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Stem Cell Patents in a Global Economy: The Legal Challenges

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Abstract

This paper reviews recent developments in the international legal landscape on stem cell patents and compares the fate of one of the early patent applications on stem cells derived from hESCs at leading patent offices around the world. Parts II and III set out the international and European legal contexts for the case study in Part IV, which reveals considerable international variance in the application of patentability criteria and examining standards. Part V argues that the difficulties attending the drawing of patent boundaries in this emerging field of science suggest that international initiatives to harmonize standards may be premature. On the other hand, there is an urgent need for major investment in the global infrastructure of patent information systems to adequately support the dissemination of patent data, not only to realize the intended function of the patent system to facilitate disclosure, but also in order to facilitate monitoring and comparative analysis of international patenting trends and their impact on innovation.

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I. INTRODUCTION

Stem cell research, and human embryonic stem cell (hESC) research in particular, offers the prospect of ground-breaking advances in the treatment and cure of major degenerative diseases.[1] As significant public and private funding initiatives are underway around the globe to support basic and translational research,[2] the adequacy of existing regulatory infrastructures to facilitate commercialization and diffusion of regenerative products and therapies will be vital to the future of the field. Intellectual property regimes on stem cells have the potential to control and encourage or stifle and delay innovation on regenerative therapies.[3] Whilst the evidence points to a complex range of factors implicated in the high rate of failure to exploit patented technologies,[4] there remains concern that overbroad and poor quality patents are liable to block or delay innovation.[5] High quality patents are perceived as vital to facilitate exploitation and ensure that the patent system maintains an adequate balance between the private interests of patentees and the wider public interest to access the benefits of the invention.[6] Yet, drawing clear and strong boundaries on what is patentable versus not patentable in the stem cell field is posing significant challenges to major patent offices and courts around the world with all the associated costs to applicants and society.[7]

This paper reviews recent developments in the international legal landscape on stem cell patents and compares the fate of one of the early patent applications on stem cells derived from hESCs at leading patent offices around the world. Parts II and III set out the international and European legal contexts for the case study in Part IV, which reveals considerable international variance in the application of patentability criteria and examining

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[1] Unlike adult stem cells, which are limited in their capacity to differentiate, embryonic stem cells are pluripotent and have the ability to differentiate into any cell type of the human body. For a basic account of the biological properties of stem cells, including human embryonic and adult stem cells, *see generally* Nat'l Inst. of Health, Stem Cell Basics, http://stemcells.nih.gov/info/basics/ (last visited Oct. 25, 2010).

[2] *See, e.g.*, The California Stem Cell Research & Cures Initiative, 2004 Cal. Legis. Serv. Prop. 71 (West); U.K. Stem Cell Initiative, Report & Recommendations (2005); Eur. Comm'n, The Seventh Framework Programme, http://ec.europa.eu/research/fp7/ (last visited Oct. 25, 2010).

[3] *See* Karl Bergman & Gregory D. Graff, *The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development*, 25(4) NATURE BIOTECHNOLOGY 419 (2007).

[4] *See* NAT'L RESEARCH COUNCIL, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (2006); Robert Cook-Deegan, Subhashini Chandrasekharan, & Misha Angrist, *The Dangers of Diagnostic Monopolies*, 458 NATURE 405 (2009) (establishing that contrary to common assumptions, patents on genes have not led to exorbitant prices or restrictions on access for tests on diseases such as Alzheimer's).

[5] *See* NAT'L RESEARCH COUNCIL, *supra* note 4, at 3; *see also* JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS AND LAWYERS PUT INNOVATORS AT RISK (2008) (questioning the fitness of the patent system as a driver to innovation in emerging fields of science); ADAM B. JAFFE, & JOSH LERNER, INNOVATION AND ITS DISCONTENTS: HOW OUR BROKEN PATENT SYSTEM IS ENDANGERING INNOVATION AND PROGRESS, AND WHAT TO DO ABOUT IT (2004); SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, REVISED DRAFT REPORT ON GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 1 (2010) (suggesting that exclusive monopolies on diagnostic tests are creating "significant" problems for doctors and patients).

[6] Herwig Schlogl, Deputy Sec'y Gen., Org. for Econ. Cooperation & Dev., Opening Remarks at the EPO-OECD-BMWA Conference on Intellectual Property as an Economic Asset: Key Issues in Valuation and Exploitation (June 30, 2005), *available at* http://www.oecd.org/dataoecd/36/15/35426089.pdf ("High quality patents facilitate exploitation and licensing by ensuring all sides in a possible transaction that the patent is valid and protects a novel, useful and non-obvious invention."); *see also* EUR. PATENT OFFICE, SCENARIOS FOR THE FUTURE: HOW MIGHT IP REGIMES EVOLVE BY 2025? WHAT GLOBAL LEGITIMACY MIGHT SUCH REGIMES HAVE? 17 (2007).

