THE RIPPLE EFFECT OF INTELLECTUAL PROPERTY POLICY: EMPIRICAL EVIDENCE FROM STEM CELL RESEARCH AND DEVELOPMENT

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I. INTRODUCTION

In recent years, there have been dramatic shifts in the patentability of biotechnological ("biotech") inventions.[1] After three decades—during which patents were routinely granted on cells and DNA segments of the human body in their isolated and purified forms[2]—the Supreme Court recently invalidated *Myriad*'s patents on the BRCA1 and BRCA2 genes linked to breast and ovarian cancer.[3] In the landmark *Association of Molecular Pathology v. Myriad Genetics Inc.* (*Myriad*) decision, the Court deviated from a long-standing stance following the 1980 *Chakrabarty* case, which stated that living organisms are patentable as long as they were generated through manmade intervention.[4] In *Myriad*, the Supreme Court held that genes that are merely isolated from their natural environment are not patentable under Section 101 of the Patent Act,[5] distinguishing between synthetically created DNA (cDNA), which does not occur naturally, and is therefore patentable, and isolated DNA, which was held to be unpatentable subject matter under the "products of nature" doctrine.[6]

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1. *Compare* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) (holding that isolated sequences of human DNA, once sufficiently defined or reduced to practice, are patentable chemical compounds), *with* Ass'n of Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2117 (2013) ("[S]eparating [a] gene from its surrounding genetic material is not an act of invention.").

2. Isolated forms of chemicals found in nature were considered patentable since the 1912 *Parke-Davis* case. *See* Parke-Davis & Co. v. H.K. Mulford & Co., 196 F. 496, 497 (2d Cir. 1912) (holding that a purified and isolated form of adrenaline, in contrast to the natural form that exists in the body, is patentable); *see also In re* Application of Bergy, 563 F.2d 1031, 1038 (C.C.P.A. 1977) (holding that a purified culture of the microorganism Streptomyces Vellosus is patentable because it cannot be found in nature in its purified form). Amgen was the first to patent isolated human genes. *See Amgen*, 927 F.2d at 1200, 1206, 1219 (upholding patents on isolated and purified human DNA sequences).

3. *See Myriad*, 133 S. Ct. at 2111.

4. Diamond v. Chakrabarty, 447 U.S. 303, 309–10 (1980). In this landmark decision, the Supreme Court drew a distinction between products of nature that can only be discovered and therefore are not patentable, and man-made inventions which are patentable subject matter. *Id.* at 310. The Supreme Court then concluded that a living bacterium that is genetically engineered and does not exist in nature in its engineered form is patentable. *Id.*

5. *Myriad*, 133 S. Ct. at 2120. ("We merely hold that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material").

6. *Id*. at 2119. The *Myriad* Court reaffirmed its previous decision in *Mayo Collaborative Servs. v. Prometheus Labs* that the three exceptions to patentability: abstract ideas, laws of nature and natural phenomena are "the basic tools of scientific and technological work" and that without these exceptions "there would be considerable danger that the grant of patents would 'tie up' the use of such tools and thereby inhibit future innovation premised upon them" which "would be at odds with the very point of patents, which exist to promote creation." *Id.* at 2116 (citing 132 S. Ct. 1289, 1293 (2012)). Following the *Myriad* decision, a memorandum providing preliminary guidance was published by the U.S. Patent and Trademark Office (USPTO) stating that

The *Myriad* decision was followed by a torrent of speculation regarding its potential implications for the biotech industry.[7] One such issue is whether this ruling will be extended to other types of "isolated" biomolecules such as proteins, cells, organisms, and other types of natural products.[8] Another is whether the ruling will affect the level of research and development (R&D).[9] Some commentators argue that the decision is narrow in scope and has only limited implications; therefore, it is likely to only affect a very small segment of research, if at all.[10] Others have suggested that by affirming that cDNA can be patented, the decision may have in fact strengthened incentives for private investment in R&D.[11]

"examiners should now reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. § 101." Memorandum from Andrew M. Hirshfeld, Deputy Comm'r for Patent Examination Policy, U.S. Patent & Trademark Office, to Patent Examining Corps. (June 13, 2013), *available at* http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf.

7. *See, e.g.*, Carmela DeLuca & Melanie Szweras, *The Myriad Decision: What is the Impact?*, LEXOLOGY (June 20, 2013), http://www.lexology.com/library/detail.aspx?g=ed2570c9-bcac-44e0-8346-c815ae42c773 (discussing the ramifications of Myriad and possible interpretations of the decision); James J. Mullen III et al., *The Nature of Patents*, CAL. LAW. (Jan. 2014), http://www.callawyer.com/clstory.cfm?pubdt =201401&eid=932737&evid=1 (noting that "[t]he Myriad decision has potentially far-reaching effects").

8. Deluca & Szweras, *supra* note 7.

9. *See, e.g.*, Amy DeCloux & Kathleen Williams, *Myriad Genetics: The Supreme Court Rules that Isolated DNA is Not Patent Eligible*, SUNSTEIN L. (June 2013), http://sunsteinlaw.com/myriad-genetics-the-supreme-court-rules-that-isolated-dna-is-not-patent-eligible/. DeCloux and Williams assert that *Myriad's* impact is limited since

> diagnostics pertaining to genetics and human diseases has reached a level of sophistication which involves analyzing tens, hundreds, if not thousands of gene mutations at once. As a consequence, holding a patent on a single gene is unlikely to preclude competitors from commercializing diagnostics aimed at hundreds of genes, only one of which is that single gene.

Id.

10. *See id*. Similarly, patent lawyer Michael S. Tuscan from Cooley LLP contends that:

> [t]he decision is actually not too disruptive for the industry, as it leaves open many ways for companies to build patent exclusivity around manipulated nucleic acids, methods of using even naturally occurring nucleic acids, etc., . . . Much of what this decision pertains to is research and discoveries that took place more than 10 years ago, not what is generally new to the life sciences industry in this day and age.

Roxanne Palmer, *Myriad Ruling Impact: How will Human Gene Patent Decision Affect Biotech Industry and Patients?*, INT'L BUS. TIMES (June 13, 2013), http://www.ibtimes.com/myriad-ruling-impact-how-will-human-gene-patent-decision-affect-bio tech-industry-patients-1306299.

11. *See* Jason Rantanen, Myriad*: Isolated DNA out, cDNA in*, PATENTLY-O (June 13, 2013), http://www.patentlyo.com/patent/2013/06/myriad-isolated-dna-out-cdna-in.html ("I'm skeptical that the Court's opinion will have a negative effect on the incentives for creating biotechnology-

Still other commentators have warned that the *Myriad* decision, by increasing uncertainty regarding what is patentable subject matter in the biotech field, might negatively impact private investments in this area of research.[12]

Similar concerns were raised a decade ago following a 2004 decision by the European Patent Office (EPO)— which refused to grant patents on human embryonic stem cells (hESCs) based on moral grounds.[13] This decision, which was later affirmed in other instances,[14] caused turmoil within the European scientific community.[15] Here, too, concerns of a chilling effect on R&D were raised.[16] The European research community feared a shortage of funding for stem cell research, and in the absence of patent protection scientists feared that stem cell research funding would be allocated elsewhere.[17] Others argued that these legal judgments would only have a limited impact on stem cell research because they narrowly apply to hESCs and do not hold hESC research illegal, simply unpatentable.[18]

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based applications. To the contrary: by affirming that cDNA can be patented, it may strengthen the incentives for investing in research in this area.").

12. Dalila Argaez Wendlandt & Joseph Van Tassel, *Feeling Funk-y: Human Gene Patents in* AMP v. Myriad, 32 BIOTECHNOLOGY L.R. 297, 301 (2013), *available at* http://www.ropesgray.com/biographies/v/~/media/Files/articles/2013/09/FeelingFunkyWendlandtetalBLR325.ashx; Palmer, *supra* note 10. For more on the effects of policy uncertainty on research, see Aaron D. Levine, *Policy Uncertainty and the Conduct of Stem Cell Research*, 8 CELL STEM CELL 132, 132–35 (2011).

13. *European Industry, Academia Watch Closely As EPO Weighs Legality of WARF hESC Claims*, Genome Web (July 11, 2008), https://www.genomeweb.com/biotechtransferweek/european-industry-academia-watch-closely-epo-weighs-legality-warf-hesc-claims-0 (noting concerns that only basic research would be conducted in Europe while more substantial commercial activity would be conducted in places with more lenient patent environments).

14. The EPO's decision was appealed and the Enlarged Board of Appeals in the EPO concluded that human embryonic stem cell research that results in the destruction of the embryo is not patentable. Decision G 2/06, Wis. Alumni Research Found., 2008 O.J. Eur. Patent Office 306, 326 ¶ 22, *available at* http://archive.epo.org/epo/pubs/oj009/05_09/05_3069.pdf. In 2011, the European Court of Justice (ECJ) also held that the destruction of the embryo renders an invention unpatentable. *See* Case C-34/10, Brüstle v. Greenpeace eV, 2011 E.C.R. I-9849, I-9875, *available at* http://curia.europa.eu/juris/celex.jsf?celex=62010CJ0034&lang1=en&type=TXT&ancre=; Nuala Moran, *European Court Bans Embryonic Stem Cell Patents*, 29 NATURE BIOTECHOLOGY 1057, 1057–59 (2011), *available at* http://www.nature.com/nbt/journal/v29/n12/full/nbt1211-1057.html%3FWT.ec_id%3DNBT-201112.

15. *See* Moran, *supra* note 14 (noting that scientific researchers have been troubled by both the implication that their research is immoral and concerns that research funding could be threatened).

16. *Id.*

17. *Id.*; Austin Smith, *No to Ban on Stem-Cell Patents,* 472 NATURE 418, 418 (2011).

18. For example, the Medical Research Council (MRC) in England has stated that it will proceed with its stem cell funding initiatives. Moran, *supra* note 14; *European Court Bans Embryonic Stem Cell Patents*, 29 NATURE BIOTECHNOLOGY 1057, 1058 (2011). Also, September 2012 saw the launch of a new research project funded within the framework of FP7 and involving

Another example of a dramatic shift in IP policy is the recent *Alice Corp. v. CLS Bank* case pertaining to the software industry.[19] In that case, the Supreme Court examined the patentability of a computer-implemented invention for electronic escrow service intended to facilitate financial transactions.[20] The Court held that the claims of the patent applications encompassed an abstract idea and thus were ineligible for patent protection.[21] In essence, *Alice Corp. v. CLS Bank* raised the bar for software patents, but while doing so it failed to provide clear guidelines indicating when software patents are acceptable and when they should be considered an 'abstract idea' and hence unpatentable.[22] As in previous policy-changing judgments, this decision provoked a similar debate: Some commentators argued that the decision was too narrow and will not, by itself, prevent the proliferation of software patents.[23] Others claimed that the decision creates uncertainty about the validity of all software patents, which could be devastating for the software industry.[24]

These controversies regarding the potential impact of IP policy changes could be traced back to the fundamental assumptions of intellectual property policy: that well-defined intellectual property rights (IPR) are necessary in order to stimulate innovation and that any change in the scope of IPR could stifle research and development.[25] While the nature of the legal change, and the pace of regulatory change, might be of great importance for shaping the behavior of firms, investors, and scientists, there is little empirical evidence supporting the impact of legal developments on R&D. With this in mind, an empirical study on such an impact is of general interest. Studying the impact of game-changing court

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hESCs. *See* CORDIS, http://cordis.europa.eu/projects/rcn/100928_en.html (last visited Jan. 17, 2015).

19. *See* Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2352.

20. *Id.*

21. *Id*. at 2357. The Supreme Court affirmed the decision given by the Court of Appeals for the Federal Circuit, which, prior to *Alice*, had been known for its liberal approach toward software patents. *See* Timothy B. Lee, *This Ruling Should Worry Every Software Patent Owner*, VOX (July 17, 2014), http://www.vox.com/2014/7/17/5910985/software-patents-are-under-seige-thanks-to-the-supreme-court.

22. *See* Brian Fung, *The Supreme Court's Decision on Software Patents Still Doesn't Settle the Bigger Question*, WASH. POST BLOG THE SWITCH (June 20, 2014), http://www.washingtonpost.com/blogs/the-switch/wp/2014/06/20/the-supreme-courts-decision-on-software-patents-still-doesnt-settle-the-bigger-question/; Daniel Nazer & Vera Ranieri, *Bad Day for Bad Patents: Supreme Court Unanimously Strikes Down Abstract Software Patent*, ELECTRONIC FRONTIER FOUND. (June 19, 2014), https://www.eff.org/deeplinks/2014/06/bad-day-bad-patents-supreme-court-unanimously-strikes-down-abstract-software; Erin Mershon, *High Court Restricts Some Software Patents*, POLITICO (June 19, 2014), http://www.politico.com/story/ 2014/06/supreme-court-software-patent-abstract-idea-108060.html; Lee, *supra* note 21.

23. *See* Fung, *supra* note 22.

24. *See* Lee, *supra* note 21.

25. ROBERT P. MERGES, JUSTIFYING INTELLECTUAL PROPERTY 32 (2011).

judgments on R&D activity could further reveal the impact of IPR in shaping R&D.

This Article offers empirical evidence on these controversies, showing that dramatic shifts in IP policy may critically affect R&D. The study focuses on game-changing milestones in stem cell policy, and analyzes their impact on the level of stem cell R&D activity. Stem cell research provides an excellent case study to examine the relationship between policy and R&D as it has been subject to numerous policy changes, stemming from ethical controversies on issues such as what should be considered the onset of human life, at what point do we have an obligation to respect that life, and to what extent should living organisms be used for life-saving research.[26] These ethical controversies also extend to legal policies.[27]

The stem cell policy milestones analyzed in the Article primarily focus on two types of policy strategies used to shape R&D funding: (1) patent protection, designed to promote innovation by creating financial incentive for private investment in R&D; and (2) public funding policies that provide, or deny, funding. We compare the impact of policy shifts in Europe and in the United States, regarding the patentability of stem cell inventions as well as the regulation of public funding for R&D in this field.[28] We then evaluate whether policy changes pertaining to hESC research, in the United States regarding federal funding and in Europe regarding patentability, have influenced the level of R&D activity as measured by patent applications volume.

