# CAN BIOPATENTS SURVIVE AS A MATTER OF PUBLIC POLICY?

BY

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# LIST OF ABBREVIATIONS

ANDA- Annotated New Drug Application process

cDNA- Complimentary Deoxyribonucleic acid

FDA- United States Food and Drug Administration

hESC- Human embryonic stem cells

ICM- Inner cell mass

IPSC- induced pluripotent stem cells

PTO- The United States Patent and Trademark Office

SCNT- somatic cell nuclear transfer

WARF -The Wisconsin Alumni Research Foundation

# ABSTRACT

Rebeca Echevarria

CAN BIOPATENTS SURVIVE AS A MATTER OF PUBLIC POLICY?

Thesis under the direction of Mark Hall, JD, Fred D. & Elizabeth L. Turnage Professor of Law and Public Health, Wake Forest University School of Law and School of Medicine, and Associate in Management, Babcock School of Management.

Bioproduct patents hold great promise for developing new and impactful medical treatments, but much of their potential depends on the ability of federal patent regulations to foster innovation and progress, both in their regulatory effect and through predictable and consistent application of patent law. Unfortunately, patent law is failing in both respects. Recent studies show that patents do not ultimately foster innovation and progress, especially in the biotechnology sector. Recent Supreme Court decisions, *Mayo v. Prometheus* and *Association for Molecular Pathology v. Myriad.* have also raised uncertainty as to the patent eligibility of stem cells. This uncertainty can ultimately block pathways to market and dampen investor interest in commercialization, slowing the overall development of new technical applications and reducing public benefit.

The Supreme Court has ruled on patent eligibility of several biopatents, but the future of stem cell patents is yet to be determined. Stem cells hold great promise for medical cures and treatments, and if stem cell research is inhibited, the public will suffer. Therefore, this thesis will explore the patent-eligibility of two types of stem cells: human embryonic stem cells and induced pluripotent stem cells as a basis for the argument that

biopatents cannot survive current patent law as a matter of public policy. After explaining how various types of stem cells are isolated and cultured, discussing what subject matter is patent-eligible, and analyzing the legal trend in bioproduct patents, this thesis posits that stem cell patents, like other biopatents, ultimately do more harm to society than the benefits they purport to provide and concludes that patent law needs to be industry specific if stem cell and other bioproduct research are to thrive.

# INTRODUCTION

As a dual JD/MA in Bioethics candidate, I was very interested in the way that the law can remedy ethical dilemmas present in our society. Courts regularly balance law and ethics through public policy analysis, which is an effective tool for remedying unethical legal outcomes, so I applied public analysis to bioproduct patent law, specifically stem cell patents, in the United States. Rather than debate whether bioproduct research itself is ethical, I decided to focus on whether the way our society uses patents to protect bioproduct research is good public policy.

The biopatent industry is unique from other patent industries because of the profound benefits it provides to society. Stem cell research is a perfect example of those possibilities. Stem cells promise to fundamentally improve medicine. Their regenerative properties mean endless possibilities for how these cells may be used in the future. Researchers are using stem cells to grow organs, reverse physical trauma, and cure diseases, but the scientific community knows that these applications are just the beginning. Theoretically human embryonic stem cell research can cure many diseases, but the challenge is in applying that research to therapeutic treatments. This requires "translation" of stem cell research into clinical research and eventually clinical medicine.[1] Stem cell research has attracted enormous interest in the United States and the rest of the world in last several decades

[1] J.A. Robertson, *Embryo Stem Cell Research: Ten Years of Controversy*,38 J.L. MED. & ETHICS

because of its scientific and medical potential, and commercial promise. By 2010, embryonic stem cell markets alone had risen to $10 billion.[2] Currently, the United States is the global leader in developing stem cell innovations and is estimated to hold 60% of the global market presently predicted to be worth $88.6 billion;[3] however, the degree to which any of these developments can be realized in the United States rest upon how effective the regulatory environment is in nurturing the technology market.[4] Patents are designed to foster this translation of research through exclusive market incentives but not all patent industries respond to the same to patent incentives. Patent law must strike a balance between encouraging investment in research and development activities, and promoting the freedom of academic research for the sake of public benefit from new discoveries.[5] For patent law to be truly successful, it must become more industry specific to meet industry's needs. Studies now show that the biotechnology industry leaders' claims that patent protection is necessary for continued growth and development of new technologies are false.[6]

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[2] R. KOROBKIN & S.R. MUNZER, STEM CELL RESEARCH AND THE LAW 3 (UCLA School of Law Research Paper No. 06-05, February 2007), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=878392.

[3] A. Warren-Jones, *Realizing New Health Technologies: Problems of Regulating Human Stem Cells in the USA* 1 (The University of Sheffield, 2012).

[4] *Id.*

[5] G. Bahadur & M. Morrison, *Patenting Human Pluripotent Cells: Balancing Commercial, Academic and Ethical Interests*, 25 HUMAN REPRODUCTION 14, 15 (2010), *available at* http://humrep.oxfordjournals.org/.

[6] *Id.*

Biopatents often result in monopolies of fundamental research tools. Unlike the majority of patents, which may be invented around through analogous mechanisms, biopatents have traditionally covered foundational and master principles, which inherently allow the right holders to control successive development of biotechnology. Stem cell patents perfectly exemplify this reality. The Wisconsin Alumni Research Foundation ("WARF"), for instance, holds patents that claim both the composition of matter and the processes used to isolate any and all human embryonic stem cells regardless of how they are generated. WARF's foundational patents created a bottleneck through which all progress relied on subsequent researchers being granted access to WARF's patents.[7] Previous papers discussing the ethics of stem cell patents have tended to focus on whether human embryonic stem cell patents violate human rights or whether stem cell research violates the idea of "human dignity" and right to life.[8] This thesis will not take that route. The moral debate over the permissibility of stem cell research has been played out to such an extent that, although not resolved, it takes little effort to think of several arguments both for and against allowing stem cell research.[9] For the sake of this thesis, I will begin with the assumption that stem cell research itself is ethically permissible and

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[7] Warren-Jones, *supra* note 3.

[8] S. KHACHIAURI, HUMAN EMBRYONIC STEM CELL CONTROVERSY: PATENTS INVOLVING ETHICAL AND HUMAN RIGHTS CONCERNS 1(Lund University, 2012).

[9] Christine N. Coughlin, Nancy M.P. King, and Anthony Atala. *Pluripotent Stem Cells: The Search for the "Perfect" Source*, 12 MINN. J. OF LAW, SCI. 715 (2011).

address the ethics of granting stem cell patents when innovation and discoveries in biotechnology are dependent on building upon fundamental techniques.[10] This thesis will use stem cell patents to illustrate why patenting fundamental biotechnology research tools violate public policy and the thesis will discuss alternative applications of patent law.

In recent years, the Federal Circuit and Supreme Court have taken particular interest in the patent eligibility of bioproducts. Because stem cell patents fall under this broad umbrella of biopatent regulation, it is essential to understand the state of current bioproduct regulation before applying the law to stem cell patents. Until recently, the Supreme Court had not discussed patentability of life issues since the *Diamond v. Chakrabarty* decision in 1980, which said products of nature are not patentable without additional human engineering making them "markedly different compositions of matter"; however, on June 28, 2010, the Court in *Bilski v. Kappos*, held that the established machine-or-transformation test was not determinative and on March 20, 2012, the Court in *Mayo v. Prometheus* said that applications of laws of nature to known structures or processes are patent eligible if they go beyond just describing the law and saying "apply it". On March 20, 2012, the Supreme Court then unanimously invalidated Myriad Genetics' ("Myriad") isolated DNA patents as products of nature but held that Myriad's synthetically created DNA, known as complimentary DNA ("cDNA"), is

[10] *See* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anti-commons in Biomedical Research*, 280 SCI. 698, 698 (1998).

patent-eligible because it does not naturally occur.[11] To date, there has been no litigation regarding stem cell patents, but as stem cell therapies eventually hit the market, stem cell patent rights will be challenged.

As biotechnology companies race to find new and innovative ways to use stem cells and profit from their successes, the future of stem cell patents is in question. That future of stem cell and other biotech research largely depends on Congress amending patent law to better suit the biotech industry, or alternatively, the courts' willingness to balance public concerns in their application of patent law. This thesis considers the holdings set forth in *Mayo v. Prometheus*, and *Association for Molecular Pathology v. Myriad* as applied to the three major types of stem cells currently used in research—Human Embryonic Stem Cells, Induced Pluripotent Stem Cells, and Somatic Cell Nuclear Transfers—and discusses why courts and Congress must adopt a new approach to biopatent law.

This thesis is divided into six parts. Chapter I provides background on form and function of the three types of stem cells discussed in this thesis. Chapter II discusses patent-eligible subject matter under §101 of the United States Code and the doctrinal tests the courts employ to determine patent eligibility. Chapter III analyzes the legal trend of bioproduct patent eligibility. Chapter IV examines the effect of recent biopatent holdings on future stem cell patent eligibility. Chapter V considers the negative impact

[11] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2114 (2013).

of biopatents on progress and innovation in medical research and consumer access to medical care. Finally, Chapter VI suggests how Congress should ament patent law and alternatively how courts should balance public policy concerns to better apply current patent law. The purpose of this thesis is to bring attention to the failing of current patent law, as applied to bioproduct research, and to provide specific recommendations for a better future of biopatent regulations.

# CHAPTER ONE

# STEM CELLS- A BRIEF OVERVIEW

Regenerative medicine aims to treat disease and illness by replacing lost or damaged cells. Because of their vast potential to become other cells as needed, stem cells are the key to regenerative medicine. Because of the various ways they are derived, the law treats various types of stem cells differently. Human embryonic stem cells (hESCs) and induced pluripotent stem cells (IPSCs) are the two major forms of stem cells being used in research today. The first type of stem cell to be isolated for research was the human embryonic stem cell. In 1998, the United States issued the first stem cell patent to James Thompson, who assigned it to the Wisconsin Alumni Research Foundation ("WARF"). The WARF patents claim both the processes used to isolate and the actual compositions of matter of any and all hESCs regardless of how they are generated.[12] Therefore, all researchers wishing to conduct research on hESCs must obtain licenses from WARF.[13]

In more recent years, researchers attempting to invent around the WARF patents have discovered how to reprogram somatic cells to become other cells through direct reprogramming, transdifferentiation, somatic cell nuclear transfer, and chromosomal transfer. The manner in which they are cultured and the potential uses vary with each type of stem cell. There are significant ethical advantages in using IPSCs rather than

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[12] Press Release, Wis. Alumni Research Found., United States Patent and Trademark Office Upholds Key WARF Stem Cell Patent (Feb. 28, 2008), http://www.warf.org/up-loads/media/Key_hES_Cell_Patent-UpheldRelease_v6-3.pdf [hereinafter WARF-PTO PR1]; Press Release, WARE, Patent Office Upholds Remaining WARF Stem Cell Patents (Mar. 11, 2008), http://www.warf.org/news/news.jsp?news id= 226 [hereinafter WARF-PTO PR2]; Press Release, WARF, U.S. Patent Office Issues Certificates to Uphold WARF Stem Cell Patents (June 26, 2008), http://www.warf.org/news/news.jsp?news_id=234.

[13] Jeanne F. Loring & Cathryn Campbell, *Intellectual Property and Human Embryonic Stem Cell Research,* 311 SCI. 1716, 1717 (2006).

hESCs in stem cell therapies because IPSCs do not require the destruction of an embryo in order to be harvested and they can alter the biological makeup of somatic cells.[14] On the other hand, reprogrammed somatic cells have low cloning efficiency and often result in various abnormalities in many stages of development.[15] There are substantial benefits to each type of stem cell, but as biotechnology companies race to secure patents on these stem cells, the questions remains how long stem cells, as bioproducts, will remain patent-eligible and whether granting a monopoly on such a basic scientific tool will severely limit subsequent research.

## HUMAN EMBRYONIC STEM CELLS

The term "stem cell" refers to a cell that is able to self-renew and has potency—the ability to differentiate into specialized cell types.[16] Differentiation describes the process by which a stem cell is assigned the cell type that it may become.[17] Stem cells are naturally present in various parts of our bodies and used to heal injuries and complete

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[14] EXPLORE STEM CELLS, THERAPEUTIC CLONING (Mar. 2013) http://www.explorestemcells.co.uk/therapeuticcloning.html
A Somatic cell is any cell that is not a germ or germ line cell. In humans, this means any cell that is not a sperm or egg.

