fluidity, and result in less cumulative innovation.²⁶³

Furthermore, biotechnology is not only an important component of our medical system, but also an important part of our entrepreneurial structure and economy as a whole.²⁶⁴ Despite being a fairly new industry,²⁶⁵ biotechnology is a multi-billion industry that accounts for over 400,000 jobs,²⁶⁶ and is a key contributor to U.S. economic stability.²⁶⁷ Stem cell industries are a rapidly growing subset within the biotechnology field.²⁶⁸ The ripple effect of diminished patent protection within these fields, especially considering the importance of patent protection to the existence of these companies, would not only have an effect on the medical industry, but to some extent on the economy as a whole.

D. U.S.-INTERNATIONAL COMPETITION

Patent applications are one indicator of commercialization activity within a field. Between 1970 and 2005, thirty-five percent of patents on

260. *Id.*

261. *Id.*

262. *See, e.g.,* Faye M. Drawnel et al., *Disease Modeling and Phenotypic Drug Screening for Diabetic Cardiomyopathy Using Human Induced Pluripotent Stem Cells*, 9 CELL REP. 810 (2014); Praful Aggarwal et al., *RNA Expression Profiling of Human iPSC-Derived Cardiomyocytes in a Cardiac Hypertrophy Model*, PLOS ONE 9:e108051 (2014).

263. *See* Arti K. Rai, *Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust*, 16 BERK. TECH L.J. 813, 834–35, 842–43 (2001) (arguing that patents can facilitate cumulative innovation where trade secrets hamper it).

264. *See* ERNST & YOUNG, *supra* note 20, at 37; GLOBAL INSIGHT & NAT'L VENTURE CAPITAL ASS'N, *supra* note 21, at 9.

265. *See* FRIEDMAN, *supra* note 226, at 3–5.

266. NAT'L VENTURE CAPITAL ASS'N, *supra* note 247, at 8.

267. *See id.* at 6–8.

268. Alexander van Servellen & Ikuko Oba, *Stem cell research: Trends in and perspectives on the evolving international landscape*, 36 RESEARCH TRENDS 1 (2014) (reporting that stem cell research is growing at a very fast rate, with iPS research showing an explosive growth).

stem cells were filed with the PTO and the European Patent Office (“EPO”).²⁶⁹ Besides the United States and Europe, the most active countries for stem cell filings were Australia, Canada, Japan, Germany, China, the United Kingdom and Israel.²⁷⁰ Stem cells, genes, and products of nature are internationally controversial topics. However, different international patent regimes have dealt with them differently.

In a globalized market, with a myriad of international commercialization opportunities, patentability plays a key role in determining where investors decide to commercialize a product. In order to incentivize globalization, the World Trade Agreement (“WTA”) became operative in 1995 and established the World Trade Organization. The Agreement on Trade-Related Aspects of Intellectual Property Rights (“TRIPS”)²⁷¹ is one of many international agreements in the WTA. TRIPS is one of the most important milestones in intellectual property harmonization, and it gave new life to the previous attempts for harmonized international intellectual property rights.²⁷² It provides the international legal framework (applicable to the countries that are signatories) for addressing patentability generally and patentable subject matter specifically.²⁷³

269. Bergman & Graff, *supra* note 246, at 420.

270. *Id.*

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

272. DANIEL GERVAIS, *THE TRIPS AGREEMENT: DRAFTING HISTORY AND ANALYSIS* 3, 24–25 (3d ed. 2003) (describing TRIPS as “the most comprehensive international agreement on intellectual property protection ever established”, and explains that TRIPS is distinguishable from both the Berne and Paris Conventions of the 19th century because of its IP provisions); *see also* SUSAN K. SELL, *PRIVATE POWER, PUBLIC LAW: THE GLOBALIZATION OF INTELLECTUAL PROPERTY RIGHTS* 7–9 (2003) (explaining that TRIPS is a dramatic expansion of the rights of IP owners which is far-reaching with important implications for innovation, research and development, economic development, the future location of industry, and the global division of labor).

273. *See* TRIPS, *supra* note 271:

Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.

Id. at art. 27.1.