Patents are considered a direct measurement of research and development and other inventive activities.[29] The volume of patent applications is often used as a proxy to indicate technological and scientific developments.[30] By tracing patent applications, threads of inventive activity in stem cell research may be unveiled.[31] The dataset

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26. *See* Kristina Hug & Goran Hermeren, *Embryonic Stem Cell Research: An Ethical Dilemma*, EURO. STEM CELL (Mar. 23, 2011), http://www.eurostemcell.org/factsheet/embyronic-stem-cell-research-ethical-dilemma.

27. *See, e.g.*, President George W. Bush, President Discusses Stem Cell Research (Aug. 9, 2001, 8:01 PM), *available at President Discusses Stem Cell Research*, WHITE HOUSE, http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html and the discussion in Part III.C.1; *see also* G-2/06, Decision of the Enlarged Board of Appeal dated Nov. 25, 2008, Official Journal of the European Patent Office, 306, 326 ¶ 22, *available at* http://www.epo.org/law-practice/case-law-appeals/pdf/g060002ex1.pdf and the discussion in Part III.B.2.

28. *See infra* Part III.

29. Zvi Griliches, *Patent Statistics as Economic Indicators: A Survey*, 28 J. ECON. LITERATURE 1661, 1701–02 (1990); ORGANISATION FOR ECON. CO-OPERATION AND DEV., OECD PATENT STATISTICS MANUAL 26 (2009) [hereinafter OECD PATENT STATISTICS MANUAL].

30. Griliches, *supra* note 29.

31. OECD PATENT STATISTICS MANUAL, *supra* note 29.

compiled for this study includes stem cell patent applications filed during the years 1990–2013 in the U.S. Patent and Trademark Office (USPTO),[32] via the Patent Cooperation Treaty (PCT), and in the European Patent Office (EPO).

Our findings show a strong correlation between a 2004 European legal decision, which denied patent protection of hESC inventions, and a consistent decline in patent activity.[33] In fact, while the legal decision denying patent protection was confined solely to human embryonic stem cells and applicable only to European patents, its implications were much broader. Our analysis indicates a steady and consistent decline in the number of patent applications in all stem cell inventions (not just human embryonic stem cells), and in all the tracks surveyed.[34] No similar impact was recorded following changes in funding policies.[35] Nonetheless, given the intensity of policy changes over a short period of time, the declining trend witnessed could be attributed to the overall effect of the policy changes rather than to just one of them.[36]

The analysis of the findings demonstrates the Ripple Effect of IP policy, showing that IP policy changes might have unintended consequences that are broader than their original scope. The findings show that the EPO's decision, denying patent protection for human embryonic stem cells, had a global effect on patent activity—one that was not limited to the EPO jurisdiction. Furthermore, even though the decision strictly applied to human embryonic stem cells it had a broad effect on stem cell patent activity in general. The analysis also suggests that frequent policy changes created uncertainty in the stem cell field, which increased the risks associated with R&D. Finally, our findings demonstrate a differentiated impact of IP policy, with a more significant impact on the private sector as compared to the public one, suggesting that the public and the private sectors react differently to IP policy changes.

This Article proceeds as follows: Part II briefly discusses stem cell research and introduces the ethical controversies it raises. Part III has three objectives: (a) to describe the legal framework for regulating research and development, identifying the major policy milestones pertaining to stem cell research in the United States and Europe; (b) to

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32. Data for U.S. patent applications starts at 2001 as data relating to previous years is not available. *See* Patent Document Authority Files, U.S. PAT. & TRADEMARK OFF. (July 4, 2009 6:38 PM), http://www.uspto.gov/patents-application-process/patent-search/patent-document-authority-files.

33. *See infra* Figure 2 and the accompanying text.

34. *Id.*

35. *See infra* Figure 3.

36. *See generally* Levine, *supra* note 12 (discussing the broad effects of uncertainty in the stem cell field on scientists and on R&D).

discuss the patentability of hESCs, comparing the European approach, which led to the denial of hESC patents, and the American approach, which led to the approval of hESC patents; and (c) to explore the different legal policies on public funding for hESC research in the United States and Europe. Part IV provides an extensive analysis of stem cell patent applications and identifies trends in stem cell patent filing following the legal milestones described in Part III. The Article reviews and analyzes the implications of these findings in Part V. Part VI summarizes the Article's main observations and conclusions.

II. WHAT IS STEM CELL RESEARCH?

Stem cell research is a highly promising yet controversial line of research, embedding ethical, legal, and financial dilemmas—which result in frequent policy changes and much uncertainty.[37] Stem cells are self-renewing, unspecialized cells that are capable of giving rise to a variety of differentiated and specialized cells in the body.[38] Stem cell research is often considered a breakthrough technology, at the forefront of the biotechnology industry.[39] Its potential uses include improved understanding of the complex events that occur during human development, primarily how undifferentiated cells turn into differentiated cells that form tissues and organs, and the causes for abnormal cell division.[40] Human stem cells are also used to test new drugs safety, for example, cancer cell lines are used to screen potential anti-tumor drugs.[41] Pluripotent stem cells (iPS) allow drug testing on a wide range of cell types.[42] Human stem cells may also be used to generate cells and tissues for cell-based therapy.[43] Due to its extensive potential uses, stem cell research provides hope for treatment and cure for an array of degenerative diseases and injuries including Alzheimer's, diabetes, spinal cord injury, and certain types of cancer.[44]

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37. *See* Levine, *supra* note 12; *see generally* R.M.L. Winston, *Does Government Regulation Inhibit Embryonic Stem Cell Research and Can It Be Effective?*, 1 CELL STEM CELL 27, 27–34 (2007) (providing information on the history of stem cells).

38. ESSENTIALS OF STEM CELL BIOLOGY, at XXV (Lanza et al. eds., 2d ed. 2009).

39. *What are the potential uses of human stem cells and the obstacles that must be overcome before these potential uses will be realized?*, subheading in *Stem Cell Information*, NAT'L INSTS. OF HEALTH, http://stemcells.nih.gov/info/basics/pages/basics6.aspx (last visited Oct. 9, 2014) [hereinafter NAT'L INSTS. OF HEALTH].

40. *Id.*

41. *Id.*

42. iPS cells are adult cells that have been genetically reprogramed to an embryonic stem cell-like state. *Id.*

43. *Id.*

44. James M. Wilson, *A History Lesson for Stem Cells*, 324 SCIENCE 727, 727 (2009).

All types of stem cells are capable of dividing and renewing themselves over long periods of times; they are unspecialized but can give rise to specialized cell types.[45] The different types of stem cells differ in their degree of specialization.[46] Adult stem cells are specialized, undifferentiated cells found among differentiated cells in a tissue or organ.[47] Their primary role is to regenerate and repair the tissue in which they are found.[48] Being specialized, adult stem cells are committed to specific directions of differentiation, whereas embryonic stem cells may give rise to most cell types.[49] Embryonic stem cells are pluripotent (*i.e.*, able to give rise to differentiated cells of all three germ layers),[50] immortal,[51] and capable of giving rise to most cell types.[52]

Embryonic stem cell research has become morally controversial.[53] This moral controversy is rooted in the fact that embryonic stem cells are typically derived from a four to five day old embryo, called a blastocyst, a procedure which results in the destruction of the embryo.[54] The moral status of the embryo, its autonomy, the degree of consent required from donors, and religious views regarding the onset of life are some of the ethical questions raised by hESC research.[55] Thus, for example, conservative Christian groups generally oppose human embryonic stem

45. There are different types of stem cells including: adult stem cells, embryonic stem cells and stem cells derived from other sources including cord blood, fetal tissues and amniotic fluid. *See* NAT'L INSTS. OF HEALTH, *supra* note 39; ESSENTIALS OF STEM CELL BIOLOGY, *supra* note 38, at 145, 151.

46. NAT'L INSTS. OF HEALTH, *supra* note 39.

47. *Id*.

48. *Id.*

49. Martin Evans, *Ethical Sourcing of Human embryonic Stem Cells – Rational Solutions?* 6 NATURE REVIEWS: MOLECULAR CELL BIOLOGY 663, 664 (2005).

50. ESSENTIALS OF STEM CELL BIOLOGY, *supra* note 38, at 527.

51. The process by which a stem cell replicates itself. *See id.* at XXV.

52. Evans, *supra* note 49, at 664.

53. *See* Bernard Lo & Lindsay Parham, *Ethical Issues in Stem Cell Research*, 30 ENDOCRINE REV. 204, 204 (2009); RUSSELL KOROBKIN, STEM CELL CENTURY: LAW & POLICY FOR A BREAKTHROUGH TECHNOLOGY 29 (2007).

54. *See* Andrew Siegel, *Ethics of Stem Cell Research*, The Stanford Encyclopedia of Philosophy (Edward N. Zalta ed., Spring 2013 ed.) (2008), *available at* http://plato.stanford.edu/entries/stem-cells.

55. For more on the ethical aspects of hESC research see *Embryonic Stem Cell Research: An Ethical Dilemma*, EUROSTEMCELL (Mar. 23, 2011), http://www.eurostemcell.org/factsheet/embryonic-stem-cell-research-ethical-dilemma; Tabinda Hasan, *Human Embryonic Stem Cells: Where to Draw the Line*, J. ARMED FORCES MED. C. BANGDL., Dec. 2011, at 40, 40; Michael J. Sandel, *Embryo Ethics – The Moral Logic of Stem-Cell Research*, 351 N. ENG. J. MED. 207, 207–08 (2004); AURORA PLOMER, THE LAW AND ETHICS OF MEDICAL RESEARCH: INTERNATIONAL BIOETHICS AND HUMAN RIGHTS 70 (2005); Erik Parens, *On the Ethics and Politics of Embryonic Stem Cell Research*, *in* THE HUMAN EMBRYONIC STEM CELL DEBATE: SCIENCE, ETHICS, AND PUBLIC POLICY 40 (Suzanne Holland et al. eds., 2001) [hereinafter THE HUMAN EMBRYONIC STEM CELL DEBATE].

cell research; they view the embryo as an entity with full rights from the moment of fertilization and therefore strongly object to hESC research that results in the destruction of the embryo.[56] At the same time, others deny the moral status of human embryos at the very early stage in which they are used for research and argue that human embryos should simply be treated as any other human tissue.[57] While even others believe that stem cell research is morally justified given the promising lifesaving treatments that it could generate, notwithstanding the moral status of the human embryo.[58] Commonly, a distinction is made between "surplus" or "leftover" embryos, (embryos which were created during an in-vitro fertilization (IVF) process, not used to reach pregnancy, and transferred for research purposes with the donor's consent), and human embryos that are created specifically for research purposes.[59] While conducting research on surplus embryos is considered ethically acceptable in many countries (subject to an appropriate informed consent process), the use of human embryos created for research purposes is typically banned.[60]

Other forms of stem cell research, such as adult stem cell research, do not raise the same ethical dilemmas as hESC research because they do

56. Sven Pompe et al., *Stem-Cell Research: The State of the Art*, 6 EUROPEAN MOLECULAR BIOLOGY ORGANIZATION (EMBO) REPORTS 297 (2005); *Embryonic Stem Cell Research: An Ethical Dilemma*, *supra* note 55; *see also Religious Groups' Official Positions on Stem Cell Research*, THE PEW FORUM ON RELIGION & PUB. LIFE (July 17, 2008), http://www.pewforum.org/Science-and-Bioethics/Religious-Groups-Official-Positions-on-Stem-Cell-Research.aspx (collecting sources that describe the different religions' views on stem cell research).

57. Patrick L. Taylor, *The Gap Between Law and Ethics in Human Embryonic Stem Cell Research: Overcoming the Effect of U.S. Federal Policy on Research Advances and Public Benefit*, 11 SCI. & ENGINEERING ETHICS 589, 592 (2005). Under Jewish Law, for example, an embryo is considered an entity with rights only 40 days after fertilization. Therefore, under the Jewish tradition, embryonic stem cells that are produced just days after fertilization do not automatically enjoy the right to live. Moreover, under Jewish Law, only an embryo in vivo has the potential to develop to a human being, and in vitro fertilization does not encompass this potential. Consequently, religious views do not stand in the way of conducting stem cell research in Israel, and the field enjoys both legal and financial support from the state. *See* THE BIOETHICS ADVISORY COMMITTEE OF THE ISRAEL ACADEMY OF SCIENCES AND HUMANITIES, THE USE OF EMBRYONIC STEM CELLS FOR THERAPEUTIC RESEARCH (2001), *available at* http://bioethics.academy.ac.il/english/PDF/Embryonic_Stem_Cells.pdf [hereinafter Committee's Report]; *see also* Laurie Zoloth, *The Ethics of the Eight Day: Jewish Bioethics and Research on Embryonic Stem Cells*, *in* THE HUMAN EMBRYONIC STEM CELL DEBATE, *supra* note 55, at 95, 98–102 (discussing the debate regarding Israeli norms and stem cell research); Michael L. Gross & Vardit Ravitsky, *Israel: Bioethics in a Jewish-Democratic State*, 12 CAMBRIDGE Q. HEALTHCARE ETHICS 247, 250–51 (2003) (same); Barbara Prainsack, *'Negotiating Life': The Regulation of Human Cloning and Embryonic Stem Cell Research in Israel*, 36 SOC. STUD. SCI. 173, 179–82 (2006) (same).

58. Taylor, *supra* note 57, at 594.

59. *See* Committee's Report, *supra* note 57, at 9.

60. *See* Winston, *supra* note 37 (discussing countries' views on stem cell research).

not entail the destruction of embryos.[61] Alternative lines of research such as those concerning induced iPS—which are adult stem cells that have been genetically reprogrammed to an embryonic stem cell-like state—are also less morally controversial.[62]

Opinion on the morality of hESC research thus varies significantly. Consequently, many countries have undertaken different regulatory approaches toward this type of research.[63] Due to moral objections, U.S. policy has placed financial restrictions on the conduct of hESC research for almost a decade.[64] Similarly, in many European countries, the destruction of human embryos is considered unethical and contrary to public morals, and consequently hESC research is not eligible for patent protection.[65] These legal policies and regulations are discussed next.