[15] *See* Marc Lewitzky & Shinya Yamanaka, *Reprogramming Somatic Cells Towards Pluripotency by Defined Factors,* 18 CURRENT OPINION IN BIOTECHNOLOGY, 467-473 (2007) *available at* http://ntp.neuroscience.wisc.edu/neuro670/reqreading/ReprogrammingSomaticCellsTowardsPluripotencyByDefinedFactors.pdf (explaining that IPSCs are difficult to proliferate and grow in culture and require multiple attempts per sample due to low cloning efficacy).

[16] *See* NAT'L INSTS. OF HEALTH, U.S. DEPT. OF HEALTH & HUMAN SERVS., STEM CELL BASICS, 1 (2009) [hereinafter Stem Cell Basics], *available at* http://stemcells.nih.gov/staticresources/info/basics/SCprimer2009.pdf (stating "When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function.").

[17] *See* L. Wolpert, *Positional Information and the Spatial Pattern of Cellular Differentiation*, 25 J. OF THEORETICAL BIO., 1–47 (1969) *available at* http://www.sciencedirect.com/science/article/pii/S0022519369800160 (defining "differentiation" as the process by which a cell is assigned a cell type).

many bodily functions.[18] Stem cells exist naturally in humans in two forms: human embryonic stem cells (hESC) and adult stem cells.[19]

Adult stem cells are mutlipotent stem cells that exist in adult organs and tissues and are limited to becoming those particular cell lineages.[20] They are used by the body to replenish particular cells in organs or tissues. Hematopoietic stem cells are an example of adult stem cells.[21] Hematopoietic stem cells continuously replace red and white blood cells, preventing minor blood loss from being fatal and making blood donations possible.[22] Adult stem cells may only replenish cells of the same type, and so hematopoietic stem cells could not replenish skin cells or brains cells when needed.[23]

In contrast, hESC are pluripotent stem cells with the ability to become nearly any cell in the body, except for zygotes which are responsible for entirely reproducing a new organism. HESC exist only in the inner cell mass (ICM) of a pre-implantation blastocyst three to five days after fertilization before any of the cells have differentiated into a specific cell type.[24] Additionally, hESC are able to self-renew and replicate for indefinite

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18 ROBERT LANZA ET AL., ESSENTIALS OF STEM CELL BIOLOGY, XXIII-XXIX (Academic Press 2009).

19 *Id.*

20 *Id.*

21 *Id.*

22 *See* Lanza *supra* note 18 at 98 (Other adult stem cell types include mesenchymal stem cells, neural stem cells, epithelial stem cells, and germ stem cells); *See also*, Stem Cell Basics, *supra* note 16, at 10–11, 20.

23 *See* Lanza & Rosenthal, *supra* note 18, at 98 (explaining that adult stem cells have very limited regenerative capabilities).

24 *See* James A. Thomson et al., Embryonic Stem Cell Lines Derived from Human Blastocysts, 282 SCIENCE 1145 (1998) (explaining that if left undisturbed a blastocyst gives rise to a human fetus upon implantation. Blastocysts used to create embryonic stem cells, are from the remainder fertilized eggs from in vitro fertilization procedures).

periods of time in a laboratory setting, making them very useful research tools.[25] Because they have no yet been assigned to any particular cell lineage, scientists are able to differentiate hESC into any desired cells (except for gametes/reproductive cells) and use them for replacement therapies.[26]

James Thomson was the first to culture hESCs in 1998 at the University of Wisconsin.[27] In order to culture hESCs, the inner cell mass from the three-five day blastocyst stage of the embryo, is separated from the rest of the embryo through the processes of immunosurgery and mechanical dissection.[28] The removed part of the embryo is the trophectoderm and is responsible for causing the cells to differentiate into extra-embryonic tissue.[29] The removed cells are plated onto fibroblasts in order to supply support and further divide and expand to become an undifferentiated hESC line.[30] These cells are given enzymes to keep them alive and continue replicating. Because they replicate so quickly, they are mechanically separated every four to seven days.[31] In order for differentiation to occur, the hESC line is removed from the supporting cells and

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[25] *See* Thomson et al., *supra* note 24, at 1145 (explaining that HESC are able to self-renew and replicate for indefinite periods of time); *see also* Stem Cell Basics, *supra* note 43, at 3.

[26] *See* Christine Mummery et al*., Differentiation of Human Embryonic Stem Cells to Cardiomyocytes: Role of Coculture with Visceral Endoderm-Like Cells*, 107 CIRCULATION 2733, 2733 (2003) (explaining that HESCs can become any cell in the body).

[27] *See* Thomson et al., *supra* note 24, at 1145 (explaining scientists have used mouse embryonic stem cells since 1981); Stem Cell Basics, *supra* note 16, at 2.

[28] *See* Stem Cell Basics, *supra* note 16,

[29] *Id.*

[30] *See* G. Martin, *Isolation of Pluripotent Cell Line from Early Mouse Embryos Culutred in Medium Conditioned by Teratocarcinoma Stem Cells*, 78 PROC. NAT'L. ACAD. SCI. U.S.A. 12, 7634–8 (1981) (explaining that HESCs simply need to be plated in order to be used in research).

[31] *Id.*

introduced to the desired differentiation signals or grafted into a three-dimensional differentiated cell scaffold.[32]

A hESC is biologically the same as a hESC found in nature. Nothing is done to alter the biology of the cell itself. The mechanisms described above are necessary to isolate the hESC and control the manner in which it replicates, but the ability of the hESC to become any cell in the human body is a trait that exists in hESC found in nature. The utility of a hESC lies in its ability to become nearly any other cell.

## INDUCED PLURIPOTENT STEM CELLS

Unlike hESC which exist naturally in the human body, reprogrammed stem cells require complex human interference to alter the very nature of a cell and allow it to become an entirely different cell as needed. HESC are naturally occurring pluripotent stem cells, but depending on which method is used, reprogrammed cells have the potential to transform differentiated somatic cells into either pluripotent or totipotent cells once again.[33] A cell that is able to differentiate into all cell types, including placental tissue necessary for reproduction, is considered totipotent.[34] In mammals, the only naturally totipotent cells present are the zygote and subsequent blastomeres.[35] There are four methods of cellular reprogramming being used in research today; The first two

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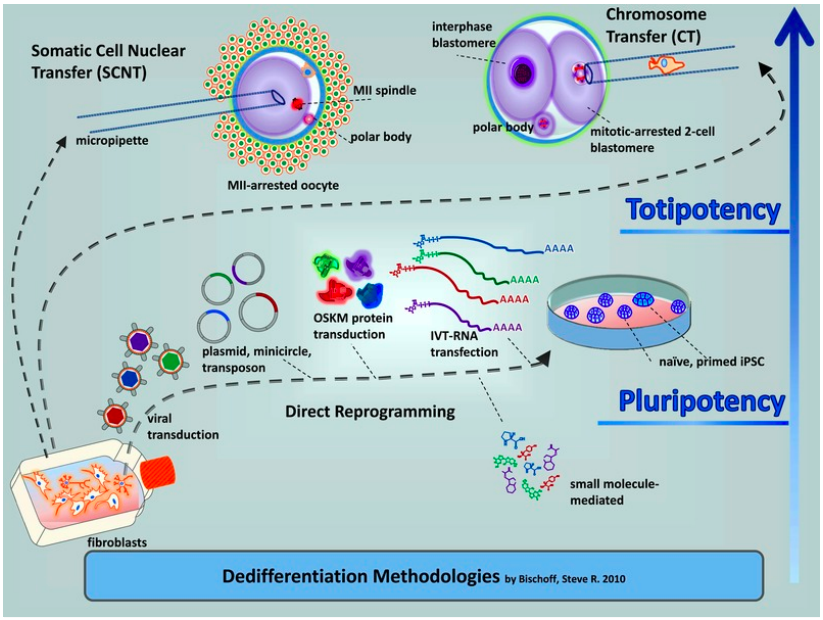
[32] *See* J.A. Thomson et al., *Embryonic stem cell lines derived from human blastocysts*, 282 SCIENCE 1145–1147 (1998) (explaining that HESCs have the ability to attach to a differentiated cell scaffold to become a completely new cell type).

[33] *See* Lewitzky & Yamanaka, *supra* note 15 (discussing the potency of IPSCs).

[34] CELL THERAPY AND REGENERATIVE MEDICINE GLOSSARY, REGENERATIVE MEDICINE S1-S124 (v. 7 May 2012).

[35] *Id.*

methods— direct reprogramming and transdifferentiation—give rise to pluripotent stem cells, while the third and fourth methods—somatic cell nuclear transfer (SCNT) and chromosome transfer—can give rise to totipotent stem cells with the ability to become absolutely any cell in the body and are the basis for reproductive cloning processes.[36]




(Figure 1)[37]

*Direct reprogramming*

In 2006, researchers Shinya Yamanaka and James Tomson, in two separate research teams, first discovered that a mammalian cell's developmental "memory" could be wiped out by inserting just four genes, creating a cell that could be made into a completely different cell type.[38] These cells are known as induced pluripotent stem cells

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36 *Id.*

37 Bischoff, Steve R., Dec. 12, 2010. PHOTO

38 *See* SCIENCE'S BREAKTHROUGH OF THE YEAR: CELLULAR REPROGRAMMING (Science Daily, Dec. 22, 2008) *available at* http://www.sciencedaily.com/releases/2008/12/081218141720.htm (discussing the discovery of "reprogramming" genes to become entirely new genes).

(IPSCs).[39] In 2007, Yamanaka successfully produced the first human IPSC.[40] Cellular reprogramming is a process where the cellular "memory" of a differentiated somatic cell is wiped clean and returns to a less differentiated state so that the cell may then be transformed into a completely new differentiated somatic cell.[41]

Today, researchers are able to use retroviruses, adenoviruses, plasmids, naked DNA, or protein compounds to insert the four requisite genes into a differentiated somatic cell to transform it into an IPSC.[42] Each delivery system has its own distinct advantage but all of these delivery systems allow researchers to break through the cell membrane and deliver the necessary genes to the cell nucleus, effectively altering its natural state. Direct cellular reprogramming does not naturally occur in mammalian somatic cells.

*Transdifferentiation*

Transdifferentiation is a process where a differentiated somatic cell transforms into a completely different differentiated somatic cell, but unlike direct reprogramming, it does not first undergo dedifferentiation.[43] The process of transdifferentiation was first observed over a hundred years ago in the regenerating lens of the newt;[44] the term

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39 *Id*.

40 THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE – 2012 PRESS RELEASE (Nobel Media AB. 8, October 2012).

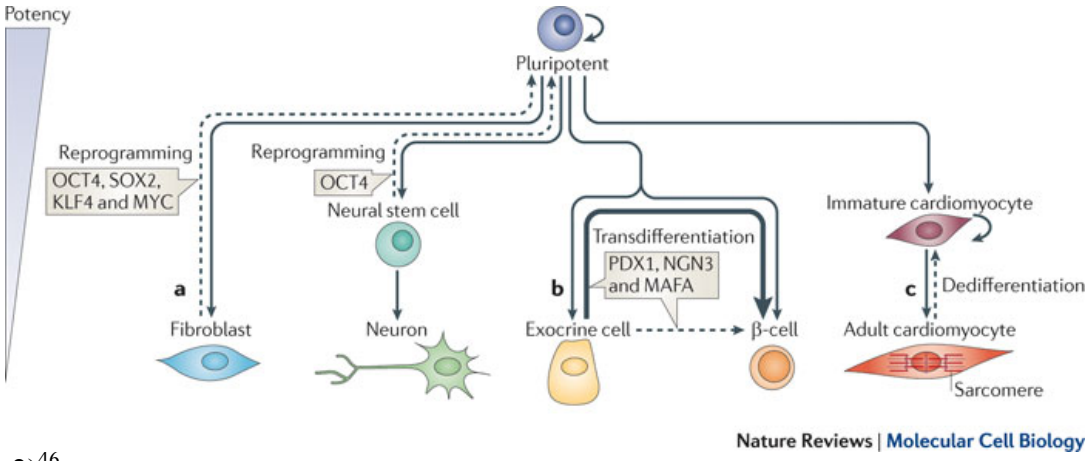
41 *See* Lewitzky & Yamanaka, *supra* note 15 (explaining that cellular reprogramming completely "wipes out" the cell memory that a cell had before).

42 *Id.*

43 *See* T. Graf & T. Enver, *Forcing Cells to Change Lineages*, 462 NATURE 587 (2009) (explaining that transdifferentiation does not require dedifferentiation to first occurr).

44 *Id.*.

'transdifferentiation' was not coined, however, until 1974, when Selman and Kafatos described the way a silk moth undergoing metamorphosis experiences changes in actual cell properties.[45] Transdifferentiation as it occurs in nature is a very rare occurrence, yet researchers have now discovered how to replicate this process and have managed to transdifferentiate human cells that would never otherwise undergo transdifferentiation.