However, it is important to note that TRIPS only provides a framework for regulations,²⁷⁴ and the signatory countries have some leeway in how they incorporate such guidelines into national law.²⁷⁵ In other words, TRIPS provides guidelines that serve as a floor to what needs to be protected, and each country—so long as they do not discriminate between citizens and non-citizens—can determine their own ceiling. Under Article 27(1) “patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.”²⁷⁶ Thus for a member state to grant a patent, the “invention” must at least satisfy these requirements, or the signatory country would be in violation of the agreement.²⁷⁷ In the United States, for example, these requirements are satisfied through the novelty, obviousness and utility requirements of the Patent Act.²⁷⁸

The United States and Europe had in place patent requirements that complied with the Paris Convention for the Protection of Industrial Property of 1883 (which preceded TRIPS), so there are shared similarities between the regimes, the evolution of the doctrines surrounding patentability, and the definition of the word “invention.”²⁷⁹ Furthermore, many countries have closely incorporated TRIPS guidelines into their patent law.²⁸⁰ Despite this, several differences exist between different patent regimes that affect the patentability of stem cells.

274. Marrakesh Agreement Establishing the World Trade Organization, art. 16.4, Apr. 15, 1994, 1867 U.N.T.S. 154 [hereinafter WTA] (“Each Member shall ensure the conformity of its laws, regulations and administrative procedures with its obligations as provided in the annexed Agreements.”).

275. See Paul Cole, *Myriad-Mayo Guidance — Consistency with International Harmonization and TRIPS*, PATENT DOCS (Aug. 26, 2014), <http://www.patentdocs.org/2014/08/guest-post-myriad-mayo-guidance-consistency-with-international-harmonization-and-trips.html>.

276. TRIPS, *supra* note 271, at art. 27.1; Agreement on Trade-Related Aspects of Intellectual Property Rights, 1869 U.N.T.S. 299 (1994).

277. WTA, *supra* note 274 (“Each Member shall ensure the conformity of its laws, regulations and administrative procedures with its obligations as provided in the annexed Agreements.”).

278. See generally 35 U.S.C. §§ 101–112 (2012).

279. The common principles are: 1) that there is a distinction between an ‘invention’ and a ‘patentable invention,’ 2) that an ‘invention’ per se must be new and useful, 3) that an ‘invention’ which is not novel, which lacks an ‘inventive step and which is not industrially applicable is not a ‘patentable invention,’ and 4) that laws of nature, physical phenomena, and abstract ideas per se are prohibited as ‘inventions.’

280. Compare TRIPS, *supra* note 271, at art. 27.1 (proclaiming that “patents shall be available for any inventions, whether products or processes, in all fields of technology,

When faced with the challenges of the patentability of purified natural products, such as purified DNA in 1998, the PTO, EPO, and Japan Patent Office (“JPO”), seemed to agree on the fact that isolated molecules are patentable since they do not exist in nature in their isolated form.²⁸¹ The Supreme Court Decision in *Myriad* shows that in the United States, this view is no longer applicable.

While different countries have limitations on the patentability of stem cells, they approach such limitations differently. For example, the EPO relies heavily on the “ordre public” exemption, which provides that subject matter can be exempt from patentability as necessary in order to protect human, animal, or plant life.²⁸² The question of whether or not embryonic stem cells violated the “ordre public” provision was decided on October 2011, when the European Court of Justice, decided in *Brüstle v. Greenpeace* that a process which involves the destruction of a human embryo, or uses a derivative of base material, derived from a process that destroys a human embryo, cannot be patented.²⁸³ On the other hand, iPSCs have been patented in the EU.²⁸⁴

provided that they are new, involve an inventive step and are capable of industrial application”), *with* European Patent Convention art 52(2), Oct. 5, 1973, 1065 U.N.T.S. 199 (establishing that “European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application”), *and* Patents Act, 1977, § 1.1 (Eng.) (describing that “A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say (a) the invention is new; (b) it involves an inventive step; (c) it is capable of industrial application; . . .”).

281. In 1988 the PTO, the EPO and the JPO issued a joint communication explaining their position regarding the patentability of Directive technologies. The communication provides:

Purified natural products are not regarded under any of the three laws as products of nature or discoveries because they do not in fact exist in nature in an isolated form. Rather, they are regarded for patent purposes as biologically active substances or chemical compounds and eligible for patenting on the same basis as other chemical compounds.