III. REGULATING STEM CELL RESEARCH

A. *Law and Policy of R&D*

R&D activity has been recognized by policymakers as a key factor to national economic strength.[66] The importance of boosting R&D activity has led governments to recognize the need to influence and direct R&D activities.[67] Governments use several mechanisms to shape R&D activity including legislation that strictly prohibits particular research activities, often based on moral grounds, such as the prohibition against human cloning for reproductive purposes[68] or the ban in some European countries and several American states against human embryonic stem cell research.[69] Another mechanism is direct allocation of public funds according to the state's priorities.[70] Additionally, incentives, or disincentives, for conducting specific lines of research may be given

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61. *See Religious Groups' Official Positions on Stem Cell Research*, PEW F. ON RELIGION & PUB. LIFE (July 17, 2008), http://www.pewforum.org/Science-and-Bioethics/Religious-Groups-Official-Positions-on-Stem-Cell-Research.aspx.

62. For more on how iPS are produced and reprogrammed, see Nat'l Insts. of Health, U.S. Dep't of Health & Human Servs., *What are Induced Pluripotent Stem Cells?*, NAT'L INSTS. OF HEALTH, http://stemcells.nih.gov/info/basics/pages/basics10.aspx (last visited Sept. 25, 2014).

63. *See infra* Part III.

64. *President Discusses Stem Cell Research*, *supra* note 27.

65. Winston, *supra* note 37, at 29.

66. *See* GREGORY TASSEY, NAT'L INST. OF STANDARDS & TECH., METHODS FOR ASSESSING THE ECONOMIC IMPACTS OF GOVERNMENT R&D 1.1–1.2 (2003).

67. *Id.*

68. *See, e.g.*, THE PRESIDENT'S COUNCIL ON BIOETHICS, HUMAN CLONING AND HUMAN DIGNITY: AN ETHICAL INQUIRY 29–30 (2002), *available at* https://bioethicsarchive.georgetown.edu/pcbe/reports/cloningreport/.

69. *See* Winston, *supra* note 37.

70. *Id*. at 29–30.

through subsidies and tax cuts or via the availability of infrastructure.[71] Intellectual property protection, especially patent rights, provides yet another tool to shape R&D activity by creating incentives for players mostly in the private sector.[72] This Article focuses on two of these policy measures: patent protection, seeking to provide incentives for private investment in R&D; and direct funding that shapes R&D by providing, or denying, public funding.

To see why financial incentives are necessary for R&D, one should take a closer look at the economic aspects of the production of knowledge. In economic terms knowledge is often considered a public good, with two distinctive characteristics: it is non-rivalrous and non-excludable.[73] Knowledge is non-rivalrous because it is not exhausted by use, in other words, the use of knowledge by one does detract from the ability of others to still use it.[74] Knowledge is also non-excludable, since it is often impossible to exclude free-riders.[75] Inventions often require large investments in R&D, but once made public could be easily copied at hardly any cost.[76] With this in mind, private investors and venture capitalists may fear they cannot secure the return on their investment and avoid the risk of investing in R&D altogether. In other words, free riding of non-payers reduces incentives for investment in generating new knowledge, and without government intervention information tends to be under-supplied.

IPRs offer one way of addressing this market failure associated with the "public good" nature of knowledge.[77] The patent system seeks to encourage private investments in R&D by granting the inventor a set of exclusive rights (a patent) over the invention for a limited period.[78] The exclusive rights granted by a patent enable the inventor to commercially exploit the invention during the patent duration, and thus secure a return

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71. *See, e.g.*, DANIEL POLLACK, BIOSCIENCE INDUSTRIES: OVERVIEW AND POLICY ISSUES 53–60 (2002) (discussing the role of government in bioscience research).

72. Josh Lerner & Julie Wulf, *Innovation and Incentives: Evidence from Corporate R&D*, 89 REV. ECON. & STAT. 634, 634 (2007).

73. *See* KENNETH J. ARROW, ECONOMIC WELFARE AND THE ALLOCATION OF RESOURCES FOR INVENTIONS 8–11 (1959); Ammon J. Salter & Ben R. Martin, *The Economic Benefits of Publicly Funded Basic Research: A Critical Review*, 30 RESEARCH POL'Y 509, 511 (2001) ("[T]his knowledge is non-rival and non-excludable."); *see generally* JOSEPH A. SCHUMPETER, CAPITALISM, SOCIALISM AND DEMOCRACY (1942).

74. MERGES, *supra* note 25.

75. *Id.*

76. *Id.*

77. *See generally* Paul Belleflamme, *Patents and Incentives to Innovate: Some Theoretical and Empirical Economic Evidence*, 13 ETHICAL PERSP.: J. EUR. ETHICS NETWORK 267 (2006) (discussing how patent systems affect this market failure).

78. NIVA ELKIN-KOREN & ELI M. SALZBERGER, THE LAW AND ECONOMICS OF INTELLECTUAL PROPERTY IN THE DIGITAL AGE: THE LIMITS OF ANALYSIS ch. 2 (2013) (describing the basics and evolution of intellectual property law in the United States).

on the investment.[79]

R&D funding is not just a function of the private sector; R&D could also be sponsored through public funding.[80] Public funding may take several forms.[81] Governments may opt to produce informational goods themselves, or sponsor R&D by funding research institutions or universities.[82] Such public funding could also be offered through governmental research grants for specific projects initiated and performed by the public or the private sectors or indeed called for by the government.[83] While IPR is an ex-post reward system, generating incentives by promising a financial reward to a commercially successful invention, public funding is usually ex-ante, offering funding to research and development projects upfront.[84]

Thus, the patent system stimulates private funding for R&D activity, which provides an alternative mechanism to public funding.[85] Therefore, a legal policy that supports patenting stem cell inventions theoretically narrows the need for public funding. Yet, even though public funding and private capital are two engines that foster innovation, they are not mutually exclusive and may co-exist in particular funding schemes.[86] Also, public funding of infrastructures or selected projects in particular areas may further increase incentives for private investments.[87]

These general mechanisms for shaping R&D activity by legal policy are particularly interesting in the context of stem cell research. The ethical controversies surrounding hESC research have crept into legal policies.[88] Some countries strictly prohibit hESC research, while other countries seek to avoid direct regulation by reducing financial incentives—that is, setting legal restrictions on public funding, or limiting the patentability

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79. Belleflamme, *supra* note 77, at 271.

80. VANNAEVAR BUSH, DIR., OFFICE OF SCIENTIFIC RESEARCH & DEV., SCIENCE: THE ENDLESS FRONTIER: A REPORT TO THE PRESIDENT ON A PROGRAM FOR POSTWAR SCIENTIFIC RESEARCH (1945), *available at* http://www.nsf.gov/about/history/vbush1945.htm (discussing the need for public funding for R&D); *see also* Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663 (1996).

81. NAT'L INSTS. OF HEALTH, U.S. DEP'T OF HEALTH & HUMAN SERVS., *Budget and Spending*, Nat'l Insts. of Health, http://www.report.nih.gov/budget_and_spending/index.aspx.

82. *Id*.

83. *Id*.

84. *See* Salter & Martin, *supra* note 73, at 528.

85. Eisenberg, *supra* note 80.

86. For example, Thomson's groundbreaking hESC research was financed by both the NIH and Geron Corp. *See also infra* note 109 and the accompanying text.

87. *See* Salter & Martin, *supra* note 73, at 519.

88. *See, e.g.*, Lori P. Knowles, *A Regulatory Patchwork—Human ES Cell Research Oversight*, 22 NATURE BIOTECHNOLOGY 157, 157 (2004); Timothy Caulfield et al., *The Stem Cell Research Environment: A Patchwork of Patchworks*, 5 STEM CELL REV. & R. 82, 83 (2009).

of hESC inventions—for this type of research.[89] The deep ethical controversy discussed above, has also led to frequent policy changes in the United States and Europe, as we discuss next.

B. *Patentability of Human Embryonic Stem Cell Inventions*

The TRIPS Agreement provides the international legal framework for addressing the patentability of stem cell inventions and particularly human embryonic stem cell inventions.[90] Under Article 27(1) "patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application."[91] Inventions may be excluded from patentability "to protect *ordre public* or morality" as needed to protect human, animal, or plant life.[92] This wording leaves considerable room for interpretation, leading different legal regimes to adopt a variety of legal rules regarding the patentability of stem cell inventions.[93] The exclusion of some inventions from patent protection for reasons of "public order" or "morality," also reflects different approaches to the social role of patent law: The American approach to patent law is neutral, granting patents on any invention as long as it is novel, inventive, and useful, assuming that the invention is sufficient to promote progress; U.S. patent law does not make a moral judgment regarding the invention. Accordingly, the United States has never raised the exception of morality or *ordre public* in patent law.[94] On the other hand, European countries did incorporate the morality and *ordre public* clause into patent legislation, assuming that an invention which offends society's morals should not be patented.[95] These different approaches have proved significant for hESC patents.[96]

1. Patentability of Stem Cell Inventions in the United States

Patentable subject matter refers to the types of inventions that are eligible for patent protection.[97] Under the U.S. Patent Act "any new and

89. *See infra* Parts III.B & C.

90. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, 1869 U.N.T.S. 299.

91. *Id*. art. 27, ¶ 1.

92. *Id.* art. 27, ¶ 2.

93. *See infra* Parts III.B.1 & B.2.

94. *See infra* Part III.B.1.

95. U.N. Convention on the Grant of European Patents art. 53, Oct. 5, 1973, 1065 U.N.T.S. 199, 258–59 [hereinafter EPC]. *See infra* Part III.B.2.

96. *See infra* Part IV.B.

97. ROBERT P. MERGES & JOHN F. DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 67 (5th ed. 2011).

useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . ." is patentable subject matter.[98] In addition, an invention is only eligible for patent protection if it is new,[99] useful,[100] non-obvious,[101] and satisfies the disclosure requirements including the "best mode" known to the inventor to practice the invention.[102]

Traditionally, living organisms were considered non-patentable subject matter.[103] However, in 1980, in the landmark case of *Diamond v. Chakrabarty*, the U.S. Supreme Court concluded that living bacterium was patentable subject matter under § 101.[104] The Court concluded that genetically engineered bacterium, which did not otherwise exist in nature, was patentable, thereby enabling patent protection on living organisms, as long as they were man-made and did not occur naturally.[105] Consequently, DNA segments and human cells, including stem cells, have been considered patentable in their "isolated and purified" form, as opposed to their naturally occurring state in the human body.[106]

In 1998, biologist James Thomson became the first scientist to successfully isolate and maintain hESCs in a stable condition,[107] granting him three foundational U.S. patents for his work (the "WARF patents") assigned to the Wisconsin Alumni Research Foundation (WARF) and its subsidiary WiCell Research Institute (WiCell).[108] An exclusive license to use the patents was given to Geron Corp., which funded the research along with federal funds received from the National Institutes of Health (NIH).[109]

These patents encompass the methods used by Thomson for isolating and purifying human and primate embryonic stem cell lines, as well as purified preparations of embryonic stem cells from humans and other

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98. 35 U.S.C. § 101 (2012).

99. *Id.* § 102.

100. *Id.* §§ 101, 112.

101. *Id.* § 103.

102. *Id.* § 112.

103. In addition to living organisms, the traditional exclusions from patentable subject matter included mathematical algorithms, laws of nature and business methods.

104. Diamond v. Chakrabarty, 447 U.S. 303, 309–10 (1980).

105. *Id*.

106. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1217–19 (Fed. Cir. 1991) (upholding patents on isolated and purified human DNA sequences). In Europe, see Directive 98/44, of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, art. 3, 1998 O.J. (L 213) [hereinafter Directive].

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

108. U.S. Patent No. 5,843,780 (filed Jan. 18, 1996); U.S. Patent No. 6.200,806 (filed June 26, 1998); U.S. Patent No. 7,029,913 (filed Oct. 18, 2001).

109. Christopher R. Carroll, *Selling the Stem Cell: The Licensing of the Stem Cell Patent and Possible Antitrust Consequences*, 2002 U. ILL. J.L. TECH. & POL'Y 435, 447 (2002).

primates.[110] The main limitation on the scope of the patents was the use of the term "embryonic" in the patent claims.[111] WARF filed for a continuation of the '806 patent, attempting to expand the scope of the patent from "embryonic" stem cells to all "pluripotent" human cells, but in December 2007, the USPTO rejected their continuation request.[112] In 2007, the USPTO also received several re-examination requests for the WARF patents.[113] In a preliminary decision, the USPTO rejected all claims of the patents as anticipated by the prior art under 35 U.S.C. § 102, or obvious in light of 35 U.S.C. § 103.[114] However, in 2008, the USPTO upheld and affirmed the claims of the three WARF patents in three separate decisions; revising its preliminary decision,[115] yet allowing re-examination of the '913 patent.[116] In April 2010, the Board of Patent Appeals and Interferences of the USPTO invalidated the '913 patent.[117] The Board concluded that the patent was anticipated in light of prior art disclosing animal embryonic stem cell cultures, and particularly mice embryonic stem cell cultures.[118] The Board also found the '913 patent obvious in light of 35 U.S.C. § 103.[119]

It remains to be seen if and how the recent *AMP v. Myriad* decision

110. The patents claim embryonic stem cells that are: pluripotent; proliferate in-vitro for over 1-year while maintaining a stable, enploid karyotype; have the potential to differentiate into "derivatives of" the 3 germ layers that represent the earliest developmental stages of an embryo; defined by the presence and absence of certain cell surface proteins and enzyme activities. '780 Patent; '806 Patent; '913 Patent.

111. Katja Triller Vrtovec & Christopher Thomas Scott, *Patenting Pluripotence: The Next Battle for Stem Cell Intellectual Property*, 26 NATURE BIOTECHNOLOGY 393, 393–95 (2008).