(Figure 2)[46]

Normally, when transdifferentiation occurs in nature, the cell must first dedifferentiate before differentiating into the new lineage (Fig. 1).[47] As explained before, a differentiated cell is a cell that has been assigned a cell type, so a dedifferentiated cell is one that was once assigned a cell type that then reverted back to an unassigned state. Take for example, the regenerating lens of the newt.[48] [38]. When the newt loses a lens, pigmented epithelial cells from the dorsal iris regenerate the missing tissue by

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45 *See* K. Selman & F.C. Kafatos, *Transdifferentiation in the Labial Gland of Silk Moths: Is DNA Required for Cellular Metamorphosis?*, 3 CELL DIFFERENTIATION 81 (1974).

46 *See* Christ Jopling et al., *Dedifferentiation, Transdifferentiation and Reprogramming: Three Routes to Regeneration,* 12 NATURE REVIEWS MOLECULAR CELL BIOLOGY 70 (2011).

47 *See supra* note 44.

48 *Id.*

transdifferentiation.[49] A pigmented epithelial cell dedifferentiates, multiplies and then differentiates into a lens cell, as needed.[50]

Unlike natural transdifferentiation, clinically-induced transdifferentiation performed by researchers does not require dedifferentiation before transdifferentiation may occur.[51] Researchers have figured out how to directly convert one cell type into another by using transcription factors to downregulate one genetic program while upregulating the new desired genetic program (Fig. 1).[52] A transcription factor is a protein that binds to specific DNA sequences, thus controlling the transcription (copy and transfer) of genetic information from DNA to mRNA.[53] By introducing these new transcription factors, researchers can essentially force a cell to become an entirely different cell. Transdifferentiated cells behave and appear to be identical to the naturally occurring versions of whatever cells they have become, but the utility of a clinically induced transdifferentiated cell is that it can theoretically be made from and made into whatever particular somatic cell a researcher chooses.[54] Not only is transdifferentiation as found in nature performed differently than clinically than clinically induced transdifferentiation, but transdifferentiation does not naturally occur in humans at all.[55] Transdifferentiation of a human cell cannot occur without the complex human intervention of introducing new transcription factors as shown in figure 3.

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49 *Id.*

50 *Id.*

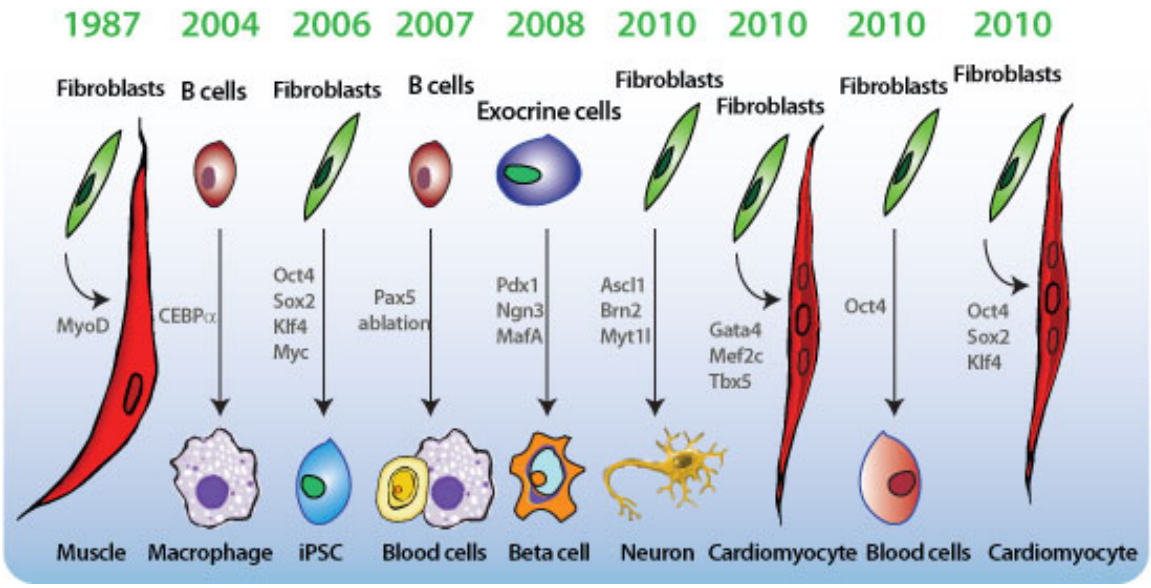
51 *Id.*

52 *Id.*

53 *See* D.S. Latchman, *Transcription Factors: An Overview*, 29 INT. J. BIOCHEM 12 (1997).

54 *Id.*

55 *Id.*




(Figure 3)[56]

*Somatic cell nuclear transfer*

Somatic Cell Nuclear Transfer (SCNT), also referred to as therapeutic cloning, describes the process where the DNA of a desired somatic cell (eg. Skin cell) is manually inserted into an enucleated egg.[57] The egg will then divide and develop into the desired cell.[58] In order to accomplish this, the DNA of the desired cell type is carefully removed from a donor cell. The nucleus of the host cell is then carefully removed by a process called 'enucleation'.[59] Because the egg's membrane is so delicate, it often takes many tries before an egg is successfully enucleated. Once the egg is enucleated, the DNA extracted from the donor cell is inserted into the egg, making an embryo, and an electric

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56 *See* DIRECT REPROGRAMMING FACTORS, SYSTEM BIOSCIENCE INNOVATIONS, *available at* http://www.systembio.com/stem-cell-research/transdifferentiation-factors/overview.

57 *See* Lanza et. al., *Human Therapeutic Cloning,* 5 NATURE MED. 975 (1999).

58 *Id.*

59 *Id.*

shock jump-starts the embryo's cellular division.[60] Once the embryo forms a blastocyst, stem cells are extracted and grown in specially selected cell cultures. [61]

A SCNT cell will completely take on the identity of the DNA inserted into its nucleus, even if the DNA is originally from a cell of a different type. Because they have the ability to become any cell type, SCNT cells are referred to as totipotent. In mammals, no somatic cells naturally possess the capability to become totipotent. Even stem cells that naturally exist in the human body are limited in the cell types they may become. SCNT is a complicated process that does not mimic any naturally occurring process.

*Chromosome transfer*

Microcell-mediated chromosome transfer (MMCT) is a process used to transfer chromosomes into host cells, creating hybrid cell lines that only contain desired genes.[62] It was first created in 1970, but in recent years it has been used to create artificial chromosomes, called hybrid chromosomes, which can be used in gene therapies.[63] Rather than transfer an entire cell nucleus as with SCNT, MMCT fuses the individual chromosomes themselves together to create an entirely new hybrid cell.[64]

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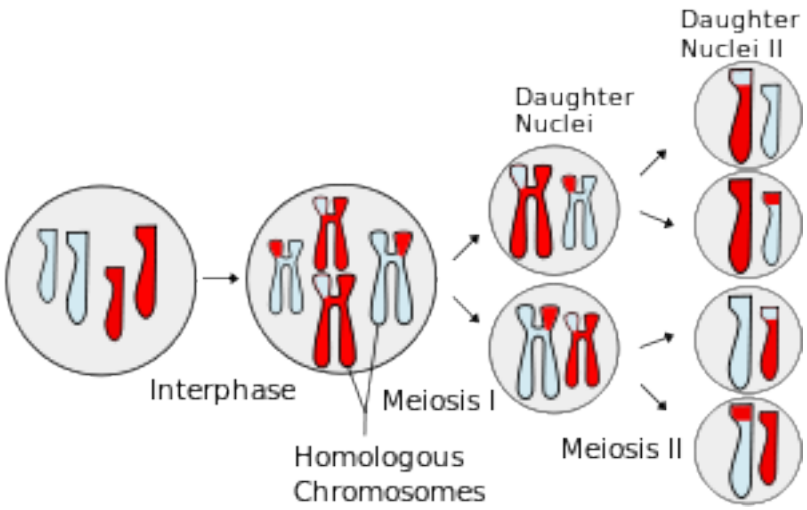
60 *Id.*

61 *Id.*

62 *See* Karen Meaburn et al., *The Manipulation of Chromosomes By Mankind: The Uses of Microcell-mediated Chromosome Transfer,* 114 CHROMOSOMA 263, 263–264 (2005) *available at* http://link.springer.com/article/10.1007%2Fs00412-005-0014-8?LI=true (explaining the mechanisms for microcell-chromosome transfer).

63 *Id.*

64 *Id.*




(Figure 4)[65]

Humans are diploid organisms, meaning human chromosomes exist as homologous pairs with one chromosome from the mother and one from the father.[66] As seen in figure 4, during the meiosis stage of reproduction the chromosomes split into pieces and rearrange themselves, with each piece possessing different alleles, which are in turn responsible for which specific genetic traits will be manifested.[67] In order to create micronuclei, researchers must performing colcemid treatments to artificially cause prolonged mitotic arrest after the chromosomes split.[68] The micronuclei are then placed into a centrifuge and essentially shaken at very high speeds to create little microcells containing only one chromosome each.[69] The micronuclei containing the desired chromosomes are then fused together to create hybrid cells containing only the desired

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65 *See A Basic Introduction to the Science Underlying NCBI Resources*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (Mar. 30, 2004) *available at* http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html.

66 *Id.*

67 *Id.*

68 *Id.*

69 *Id.*

chromosomes.[70] Nothing that follows the mincronucleation of the chromosomes occurs naturally in cell division and is an entirely artificial process.[71]

[70] *Id*

[71] *See* Egli, Dieter et al., *Developmental Reprogramming After Chromosome Transfer into Mitotic Mouse Zygotes,* 447 NATURE 679 (2007) *available at* http://www.nature.com/nature/journal/v447/n7145/suppinfo/nature05879_S1.html.

# CHAPTER TWO

# PATENT LAW- RELEVANT BACKGROUND

Just as the previous chapter gave relevant background on the various types of stem cells used in research today, this chapter will briefly summarize current patent law. Patent law does not directly address stem cell research, and so it is necessary to grasp several patent law principles before one can begin to discuss the effect of patent law on stem cell research. This chapter will provide the necessary background on relevant patent law, both as defined by statute and as interpreted by the courts.

Stem cell patents can take the form of method claims or composition of matter claims. Method claims cover the manner in which HESSCs are isolated and IPSCs caused to differentiate.[72] Composition of matter claims cover HESSCs themselves and the transcription and neural differentiation factors used to create IPSCs.[73] Since the WARF patents, encompassing all HESSCs, patents for nonembryonic human stem cells continue to be broadly granted; however recent Supreme Court decisions on biopatents have opened the door for new stem cell patent challenges. This chapter will explore present patent law and provide the necessary background of both the scope and purpose of patent law for the later discussion of the ethics of stem cell patents.

Article I, Section 8, Clause 8 states that Congress has the authority, "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries;" to that end,

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[72] Benjamin E. Reubinoff et al., *Neural Progenitors from Human Embryonic Stem Cells*, 19 NATURE BIOTECH. 1134, 1135 (2001).

[73] J.H. Shim et al., *Directed Differentiation of Human Embryonic Stem Cells Towards a Pancreatic Cell Fate*, 50 DIABETOLOGIA 1228, 1231 (2007).

Congress enacted the federal Patent Act codified in §35 of the U.S.C.. [74] A patent is a government granted intellectual property right of an inventor "to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" for a designated period of time in exchange for public disclosure of the invention.[75] Patent systems are justified by the assumption that they foster scientific progress and technological innovation.[76] If this is true, then patents should lead to higher rates of progress and innovation than their alternative. Courts have determined that the main underlying goal of patent law is to benefit the public rather than rewarding the inventor for his or her efforts.[77]

Anyone may challenge an issued patent by requesting the PTO to re-examine the patent, but such challenges must be based upon prior art consisting of patents or printed publications. This limits re-examination challenges to arguments of lack of novelty or nonobviousness in light of prior art. Challengers may also challenge a patent's validity in court by raising an argument that a patent claim is directed to unpatentable subject matter under § 101 of the Patent Act. Although no such claim has yet been raised in the courts, this thesis also suggest a third grounds for challenging a patent's validity on the basis of public policy violations, such as impeding progress and innovation.

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74 35 U.S.C.

75 *See* UNITED STATES PATENT AND TRADE OFFICE (Mar. 2012), *available at* http://www.uspto.gov/patents/index.jsp (explaining the rights granted by patent).

76 Dr. Andrew W. Torrance & Dr. Bill Tomlinson, *Patents and the Regress of Useful Arts*, 10 Colum. Sci. & Tech. L. Rev. 130, 132 (2009)

77 In Quanta Computer, Inc. v. LG Elecs., Inc., 553 U.S. 617, 626 (2008); *See also* Bilski v. Kappos, 130 S. Ct. 3218, 3252 n. 44 (2010) (Stevens, J., concurring). Edward Rothstein, Connections; Swashbuckling Anarchists Try to Take the $; Out of Cyberspace, N.Y. TIMES, June 10, 2000, at B1.