NUFFIELD COUNCIL ON BIOETHICS, THE ETHICS OF PATENTING DNA: A DISCUSSION PAPER 26 (2002); *see also* Anita Varma and David Abraham, *DNA Is Different: Legal Obviousness and the Balance between Biotech Inventors and the Market*, 9 HARV. J. L. & TECH. 53 (1996).

282. TRIPS, *supra* note 271, at arts. 27.2, 27.3.

283. Oliver Brüstle v Greenpeace e.V., Case C-34/10, EUR-Lex CELEX LEXIS 62010CJ0034, 52 (Oct. 18, 2011) (Belg.).

284. The United Kingdom Intellectual Property Office (“UKIPO”) and EPO have granted iPSC patents. *See, e.g.*, G.B. Patent No. 2,450,603 (Jun. 13, 2008); E.P.O. Patent No. 1970446 (Dec. 6, 2006).

Australian patent law does not explicitly include an exemption to the patentability of products of nature.²⁸⁵ This doctrine is defined differently in Australia than in the United States. The High Court of Australia defined this doctrine in *National Research and Development Corp. v. Commissioner of Patents* (“NRDC”).²⁸⁶ In *NRDC*, the Court explained that any distinction by the courts of “discovery” and “invention” is not precise enough to be useful but would rather be misleading and confusing to the discussion governing subject matter eligibility.²⁸⁷ Rather than focusing on the distinction between “discovery” and “invention” in terms of what is a natural phenomenon, law of nature, or abstract idea, subject matter eligibility in Australia focuses on the end result of the intellectual process involved.²⁸⁸ The disparity in the reliance on the distinction between “discovery” and “invention” in the United States vs. Australia is best observed in the *Myriad* cases in which the U.S. and Australian courts reached different conclusions when evaluating the same patents. The Federal Court of Australia, unlike the U.S. Supreme Court, concluded that both isolated DNA and cDNA are patentable subject matter under Australian law.²⁸⁹ The Australian court noted, that it is not within the role of the court to decide “whether, for policy or moral or social reasons, patents for gene sequences should be excluded from patentability,”²⁹⁰ noting that the Australian Parliament had considered the subject matter patentability question and decided on the codification of the law.²⁹¹ The Australian court’s decision is not only prudent in giving credit to the deliberations of parliament, but also scientifically correct in interpreting distinctions between cDNA, isolated DNA, and genomic DNA. The Australian Parliament passed legislation that restricted embryonic stem cell research to embryos that are less than fifteen days old and that have

285. See *D'Arcy v. Myriad Genetics, Inc.* (2014) 224 FCR 479, 115 FCAFC ¶ 114 (Austl.) (stating that “There is no requirement for: a consideration of whether the composition of matter is a “product of nature”; or whether a microorganism is “markedly different” from something that already exists in nature.”).

286. *Nat'l Res. Dev. Corp. v. Comm'r* (1959) 102.CLR 252 (Austl.).

287. *Id.* at ¶ 8.

288. See *id.* at ¶¶ 25–26.

289. See *D'Arcy v. Myriad Genetics, Inc.*, (2014) 115 FCAFC ¶ 92, ¶¶ 212–218 (Austl.).

290. *Id.* at ¶ 205.

291. *Id.*

been obtained with proper consent.²⁹² Thus, Australia is one of the more accommodating patent regimes for stem cell innovation and patentability, as applied to all types of stem cells currently known.

Similar to the patent regimes in Australia and most developed Asian countries (such as those of China, India, South Korea, Singapore, and Taiwan), Japan's patent regime has limited or no regulations regarding the patentability of stem cells²⁹³ and allows greater flexibility to scientists in the area of stem cell research.²⁹⁴ Japan grants patents for iPS and ES cells.²⁹⁵ Similar to the European Union, Japan excludes from patentable subject matter inventions that are likely to "contravene public order, morality, or public health."²⁹⁶ However, these restrictions are implemented differently. ESTs, SNPs and smaller DNA fragments that are not patentable in the United States have been patented in Japan. One key way in which Japan differs from the United States is in its reliance on novelty and obviousness rather than patentable subject matter, which is where most applications fail.²⁹⁷ Japan, which generally grants a smaller portion out of the total number of applications, has granted iPS cell patents in the past that remain unchallenged.²⁹⁸

When comparing the United States to these regimes, it is worth noting that unlike the United States, Europe, Japan, and Australia take a targeted approach in banning only specific products, which for either moral or other reasons, they deem to be unpatentable. Changes in IP protection in a field that relies on such protection for funding could have an impact that is larger than their intended scope. The EPO's 2004 decision that human ES cells were not patentable resulted in a significant drop in patent applications and scientific publications on all types of stem

292. Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act, 2006, sched. 2 (Act No. 172, 2006) (Austl.) (amending Research Involving Human Embryos Act 2002).