[7] *See* BESSEN & MEURER, *supra* note 5, at ch. 6.

standards. Part V argues that the difficulties attending the drawing of patent boundaries in this emerging field of science suggest that international initiatives to harmonize standards may be premature. On the other hand, there is an urgent need for major investment in the global infrastructure of patent information systems to adequately support the dissemination of patent data, not only to realize the intended function of the patent system to facilitate disclosure, but also in order to facilitate monitoring and comparative analysis of international patenting trends and their impact on innovation.

II. THE GLOBAL STEM CELL PATENT LANDSCAPE

The leading study of the global stem cell patents landscape, published by Bergman and Graff in 2007, shows a dramatic growth in the number of applications and grants of patents on stem cell inventions, with a total 10,681 applications and grants worldwide from 1986 to 2005.[8] Patents granted by the U.S. Patent and Trademark Office (USPTO) far outstripped those granted by other patent offices, with a total of 1724 at the USPTO, as against 421 granted by the European Patent Office (EPO), although patent applications and grants at the USPTO have been in gradual decline since 2001. When expanded to include the full "patent family" for each document, the corresponding patent filings show a global collection of stem cell patent families consisting of 47,467 documents. The distribution of the enlarged data set shows that patenting activity is concentrated in the United States (21%), the World Intellectual Property Organization (WIPO) (PCT) (19%), EPO (14%), Australia (12%), Canada and Japan (7%), Germany (3%), and China and the United Kingdom (2%).

The data collected by Bergman and Graff highlights the limitations of the patent classification system, the difficulties in aligning new technologies and their application to the existing codes, and the consequent methodological challenges in tracking patent applications and prior art in an emerging field of science. In the absence of a single category in the international patent classification (IPC) system capturing all the stem cell technologies, the figures are the result of combined aggregate searches including both human embryonic and adult stem cell lines, as well as culture media, growth factors, enzymes, and technologies relating to tissue engineering. Although WIPO has recently proposed changes to the IPC system to differentiate embryonic stem cells (C12N5/0735) from adult stem cells (C12N5/074), the new classifiers have not yet been formally adopted and cannot, in any event, be used to track patents already granted.[9] Bergman and Graff's study found that the largest class present were the stem cell lines and culture media covered by the international classification codes C12N5/06 (animal cells or tissues) and C12N5/08 (human cells and tissues) covering stem cell lines and cultures. Further filtering of the dataset to identify the fifty most potentially dominant patents was based on frequency of citation of the patent in subsequent patent documents and/or journals.

Whilst the data from Bergman and Graff does not specifically disaggregate patents on hESCs from those on adult stem cells, there are a number of limitations with Bergman and Graff's filtering strategy to identifying the most potentially dominant patents that are generic to the structure of the patent system. Quality of drafting styles and completeness of information on patent applications is highly variable.[10] In Europe, there is no explicit

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[8] Bergman & Graff, *supra* note 3.

[9] *See* World Intellectual Prop. Org. [WIPO], Special Union for the Int'l Patent Classification, IPC Revision Working Group, *Report, Nineteenth Session, Geneva, May 26 to 30, 2008*, IPC/WG/19/2 (June 20, 2008) (providing an update on the "C436 project," which concerns the reclassification of the C12N5 group and includes a proposal to introduce a subdivision distinguishing embryonic stem cells from adult stem cells).

[10] DOMINIQUE GUELLEC & BRUNO VAN POTTELSBERGHE DE LA POTTERIE, THE ECONOMICS OF THE EUROPEAN PATENT SYSTEM: IP POLICY FOR INNOVATION AND COMPETITION 160 (2008).

requirement for the applicant to cite all relevant prior art, although Rule 42(1)(b) of the European Patent Convention (EPC) points to the "useful[ness]" of the applicant doing so.[11] In the United States, applicants need only submit "material" references of which they are aware.[12] Furthermore, patent examiners often have many reasons to cite documents that may not say anything about the strength of the patent or novelty of the work.[13] In addition, as the EPO esp@cenet portal warns, it may not be to the commercial advantage of patentees to bring the patent application (or, indeed, existing prior art) to the attention of competitors.[14] This is particularly true in a field like stem cells where there are, as of yet, no downstream therapeutic applications. Indeed, the U.S. Food and Drug Administration initially put a hold on authorization of the first world trial by Geron, and only approved the trial finally in July 2010.[15] Crucially, the early stage of development of stem cell science, the basic nature of the knowledge and research relating to stem cell inventions, and the relative paucity of a downstream chain of translational therapeutic applications all suggest that frequency of citation may not be a reliable indicator of the potential dominance of a patent.