112. Vrtovec & Scott, *supra* note 111.

113. *Inter Partes*, Reexamination No. 95/000,154, Action Closing Prosecution Communication from Gary L. Kunz, Primary Examiner, U.S. Patent & Trademark Office, http://licensinglaw.net/Litigation_files/In_re_US_Patent_7029913.pdf; *Ex Parte* Reexamination No. 90/008,139 Communication from Bennett Celsa, Primary Examiner, U.S. Patent & Trademark Office to Drinkler, Biddle & Reath (Mar. 30, 2007), http://www.pubpat.org/assets/files/warfstemcell/806rejected.pdf; *Ex Parte* Reexamination No. 90/008,102 Communication from Padmashri Ponnaluri, Primary Examiner, U.S. Patent & Trademark Office to Drinker, Biddle & Reath (Mar. 30, 2007), http://www.pubpat.org/assets/files/warfstemcell/780rejected.pdf.

114. *Inter Partes* Reexamination No. 95/000,154 Communication from Gary L. Kunz, Primary Examiner, U.S. Patent & Trademark Office to Drinker, Biddle & Reath (Mar. 30, 2007).

115. Notice of Intent to Issue *Ex Parte* Reexamination Certificate, Reexamination No. 90/008,139 from Bennet Celsa, Primary Examiner, U.S. Patent & Trademark Office to Drinker, Biddle & Reath (Mar. 5, 2008) (withdrawing objections to the '806 patent), *available at* http://www.warf.org/media.acux/f71d94db-0292-4791-b59a-835696210d9e; Wis. Alumni Research Found., *U.S. Patent Office Issues Certificates to Uphold WARF Stem Cell Patents*, WIS. ALUMNI RESEARCH FOUND. (June 26, 2008), http://www.warf.org/news-media/news/releases-and-announcements/u-s-patent-office-issues-certificates-to-uphold-warf-stem-cell-patents.cmsx.

116. *Inter Partes*, Reexamination No. 95/000,154, *supra* note 113.

117. Found. for Taxpayer & Consumer Rights v. Wis. Alumni Research Found., No. 2010-001854, 2010 Pat. App. LEXIS 15017, *54–56 (B.P.A.I. Apr. 28, 2010).

118. *Id*.

119. *Id*.

will affect the validity of the other two WARF stem cell patents. Already, Consumer Watchdog[120] has asked the Federal Circuit to apply the ruling in the *AMP v. Myriad* case and the same "products of nature" analysis to hESC cultures and consequently hold them non-patentable subject matter under 35 U.S.C. § 101.[121] Consumer Watchdog claims that hESCs are products of nature not eligible for patent protection because they are "not markedly different from naturally occurring hESCs."[122] At the same time, others argue that isolated stem cells are sufficiently different from their natural environment because they undergo manipulation during the culture process in which they are grown.[123]

2. Patentability of Stem Cell Inventions in the European Union

Patenting stem cell inventions in Europe raises a different challenge. Patentable subject matter for European patents is essentially set by the European Patent Convention (EPC).[124] The EPC provides the legal framework for granting European patents by filing a single patent application with the EPO.[125] It also has a great influence on shaping patent laws in different European countries.[126] The EPC was signed in October 1973 and creates the infrastructure for an independent legal system, under which European patents are currently registered.[127] Thus, the popular term "European Patent" refers to patents that are registered in accordance with the EPC.[128]

Generally, according to Article 52(1) of the EPC, European patents

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120. Consumer Watchdog is a nonprofit consumer advocate organization. For more information on the organization, see CONSUMER WATCHDOG, http://www.consumerwatchdog.org/ (last visited Oct. 4, 2014).

121. Opening Brief of Appellant at 13–16, Consumer Watchdog v. Wis. Alumni Research Found., 753 F.3d 1258 (Fed. Cir. 2014) (No. 13-1377).

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

123. DeLuca & Szweras, *supra* note 7.

124. EPC, *supra* note 95, at 258–59.

125. *Id.* art. 2.

126. *See* Shobita Parthasarathy & Alexis Walker, *Observing the Patent System in Social and Political Perspective*, *in* PATENT LAW IN GLOBAL PERSPECTIVE 321, 330 (Ruth L.Okediji & Margo A. Bagley eds., 2014).

127. EPC, *supra* note 95, arts. 1 & 2.

128. In a way, this term is misleading because a "European Patent" is not protected in the European countries which are members of the Convention. Furthermore, this is not a European Patent in the sense of the European Union, except for the fact that all member countries of the European Union are members of the Convention. *See* EUR. GRP. ON ETHICS IN SCI. & NEW TECHS. TO THE EUR. COMM'N, STUDY ON THE PATENTING OF INVENTIONS RELATED TO HUMAN STEM CELL RESEARCH 40 (2002) [hereinafter EGEST], *available at* https://scholarworks.iupui.edu/handle/1805/935.

are granted to inventions (1) in all fields of technology;[129] (2) provided that they are new (do not form part of the state of the art);[130] (3) involve an inventive step (not obvious to a person skilled in the art);[131] and (4) are susceptible to industrial application (can be made or used in any kind of industry, including agriculture).[132] Article 53 of the EPC defines the exceptions to patentability, and includes: inventions the commercial exploitation of which would be contrary to "*ordre public*" or morality,[133] plant or animal varieties or essentially biological processes for the production of plants or animals and methods for treatment of the human or animal body by surgery or therapy,[134] and diagnostic methods practiced on the human or animal body.[135]

The ambiguous terms "*ordre public*" and "morality" are examined on a case-by-case basis.[136] The Board of Appeals of the European Patent Office[137] has referred to this issue on several occasions[138] and has stated that these exceptions should be given a limited interpretation.[139] It has deemed that "[i]t is generally accepted that the concept of '*ordre public*' covers the protection of public security and the physical integrity of individuals as part of society."[140] Regarding "morality," the Board of Appeals has stated that:

> [t]he concept of morality is related to the belief that some behavior is right and acceptable whereas other behavior is wrong . . . For the purposes of the EPC, the culture in question is the culture inherent in European society and civilisation [sic]. Accordingly, under Article 53(a) EPC, inventions the exploitation of which is not in conformity with the conventionally accepted standards of conduct pertaining to this culture are to be excluded from patentability as being contrary to morality.[141]

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129. Subject to the reservations set out in Article 52(2) of the EPC. EPC, *supra* note 95, art. 52, ¶ 2.

130. *Id.* art. 54.

131. *Id.* art. 56.

132. *Id.* art. 57.

133. *Id.* art. 53(a).

134. *Id.* art. 53(b).

135. *Id.* art. 53(c).

136. *See* T-356/93 Plant Genetics Sys. N.V. v. Greenpeace, Ltd., 1995 O.J. Eur. Patent Office 511, 560, *available at* http://archive.epo.org/epo/pubs/oj1995/p511_594.pdf.

137. For a full explanation of the structure of the EPO and the status of the different boards of appeals, see Eur. Patent Office, *Boards of Appeal*, EUR. PATENT OFFICE, http://www.epo.org/about-us/boards-of-appeal.html (last updated Mar. 12, 2013).

138. T-356/93, Plant Genetics Sys., 1995 O.J. Eur. Patent Office at 560.

139. *Id.* at 558.

140. *Id.* at 557.

141. *Id.*

The Implementing Regulations to the Convention on the Grant of European Patents (2006) provides an additional source for interpreting what is patentable subject matter in Europe.[142] Under Rule 28(c) "uses of human embryos for industrial or commercial purposes" fall under the exceptions to patentability.[143]

In other words, human embryonic stem cells that are used for industrial or commercial purposes are not eligible for a European patent under Rule 28(c). The Rule does not address the question whether human embryonic stem cells used for research purposes are patentable subject matter. In addition, Rule 28 does not answer the question whether uses of surplus embryos can be patented.[144] In light of the uncertainty regarding the patentability of biological materials and the varied interpretations given by different European countries,[145] the European Commission[146] decided to harmonize this issue for European member countries.[147] After a decade of discussion, the Directive on the Legal Protection of Biotechnological Inventions was adopted in 1998, and took effect in September 1999.[148]

The Directive recognizes biological material as patentable subject matter[149] and emphasizes that biological material which is isolated from

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142. The goal of these regulations is to assist in the interpretation of the EPC instructions. *See* Administrative Council of the European Patent Organisation of Dec. 13, 2013 on Implementing Regulations to the Convention on the Grant of European Patents, EUR. PATENT OFF., http://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ma2.html.

143. *Id.* R.28.

144. *See id.* R.28: Under article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:

> (a) Processes for cloning human beings;
> (b) Processes for modifying the germ line genetic identity of human beings;
> (c) Uses of human embryos for industrial or commercial purposes;
> (d) Processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

145. Gerard Porter et al., *The Patentability of Human Embryonic Stem Cells in Europe*, 24 NATURE BIOTECHNOLOGY 653, 654 (2006); Aurora Plomer et al., *Challenges to Human Embryonic Stem Cell Patents*, 2 CELL STEM CELL 13, 15 (2008); AURORA PLOMER, STEM CELL PATENTS: EUROPEAN PATENT LAW AND ETHICS REPORT 23 (2006), *available at* http://www.nottingham.ac.uk/~llzwww/StemCellProject/project.report.pdf.

146. *See* EUR. COMM'N, *available at* ec.europa.eu/index_en.htm (last visited Oct. 14, 2014).

147. Directive, *supra* note 106.

148. EGEST, *supra* note 128, at 45.

149. Directive, *supra* note 106, art. 3, ¶ 1.

> For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product *consisting of or containing biological*

its natural environment may be the subject of an invention even if it previously occurred in nature.[150] The Directive defines "biological material" as "any material containing genetic information and capable of reproducing itself or being reproduced in a biological system."[151] With that, it excludes the "human body, at the various stages of its formation and development," from being a patentable invention, and specifically states that "the simple discovery of one of its elements, including the sequence or partial sequence of a gene, *cannot constitute patentable inventions*."[152] However, the Directive adds that "[a]n element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element."[153]

The Directive repeats Rule 28 of the Implementing Convention on the Grant of European Patents Regulations and states that "uses of human embryos for industrial or commercial purposes" shall be considered unpatentable.[154] Paragraph 16 of the Directive emphasizes that "patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person . . ."[155] Subsequently, paragraph 38 specifies that "processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability."[156]

In spite of the fact that the EPO is not officially subject to the decisions of the European Union institutions, in June 1999 it adopted the Directive's instructions, primarily in order to maintain coherency and harmony between the various patent laws in different European countries.[157] Ironically, despite the fact that one of the main goals of the Directive is to harmonize the sundry of European patent laws in order to increase the competitiveness of the European biotechnology industry, in

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> *material or a process by means of which biological material is produced, processed or used.*

Id.

150. *Id.* art. 3, ¶ 2 ("Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.").

151. *Id.* art. 2, ¶ 1(a).

152. *Id.* art. 5, ¶ 1.

153. *Id.* art. 5, ¶ 2.

154. *Id.* art. 6, ¶ 2(c).

155. *Id.* ¶ 16.

156. *Id.* ¶ 38.

157. Press Release, Eur. Patent Office, The EPO follows the EU's Directive on Biotechnology Patents (Oct. 27, 2005) (on file with authors).

practice, it has created considerable uncertainty.[158] The Directive was completed just a few months before researcher James Thomson, from Wisconsin University in the United States, first reported in 1998 that he had successfully isolated human embryonic stem cells.[159] Hence, the issue of stem cell research was never specifically discussed within the Directive's framework.[160]

The uncertainty regarding the Directive's provisions is also reflected in the EPO decision concerning WARF's patent application for a European patent.[161] In addition to its U.S. patents on hESCs, which were granted by the USPTO, WARF filed for patent protection in the EPO.[162] On July 13, 2004, the EPO refused to accept the application on moral grounds because the invention included the use of human embryos.[163] WARF appealed the decision to the Enlarged Board of Appeals in the EPO which stated that WARF's application violated Rule 28 of the Implementing Rules, because at the time the patents were filed, production of the claimed human embryonic stem cells led to the destruction of the embryo.[164] The Board reasoned that the examination of a patent application under Rule 28 of the Implementing Rules demanded examining not just at the wording of the patent claims but the invention as a whole, including the process used in the invention.[165] In that particular case, according to the Board, the process required destroying the embryo and as such rendered it unpatentable.[166] It should be noted that the Board did not deny the patentability of human embryonic stem cells in general, and thus the question whether human embryonic stem cells are patentable if the invention does not lead to the destruction of the embryo remains open.[167]

In 2011, the European Court of Justice (ECJ) also considered the patentability of stem cell inventions.[168] The organization Greenpeace appealed to the German Federal Court to invalidate a German patent that

158. Laura Bonetta, *European Stem Cell Patents: Taking the Moral High Road?*, 132 CELL 514, 515 (2008).

159. *Id*.

160. *Id*.

161. Eur. Patent Application No. 96903521.1 (filed Jan. 19, 1996).

162. *Id.*

163. *Primate Stem Cells Denied in Europe*, 3 NATURE REVIEWS DRUG DISCOVERY 820 (2004).

164. Decision G 2/06, 2008 O.J. Eur. Patent Office 306, ¶ 22, *available at* http://www.epo.org/law-practice/case-law-appeals/pdf/g060002ex1.pdf.

165. *Id.* ¶ 22.

166. *Id.* ¶¶ 25, 29.

167. *Id.* ¶ 35.