Patents confer on their owners a limited monopoly right to exclude others from using their inventions.[78] This should, in theory, incentivize more invention. As Lawrence Lessig summarizes it, if an inventor cannot get a patent for his invention, then his idea could simply be taken by others who wish to benefit from his invention without bearing the cost that went into its creation.[79] This might result in fewer inventors and thus, less progress in "science and useful arts." If, however, this theory is inaccurate and biopatents actually impeded progress and have little benefit to the public medical consumers, then biopatents may violate public policy. Regulations which unjustifiably prevent innovations from reaching the market, being fully developed, or reaching consumers are clearly not in the interest of society, especially in the context of medicine.[80]

In the United States, patent law does not provide industry-specific variations, unlike the European Union, which has industry-specific rules for compulsory licensing of pharmaceuticals and for the patentability of software and business methods.[81] The United States has employed *sui generis* laws to give additional protection to specific technologies, as with the Semiconductor Chip Protection Act of 1984, but has not instituted compulsory licensing schemes to patent law.[82] Unlike *sui generis* technology specific laws, which quickly become obsolete as technology evolves, compulsory licenses apply to an entire industry to ensure both that inventors are reasonably

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78 *Id.*

79 *See* Torrance, *supra* note 76.

80 *See* Warren-Jones, *supra* note 3.

81 Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1634 (2003).

82 *Id.* at 1636-1637.

compensated for their work and the public has access to those inventions.[83] Under a compulsory license, an individual or company seeking to use another's patent can do so without seeking the patent holder's consent and merely pay the rights holder a predetermined set fee for the license. Generally the fees are determined by Administrative Law Judges using several market factors.[84] The United States does not employ any compulsory licensing of patents, instead favoring market competition to set pricing and demand on research patents and allowing inventors exclusive rights. The only instance in which the United States government threatened to initiate compulsory licensing was during the 2001 anthrax postal service attacks.[85] The government wanted to require Bayer to license its anthrax antibiotic, but Bayer agreed to voluntarily lower the price and freely license the drug without government intervention.[86]

To date, patents apply consistently to all industries and grant exclusive rights to their inventors subject to the statutory eligibility requirements of the Patent Act. The statutory requirements found in §§ 112 (written description) 101 (eligible subject matter), 102 (novelty), and 103 (non-obviousness) are then interpreted and applied by the PTO and on appeal, by the courts.[87] In recent years the Supreme Court has given special attention to the § 101 patent eligibility requirements.

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83 *Id.*

84 *See* 17 U.S.C. § 115(c)

85 Reichman, Jerome H, *Compulsory licensing of patented pharmaceutical inventions: evaluating the options*, 37 J. OF L. AND MED. ETHICS 247 (2009).

86 *Id.*

87 Manual of Patent Examining Procedure (MPEP) , *available at* http://www.uspto.gov/web/offices/pac/mpep/.

## STATUTORY PATENT-ELIGIBILITY

Section 101 of the Patent Act states that "[w]hoever 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." 35 U.S.C. § 101 (2006). A patent examiner will generally grant a patent unless an invention is not useful, novel, and non-obvious to someone of ordinary skill in that area of technology.[88] The claims contained in the patent application must also be written with enough specificity to enable one of ordinary skill in the art to duplicate the invention when the patent term expires.[89] In order for an invention to be patent-eligible, an invention must fit within the scope of patentable subject matter codified in 35 U.S.C. § 101, as interpreted by the courts.[90] Even if useful, novel, and non-obvious, the question remains whether a patent fits within the scope of §101.

The United States Patent and Trademark Office (PTO) is the administrative agency responsible for reviewing patent applications in the United States. The PTO lists three types of patents: design patents, plant patents, and utility patents.[91] Design patents are granted for "new, original, and ornamental design[s] for an article of manufacture."[92] Plant patents are granted for distinctly new varieties of plants that are

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88 *See* Simone A. Rose, *Semiconductor Chips, Genes, and Stem Cells: SEMICONDUCTOR CHIPS, GENES, and STEM CELLS: NEW WINE for NEW BOTTLES?,* 38 AM. J. OF L. 113, 116 (2012) (discussing why an invention must be useful, novel, and non-obvious to someone of ordinary skill in that area of technology in order to be eligible for patent protection).

89 35 U.S.C. §112.

90 35 U.S.C. §101.

91 *See* United State Patent and Trademark Office (Mar. 2012) *available at* __ http://www.uspto.gov/patents/index.jsp (describing the three types of patents: design patents, plant patents, and utility patents).

92 *Id.*

discovered and then asexually reproduced.[93] Utility patents are granted for the invention or discovery of "any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof."[94] The PTO guidelines serve as a useful aid for courts deciding whether a given invention fits within the umbrella of patent-eligible subject matter of §101 of the Patent Act, but it is ultimately up to the courts to make that decision.[95] Looking to the plain language, legislative history, and supporting case law, courts must decide what qualifies as patent-eligible under the Patent Act and the IP Clause's mandate to "promote the Progress of the useful arts."[96]

As a federal agency, the PTO's guidelines and decisions receive no deference from the courts and recent court trends have caused the PTO to reevaluate how patent examiners determine eligibility of applications claiming processes involving laws of nature and compositions of matter. On July 3rd, the PTO released a thirteen-page memorandum entitled, "2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature."[97] The new PTO guidelines set forth a three-part inquiry to help examiners determine patent eligibility: (1) "Is the claimed invention directed to a process…or a series of acts or steps?" (2) "Does the claim focus on use of a law of nature, a natural phenomenon, or naturally occurring relation or correlation?" And

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93 *Id.*

94 *Id.*

95 *See* Rose, *supra* note 88, at 121 (explaining that it is the role of the courts to interpret a statute's meaning).

96 *Id*. at 133

97 *Id.*

(3) Does the claim include additional elements/steps or a combination of elements/steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied, and are sufficient to ensure that the claim amounts to significantly more than the natural principle itself? "(Is it more than a law of nature and the general instruction to simply "apply it")?[98] If a given process claim passes the first two inquiries, it *must* pass the third inquiry in order to be patent-eligible.[99]

**JUDICIAL APPLICATION OF 35 U.S.C. § 101**

Patent categories have historically been viewed very broadly, but there are three judicially created exclusions to patentability:[100] "laws of nature, physical phenomena, and abstract ideas" are ineligible for patents.[101] The constitutional mandate to promote progress in the useful arts includes safe-guarding the right to reasonable access to basic knowledge.[102] Because laws of nature, physical phenomena and abstract ideas are considered basic knowledge, the courts have made these absolute bars to patent-eligibility.

Though laws of nature are barred from patent-eligibility, *products* of nature and *applications* of laws of nature are not automatically barred from patent-eligibility. Although neither physical phenomena nor laws of nature are patentable, the Court in

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98 *Id.*

99 *Id.*

100 *See* Diamond v. Chakrabarty, 447 U.S. 303, 303 (1980) (stating "[L]aws of nature, physical phenomena, and abstract ideas are not patentable.").

101 *Id.*

102 *See* Rose, *supra* note 88, at 121 (examining the Constitutional mandate to promote progress).

*Diamond v. Chakrabarty* held that products of nature are patent-eligible with additional human engineering making them "markedly different compositions of nature". [103] A mere "discovery of some of the handiwork of nature" is not patent-eligible because information that is "part of the storehouse of knowledge of all men . . . [is] . . . reserved exclusively to none." [104] To put it differently, laws of nature are not patent-eligible, but process claims *involving* laws of nature may be patent-eligible.

Like physical phenomena and laws of nature, the Court in *Mayo v. Prometheu*s said abstract ideas that do more than simply state the idea are not automatically barred form patent eligibility. "An *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection."[105] It is not enough to simply state a law and say "now apply it", but "a particular, inventive application of the law" may have enough human involvement to make the matter patent-eligible.[106]

There is no clearly defined test that courts must employ to determine whether a given invention conforms to the Patent Act and is thus patent-eligible. As science evolves, it becomes increasingly more difficult for courts to distinguish between patent-eligible and patent-ineligible subject matter. The courts have historically relied on two major doctrinal tests for patent-eligibility—the machine-or-transformation test and the

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103 Chakrabarty, 447 U.S. at 310.

104 *See* Funk Bros. Seed v. Kalo Innoculant, 333 U.S. 127, 130–31 (1948) (explaining why laws of nature are not patent-eligible)

105 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 U.S. 1289, 1293–94 (2012); *emphasis added* (holding that the mere description of a correlation between thiopurine metabolite levels and toxicity/efficacy of thiopurine drugs was insufficient to make the application patent-eligible because it did not apply the law of nature to a known structure or process. A patent application must do more than simply state a law and say "apply it").

106 *Id.* at 1290.

preemption test—but modern science often manages to blur the lines of patent-eligible subject matter that these tests attempt to establish.

## THE MACHINE-OR-TRANSFORMATION TEST

When determining whether a given invention or process is patent eligible, the courts have long employed the machine-or-transformation test. The machine-or-transformation test states that a claim is likely patent-eligible when "(1) it is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing."[107] Although still employed in courts today, the Supreme Court in *In re Bilski* said the machine-or-transformation test "is not the sole test for determining the patent eligibility of a process . . . but rather "is a useful and important clue, an investigative tool, for determining whether some claimed inventions are patent-eligible processes."[108]

The court in *In re Bilski*, noted that the machine-or-transformation test had been created during the Industrial Revolution, a time in which inventions were expressly tethered to machines or other physical forms.[109] In today's technological age, inventions are not always tethered to a machine or physical transformation and the way in which the courts make their determinations must evolve along with the technologies they deal with.[110] The Court noted that the machine-or-transformation test does not work for all

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107 *See* Bilski v. Kappos, 130 U.S. 3218, 3226 (2010) (stating the rules of the machine-or-transformation test).

108 *Id.*

109 *Id.* at 3227.

110 *Id.*

cases. There may be inventions that satisfy the test but are patent-ineligible and some that do not satisfy the test but are still patent-eligible.[111]

The machine-or-transformation test ultimately tries to answer whether there is 'inventiveness' present in a given invention. As Chief Justice Marshall explained, if the invention results in something that is "markedly different from a naturally occurring phenomenon" or idea, it will likely be patent-eligible.[112] Building upon this principle, the Court in *In re Bilski* explained that post-solution steps do not contribute to patentability because the core invention still requires inventiveness.[113] Post-solution steps are insignificant if they do no more than "recit[e] a specific machine or a particular transformation of a specific article. An insignificant step, such as data gathering or outputting, is not sufficient to pass the test" without further inventiveness.[114]

In *Funk Bros.,* the Supreme Court said a bacteria-mixture patent was not patent-eligible because the interaction of the two species, though useful and novel, was nothing more than a naturally occurring phenomenon. In *Diamond v. Chakrabarty*, however, the Court said a patent claiming a genetically engineered bacterium was patent-eligible because the bacteria in their genetically modified state were unlike any found in nature. By inserting two plasmid coding for hydrocarbon degradation enzymes, Chakrabarty transformed the bacteria into a new composition possessing characteristics "possessed by

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111 *Id.*

112 Davis v. Palmer, 7 F. Cas. 154, 159 (C.C. Va. 1827).

113 *See* Bilski v. Kappos, 130 U.S. 3218, 3230 (2010) (explaining that post-solution steps do not contribute to patentability without inventiveness).

114 PTO Guidance Memo (July 3, 2012), *available at* http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf.

no naturally occurring bacteria."[115] The Court found the fact that the engineered bacteria could clean up oil spills and serve a useful purpose irrelevant and relied on the fact that Chakrabarty had "produced a new bacterium with markedly different characteristics from any found in nature" to validate the biopatent.[116]

*Diamond v. Chakrabarty* marked the first time the Court granted a non-plant patent of a living thing.[117] With the arrival of biotechnology, mankind is now able to manipulate and alter living things resulting in markedly different products.[118] Researchers can also now adequately explain their processes in enough detail for them to be replicated upon the expiration of the patent term. Biopatent introduced a new era of patents, but the advent of bioproducts challenged the practicality of the machine-or-transformation test.[119] Courts may still use the machine-or-transformation test as a helpful tool to determine inventiveness, but as the Supreme Court explained in *Mayo v. Prometheus*, the Court's inquiry may not stop there.[120] Courts must also ask if a given

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115 *See* Chakrabarty, 447 U.S. at 305 (discussing the novel characteristics of the bacteria synthesized by Chakrabarty).

116 *Id.* at 310.

117 *See* John F. Duffy, *Rules and Standards on the Forefront of Patentability*, 51 WM. & MARY L. REV. 609, 625–29 (2009) (examining the history of biological product patents, beginning with *Chakrabarty*).