293. Kenneth C. Cheney, *Patentability of Stem Cell Research under TRIPS: Can Morality-Based Exclusions Be Better Defined by Emerging Customary International Law?* 29 LOY. L.A. INT'L & COMP. L. REV. 503, 512 (2007).

294. *Id.*

295. *Id.*

296. Patent Law, Law No. 121 of 1959, amended by Law No. 220 of 1999, art. 32 (Japan).

297. See Katherine Dover, *Epigenetics and the Patentability of Methylation Patterns in Japan*, 10 ASIAN-PAC. L. & POL'Y J. 434, 443-45 (2009).

298. See David Cyranoski, *Japan Fast Tracks Stem-Cell Patent*, 455 NATURE 269 (2008) (commenting on fast-tracking iPS patents from Yamanaka).

cells in Europe between 2002–2012.²⁹⁹ The short-term ban on federal funding for ES research in the United States had similar effects.³⁰⁰ On the other hand, Japan saw a rise in stem cell research as evidenced by stem cell related publications, stem cell patents, and the successful reprogramming of the first iPS cell, granted the Nobel Prize in 2012.³⁰¹ The recent shift in IP protection granted to stem cells in the United States can have a similar chilling effect on stem cell research, innovation, and shift such innovation to countries with patent systems that are more receptive to stem cell innovations.

V. CONCLUSION

Recent developments in subject matter patentability have made it more challenging to obtain patent protection for stem cell innovations in the United States. Weaker patent protection for stem cell technologies in the United States could have a chilling effect on stem cell innovation and successful clinical commercialization.

Since the first isolation of human embryonic stem cells less than twenty years ago, the field has grown at a very rapid pace. Stem cells, by definition, hold the potency to differentiation into most or all cell types. This inherent potency, makes them not only incredibly interesting to study scientifically, but also confers unparalleled utility potential in treating the most pressing medical issues of our time. However, it is not enough for scientists to discover and perfect these useful treatments. The treatments also need to get to patients, and the road from the bench side to the bed side is long and expensive.

Stem cell technologies, like most other medical and biotechnology fields, are under great regulation and require long and extensive testing before a final product is approved. This process takes time and substantial investment with long-term returns. This is an important reason why patents have been particularly important in the development of the pharmaceutical and biotechnology industries. This is particularly true in fields with both big and small industry players in them, such as stem cell

299. Yael Bregman-Eschet et al., *The Ripple Effect of Intellectual Property Policy: Empirical Evidence from Stem Cell Research and Development*, 20 J. TECH. L. & POLY (forthcoming 2015) (manuscript at 7, 35) (on file with the author).

300. *Id.* at 30.

301. Nobel Prize in Physiology or Medicine, 2012 Press Release, http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html (last visited Feb. 12, 2015).

technologies. Patents are particularly important for small companies, which rely heavily on third party investors and do not have the resources to be entirely self-sufficient and produce everything in-house.

The recent developments in subject matter patentability provide scientifically unclear guidelines at best, and possibly little to no patent protection at all. A diminished or total lack of patent protection is likely to push big companies into increased secrecy and further complicate the struggle of small companies to acquire funding and survive. Neither decreased competition, nor decreased collaboration, is likely to incentivize or sustain innovation in this promising medical field.

In the past century and a half, the United States has emerged as a leading player in the pharmaceutical and biotechnology fields. Other countries might have cheaper drugs, but they do not necessarily have better drugs. While the EPO has liberalized its position towards stem cell technologies and their patentability, Japan and Australia continue to maintain a patent landscape that greatly favors these industries. In an increasingly globalized market, which allows scientific mobility, countries that provide the most advantageous collaborative and innovative environments, are more likely to sustain growth in a particular field. Most Americans die of cardiovascular disorders, neurodegenerative disorders, or cancer. Based on the current review, modern and scientific needs and patent law are at odds with each other. It is the responsibility of Congress and the courts to fix these legal disparities, leading to a more harmonized system that prioritizes medical innovation and commercialization and benefits patients.