168. *See generally* Case C-34/10, Brüstle v. Greenpeace eV, 2011 E.C.R. I-9849, I-9875, *available at* http://curia.europa.eu/juris/celex.jsf?celex=62010CJ0034&lang1=en&type=TXT&ancre=; *see also* Moran, *supra* note 14, at 1057.

had been granted to Dr. Oliver Brüstle, Professor of Reconstructive Neurobiology at the University of Bonn Medical Center.[169] Greenpeace claimed that the patent at issue was invalid under Article 6(2) of the Biological Directive, because it covered precursor cells obtained from human embryonic stem cells and processes for the production of those precursor cells.[170] Article 6(2) of the Biological Directive does not allow the use of human embryos for industrial or commercial purposes.[171] The German Federal Court of Justice accepted Greenpeace's claims and invalidated the patent.[172] Brüstle appealed and the case was redirected to the ECJ.[173]

The ECJ discussed three main issues.[174] First, the Court held that the term "human embryo" must be broadly interpreted, stating that "any human ovum must, as soon as fertilized, be regarded as a 'human embryo' within the meaning and for the purposes of the application of Article 6(2)(c) of the Directive, since that fertilization is such as to commence the process of development of a human being."[175] Consequently, the ECJ instructed the courts to examine whether the cells, which were the subject of the invention, had the capability of developing into a human being.[176] Second, the ECJ determined that the concept of Article 6(2)(c) of the Directive that discusses the "uses of human embryos for industrial or commercial purposes" also covered the use of human embryos for purposes of scientific research,[177] thus adopting the EPO's interpretation of the Directive.[178] Third, the ECJ concluded that the destruction of the embryo rendered the invention unpatentable, even if the destruction of the embryo had occurred long before the invention was achieved, adopting once again the EPO's decision:

> Article 6(2)(c) of the Directive excludes an invention from patentability where the technical teaching which is the subject-matter of the patent application requires the prior destruction of human embryos or their use as base material, whatever the stage at which that takes place and even if the description of the technical teaching claimed does not refer to the use of human embryos.[179]

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169. *Id.*
170. *Id.* at I-9851.
171. Directive, *supra* note 106, art. 6, ¶ 2.
172. *Brüstle*, 2011 E.C.R. at I-9865.
173. *Id*.
174. *Id*. at I-9867–68.
175. *Id*. at I-9871.
176. *Id.* at I-9872.
177. *Id.* at I-9874.
178. *Id.* at I-9865.
179. *Id.* at I-9876.

In sum, at the European level, regulation of stem cell research is quite complex and varies from country to country according to the specific legal system applied. Many countries regulate human embryonic stem cell research indirectly, for example, through in vitro fertilization regulations, and interpretation is necessary to determine whether stem cell research is allowed.[180]

C. *Regulation of Stem Cell Public Funding*

The analysis of stem cell patenting policies shows a much stricter European stance toward stem cell patents than that of the United States.[181] We now turn to examine each stem cell funding policy.

1. Public Funding in the United States

While the United States displays a very lenient approach toward patenting stem cells, including human embryonic stem cells, its funding policies are considerably more stringent and include a decade-long specific restriction on federal funding for hESC research placed by the George W. Bush administration.[182] In addition, several federal laws indirectly affect funding for stem cell research. The Dickey-Wicker Amendment, which is attached to the appropriations bills for the Department of Health and Human Services, prohibits the use of federal funding for experimentation using human embryos.[183] The amendment

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180. Christiane Druml, *Stem Cell Research: Toward Greater Unity in Europe?*, 139 CELL 649, 650 (2009). The multitude of national laws on human embryonic stem cells across the different European countries can be classified on the basis of four main approaches: (1) Permissive approach: Belgium, Spain, Sweden and the United Kingdom. In these countries, specific legislation covers the procurement of hESCs and their use for research, and the creation of human embryos for research purposes is allowed. (2) Permissive approach with restrictions: The Czech Republic, Denmark, Finland, France, Greece, The Netherlands and Portugal. In these countries specific legislation allows the derivation of new hESC lines from human embryos created by assisted reproduction technology or in vitro fertilization for the purposes of pregnancy but only when the embryos can no longer be used for that purpose. (3) Restrictive approach: Germany, Italy. In these countries, scientists are not allowed to derive new hESC lines but may import them from other countries. (4) Countries with no specific legislation: Bulgaria, Cyprus, Estonia, Ireland, Hungary, Latvia, Luxemburg, Romania and Slovenia. The legislation in these countries does not directly address hESC research. *Id.* at 649.

181. *See supra* Part III.B.

182. *President Discusses Stem Cell Research*, *supra* note 27.

183. The Amendment does not, however, prohibit experimentation with human embryos. SEC. 509. (a) None of the funds made available in this Act may be used for—(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 C.F.R. 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 C.F.R. 46

was first passed in 1996 and has been renewed by Congress yearly.[184] Another provision that could restrict federal funding is the Weldon Amendment, which was part of the 2004 Omnibus Appropriation Bill.[185] The Amendment prohibits "the use of funds under this Act to: (1) issue patents on claims directed to or encompassing a human organism. . . ." and has been interpreted as a prohibition on patenting human clones or reproductive cloning.[186] In September 2011, as part of the America Invents Act (AIA) patent reform, the Weldon Amendment was merged into the U.S. Patent Act.[187]

Beyond these amendments, U.S. federal policy pertaining to human embryonic stem cell research can be divided into two main time frameworks. The first began in 2001 and ended in 2009, during which President George W. Bush placed strong limitations on federal funding for human embryonic stem cell research.[188] The second began in 2009, when President Barak Obama lifted the aforementioned restrictions.[189]

In 2001, in an attempt to address some of the moral objections against hESC research, the Bush administration restricted federal funding to hESC research.[190] Under the 2001 policy, federal funding was permitted only to hESC lines that had been isolated prior to August 2001 and authorized by the National Institutes of Health (NIH).[191] All in all, approximately twenty hESC lines were eligible for federal funding.[192] None of the research that involved hESC lines that were isolated at a later date was eligible for NIH funding, mandating alternative funding

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as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Dickey-Wicker Amendment of 1995, Pub. L. No. 104-99, § 128, 110 Stat. 26, 34 (1996).

184. Ann A. Kiessling, *The History of the Dickey-Wicker Amendment*, BEDFORD STEM CELL RESEARCH FOUNDATION (Aug. 24, 2010), http://www.bedfordresearch.org/article/dickey-wicker-amendment-human-embryo-research-25912.

185. Andrew W. Torrance, *Weldon Amendment Welded onto the Patent Act*, BIOLAW (Sept. 16, 2011), http://biolaw.blogspot.com/2011/09/weldon-amendment-welded-onto-patent-act.html.

186. *Id*.

187. Pub. L. No. 112-29, § 33, 125 Stat. 340 (Sept. 16, 2011) ("Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism"). However, the scope of this restriction remains ambiguous and open to interpretation. *See* Torrance, *supra* note 185; Jeremy Kryn, *Amendment Banning Human Embryo Patents Becomes Permanent U.S. Law*, LIFESITE (Sept. 20, 2011), http://www.lifesitenews.com/news/congress-makes-amendment-banning-human-embryo-patents-permanent.

188. *President Discusses Stem Cell Research*, *supra* note 27.

189. NAT'L INSTS. OF HEALTH, U.S. DEP'T OF HEALTH & HUMAN SERVS., *Federal Policy*, NAT'L INSTS. OF HEALTH (2009), http://stemcells.nih.gov/policy/Pages/Default.aspx.

190. *President Discusses Stem Cell Research*, *supra* note 27.

191. Varnee Murugan, *Embryonic Stem Cell Research: A Decade of Debate from Bush to Obama*, 82 YALE J. BIOLOGY & MED. 101, 101 (2009), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2744932/.

192. *Id*.

sources.[193] Research that did enjoy federal funding had to be conducted in separate labs, using separate equipment and even different personnel in order to ensure that federal funds were not used on unauthorized research. Consequently, a research dichotomy was created between federally eligible hESC research and non-eligible hESC research.[194] This policy restricted information sharing among researchers, limited the number of research collaborations with international scientists, and generally made hESC research in the United States more difficult to pursue.[195] At the same time, the administration proclaimed its support for alternative lines of research that did not entail the destruction of embryos, such as iPS.[196]

The restrictive funding approach adopted by the Bush administration, created the need for alternative funding sources, and several states stepped up to the plate.[197] In January 2004, New Jersey became the first state to allocate $10 million from state funds for stem cell research, including hESC research; although the funding was later halted.[198] New Jersey was followed by California, which allocated in November 2004 $3 billion dollars in state bonds for stem cell research;[199] other states such as New York, Maryland, Connecticut, Wisconsin, and Massachusetts followed suit.[200] In contrast, some states, such as Virginia,[201] restricted even further stem cell research, while six states, North Dakota, South

193. *Id*. at 102.

194. *Id*. at 101.

195. *Id*.

196. *Id.* at 102.

197. *See* Susan Stayn, *A Guide to States Laws on hESC Research and a Call for Interstate Dialogue*, 5 MED. RES. L. & POL'Y 718 (2006).

198. *See* Meredith Wadman, *Stuck in New Jersey*, 451 NATURE 622, 622 (2008), *available at* http://www.nature.com/news/2008/080206/pdf/451622a.pdf.

199. *Id*. Following the passage of the California initiative, known as Proposition 71, a detailed policy concerning stem cell research and its funding was adopted. *See* Stayn, *supra* note 197, at 1–2. The regulations deal, *inter alia*, with the ownership and licensing aspects of stem cell research, revenue sharing requirements, access and pricing requirements, publications, and march-in rights. *See generally* CAL. CODE REGS. tit. 17, §§ 100300–100410 (2014). Up to the end of 2009, non-profit and for-profit institutions were subject to different IP and revenue sharing requirements; after December 17, 2009 all grants are subject to the same requirements. *See id.* Under these requirements, the state of California is entitled to a pre-determined fraction of licensing revenue received under a license agreement for a CIRM-funded invention or technology. *Id*. § 100408. Funding will not be available for research projects involving human reproductive cloning and the introduction and breeding of human and non-human cell lines. *Id.* § 100030(a), (d).

200. MASS. GEN. LAWS ANN. ch. 111L § 6 (2014); Wadman, *supra* note 198, at 622, 626.

201. Virginia law bans all state funding for research involving human embryonic stem cells. *See* VA. CODE ANN. § 23-286.1(C) (West 2014); Peter Hamby, *Kaine Blocks Funding for Embryonic Stem Cell Research*, POL. TICKER (Mar. 31, 2009), http://politicalticker.blogs.cnn.com/2009/03/31/kaine-blocks-funding-for-embryonic-stem-cell-research.

Dakota,[202] Arkansas, Louisiana, Indiana, and Michigan, criminalized it.[203]

In 2009, eight years after the Bush administration placed funding restrictions on hESC research; the Obama administration lifted these restrictions, leading the NIH to revise its hESC funding policy.[204] Under the new funding policy, federal funds have become available to research hESC lines[205] that are posted on the new NIH Registry or have been derived from human embryos that (1) have been created using IVF for reproductive purposes and are no longer needed for this purpose; (2) have been donated by individuals who seek reproductive treatment and have voluntarily given their written consent to use the human embryos in research; and for which (3) documentation, such as consent forms and written policies, can be provided.[206] No payment may be offered for the donated embryos.[207]

The new informed consent requirements are particularly rigid.[208] Eligibility may be established in respect of embryos that were donated in the United States before the guidelines came into effect through the submission of materials to a Working Group of the Advisory Committee

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202. S.D. CODIFIED LAWS § 34-14-16 (2014) ("No person may knowingly conduct nontherapeutic research that destroys a human embryo. A violation of this section is a Class 1 misdemeanor.").

203. *See* Wadman, *supra* note 198, at 626.

204. NAT'L INSTS. OF HEALTH, *supra* note 189.

205. "For the purpose of [the NIH] guidelines, 'human embryonic stem cells (hESCs)' are cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although hESCs are derived from embryos, such stem cells are not themselves human embryos." NAT'L INSTS. OF HEALTH, U.S. DEP'T OF HEALTH & HUMAN SERVS., NATIONAL INSTITUTES OF HEALTH GUIDELINES FOR RESEARCH USING HUMAN STEM CELLS § II, NAT'L INSTS. OF HEALTH (2009), http://stemcells.nih.gov/policy/pages/2009guidelines.aspx [hereinafter NIH GUIDELINES].

206. *Id.* § II(A).

207. *Id*. § II(A)(3)(b).

208. Donors must be informed:

> (i) that the embryos will be used to derive hESCs for research; (ii) what would happen to the embryos in the derivation of hESCs for research; (iii) that hESCs derived from the embryos might be kept for many years; (iv) that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants.; (v) that the research was not intended to provide direct medical benefit to the donor(s); (vi) that the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development; [and] (vii) whether information that could identify the donor(s) would be available to researchers.

Id. § II(A)(3)(e).

to the Director, which in turn makes recommendations to the NIH Director.[209] The NIH Director makes the final decision regarding eligibility for NIH funding.[210] Embryos donated outside the United States before the guidelines came into effect must comply with the same standards; alternatively, assurances must be submitted to the effect that the alternative procedural standards of the foreign country where the embryo was donated provide protection that is at least equivalent to that required under the NIH guidelines.[211]

NIH funding will not be provided for: (1) research in which hESCs or human iPS cells are introduced into non-human primate blastocysts; or (2) research involving the breeding of animals where the introduction of hESCs or human iPS cells may contribute to the germ line.[212] Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is also ineligible for NIH funding.[213]

In August 2010, Judge Royce Lamberth of the U.S. District Court for the District of Columbia issued a preliminary injunction stopping all NIH funding under the new NIH guidelines, reasoning that such funding violated the Dickey-Wicker Amendment.[214] The Justice Department appealed and in April of 2011, the appeal court suspended the injunction.[215]

In 2012, the U.S. Court of Appeals for the District of Columbia lifted the injunction, holding that the NIH had reasonably interpreted the Dickey-Wicker Amendment and that the law's wording was sufficiently ambiguous to allow the NIH to fund research on the cell lines, if not their derivatives.[216] The plaintiffs then appealed to the Supreme Court; however, the Court refused to hear the case, thus ending the effort to halt NIH funding of hESC research.[217]

2. Public Funding in the European Union

In spite of challenges to the patentability of hESC inventions, the European Union has demonstrated a liberal policy in terms of funding

209. *Id.* § II(B).
210. *Id.* § II(B)(2).
211. *Id.* § II(B)(2).
212. *Id.* § IV.
213. *Id.* § V.
214. Sherley v. Sebelius, 704 F. Supp. 2d 63, 71 (D.D.C. 2010).
215. Sherley v. Sebelius, 644 F.3d 388, 390 (D.C. Cir. 2011).
216. Sherley v. Sebelius, 689 F.3d 776, 779, 781 (D.C. Cir. 2012).
217. Meredith Wadman, *High Court Ensures Continued U.S. Funding of Human Embryonic-Stem-Cell Research*, NATURE NEWS (Jan. 7, 2013), http://www.nature.com/news/high-court-ensures-continued-us-funding-of-human-embryonic-stem-cell-research-1.12171.

stem cell research.[218] In 2000, the European Union established joint European research programs within the European Research Area (ERA) to encourage the unification of research efforts in various fields.[219] Research involving hESC is a notable example of one of the major challenges facing the ERA, primarily because of the great differences between the diverse research policies of the various member states.[220] Under the joint programs, European funding for research that includes the use of human embryos and hESCs is allowed, as long as the research activity is permitted by each of the countries involved.[221] Until 2013, the Sixth[222] and the Seventh[223] Framework Programme (FP6 and FP7 respectively) were the main legal and financial tools through which the ERA program was applied.[224]

Until 2003, funding for hESC research could only be obtained for projects involving banked hESC cultures.[225] This was changed following the recommendations of the Commission of the European

218. Porter et al., *supra* note 145, at 653; *European Research Area: More Effective National Research Systems*, EUROPEAN COMM'N: RESEARCH & INNOVATION, http://ec.europa.eu/research/era/more-effective-national-research-systems_en.htm (last updated Apr. 30, 2013).