118 *See* Christopher M. Holman, *Bilski: Assessing the Impact of a Newly Invigorated Patent-Eligibility Doctrine on the Pharmaceutical Industry and the Future of Personalized Medicine*, SOC. SCI. RESEARCH NETWORK, 4 (June 23, 2009) (unpublished manuscript), *available at* http://ssrn.com/abstract=1424493. "[T]he key distinction is human intervention; products and processes arising out of active human invention are patent-eligible...." *Id*.

119 *See* Duffy, *supra* note 117, at 630 (explaining a weakness in only using a *per se* exclusion to patentability for living inventions is that the rule could still be circumvented by claiming a living invention in conjunction with an inanimate carrier material, such as a bacteria on top of a petri dish).

120 *See* Mayo Collaborative Serv., 132 U.S. 1289 (2012).

invention would preempt others from employing fundamental principles that would benefit society.[121]

**THE PREEMPTION TEST**

Patent claims that may preempt ideas already in "the storehouse of knowledge of all men," including basic tools of science and abstract ideas are not patent-eligible because they prevent future inventions.[122] The preemption test goes beyond the machine-or-transformation test and asks whether a patent could prohibit another inventor from employing a fundamental principle that would be necessary for scientific progress. Fundamental principles are necessary for other inventors to use when inventing around them would be nearly impossible.[123] Congress has tasked the PTO and the courts to ensure that fundamental principles and basic ideas remain freely available to the public for the sake of scientific progress.[124]

In *In re Bilski*, the Court found that the processes claimed passed the machine-or-transformation test, but were still not patent-eligible because they covered fundamental principles preempting any future innovation in the present field. The processes claimed were too broad to invent around and no one should have exclusive control over basic

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121 *See* John M. Golden, *Patentable Subject Matter and Institutional Choice*, 89 TEX. L. REV. 1041, 1055, 1067–74 (2011) (discussing the preemption test courts employ to determine if an invention is ineligible for patent protection).

122 *See* Bilski v. Kappos, 130 U.S. 3218, 3225 (2010) (quoting Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)) (internal quotation marks omitted).

123 *See* Dreyfuss, Rochelle & Evans, James, *From Bilski Back to Benson: Preemption, Inventing Around, and the Case of Genetics Diagnostics*, 63 STAN. L. REV. 1349, 1352 (2011) (examining when fundamental principles are necessary to remain in the pubic domain).

124 *See* Golden, *supra* note 121 (discussing the role of the PTO in ensuring progress is being pursued).

ideas.[125] Conversely, the court in *Diamond v. Diehr* granted a patent for the use of a well-known mathematical formula in a process for curing synthetic rubber because the Court found no preemption issue.[126] The patent claimed a formula that contained a fundamental principle, but the patentees did "not seek to pre-empt the use of that equation" and only sought to prevent others from using the equation in conjunction with all of the other steps described in their claim."[127] Patent applicants can pass the preemption test by claiming a specific application of a fundamental principle accompanied by additional conditions, rather than the fundamental principle itself. [128]

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125 *See* Bryan Treglia, *Patentable Subject Matter: Separating Abstract Ideas and Laws of Nature from Patentable Inventions*, 48 JURIMETRICS J. 427, 437 (2008) (discussing how no one should have exclusive control over basic ideas).

126 *See* Diamond v. Diehr, 450 U.S. 175, 186 (1981) (granting a patent for the use of a well-known mathematical formula because patentees did "not seek to pre-empt the use of that equation", and only sought to prevent others from using the equation in conjunction with all of the other steps described in their claim.").

127 *Id.* at 187. Unlike in *Flook* where the claims to a formula for setting alarm limits were limited in scope that they did not actually prevent the use of the formula in other applications, in Diehr, the Court said the limitation of the scope of application was merely "post-solution activity." Parker v. Flook, 437 U.S. 584, 590 (1978). The courts make it clear that post-solution activities without any inventive step do little to ameliorate preemption concerns.

128 *See* Diehr, 450 U.S. at 187 (explaining that the proper inquiry in preemption is whether a patent preempts the use of a natural phenomenon.).

# CHAPTER THREE

# LEGAL TRENDS IN BIOPATENT LAW

Biopatents, including stem cells patents, generally fall into two categories: (1) process claims involving laws of nature; and (2) compositions of matter. The Supreme Court addressed the eligibility of bioproduct process patents in *Mayo v. Prometheus*, holding them eligible if they do more than state a law of nature and say "apply it". More recently, the Supreme Court addressed the eligibility of composition of matter patents in *Myriad*, holding them eligible if the final product is not found in nature in its patented form. Although the Supreme Court has not directly addressed stem cell patent-eligibility, because stem cells comprise a specific category of biopatents, the legal principles in both of these landmark cases will define the future eligibility of stem cell patent eligibility.

## PROCESS CLAIMS INVOLVING LAWS OF NATURE

Bioproduct process patents must do more than simply state a law of nature and say "apply it". On March 20, 2012, the Supreme Court unanimously held in *Mayo v. Prometheus* that the personalized medicine dosing method invented by Prometheus Laboratories (Prometheus) was ineligible for patent protection as a law of nature. The Court of Appeals for the Federal Circuit had previously held that the claims were patent-eligible because they included substantial physical limitations and included a transformative step, but the Supreme Court overruled this decision and cited *In re Bilski*, to say that the machine-or-transformation test was not definitive and the process claimed was merely an unpatentable law of nature.

Prometheus is a specialty pharmaceutical and diagnostics company that researched the use of thiopurine drugs in the treatment of certain autoimmune diseases, such as Crohn's disease and ulcerative colitis.[129] Prometheus filed patents for a diagnostic test that could determine the proper dosage of thiupurine drug for any given patient.[130] Every individual metabolizes drugs differently and before the age of personalized medicine, doctors could only use trial-and-error methods to determine the proper dosage.[131] If a dose is too high or too low, there may be adverse side effects and lower efficacy of the drug. Prometheus's diagnostic test calculates the concentration of metabolites in the patient's blood and determines the likelihood that a dosage of a thiopurine drug will be effective without harmful side effects. [132] When Prometheus Laboratories filed for its patents, the exact correlation between metabolites and thiopurine drug efficacy was unknown but the active metabolites responsible for thiopurine drug efficacy had already been identified and were commonly known to researchers.[133]

Each of Prometheus's claims recites an "administering" step, a "determining" step, and a "wherein" step.[134] The administering step merely instructs physicians to administer the drug to the patient, the determining step tells physicians to then measure resulting metabolite in the patient's blood, and the wherein step instructs physicians to

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129 *See* Mayo Collaborative Services, 132 S. Ct. at 1290–91.

130 *Id.*

131 *Id.*

132 *Id.*

133 *Id.* at 1295.

134 *Id.* at 1290.

decrease or increase the dosage if the metabolites are outside the ideal range.[135] The methods for making these determinations were already well known in the art before Prometheus came along, and the Court said that simply telling doctors to engage in "well-understood, routine, conventional activity previously engaged in by scientists in the field" was insufficient to make an patentable-ineligible law of nature patent-eligible.[136]

As previously explained in the section on patent-eligible subject matter, laws of nature are barred from patent-eligibility, but applications of laws of nature are not automatically barred from patent-eligibility so long as there is additional human engineering making them "markedly different compositions of nature".[137] Employing the machine-or-transformation test to determine whether there was sufficient additional human engineering involved, the Federal Circuit held that Prometheus's patent was valid because the "asserted claims involve a particular transformation of a patient's body and bodily sample and use particular machines to determine metabolite concentrations in a bodily sample"; [138] the Supreme Court, however, did not agree with this assessment and reversed the Federal Circuit's holding, clarifying that satisfying the Machine-or-transformation test does not *ensure* patent-eligibility.[139]

The Supreme Court held that the correlation between thiopurine drug efficacy and the prevalence of metabolites in a person's body is an entirely natural process, thus

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135 *Id.*

136 *Id.* at 1291, citing *Parker v. Flook,* 437 U.S. 584, 590.

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

138 *See* Prometheus Laboratories, Inc. v. Mayo Collaborative Services, 628 F.3d 1347, 1354 (Fed. Cir. 2010).

139 *See* Mayo Collaborative Services, 132 S. Ct. at 1290–91.

making Prometheus's patents invalid for simply putting forth a natural law. Prometheus's patent attorneys attempted to draft the patents as though there was an application of a law nature and not the law itself, but the Court was unconvinced.[140] The Court reiterated that an application of a law of nature must be limited in scope so as not to broadly preempt use of the law, and include an "inventive concept" that is significant and separate from the natural law itself; [141] A mere statement of a naturally occurring correlation, despite being newly discovered, fails this inquiry.[142] "Drafting efforts designed to monopolize the correlations" do not satisfy this requirement.[143]

*Mayo* has already had a huge impact on the question of whether process claims involving laws of nature will be patent-eligible. Less than four months after the Supreme Court's decision in *Mayo*, the PTO issued interim guidelines for patent examiners determining whether a process claim involving a law of nature is patent-eligible;[144] the guidelines quote heavily from the Supreme Court's decision in *Mayo* but attempt to apply the holdings from *Mayo* to a wider array of patent claim categories to assist patent examiners.

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140 *Id*.

141 *Id*. at 1292.

142 *Id.*

143 *Id.* at 1291.

144 *See* INTERIM PROCEDURE FOR SUBJECT MATTER ELIGIBILITY ANALYSIS OF PROCESS CLAIMS INVOLVING LAWS OF NATURE, U.S. Patent & Trademark Office (2012) *available at* http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf.

**COMPOSITIONS OF MATTER**

After the Supreme Court's landmark decision on bioproduct process patents in *Mayo*, the Court ruled on bioproduct composition of matter patent eligibility. Much of the Supreme Court's reasoning in *Mayo* laid the foundation for its *Myriad* decision. On March 20, 2012, the Supreme Court unanimously invalidated Myriad Genetics's ("Myriad") isolated DNA patents as products of nature but held that Myriad's synthetically created DNA, known as complimentary DNA ("cDNA"), is patent-eligible because it does not naturally occur.[145]

Unlike the patent holder in *Mayo* who had claimed a process involving a law of nature, Myriad claimed a process for isolating and creating cDNA and claimed the individual compositions of matter.[146] The Federal Circuit had previously held both isolated DNA and cDNA patent-eligible, finding that isolated DNA is chemically distinct from naturally occurring DNA and cDNA is both biologically and chemically distinct from its natural form.[147] The Supreme Court's decision largely echoed Federal Circuit Judge Bryson's dissent, which argued that isolated DNA should not be patent-eligible because "extracting a gene is akin to snapping a leaf from a tree".[148]

Myriad Genetics (Myriad) discovered that "certain mutations in the BRCA 1/2 genes correlate with an increased risk of breast and ovarian cancer" and marketed the only genetic test for cancer.[149] The PTO granted Myriad patents for its isolated DNA

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145 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2114 (2013).

146 Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303, 1324 (Fed. Cir. 2012).

147 U.S. Patent & Trademark Office 689 F.3d 1303.

148 *Id.* at 1352.

149 Myriad, 133 S. Ct. 2109.

sequences containing the BRCA 1/2 mutations, the cDNA synthesized from the mutated genes for further research, and the diagnostic methods of identifying mutations in those DNA sequences.[150] When other medical professionals began performing cheaper versions of Myriad's genetic test Myriad filed patent infringement suits, but the infringers counterclaimed that Myriad's patents were invalid.[151] After the Supreme Court vacated and remanded the case to the Federal Circuit in light of *Mayo*, the Federal Circuit held that Myriad's method claims directed at "comparing" or "analyzing" DNA sequences were patent-ineligible because they merely claimed an "abstract mental process" and contained no transformative steps, but Myriad's claims over the isolated DNA and cDNA were patent-eligible compositions of matter. [152] The Supreme Court affirmed in part and reversed in part.[153]

The Supreme Court unanimously agreed that cDNA was patent eligible, but isolated DNA was not.[154] Isolated DNA is biologically identical to naturally occurring DNA; the nucleotide sequence found in isolated DNA, which in turn codes for the proteins that make up the BRCA 1/2 genes, appears identically in isolated DNA as it does in naturally occurring DNA.[155] In order to isolate the relevant DNA sequence, Myriad breaks the chemical bonds holding the DNA sequence to the rest of a subject's DNA.[156]

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150 *Id*.

151 *Id.* at 2114.

152 U.S. Patent & Trademark Office, 689 F.3d at 1333.

153 Myriad, 133 S. Ct. at 2111.

154 *Id.*

155 *Id.* at 2116

156 *Id.*

The Federal Circuit concluded that this chemical difference was sufficiently transformative to qualify isolated DNA as a composition of nature, but the Supreme disagreed. Unlike isolated DNA, cDNA is artificially synthesized through the splicing of genetic material and is both chemically and biologically different than naturally occurring DNA.[157] The cDNA is synthesized from mRNA after transcription, in which non-coding intron sequences are naturally cut out.[158] DNA does not naturally exist in the nucleotide sequence formed in cDNA and is thus biologically distinct from naturally occurring DNA.[159] Additionally, the chemical bonds joining the nucleotide sequences have to be broken and remade in order to bind the new nucleotide sequence together, also making cDNA chemically distinct from naturally occurring DNA.[160] The court unanimously held cDNA to be patent-eligible as "compositions of matter distinct from natural DNA as a result of human intervention into nature".[161]

Unlike cDNA, isolated DNA retains the same nucleotide sequence as naturally occurring DNA.[162] In order to isolate the DNA sequences, the chemical bonds of the DNA must be broken through human intervention, making it a chemically distinct molecule from naturally occurring DNA, but the isolated DNA retains the same biological identity.[163] The Federal Circuit held that this chemical distinction was

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157 Myriad, 133 S. Ct. at 2119.

158 *Id.*

159 *Id.*

160 *Id.*

161 *Id.*

162 *Id.* at 2118.

163 *Id.*

sufficient to render isolated DNA patent-eligible because "genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions."[164] In dissent, Judge Bryson opined that, "merely isolating the products of nature by extracting them from their natural location and making those alterations that are attendant to their extraction does not give the extractor the right to patent the products themselves."[165] The Supreme Court agreed with Judge Bryson's reasoning and held isolated DNA patent-ineligible, finding that the utility of isolated DNA lies in its nucleotide sequence, which codes for targeted genes, like BRCA1/2.[166] This decision, along with *Mayo*, will largely shape the future of stem cell patent eligibility.

**COURTS' USE OF § 101 AS A POLICY LEVER**

These cases demonstrate the Federal Circuit and Supreme Court's use of § 101 of the Patent Act as a policy lever to tailor patent law to the needs of the biotech industry. In 2003, Dan Burke and Mark Lemley published an article calling for courts to use a variety of policy levers to allow for industry specific applications of patent law.[167] Their article explained that the patent statute gives substantial discretion to courts to build industry-sensitive policy analysis in their decisions. They went on to offer a long list of factors could consider in their analyses as various "levers" the courts could adjust to each fact pattern. While the courts have been reluctant to admit that they are creating new

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164 U.S. Patent & Trademark Office, 689 F.3d at 1330.

165 *Id.* at 1350.

166 *See* Rose, *supra* note 88, at 131–32.

167 Burke, *supra* note 81 at 1630.

policies to suit particular industries, *Mayo* and *Myriad* evidence that in practice, that is exactly what the courts are doing. The courts have cautioned against creating industry specific tests for patentability because of a court's inability to dictate in detail the right patent rules for each industry, especially industry converging technologies, but the courts have been giving greater weight to certain sections of the patent statute as each industry requires.[168] Rather than consider, however, the long list of "levers" suggested by Burke and Lemley, the courts over the years have relied on the various sections of the actual patent statute found in §§ 112, 101, 102, and 103 as policy levers. This trend suggests the courts' willingness to apply patent law in an industry specific manner.

[168] Burke, *supra* note 81 at 1634.

# CHAPTER FOUR

# THE FUTURE OF STEM CELL PATENT ELIGIBILITY

The *Mayo* and *Myriad* holdings have profoundly altered the eligibility of bioproduct patents. Courts will likely treat stem cells the same as other bioproducts and apply the Supreme Court's holdings in *Mayo* and *Myriad*. To date, no court has directly addressed patent eligibility of stem cells, but less than two months after the Supreme Court's *Myriad* decision, Consumer Watchdog ("*CW*")—a public charity dedicated to provide a voice for taxpayers and consumers—challenged the validity of Wisconsin Alumni Research Foundation's ("*WARF*") primate embryonic stem sell patent No. 7,029,913 in the Federal Circuit.[169] The Federal Circuit asked each party to file briefs on the issue of CW's standing. If the Federal Circuit finds that CW has standing to bring suit against WARF, this case will be the court's first application of the *Myriad* decision to stem cell patents.[170] When the Federal Circuit does choose to rule on the patent eligibility of stem cells, the court will likely have to address hESCs and IPSCs separately since the § 101 tests for eligibility would bar hESCs, but the various methods of creating IPSCs previously discussed in chapter one involve enough human intervention to make them markedly different compositions of matter than as they naturally occur. Therefore, IPSCs will likely be held as patent eligible subject matter, unless the courts find that stem cell patents violate public policy

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169 Consumer Watchdog v. Wisc. Alumni Research Foundation, No. 13-1377 (Fed. Cir. 2013).

170 *Id.*

**HUMAN EMBYONIC STEM CELLS ARE NOT MARKEDLY DIFFERENT COMPOSITIONS OF MATTER**

Future patent-eligibility will depend on how future courts interpret the holdings in *Mayo* and *Myriad*. Though *Mayo* was directed to process claims involving laws of nature, the major holding—that an application of a law of nature must be limited in scope so as not to broadly preempt use of the law, and include an "inventive concept" that is significant and separate from the natural law itself—will certainly apply to stem cell patent-eligibility. [171] The purification assays, which allow cells to proliferate in culture for over a year and maintain their pluripotency, are not found in nature and thus would be eligible for patent protection, but the question is whether hESCs themselves are eligible for patent.[172] *Myriad* addressed whether a composition of matter that contains an inventive concept and does not broadly preempt is patent-eligible, but how the *Mayo* and *Myriad* holdings will be applied to stem cells remains to be seen .

If the Supreme Court's holdings in *Myriad* and *Mayo* are properly applied, the USPTO and/or future courts will invalidate existing hESC patents and make future hESCs ineligible for patent protection. Sufficient inventiveness for patent-eligibility will not be found if the 'utility' of hESC are not a result of human intervention, and are found in nature. Judge Bryson argued against patent-eligibility for isolated DNA because "merely isolating the products of nature by extracting them from their natural location and making those alterations that are attendant to their extraction does not give the

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171 *Id.*at 1292.

172 For example, U.S. Patent No. 6,200,806 col.21 ll.1-9 (filed June 26, 1998); the 7,955,851 Patent claims an HESC culture grown "on an extracellular matrix in a culture medium" which allow HESCs to proliferate in an in vitro culture for over one year .

extractor the right to patent the products themselves."[173] Because the utility of isolated DNA is in its nucleotide sequence and the nucleotide sequence in isolated DNA is entirely untouched, isolated DNA, as the Supreme Court agreed, is not patent-eligible. Likewise, it is the pluripotency of hESCs that make them useful; a quality present in naturally occurring hESCs.

Like the isolated DNA sequences in *Myriad*, hESCs extracted in a laboratory (*in vitro*) are no biologically different than those found naturally (*in vivo*) in the inner cell mass (ICM) of a pre-implantation blastocyst. A hESC in a pitri dish is biologically identical to a hESC found naturally within an embryo. The utility of a hESC lies in its ability to become nearly any other cell; a trait with exists in hESCs found in nature. Like the isolated DNA at issue in *Myriad*, nothing is done to alter the biology of the cell itself. The process of isolating the cells from their natural state and causing them to grow in a laboratory may require a degree of inventiveness, but like the researcher who trims a leaf of a plant, the researcher who extracted the hESC cannot then claim a patent on extracted material that is not "markedly different" than its natural form.[174] Therefore, hESC patents will likely be invalidated under the holding of *Mayo* and *Myriad*.

## ALL INDUCED PLURIPOTENT STEM CELLS WILL REMAIN PATENT-ELIGIBLE

All IPSC methods and compositions of matter will remain patent-eligible because they are not found naturally in any form, making them analogous to the new bacteria held to be patent-eligible in *Chakrabarty*. Unlike hESC which exist naturally in the human

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173 Consumer Watchdog *supra* note 169 at 1350.

174 Myriad at 1352 (quoting Chakrabarty, 447 U.S. at 310.)

body, IPSCs require complex human interference to alter the very nature of a cell and allow it to become an entirely different cell as needed. While hESCs are naturally occurring pluripotent stem cells, IPSCs are adult differentiated somatic cells that have been reprogrammed to transform into either pluripotent or totipotent cells once again.[175]

In nature, a differentiated cell stays that way. Each of the four methods of creating IPSCs— direct reprogramming, transdifferentiation, somatic cell nuclear transfer (SCNT), and chromosome transfer—reprogram adult differentiated cells into entirely different cells.[176] Direct Reprogramming is performed by using retroviruses, adenoviruses, plasmids, naked DNA, or protein compounds to insert four genes into a differentiated somatic cell to transform it into an IPSC.[177] Direct cellular reprogramming does not naturally occur in mammalian somatic cells. Likewise, transdifferentiation of a human cell cannot occur without the complex human intervention of introducing new transcription factors. Unlike natural transdifferentiation, clinically-induced transdifferentiation performed by researchers does not require dedifferentiation before transdifferentiation may occur.[178] Not only is transdifferentiation as found in nature performed differently than clinically than clinically induced transdifferentiation, but transdifferentiation does not naturally occur in humans at all.[179] Somatic Cell Nuclear Transfer is another complicated process that does not mimic any naturally occurring

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175 *MARC LEWITZKY AND SHINYA YAMANAKA, REPROGRAMMING SOMATIC CELLS TOWARDS PLURIPOTENTCY BY DEFINED FACTORS*, 1 (ELSEVIER, 2007) , available at http://ntp.neuroscience.wisc.edu/neuro670/reqreading/ReprogrammingSomaticCellsTowardsPluripotencyByDefinedFactors.pdf.

176 *Id.*

177 *Id.*

178 *Id.*

179 *Id.*

process. In mammals, no somatic cells naturally possess the capability to become totipotent. Even stem cells that naturally exist in the human body are limited in the cell types they may become, unlike SCNT cells. And lastly, Chromosome Transfer is entirely man-made invention. Micronuclei are artificially created and then fused together in order to create hybrid cells only containing the desired chromosomes[180] Each form of IPSC creation requires vast amounts of human intervention resulting in cells that are both biologically and chemically distinct than any stem cells found in nature. All IPSCs are "markedly different" than stem cells existing in nature and require extreme inventiveness to be created, therefore, IPSCs would remain patent eligibile under the *Mayo* and *Myriad* holdings.

## THE FUTURE OF STEM CELL RESEARCH

The biotechnology industry relies on patents to garner investments and generate licensing revenue in order to cover the cost of continued isolated bioproduct research and development.[181] Because federal funding for stem cell research is extremely limited, some researchers fear that if stem cells become ineligible for patent protection, economic growth and future development of stem cell research will halt.[182] This would be true if all stem cells were found to be ineligible for patent protection, but the legal trends show that likely only hESCs, if any stem cells, will become ineligible for patent protection.

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180 *Id.*

181 *See* Rose, *supra* note 88, at 120–21.

182 *Id.*

Under the *Mayo* and *Myriad* holdings, hESCs will become patent-ineligible. The process of isolating the cells from their natural state or removing hESCs from an embryo is much like the researcher who trims a leaf of a plant. The researcher who extracted the hESC cannot then claim a patent on extracted material that is not "markedly different" than its natural form.[183] "Like a gene, a leaf has a natural starting and stopping point. It buds during spring from the same place that it breaks off and falls during autumn. Yet prematurely plucking the leaf would not turn it into a human-made invention." Man cannot obtain ownership right in that which belongs to all man.[184] Isolated hESCs, being identical to naturally occurring hESCs in both biological and chemical make-up, should not be patent-eligible because they are not the result of man's invention.

The USPTO has been conservative in granting patent protection to hESCs, and for good reason. Stem cells hold great promise for the future of medicine as a whole, but there are countless ethical concerns in relation to individual ownership of products of nature, including laws of nature and compositions of matter. Making hESCs ineligible for patents would do little to no harm the biotechnology industry, but allowing hESCs to remain patent-eligible sets a dangerous precedent for the patentability of biological products, which often embody fundamental research tools.

However, the majority of stem cell patents are granted to IPSCs and other adult stem cells, both of which will likely remain patent-eligible. Although hESC research was instrumental to our understanding of stem cells as a whole, the majority of research is going in the direction of IPSCs and the current legal trend will do nothing to stop that.