219. *European Research Area: The Concept*, EUROPEAN COMM'N: CORDIS, http://cordis.europa.eu/era/concept_en.html (archived Nov. 1, 2010); *see also European Research Area*, EUROPEAN COMM'N, http://ec.europa.eu/research/era/index_en.htm (last updated Feb. 27, 2014).

220. Druml, *supra* note 180, at 649.

221. *Id*.

222. The Sixth Framework Programme (FP6) was in effect during the years 2002–2006. *See Sixth Framework Programme*, EUROPEAN COMM'N, http://ec.europa.eu/research/fp6/index_en.cfm (last updated Nov. 5, 2006); *see also The Sixth Framework Programme in Brief,* EUROPEAN COMM'N (2002), http://ec.europa.eu/research/fp6/pdf/fp6-in-brief_en.pdf.

223. The Seventh Framework program was in effect during the years 2007–2013. *See Seventh Framework Programme (FP7)*, EUROPEAN COMM'N, http://cordis.europa.eu/fp7/home_en.html (last updated Apr. 3, 2014).

224. The two programs make up the European Community Framework Programme for Research, Technological Development and Demonstration and consist of a collection of actions at EU level to fund and promote research. In December 2013, the European Commission launched a new research and innovation program with nearly €80 billion of funding available over a period of seven years (2014–2020). *See What is Horizon 2020?*, http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020 (last visited Oct. 2, 2014); *see also Horizon 2020: Press Release*, EUROPEAN COMM'N, http://ec.europa.eu/programmes/horizon2020/en/newsroom/599/ (last visited Oct. 2, 2014); *see generally Horizon 2020*, EUROPEAN COMM'N, http://ec.europa.eu/programmes/horizon2020/en (last visited Sept. 30, 2014).

225. *See* Isabelle Huys et al., *The Impact of Legislative Framework Conditions on the Development of Stem Cell Technology: Assessment of National Innovation Systems*, 30 BIOTECH. L. REP. 191, 192 (2011); Philippe Busquin, Eur. Parliament, Ethical Aspects of Stem Cell Repositories and Stem Cell Databases (Feb. 17, 2005), transcript, *available at* http://archive.eurostemcell.org/Documents/Ethics/Philipe_Busquin.pdf.

Communities,[226] allowing funding on a case-by-case basis.[227]

FP7 was designed in light of recommendations by the European Group on Ethics in Sciences and New Technologies.[228] The Group concluded that all research proposals involving hESCs should detail its research targets and the legislative infrastructure in each member country.[229] The Group also set guidelines for the ethical examination of hESC research funded under FP7 and emphasized the need to encourage responsible stem cell research to promote public interest and preserve the public's trust.[230] The Group emphasized that only use of excess embryos, created for IVF purposes and left unused, would be permitted; and if an alternative research route with similar scientific potential was available, the alternative route would be preferred.[231]

D. *Legal Milestones in Stem Cell Regulation*

The legal milestones in stem cell legal policy described above are summarized in Table 1 below. As seen, policy changes in Europe primarily addressed patentability of hESC inventions, while the American ones were directed at the availability of federal funding for hESC research.

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226. Commission of the European Communities, *Report on Human Embryonic Stem Cell Research*, at 70, SEC (2003) 441 (Apr. 3, 2003), *available at* http://ec.europa.eu/research/press/2003/pdf/sec2003-441report_en.pdf.

227. Under the new policy, it was recommended that EP6 funding will only be given to research project that received, among other things, free and informed consent by the donors, approval of the research project by a centralized authority, and displayed transparency regarding research results. *Id*. at 35–37.

228. *Recommendations on the Ethical Review of hESC FP7 Research Projects: Opinion No. 22*, EUR. GROUP ON ETHICS IN SCI. & NEW TECHS. TO THE EUR. COMM'N (June 20, 2007) [hereinafter *Recommendations on the Ethical Review of hESC FP7 Research Projects*], *available at* http://www.hescreg.eu/docs/downloads/opinion_22_final_follow_up_en.pdf; Ethics Group Adopts Opinion on Human Embryonic Stem Cell Use in FP7 Projects, CORDIS, http://cordis.europa.eu/news/rcn/28047_en.html.

229. *Recommendations on the Ethical Review of hESC FP7 Research Projects*, *supra* note 228, at 29, 35.

230. *Id.* at 3–4, 36.

231. *Id.* at 3–4.

Table 1: Legal Milestones in Stem Cell Regulation

		United States	Europe
Patentability of hESC inventions	1998–2004	Granting patents on hESCs inventions (+)	Uncertainty (?)
	2004 and onward	No change (+)	Limitations on patenting hESC inventions (-)
Funding for stem cell research	1998–2001	Uncertainty (Dickey-Wicker Amendment) (?)	Public funding for all types of stem cell research (+)
	2001–2009	Limitations on federal funding for hESC research (-)	No change (+)
	2009 and onward	Lifting limitations on federal funding for hESC research (+)	No change (+)

Frequent policy changes over such a short period give rise to considerable uncertainty[232] and consequently increase the risks involved in making financial investments in this field of research.

IV. STEM CELL RESEARCH ACTIVITY: EMPIRICAL EVIDENCE

This Part presents a comprehensive empirical study of patent applications in stem cell inventions, filed during the years 1990–2013 in the USPTO, EPO and PCT.[233] The aim of the study is to explore the potential impact of legal and policy changes on R&D activity, by analyzing trends in patent filing following the stem cell policy milestones described above. The following sections introduce our methodology, the

232. Levine, *supra* note 12, at 132; Timothy Caulfield et al., *The Evolution of Policy Issues in Stem Cell Research: An International Survey*, 8 STEM CELL REV. & REP. 1037, 1039–40 (2012); Caulfield et al., *supra* note 88, at 83–85.

233. The Patent Cooperation Treaty (PCT) is an international treaty which was drafted in 1970 and came into effect in 1978. *See Patent Cooperation Treaty*, 92 J. PAT. & TRADEMARK OFF. SOC'Y 192, 194 (2010) (entered into force Jan. 24, 1978). One hundred forty-eight countries have signed the treaty. The PCT is run by WIPO, The World Intellectual Property Organization. *See WIPO-Administered Treaties,* WIPO, http://www.wipo.int/treaties/en/ShowResults.jsp?treaty_id= (last visited Oct. 2, 2014). The PCT has become one of the most popular and significant tracks for patent applications.

dataset created, as well as the study's findings. Part V analyzes the findings and discusses some of their implications.

A. *Study Methodology*

1. Patent Application Analysis

The empirical methodology used herein is based on patent application analysis. While patents define exclusive legal rights granted by the State, they also provide valuable information on existing knowledge, such as prior art, technological advances, and the identity of the inventors and assignees.[234] Consequently, patent applications are considered a common indicator for R&D activity in a given field and provide a useful tool for conducting statistical analysis.[235] Moreover, patent data is publicly available.[236]

Patents and patent applications are frequently used as statistical indicators for inventive activity and as a proxy to measure technological and scientific developments.[237] Patent-based statistics are used to measure inventiveness, R&D activity, and predict economic and technological performance.[238] The assumption is that patents reflect inventive output and that more patents imply more inventions.[239] Patents are also used to map dynamics of the innovation process such as cooperation in research and the diffusion of technology across industries or countries; the competitive process, for example, business strategies; and other issues such as the internationalism of research, co-inventions, and the global mobility of inventors.[240] Because patents can be obtained at different stages of the R&D process, they can reflect R&D (upstream inventions) as well as provide input to innovation (downstream inventions).[241] Therefore, patent data provides a useful bridge between data regarding investments in R&D and data on innovation.[242] All these facets make patent analysis a useful statistical tool for measuring

234. *See* OECD PATENT STATISTICS MANUAL, *supra* note 29, at 25.

235. *Id.* at 26. Nonetheless, while patent applications indicate successful research they do not reflect all the research efforts behind an invention. *Id.*

236. *Id.* at 27.

237. Griliches, *supra* note 29, at 1701–02. *See also* Shyama V. Ramani & Marie-Angele de Looze, *Country-Specific Characteristics of Patent Applications in France, Germany and the UK in the Biotechnology Sectors*, 14 TECH. ANALYSIS & STRATEGIC MGMT. 457, 459–60 (2002).

238. OECD PATENT STATISTICS MANUAL, *supra* note 29, at 26.

239. *Id.*; *see generally* ZVI GRILICHES, R&D AND PRODUCTIVITY: THE ECONOMETRIC EVIDENCE 335 (1998).

240. OECD PATENT STATISTICS MANUAL, *supra* note 29, at 26.

241. *Id.* at 27.

242. *Id.*

inventive activity.[243]

Notwithstanding, when analyzing patent data one must take into account the fact that not all inventions are patented.[244] Financial constraints or strategic considerations may prevent inventors from patenting their inventions.[245] Moreover, patents do not fully reflect the innovative effort or the degree of originality and creativity of a given invention.[246] In fact, some patents have no industrial application and therefore are of little, or no, benefit to society other than in terms of the disclosure of information in the patent.[247] In addition, some fields of technology, such as the software industry, tend to have more patents than other fields.[248] Another issue that should be taken into account when relying on the analysis of patent applications concerns the high cost of patent application that makes patents more accessible to larger companies than smaller companies and individuals.[249] Finally, patent laws and practices vary across countries, making it more difficult to draw comparisons unless the same set of patent offices is analyzed.[250] Keeping in mind these limitations, patent data provides a useful tool for identifying R&D trends.

2. Creating a Stem Cell Patent Dataset

The study's dataset consists of stem cell patent applications filed in the USPTO, EPO, and PCT using PatBase.[251]

Our dataset focused on stem cell patents with an Israeli assignee[252] from 1990 up to May 2013. However, because patent applications are generally published only after 18 months and during this time period the

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243. *Id*.

244. *Id.*

245. *Id.* at 27-28.

246. *See* William S. Comanor & F.M. Scherer, *Patent Statistics as a Measure of Technical Change*, 77 J. POL. ECON. 392, 393 (1969). A similar argument can be made regarding the use of researcher numbers and research expenditure figures, which nonetheless are accepted statistical tools to measure innovation/inventive activity. *Id.*; *see also* F.M. Scherer, *Firm Size, Market Structure, Opportunity, and the Output of Patented Inventions*, 55 AM. ECON. REV. 1097, 1098 (1965).

247. OECD PATENT STATISTICS MANUAL, *supra* note 29, at 28.

248. *Id.*

249. *Id.*

250. *Id.* at 27–28.

251. *See* PATBASE, http://patbase.com/ (last visited Sept. 30, 2014). PatBase is an online patent database which includes over 40 million patent families registered in approximately 95 patent offices around the world. *Id.* This database enabled us to create a dataset consisting of all patent families in the stem cell field.

252. "Israeli assignee" refers to an Israeli entity that is active in Israel and has an Israeli address. *See generally* ADAM B. JAFFE & MANUEL TRAJTENBERG, PATENTS, CITATIONS & INNOVATIONS: A WINDOW ON THE KNOWLEDGE ECONOMY 355–56 (2002).

data available may be partial,[253] our analysis below refers to patent applications filed up to the end of 2011. The Israeli stem cell industry provides an excellent case study for understanding the impact of regulation on stem cell R&D for several reasons. First, it is a liberal legal regime[254] with relatively few restrictions on stem cell research, which facilitated the development of a flourishing stem cell industry.[255] Second, the relatively small number of players allowed us to analyze the entire Israeli scientific population in the stem cell field including the private sector, research institutions, hospitals and academia, and provide a unique and detailed picture of the patent trends in the stem cell research field. Third, the Israeli case study offers a good opportunity to study the global effect of legal rules. Due to the small size of the Israeli market, the local innovative industry is export-oriented and thus more susceptible to legal changes in countries perceived as export destinations.[256]

Our dataset consists of 1047 stem cell patent families,[257] including

253. 35 U.S.C. 122(b) (2014).

254. Stem cell research outputs in Israel are protected under the Israeli Patents Law. In 2001, three years after Thomson's hESC discovery, a report issued by the Bioethics Advisory Committee of the Israeli Academy of Sciences and Humanities specifically referred to the issue of stem cell research in Israel. *See generally* BIOETHICS ADVISORY COMMITTEE OF THE ISRAEL ACADEMY OF SCIENCES AND HUMANITIES, THE USE OF EMBRYONIC STEM CELLS FOR THERAPEUTIC RESEARCH (2001). The Committee discussed the use of embryonic stem cells for medical research. *Id.* § 6. The Committee noted that the moral legitimacy of conducting research in human embryos depends largely on the status attributed to the embryo and on the manner in which embryos are defined and classified during the stages of development. *Id.* § 4, ¶ 14. The Committee distinguished between embryos created during IVF treatments for reproduction purposes, surplus embryos, and embryos created specifically for research purposes. *Id.* § 6. The Committee's position is that while, under certain circumstances, embryos belonging to the first and second categories may be used for research purposes, explicitly permitting the creation of embryos for research purposes (third category) should be prohibited due to strong moral reservations. *Id.* The Committee also declared that the creation of embryonic stem cell lines should be permitted. *Id.* Once a stem cell line is created, research should be allowed without further need for ethical approval, allowing to further culture these cells. *Id.* Following the Committee's report, the Israeli Patent Office has adopted a liberal stand point pertaining to stem cell patents and does not consider embryonic stem cell research to be morally wrong or against public order.

255. *See* Winston, *supra* note 37, at 29.

256. *See generally* Jacques Morisset & Neda Pirni, *How Tax Policy and Incentives Affect Foreign Direct Investment: A Review* 9–10 (World Bank & Int'l Fin. Cooperation Foreign Inv. Advisory Serv., Policy Research Working Paper No. 2509, 2000); *see also* Thomas L. Brewer, *Government Policies, Market Imperfections, and Foreign Direct Investment*, 24 J. INT'L BUS. STUD. 101, 117 (1993). Israel's biotech industry is export-oriented. *See Biotech-tailor-made for Israel*, ISRAEL MINISTRY OF FOREIGN AFFAIRS (Nov. 2, 2010), http://mfa.gov.il/MFA/Innovative Israel/Pages/Biotech-tailor_made_for_Israel_%28Nov-2010% 29.aspx.

257.

> A patent family is a set of either patent applications or publications taken in multiple countries to protect a single invention by a common inventor(s) and then patented in more than one country. A first application is made in one country –

granted patents and patent applications. Of those, only 50 patent families (less than 5% of the dataset) include the terms "Human Embryonic Stem Cell" or "Human Embryonic Stem Cells."

One challenge in our research was isolating the impact of policy intervention and verifying that the patent trends identified were not associated with a general decline in R&D activity. For this purpose, we have assembled a second dataset that acts as a control group—which includes all PCT applications filed by any researcher throughout the world. The data was collected by searching applications with the suffix WO within PatBase.

B. *Patent Application Analysis*

The stem cell patent filing trends at the USPTO,[258] PCT, and EPO are quite consistent.[259] The year 2001 was a peak year for stem cell patent applications in the three venues.[260] The number of applications in the years 2002–2003 dropped but recovered again in 2004–2005.[261] Since 2005, there has been a steady decline in the number of stem cell patent applications with the exception of 2007.[262]

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the priority – and is then extended to other offices.

EUROPEAN PATENT OFFICE, http://www.epo.org/searching/essentials/patent-families.html (last visited Oct. 2, 2014).

258. Data concerning patent applications at the USPTO begins in 2001.

259. *See infra* Figure 1.

260. *Id*.

261. *Id*.

262. *Id*.

Figure 1

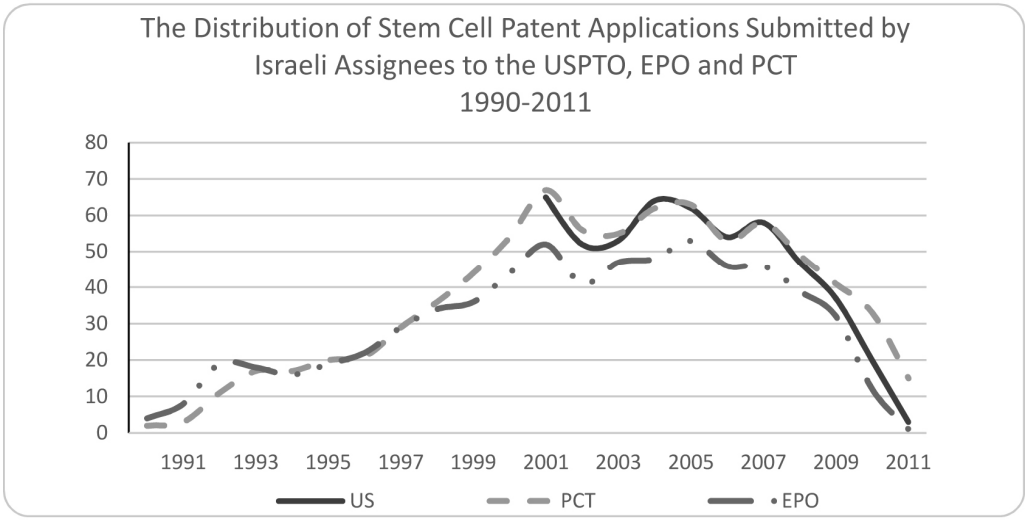


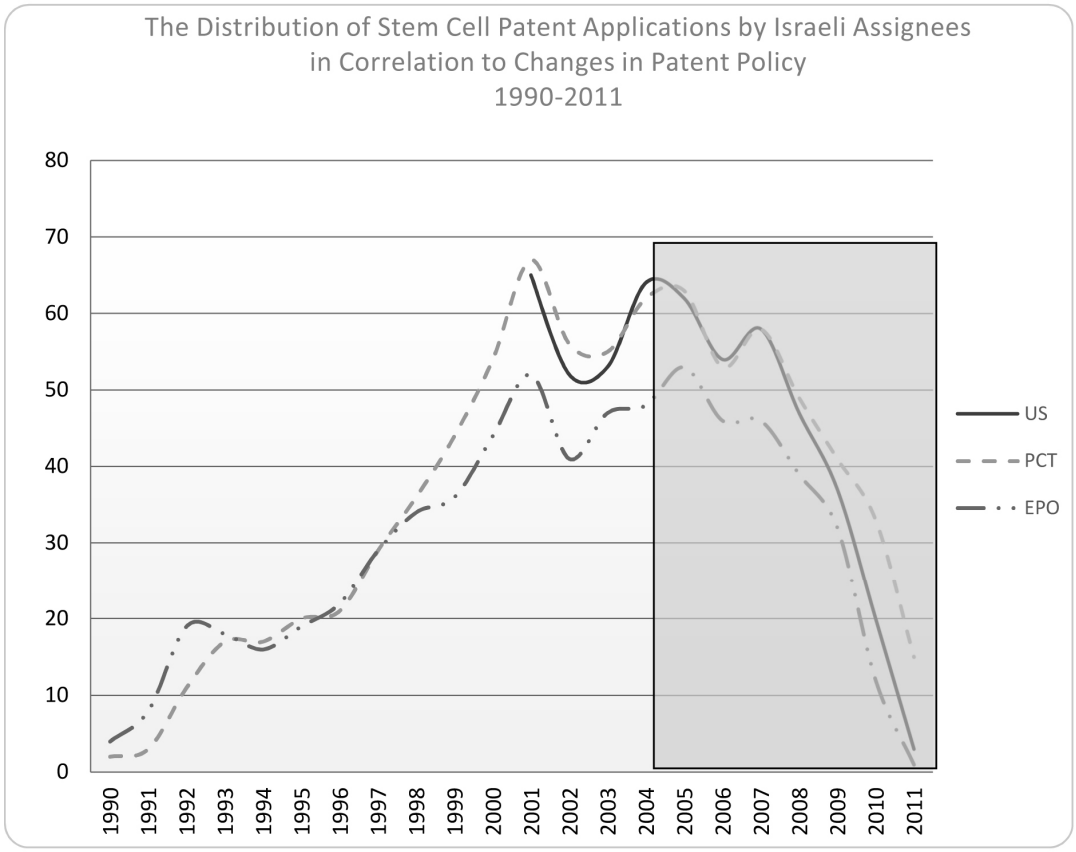
Figure 2 depicts these patent application trends in the USPTO, PCT, and EPO in correlation with changes in stem cell patentability policies.[263] As seen, following the EPO's 2004 decision to deny patents to hESC inventions,[264] there was a significant drop in the number of embryonic and non-embryonic stem cell patent applications across the registration tracks examined.[265]

263. *See infra* Figure 2.

264. Decision G 2/06, Wis. Alumni Research Found., 2008 O.J. E.P.O. 306, *available at* http://www.epo.org/law-practice/case-law-appeals/pdf/g060002ex1.pdf.

265. We assumed that changes in patent policy in 2004 would be reflected in the patent application data a year later, at minimum, and therefore we expected to see a significant drop in the number of patent applications during the years 2005–2006 and thereafter.

Figure 2



No similar trends were found with respect to changes in funding policies.[266] Following the 2001 restrictions on federal funding for hESC research,[267] the years 2002–2003 show a decline in the number of stem cell patent applications.[268] With that, 2004 indicates a recovery in the number of patent applications, which suggests a behavioral response by stem cell scientists to the new restrictions—such as finding alternative funding sources for example from the European Union.[269] However, since 2007 there has been a steady decline in the number of stem cell

266. *See infra* Figure 3.

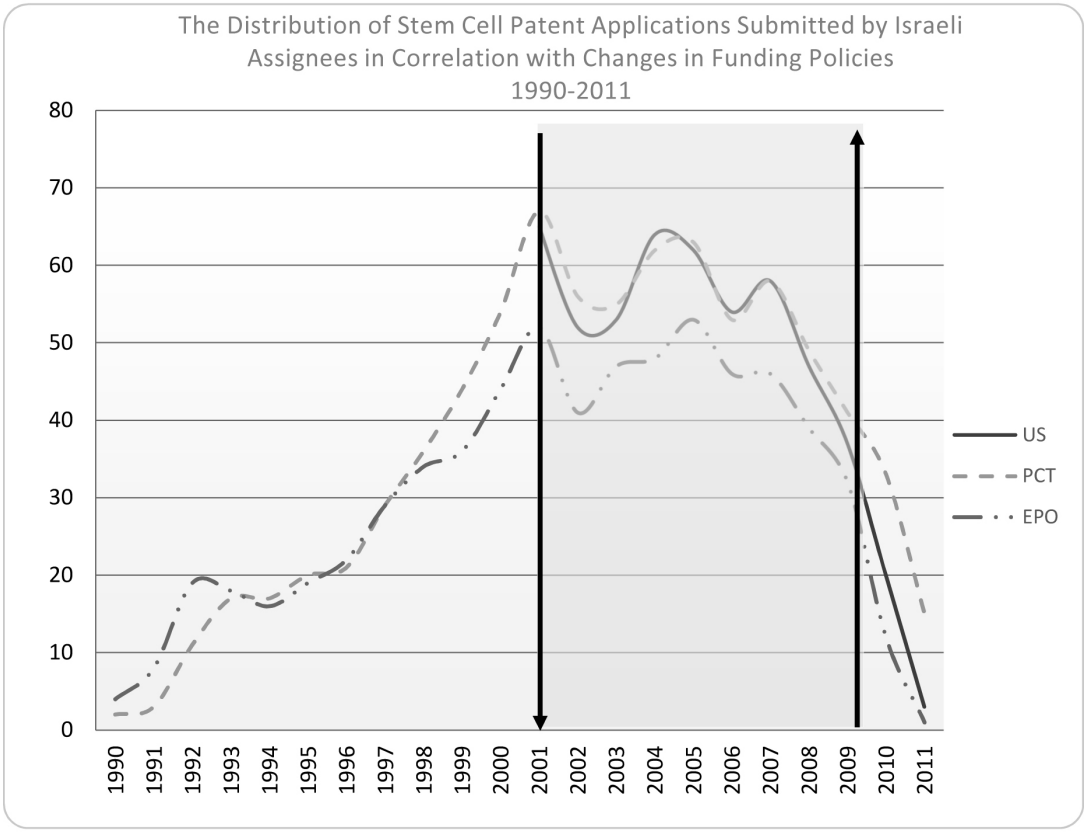
267. Address to the Nation on Stem Cell Research, 2 PUB. PAPERS 953 (Aug. 9, 2001); *see also* Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 20, 2007).

268. *See infra* Figure 3.

269. *See* Jeffrey L. Furman et al., *Growing Stem Cells: The Impact of Federal Funding Policy on the U.S. Scientific Frontier*, 31 J. POL'Y ANALYSIS & MGMT. 661, 662–63 (2012).

patent applications.[270] In 2009, the Obama administration lifted the restrictions on federal funding for stem cell research,[271] but this action did not stop the decline in the number of stem cell patent applications as could have been expected.[272]

Figure 3



Interestingly, however, while there has been a significant decline in the number of stem cell patent applications submitted by Israeli assignees, scientific research in stem cells, measured by the number of scientific publications by Israeli scientists during the same period of time, has not declined.[273] This finding possibly indicates a change in the nature

270. *See infra* Figure 3.

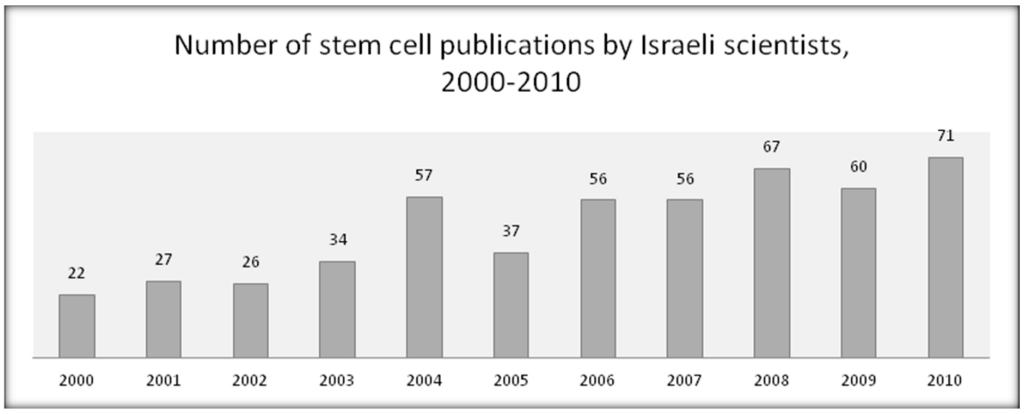
271. *See* Exec. Order No. 13,505, 74 Fed. Reg. 10,667, 10,667 (Mar. 11, 2009) (revoking President Bush's directive).

272. *See infra* Figure 3.

273. *See infra* Figure 4; Niva Elkin-Koren et al., *Facilitating Collaboration in Stem Cell Research through Intellectual Property*, 185 (2013) (Hebrew), abstract *available at* http://weblaw.haifa.ac.il/en/research/researchcenters/techlaw/researchprojects/pages/stemcells.aspx.

of stem cell research, shifting from privately funded R&D, which is profit-oriented and therefore depends on patents, to scientific research that relies on other sources of funding.