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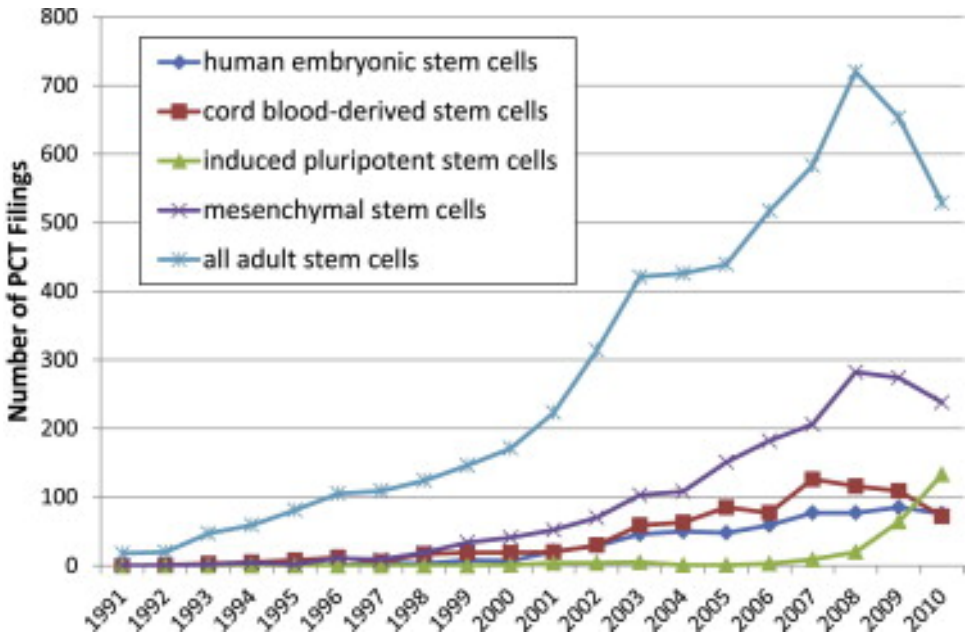
183 Myriad at 1352 (quoting Chakrabarty, 447 U.S. at 310.)

184 U.S. Constitution, Article I, Section 8.

Unfortunately, this means that *Mayo* and *Myriad* have done little to prevent the negative consequences of biopatents on subsequent research and innovation. Those consequences, which are discussed in the next chapter, will continue until the Federal Circuit and Supreme Court are willing to consider the public policy concerns relating to biopatents.




(Figure 5)[185]

185 Debra J.H. Mathews, Robert Cook-Deegan & Tania Bubela, *Patents and Misplaced Angst: Lessons for Translational Stem Cell Research from Genomics*, 12 SCI. DIRECT 1 (May 2, 2013) at available athttp://www.sciencedirect.com/science/article/pii/S1934590913001513.

# CHAPTER FIVE
# THE NEGATIVE EFFECTS OF BIOPATENTS

If stem cell patent eligibility is solely determined based on the factors discussed in the previous four chapters, there will be profoundly negative consequences for scientific innovation, which could reduce medical benefits for society. This chapter will discuss the negative effects of biopatents, particularly as they affect stem cell research. Current patent law may have profound effects on the availability of new medical treatments and the funding for continued research into promising stem cell therapies.

## PATENTS LIKELY DO NOT FURTHER PROGRESS

Recent studies argue that there is little evidence to show that patents do, in fact, further innovation and scientific progress and suggest that the opposite may be true.[186] Several studies attempting to analyze the correlations between innovation and patent protection have shown that in certain scenarios, patents slow down innovation, rather than help speed it up.[187] These studies generally take two forms: 1) the first relies on economic frameworks to determine if patents promote innovation, and thus increased amounts of new technologies are hitting the market; 2) the second employs mathematical models which either measure technological innovation in a single economy of interest or compare rates of technological innovation among countries offering different levels of patent protection.[188]

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186 *See* Torrance, *supra* note 76.

187 *See* Torrance, *supra* note 76.

188 *See* Torrance, *supra* note 76.

In Helsinki, Finland, a group of economists using the first model of patent efficacy studies determined that, "while the effect of patents is to raise the rents on and thereby the potential amount of innovations, it also tends to slow down market introduction."[189] Similarly, an empirical study done at Columbia University School of Law, supported the same finding. In order to test the hypothesis that patent systems promote innovation in the United States, Dr. Andrew W. Torrance and Dr. Bill Tomlinson created a program to simulate the behavior of inventors and competitors experimentally in both patent and non-patent systems.[190] The study employed a multi-user interactive simulation of patent and non-patent systems called, "PatentSim".[191] Following a model of the invention process, PatentSim allowed law students to access a database of potential innovations, then patent, or open source these innovations. Users could then license, assign, buy, infringe, or enforce patents against each other. The results of the simulation suggest that a system "combining patent and open source protection for inventions (that is, similar to modern patent systems) generates significantly lower rates of innovation" than non-patent systems.[192]

In 2003, the National Academies published one of the most comprehensive reviews of the United States patent system, entitled "Patents in the Knowledge-Based

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189 Takalo, Tuomas & Kanniainen, Vesa, *Do Patents Slow Down Technological Progress?: Real Options in Research, Patenting, and Market Introduction*, 18 INT'L J. OF INDUS. ORG. (2000), http://www.sciencedirect.com/science/article/pii/S0167718798000496.

190 *See* Torrance, *supra* note 76.

191 *See* Torrance, *supra* note 76.

192 *See* Torrance, *supra* note 76.

Economy".[193] Instead of supporting the hypothesis that patents spur invention and innovation, the National Academies concluded that "[t]here are theoretical as well as empirical reasons to question whether patent rights advance innovation in a substantial way in most industries."[194] Firstly, the benefits of retaining a patent monopoly for a limited time might be outweighed by the ultimate cost of detailed disclosure that patents require.[195] Secondly, technological advances are, more often than not, built cumulatively upon other inventions, but broad patent protection on upstream discoveries impedes subsequent innovations.[196] In an empirical study surveying fifty-three biotechnology companies in Switzerland, a group of researchers concluded that a broad research exemption from patent protection, combined with compulsory licensing arrangements for DNA patents are feasible remedies for overcoming the stifling effect the current patent system can often have.[197]

The current patent system arguably does not further progress, and at the very least, it is questionable.[198] If the patent system is only valid so long as it furthers progress, then it may be time for Congress to reassess whether the current patent regime is still constitutionally valid. Furthermore, any possible value patents provide must also be weighed against their potential harms. Particularly with regard to biopatents, limiting

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193 *See* Torrance, *supra* note 76.

194 Nat'l Res. Council, *Comment on Intellectual Property Rights in Knowledge-Based Econonomies* 2 (Wesley M. Cohen & Stephen A. Merrill eds., 2003) [hereinafter Cohen & Merrill].

195 *Id.*

196 *Id.*

197 Thumm, Nikolaus, *Patents for Genetic Inventions: A Tool to Promote Technological Advance or a Limitation for Upstream Inventions?,* 25 TECHNOVATION (2005), http://www.sciencedirect.com/science/article/pii/S0166497204001154

198 *See* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998).

patients' access to secondary medical opinions and affordable drugs and treatments may ultimately be against public policy.

## BIOPATENTS RAISE MEDICAL COSTS AND LIMIT PATIENT ACCESS TO TREATMENTS

Bioproduct manufacturers claim that patents are necessary to recoup research and development costs, thereby allowing manufacturers to offer drugs and treatments at affordable prices, but the evidence has overwhelmingly shown that in practice, patents greatly increase medical costs.[199] This result, however, should not be surprising. Patents grant monopoly rights to inventors. The United States and much of the rest of the world heavily regulate monopolies in every other area of the law because of the known anti-competitive nature of monopolies. The United States permits monopoly rights in new and useful inventions only in order to incentivize further progress, but limits that right to a predetermined amount of years and in return for full disclosure of the invention. The drafters of § 112 of the Patent Act's written description requirements understood that disclosure of an invention is necessary for competition to ensue once a patent term expires, ultimately making the invention affordable; however, because patent holders may freely determine the price for access to their invention, patents nearly always initially increase healthcare costs.[200]

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[199] A. Saha , H. Grabowski, et.al., *Generic Competition in the US Pharmaceutical Industry*. INT J ECON BUS 13, 15–38 (2006).

[200] R. Cook-Deegan, et.al., *The dangers of diagnostic monopolies*. 458 NATURE 405 (2009).

**BIOPATENTS PREVENT CERTAIN POPULATIONS' ACCESS TO MEDICAL TREATMENTS AND TESTS**

One particularly concerning aspect of biopatents is that they result in particular populations being prevented access to approved medical treatments and diagnostic tests. As previously discussed, biopatents prevent often-necessary follow-on research. Follow-on research often consists of additional clinical trials involving previously excluded populations or further testing to understand result variations in select populations.[201] Without this follow-on research, physicians do not know how effective the treatment or diagnostic test is in higher risk or less responsive population groups.

This very problem resulted from Myriad's BRCA 1/2 cancer test. Because of Myriad's patents, researchers are prevented from conducting further clinical trials on higher-risk population groups to better understand the test's efficacy.[202] Women who receive test results indicating that they have a "variant of uncertain significance" have no way to access further testing to find out if they are at elevated risk for cancer. Despite the many researchers requesting licenses to conduct further research to increase the test's efficacy, Myriad prevents follow-on research using its patented genes. Unfortunately, African-Americans, Hispanics, and Asian-Americans are disproportionately likely to receive these ambiguous test results. Therefore, these populations as a whole have less

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201 Wendy Chung, "Statement to the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with a Hearing on Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing," October 25, 2007.

202 Shobita Parthasarathy, *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*, MIT PRESS (2007).

access to preventative treatments for cancer.[203] This disproportionate result in minority populations is a particularly concerning public policy issue.

**BIOPATENTS DENY PATIENTS ACCESS TO SECOND MEDICAL OPINIONS**

Biopatent are particularly concerning because they may deny patients access to secondary medical opinions. Consider the following example: CancerX sells the only uterine cancer test. Using CancerX's test, Lisa's doctor diagnoses her with uterine cancer. He recommends that Lisa undergo surgery to remove her uterus and have chemotherapy to rid Lisa of the cancer. Lisa's insurance will not cover any of the costly treatments and if she chooses to proceed with the treatment, she will be unable to bear children of her own. Because CancerX holds the patent to the only test for uterine cancer, Lisa is unable to get a second medical opinion before making a life-changing decision.

Courts have consistently recognized a patient's right to a second medical opinion as a matter of public policy.[204] There is often more than one way to approach any set of medical facts and doctors may misdiagnose a condition.[205] Most doctors and insurance plans, including Medicare, frequently require that patients receive a second medical opinions before having nonemergency surgeries and treatments. [206] In *Rush Prudential*

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[203] Secretary's Advisory Committee on Genetics, Health, and Society, "Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests," March 2009.

[204] Rush Prudential HMO, Inc. v. Moran, 536 U.S. 355, 400, 122 S. Ct. 2151, 2178 (2002).

[205] Dr. Gail Gazelle, *Half of Americans don't get a second opinion*, at http://www.nbcnews.com/id/22829371/ns/health-health_care/t/half-americans-dont-get-second-opinion/.

[206] Dr. Robert Klitzman, *"When Doctors Become Patients", at http://www.nytimes.com/2008/02/12/health/views/12essa.html?_r=0*

*HMO, Inc., v. Moran*, the Supreme Court upheld laws in 42 states that give patients a right to a second medical opinion from outside doctors if their HMOs turn them down for a medical treatment or a drug benefit.[207] Both patients and insurers have an interest in obtaining second opinions because they help to guard against unnecessary surgeries and treatments that may be costly and life changing.[208] When the federal government recognized these benefits, Medicare became the first indemnity insurance plan to pay for beneficiaries to receive second medical opinions.[209] By the mid-1980s, second opinions were a well-established feature of almost all other indemnity insurance programs in the United States.[210] In 1986, the federal government considered "making second opinions mandatory for all Medicaid recipients for ten common elective surgical procedures" but the government considered second medical opinions a patient's right, rather than a burden.[211]

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[207] Rush Prudential, 536 U.S. at 374, 122 S. Ct. at 2163; *See also A Second Opinion*, ABA J., AUGUST 2002, at 36.

[208] *See* Eugene G. McCarthy & Geraldine W. Widmer, *Effects of Screening By Consultants on Recommended Elective Surgical Procedures*, 291 New Eng. J. Med. 1331 (1974); Suzanne Grisez Martin et al., *Impact of a Mandatory Second-Opinion Program on Medicaid Surgery Rates*, 20 Med. Care 21 (1982); Hirsch S. Ruchlin et al., *The Efficacy of Second-Opinion Consultation Programs: A Cost-Benefit Perspective*, 20 Med. Care 3 (1982).

[209] *See* Health Care Fin. Admin., U.S. Dep't of Health and Human Servs., Getting a SecondOpinion--Your Choice Facing Elective Surgery (visited May 20, 1998) <http://www. hoptechno.com/book17.htm>; Agency for Health Care Policy and Research, Be Informed: Questions to Ask Your Doctor Before You Have Surgery (visited May 20, 1998) <http://www.ahcpr.gov/consumer/surgery.htm>.