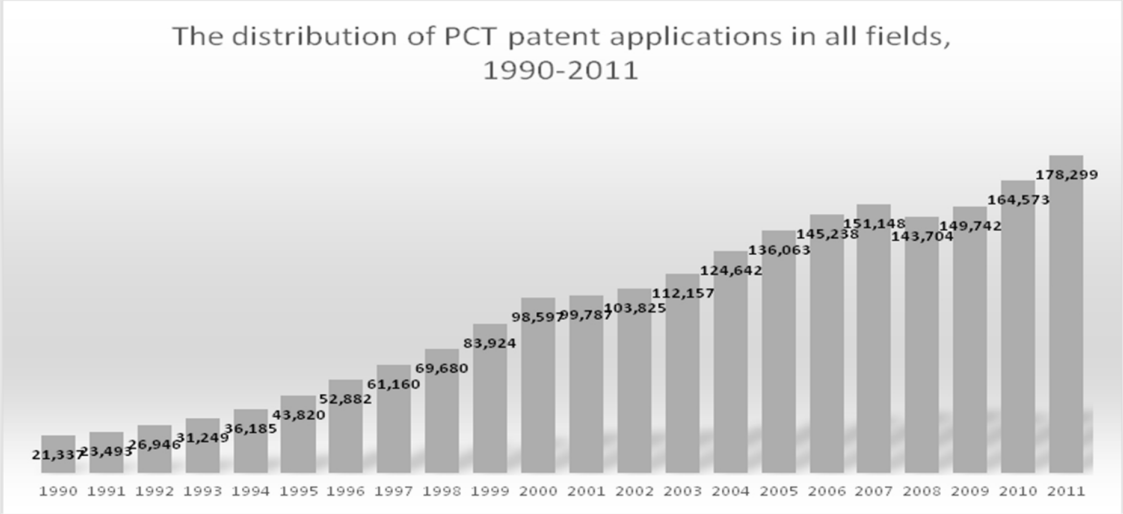
Figure 4



The control group, consisting of all patent applications in all fields of technology submitted to the PCT during the years 1990–2011, allowed for a determination as to whether the declining patent filing trend was specific to the stem cell field or part of a larger trend.[274] The distribution of these patent applications is depicted in Figure 5 below and shows a steady upward trend in the number of general patent applications submitted to the PCT during the same period, indicating that the decline in stem cell patent filings does not reflect a general slowdown or decline in the use of patents, but is rather specific to the stem cell field.

274. *See infra* Figure 5.

Figure 5



Our findings are consistent with findings reported in previous studies, which examined the correlation between policy changes and stem cell R&D output (using different methodologies).[275] Furman, Murray & Stern used a citation-based approach to track the impact of U.S. policy changes (1998–2008) on the scope of hESC research in the United States.[276] They found that U.S. policy, restricting federal funding for hESC research, led to a decline in stem cell output in the United States during the years 2001–2004 with some recovery from 2004–2007, causing stem cell research in the United States to lag behind its international peers.[277] Levine surveyed stem cell scientists in order to investigate the impact of the policy changes in the stem cell field.[278] He concluded that the frequent policy changes concerning human embryonic stem cells caused uncertainty that negatively affected all stem cell scientists, not just those working on human embryonic stem cells.[279] Similarly, a study by Huys et al., found a correlation between national legal policy and the level of stem cell R&D.[280] It discovered that countries with more lenient stem cell policies showed higher levels of stem cell R&D, concluding that "technological trajectories are modulated by research legislation."[281] These studies and

275. Furman et al., *supra* note 269; Levine, *supra* note 12; Huys et al., *supra* note 225.
276. Furman et al., *supra* note 269.
277. *Id.* at 696.
278. Levine, *supra* note 12, at 132.
279. *Id.* at 134.
280. Huys et al., *supra* note 225, at 191.
281. *Id.* at 196.

their findings suggest that the trends identified in this Article are not specific to Israeli stem cell scientists, but rather part of a larger phenomenon that affects stem cell scientists worldwide.

To summarize, our data shows a significant declining trend (from 2005 onward) in the number of stem cell patent applications submitted by Israeli assignees to the USPTO, PCT, and EPO. This decline in stem cell patents correlates with the 2004 European decision denying patent protection of hESC inventions. Changes in U.S. stem cell funding policies did not have the same systematic impact on the number of stem cell patent applications. This was not the case in 2001 when restrictions were placed and even less so when restrictions were lifted in 2009.

V. THE IMPACT OF IP POLICY ON R&D: PRELIMINARY LESSONS

This study presents important evidence showing the impact of policy changes on the scope of R&D in the stem cell field. Our data shows a significant and constant decline in the number of stem cell patent applications submitted by Israeli assignees to the USPTO, PCT, and EPO, following the dramatic changes in European patent policy in 2004 concerning hESC inventions.[282] Interestingly, the number of stem cell academic publications by Israeli scientists did not decline during the same time period.[283]

These findings are particularly striking as they show that changes in IP policy may cause an impact that is broader and wider than their intended scope. We divide the impact of the IP policy changes on R&D into four categories: global effect, extensive effect, differentiated impact and the chilling effect of uncertainty. Collectively, we call these outcomes the Ripple Effect of IP policy.

First, the EPO ruling applied only to patent applications submitted to the EPO, yet the declining effect can be seen in patent applications submitted by Israeli assignees to the EPO, PCT, and USPTO.[284] This suggests that national regulations that affect the incentives for research and development may be felt not just locally, but also globally, influencing the level of R&D in additional markets across borders. While previous studies have indicated that national regulation restricting stem cell R&D reduced the scope of stem cell research, measured by patents, in the regulated states,[285] this study shows the cross-national impact of local IP regulation.

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282. *See supra* Part IV.
283. *See supra* Figure 4.
284. *See supra* Figure 2.
285. *See* Huys et al., *supra* note 225, at 192.

Innovation and technological advancement occur at a global level,[286] hence it is not surprising that national regulation concerning the scope of research, its nature, or funding possibilities, could impact scientists globally, not just locally. Industries that are export-oriented are particularly susceptible to legal changes in other countries.[287] Thus, inability to receive patent protection for hESC inventions in Europe could also diminish incentives to conduct commercial hESC R&D outside of Europe (assuming that the European market is significant for the dissemination of hESC research products). Moreover, given that scientific developments in this area are often based on global collaboration,[288] all players in stem cell research are likely to monitor global legal developments and assess potential risks accordingly. For example, American entrepreneurs who seek to patent a hESC invention in the United States may fear that competitors will "free ride" the invention since it is unpatentable in Europe, thus lowering the expected return on their private investment or even rendering it worthless altogether. At the same time, scientists who are unable to obtain public funding for their research in the United States due to legal restrictions, may be the ones most likely to seek international collaboration, for example, cooperation with European scientists in order to obtain ERA funding. Consequently, local policy changes may have a global effect, as seen in the stem cell data analysis presented. This is the *global effect* of IP regulation.

Second, the 2004 European ruling applies only to patents for hESC research that results in the destruction of the embryo.[289] While these inventions comprise only 5% of the study's dataset, the findings indicate that since 2005 there has been an overall decline in the number of stem cell patent applications (both embryonic and non-embryonic).[290] Consequently, even though the 2004 ruling is narrow, its impact has extended to the inventive activity in the stem cell industry as a whole.

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286. Manfred M. Fischer, *Innovation, Knowledge Creation and Systems of Innovation*, 35 ANN. REG. SCI. 199, 211 (2000) (discussing the increasing recognition that the innovation process is global rather than national).

287. *See generally* Morisset & Pirni, *supra* note 256 (giving the example of a study that found that the impact of tax policy at host country on export-oriented firms is higher than on domestic firms); Brewer, *supra* note 256 (explaining that the host country's government's decision to subsidies export-oriented projects increases foreign direct investments (FDI)).

288. *See generally* Matthew Herder, Proprietary Interests and Collaboration in Stem Cell Science: Avoiding Anticommons, Countering Canalyzation, *in* TRANSLATIONAL STEM CELL RESEARCH, STEM CELL BIOLOGY AND REGENERATIVE MEDICINE 267 (Kristina Hug & Goran Hermeren eds., 2011) (discussing two initiatives to create international collaboration in the stem cell field).

289. Decision G 2/06, Wis. Alumni Research Found., 2008 O.J. Eur. Patent Office 306, 326 ¶ 22, *available at* http://www.epo.org/law-practice/case-law-appeals/pdf/g060002ep1.pdf

290. *See supra* Figure 2.

Accordingly, it seems that public policy concerning the patentability of hESC research has had an *extensive effect* on stem cell R&D, leading to a decline in the number of stem cell patent applications that goes well beyond the specific hESC research field to which the policy applies. These findings are further supported by recent studies using different methodologies. For instance, a survey among U.S. stem cell scientists has found that the uncertainty resulting from the frequent policy changes concerning human embryonic stem cell research has had a negative scientific and economic impact on stem cell scientists across the board, not just on hESC scientists.[291]

Third, the decline in the number of patent applications stands in sharp contrast to the steady increase in academic publications over the same period of time.[292] These conflicting trends in patent applications and scientific publications, suggest that intellectual property policy may carry a more limited effect on scientific progress as compared to private investment. As explained in Part III, patents act as a legal tool to incentivize and attract private R&D funding and may well complement public R&D funding.[293] For instance, the availability of public funding could promote private investment by spreading the monetary risks. Alternatively, lack of one source of funding (public or private) will likely increase the need for the other. As a result, public policy that supports patent protection for stem cell R&D diminishes the need for public funding, while denying patent protection of hESC research increases the need for public funding.[294] It seems that lack of public funding can more easily be remedied by alternative sources of funding; as a result, changes in public funding policies are reflected to a lesser degree in the number of patent applications.[295] Stem cell scientists have been quick to adapt to funding policy changes and alternatives to federal funds have been found, primarily in the form of international funding and state funding.[296] In contrast, private investments are based on the expectation of future revenue gain. When the likelihood of revenue diminishes, as is the case in uncertain, high-risk, research environments, the level of private investment will likely decrease. The decline in the number of stem cell

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291. *See* Levine, *supra* note 12, at 134.

292. *See supra* Figure 4.

293. *See supra* Part III.A.

294. This is seen in the American and European approaches. During the Bush administration U.S. stem cell policy allowed patent protection on hESC research outputs while restricting NIH funding. In contrast, European policy denies patent protection on hESCs but at the same time provides public funding for said research. *See supra* Part III.

295. *See supra* Figure 3. Yet other studies found that these changes were reflected in U.S. publication rates. *See* Furman et al., *supra* note 269, at 663 (showing that the publication rates of hESC scientists in the United States started to lag behind other countries following the 2001 restrictions on federal funding).

296. *Id.* at 676–77; *see also supra* Part IV.B.

patent applications, while the number of publications continued to rise, suggests that the policy changes had a more substantial impact on the private sector, which depends more on private funding, as compared to the public sector.[297] This indicates that IP policy has a *differentiated impact*.

Fourth, our data shows a correlation between changes in the patentability of hESCs and the decline in the number of stem cell patent applications, but it does not show a similar systematic correlation between the number of stem cell patent applications and changes in funding policy.[298] Admittedly, the fact that numerous dramatic changes occurred within a relatively short period of time, makes it difficult to evaluate the consequences of each distinct policy change on its own. Rather, the decline in the number of stem cell patent applications could be attributed to the overall effect of the policy changes in the United States and in Europe, as well as the short period in which they occurred. The frequent policy changes in the stem cell field, created legal uncertainty and increased the risk associated with private investment,[299] likely causing the number of stem cell patent applications to decline. Previous studies also reached similar conclusions.[300] Put differently, uncertainty seems to diminish private investment in R&D.

These findings not only support the assumption that legal regulation influences the level of R&D activity at the national level as previously suggested by Huys et al.,[301] but also further indicate that IP policy changes have a more extensive Ripple Effect.

VI. CONCLUSION

This study identified a Ripple Effect associated with changes in IP policy. Our findings demonstrate the global effect of IP policy showing that IP policy has a cross-national impact on R&D. Furthermore, our findings show that IP policy may have an extensive effect, affecting R&D in areas beyond its actual scope. The EPO's 2004 groundbreaking decision applied only to patents on human embryonic stem cells, which comprised just 5% of our dataset. Therefore we would have expected to see a decline only in the number of hESC patents submitted to the EPO. Yet, our data shows a decline in the number of all stem cell patent applications, and not just at the EPO but at the USPTO and PCT as well,

297. The Israeli academia is part of the public sector.

298. *See supra* Part IV.B.

299. *See* Levine, *supra* note 12, at 132; *see also* Caulfield et al., *supra* note 232, at 1039–40; Caulfield et al., *supra* note 88, at 85.

300. *See, e.g.*, Levine, *supra* note 12, at 132.

301. Huys et al., *supra* note 225, at 195.

suggesting that the impact on the market is not limited to the narrow legal rule.

Our findings also support the conclusion that legal uncertainty, created by frequent changes in stem cell policy, adversely affected private investment in R&D.[302] In other words, IP policy impacts R&D beyond its defined substance.

Lastly, the findings suggest a differentiated impact of IP policy: restrictions on patenting hESCs had a greater impact on the private sector, which depends more on private investment, as compared to the public sector. The data presented shows a decline in the number of stem cell patent applications submitted by Israeli researchers to the USPTO, EPO, and PCT following the European policy changes denying hESC patents. At the same time, the number of academic publications by Israeli scientists did not decline. In other words, while stem cell patenting activity decreased, stem cell research did not. Hence, our findings suggest that the private and public sectors are influenced differently by policy changes.

Returning to the *Association for Molecular Pathology v. Myriad Genetics* and *Alice Corp. v. CLS Bank* aftermath, this study could shed light on the potential consequences of IP policy changes. Our findings suggest that even narrowly tailored legal changes could have a broad effect on private investments in R&D. Put differently; the impact on R&D activity could exceed the boundaries of the legal decision due to the Ripple Effect of IP regulation. The Ripple Effect of IP policy calls for caution among judges and policymakers in making sharp policy shifts, since such shifts may involve some unintended consequences for R&D.

302. *See also* Levine, *supra* note 12, at 132.