[210] *See* Friedman, supra note 85, at 105 (noting growing interest in second-opinion programs); Second-Opinion Surgery: *What the Doctor Ordered?*, Changing Times, June 1985, at 18, 18 ("A majority of Blue Cross/Blue Shield Plans now require second opinions, and the momentum is picking up among other insurers.").

[211] *See* Mandatory Second Surgical Opinion Requirements for Medicaid Recipients, 51 Fed. Reg. 21,933 (1986) (proposed June 17, 1986).

Today, patients do not seek second opinions as often as they did in the 1980's.[212] The current American healthcare system has moved away from indemnity insurance and fee-for-service medical care to integrated systems of coverage and care, which shift financial risk to providers;[213] however, for procedures that insurance may not cover—i.e. expensive cancer treatments—doctors often still recommend that patients seek a second medical opinion.[214] Even if most second opinions just confirm what a patient's original physician recommended, they still play an important role because they offer patients peace of mind before they have to make life changing decisions.[215] In the instances in which primary physicians misdiagnose patients, second opinions can have profound economic and physical effects.

**THE RESEARCH EXEMPTION IS NOT ENOUGH TO FIX THE PROBLEM**

Some commentators call for an expansion of the current research exemption to patents in order to cure these dilemmas, but a research exemption would not solve either the harm to innovation and progress or consumer access to secondary medical opinions.

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212 David A. Hyman, *A Second Opinion on Second Opinions*, 84 Va. L. Rev. 1439, 1457 (1998)

213 *Id.*

214 Dr. Jan C. Buckner chair of medical oncology, Mayo Clinic, Rochester, Minn. Harold J. Burstein, MD, staff oncologist, Dana-Farber Cancer Institute; assistant professor of medicine, Harvard Medical School, Boston.

215 *See* Second Opinions, Harv. Med. Sch. Health Letter, Feb. 1989, at 1; *See also* Breastlink Consultation Services (visited Nov. 3, 1998) < http:// www.breastlink.com/ consult.html> (noting the importance of getting a second opinion in dealing with breast cancer, especially when, "because of managed care, some women are given little choice in selecting physicians or treatment options and they want to make sure their medical system will do the right thing"); Propositions 214 and 216, which were on the ballot in California in 1996, would have required HMOs to obtain a second opinion before denying care. See David R. Olmos, Backers of HMO Reform Initiatives Launch Ad Blitz, L.A. Times, Nov. 1, 1996, at D2; Marvin L. Lipman, Office Visit: Are Two Medical Opinions Better Than One?, Consumer Rep. on Health, July 1994, at 83, available in WESTLAW, Consumer (Dialog) Database.

The research exemption is a common law affirmative defense to patent infringement, which may be invoked where the alleged infringer uses a patented invention for research purposes only. A crucial limitation on the research exemption is that the innovation may not actually be performed on the public.[216] Any public or commercial involvement prevents a researcher from invoking the research exemption. Justice Joseph Story first wrote of the research exemption in the 1813 case, *Whittemore v. Cutter*;[217] however, the research exemption has since been limited by subsequent cases, generally depending on the commercial nature of the research.

Contrary to common belief, the United States patent system does not exempt noncommercial and purely academic research from liability.[218] In 2002, in *Madey v. Duke University ("Madey"),* the Court of Appeals for the Federal Circuit "very narrowly and strictly limited [the] experimental use defense" for "amusement, to satisfy idle curiosity, or for strictly philosophical inquiry…" and excluded research done "in furtherance of the alleged infringer's legitimate business."[219] The court held that universities, such as Duke, conduct research as part of its legitimate business, and thus cannot invoke the research exemption as a defense to patent infringement.[220] The Federal Circuit essentially made it impossible for university and clinical researchers to use the

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216 Madey v Duke University 307 F.3d 1351 (Fed. Cir. 2002).

217 Whittemore v. Cutter, 29 Fed. Cas. 1120 (C.C.D. Mass. 1813), (the intent of the legislature could not have been to punish someone who infringes "merely for [scientific] experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.)

218 *See* Katherine J. Strandburg, *What Does the Public Get? Experimental Use and the Patent Bargain*, 1WIS. L. REV. 81, 93-100 (2009).

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

220 *Id.*

exemption as a shield from infringement liability even if the sole purpose of the research is to invent around patented method.[221]

If *Madey* were overruled and research universities permitted to invoke the research exemption regardless of their commercial applications, progress and innovation might increase. This would still require, however, that courts permit universities to profit from their research through subsequent patents. Such a ruling would entirely undermine the present patent system. This would leave only private companies subject to patent limitations, which would removed any incentives for private companies to invest in scientific research, thereby effectively leaving no parties subject to patent limitations.

Furthermore, an expanded research exemption would do nothing to give consumers access to secondary medical opinions. If the research exemption depends on the commercial nature of the research, then researchers will have to be careful about that innovation reaching the marketplace, which ultimately would have little benefit to the public. If innovation and progress is occurring but consumers are not benefiting from the innovation, then the IP Clause's constitution mandate will still be unfulfilled. Progress and innovation must reach the consumer, but the research exemption, even an expanded one, could not do this.

[221] Strandburg, *supra* note 218 at 86-87.

# CHAPTER SIX

# RECOMMENDED CHANGES TO PATENT LAW

The Supreme Court arguably came to the correct legal conclusion in the *Mayo* and *Myriad* cases, appropriately applying all doctrinal tests, but the "correct" holding may have profound negative consequences for scientific progress and innovation and consumer access to medical care. A strict reading of the constitutional social utility rationale for intellectual property implies that failure to facilitate scientific progress and development of useful and affordable for the public's benefit undermines the legitimacy of current patent law, warranting fundamental changes.[222] Patent law derives from the constitution mandate for congress "[t]o promote the Progress of Science and useful Arts…" and it arguably only remains valid so long as that mandate is met. [223] If the constitutional mandate to further progress and innovation is no longer being met and biopatents violate public policy, then a change must be made to American patent law either through the legislature or through judicial application. This change ought to come from the legislature if the constitutional mandate is no longer being met; however, even if constitutional, courts may carve out an exception for the remaining eligible stem cell patents if courts find that they violate other public policies.

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222 A. Chapman, *Article: Religious Contributions to the Debate on the Patenting of Human Genes*, 10 U. ST. THOMAS L.J. 650.

223 U.S. Const. art. I, § 8, cl. 8.

**LEGISLATIVE CHANGE**

Because of the profoundly negative impact on public health risks that stem cell patents present, Congress should enact compulsory license legislation for stem cell and all bioproduct patents. Some proponents of change call for Congress to broaden the experimental use exemption currently available to academic researchers to make stem cells freely available to those in research, but this does not remedy all of the public harms of these patents. [224i] While this would allow biomedical research taking place at nonprofit academic research laboratories to openly infringe bioproduct patents, it would not allow any of those discoveries to make their way to the market to benefit consumers.

Compulsory licensing would not undermine the intended purpose of patent protection to incentive innovation and progress. Patents grant inventors negative rights in their inventions so that they may recoup costs and profit from their development, incentivizing innovation. Patentees can still recoup costs and profits if they were federally compelled to license their patented bioproducts in exchange for a statutory set fee. This is evidenced by the fact that WARF, in response to public pressures, has chosen to freely license its stem cells and is still profiting handsomely from its patents.[225] As WARF did, the licensing fee could be "tied to the commercial value of the product developed as a result of the licensee's research." [226ii] In response to political pressure, WARF chose to successfully self-impose a compulsory scheme for its patents. WARF has continued to thrive financially even after enacting this scheme. Compulsory licensing of bioproduct patents thus would not remove the financial incentives that

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224 17 DCBABR 22, 24

225 US patent number 7029913 (March 2001).

226 17 DCBABR 22, 26

patents provide. Compulsory licensing merely ensures that available inventions might be improved upon and allows physicians to practice medicine by using the patented inventions to give secondary diagnoses and treatment options..

This also would not be the first time Congress has acted to protect the interests of medical consumers. In 1984, Congress acted to safeguard consumer access to healthcare by enacting the "Drug Price Competition and Patent Term Restoration Act of 1984"—also known as the Hatch-Waxman Act—which established the Annotated New Drug Application process ("ANDA").[227iii] ANDAs allow the United States Food and Drug Administration ("FDA") to speed up the timeframe in which drug manufacturers can provide to the public safe, effective, low cost alternatives to name-brand drugs.[228iv] Similarly, compulsory licensing for stem cell gene patents would ensure that medical consumers could access inventions, as the IP Clause intends. Compulsory licensing would increase downward flow of research and innovation, while maintaining patent incentives. Furthermore, compulsory licensing currently is automatically granted for government use of any patented innovation, in exchange for reasonable compensation.[229] Courts may also use compulsory licenses to remedy anti-competitive practices such as paying competitors not to enter the market, wherever they believe is necessary.[230]

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227 United States Food & Drug Admin., Development and Approval Process (Dep't of Health & Human Services 2013), available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm.

228 *Id.*

229 NIH, *Report of the National Institute of Health Working Group on Research Tools* (1998) <http://www.nih.gov/news/researchtools/> accessed July 2010.

230 *See* Innnogenetics v Abbott Labs (Fed. Cir. 2008).

## JUDICIAL USE OF PUBLIC POLICY AS A BALANCING FACTOR IN DETERMINING PATENT ELIGIBILITY

While fundamental patent reform must originate from Congress, courts may still balance public policy concerns to remedy the negative effects of bioproduct patents,previously discussed. Rather than merely focus on the application of § 101 of the Patent Act, as courts presently do, courts should also look to the public policy effect of bioproduct patents when considering patent eligibility. As the Supreme Court did with the machine-or-transformation test in *In Re Bilski*, courts should rule that, on public policy grounds, the holdings of *Mayo* and *Myriad* are not conclusive of patentability. Lower courts are bound by the "four corners" of Supreme Court decisions, but they may decide to apply different principles to different situations. If *Mayo* and *Myriad* were not conclusive on the matter of patentability, the courts could balance the public policy concerns of biopatents, and stem cells in particular. After decades of judicial dicta on the matter and a strong medical lobby, in 1996, Congress amended the patent act to immunize medical professionals from patent infringement of patented surgical techniques as a matter of public policy due to the unique need for unrestricted access to healthcare.[231] Likewise, the medical applications of bioproduct research warrant special judicial balancing of public policy considerations when determining biopatent eligibility and validity.

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[231] 35 U.S.C. § 287(c) (2) (A); *See also* Cynthia Ho, *Patents, Patients, and Public Policy: an incomplete intersection at 35 U.S.C. § 287 (c)*, 33 U.C. DAVIS L. REV. 601 (1999-2000).

# CONCLUSION

Biopatents embody a unique combination of medical research tools aimed at improving patient health. The effect of biopatents on public health warrants special treatment of the biotechnology industry. The Supreme Court ruled on the patent eligibility of method claims involving laws of nature in *Mayo* and compositions of matter in *Myriad*; however, the fate of stem cell patents is not yet certain. Because of their nearly infinite medical applications, stem cells are arguably one of the most crucial research tools for the future. The Supreme Court's holdings in *Mayo* and *Myriad* will likely result in the invalidation of hESCs because they are not "markedly different" than stem cells found in nature. The same holdings, however, will likely do nothing to prevent IPSCs from remaining patentable.

Unfortunately, biopatents, especially stem cell patents, violate public policy in several respects. The evidence establishes that biopatents inhibit further progress and innovation by preventing follow-on research, raise medical costs, limit patient access to treatments, prevent minority populations access to medical treatments and diagnostic tests, and deny patients access to second medical opinions. Patent law was created to benefit the public rather than to reward the inventor for his or her efforts. These public policy concerns warrant special consideration to be given to biopatent eligibility.

It is time for Congress to amend the patent act to prevent these public harms. I recommend that Congress enact compulsory licensing for biopatents; however such a radical change is highly unlikely to occur any time soon. The Leahy-Smith America Invent Act was long overdue when it was enacted in 2011 and only made minor changes to the present patent structure, so it is unlikely Congress will do much further.

Alternatively, courts should balance public policy concerns when determining biopatent eligibility. By balancing public policy considerations, the courts would be able to apply current patent law in an industry-specific manner to remedy the public policy violations which often result from biopatents. The Supreme Court already balances the various statutory provisions of the patent act when making its determinations, but additional public policy considerations are necessary to reach the correct result for the public, as patent law intended.

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- Rebeca Echevarria, Note, *Valid but Harmful: Why Congress Should Amend the Patent Act to Compulsory Licensing of Disease Gene Patents*, 2014 WAKE FOREST J. OF BUS. & INTELL. PROP. L. (citation forthcoming).
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