In addition, there is mounting evidence of significant variances in the evaluation of prior art and interpretation of patent standards across major patent offices around the world.[16] As a result, the outcome of the same application can vary dramatically from outright rejection to grant in regional and national patent offices. Last, but not least, the legal boundaries of the criteria of novelty, non-obviousness/inventive step, and utility/industrial application in this emerging field of science may be subject to readjustment, as policies originally developed by patent offices are challenged in the courts and/or subject to administrative or legal revisions.[17] In Europe, the legal status of stem cell patents is further complicated by the uncertain reach of the scope of moral exclusions on hESCs.[18] Together, these considerations suggest that a close examination of the outcome of international patent filings in the stem cell field through a comparative analysis of patents filed and granted could shed valuable light on the potential value of existing patent applications. The next section reviews major developments in Europe to set the context for the case study in Part IV.

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[11] Implementing Regulations to the Convention on the Grant of European Patents R. 42(1)(b), Dec. 7 2006, *in* Convention on the Grant of European Patents, Oct. 5, 1973, 13 I.L.M. 270 (as amended by Revision Act of Nov. 29, 2000), *available at* http://www.epo.org/patents/law/legal-texts/epc.html.

[12] 37 C.F.R. § 1.56 (2010); Manual of Patent Examining Procedure § 2001(a) (8th rev. ed. 2010).

[13] *See generally* Jeanne C. Fromer, *Patent Disclosure*, 94 IOWA L. REV. 539, 539-606 (2009).

[14] Eur. Patent Office, Seven Points to Consider Before Starting Your Search, http://ep.espacenet.com/ (last visited Oct. 25, 2010).

[15] Press Release, Geron, Geron to Proceed with First Human Clinical Trial of Embryonic Stem Cell-Based Therapy (July 30, 2010), *available at* http://www.geron.com/media/pressview.aspx?id=1229.

[16] *See* Press Release, WIPO, WIPO Symposium to Address Operation Deficiencies in Global IP Systems (Aug. 28, 2009), *available at* http://www.wipo.int/pressroom/en/articles/2009/article_0031.html (announcing the first Global Symposium of Intellectual Property Authorities to take place on September 17-18, 2009 and its goals); *see also* Shinjiro Ono, *Trilateral Cooperation – Mutual Exploitation of Search and Examination Results Among Patent Offices with a View to Establishing a System of Rationalized Work-Sharing*, *in* PATENT LAW AND THEORY 271, 273 (Toshiko Takenaka ed., 2008) (noting former USPTO Commissioner Bruce Lehman's alarm at "evidence of a looming crisis in the international patent system").

[17] *See, e.g.*, Bilski v. Kappos, 130 S. Ct. 3218 (2010) (narrowing the scope of eligible patentable subject matter); Eli Lilly & Co. v. Human Genome Sciences, Inc. [2010] EWCA Civ 33 (affirming the ruling of the court below invalidating a patent granted to Human Genome Science on a protein and the polynucleotide sequence encoding for it as lacking a credible "industrial application"); Press Release, Pub. Patent Found., Consumer Groups File Appeal on Challenge of Human Stem Cell Patent Held by WARF (July 18, 2008), *available at* http://www.pubpat.org/stemcellappeal.htm (noting that the USPTO Board of Appeals dismissed prior art publications cited by opponents of the WARF U.S. Patent No. 7,029,913, entitled "Primate embryonic stem cells," but opponents remain bent on pursuing the challenge in the courts).

[18] *See infra* Part III.

III. THE EUROPEAN LANDSCAPE

In Europe, the legality of patenting hESCs is shrouded in uncertainty as national and European patent offices and courts have adopted divergent interpretations of the scope of application of the moral exclusion clause on patenting "industrial and commercial uses of human embryos" adopted by the European Union in the Directive on the Legal Protection of Biotechnological Inventions of 1998.[19] Whilst the Wisconsin Alumni Research Foundation (WARF) patent was challenged on technical grounds at the USPTO,[20] a corresponding WARF European application on embryonic stem cell cultures was judged contrary to the specific moral exclusion by the Enlarged Board of Appeal (EBA) of the EPO,[21] on the grounds that, at the time of the application, the practice of the invention necessarily involved destruction of human embryos. The decision was made notwithstanding the fact that the applicants' claims were exclusively to the cell cultures and not to the prior process of obtaining the stem cells.[22]

A rapidly mounting backlog of patent applications on downstream embryonic stem cell cultures awaits examination at the EPO; meanwhile, the EPO granted to the German neuroscientist, Oliver Bruestle, a European patent on neuroprogenitor stem cells—seemingly following the inclusion of amendments expressly stating that the practice of the invention did not require destruction of human embryos.[23] The patent was granted in June 2006; but in a legal twist, only six months after the grant of the European patent by the EPO, the corresponding national German patent (which had been filed before the European patent and granted by the German patent office in 1999) was partially invalided on moral grounds by the German Federal Patent Court as contrary to the moral exclusions in the Directive.[24] Oliver Bruestle's appeal prompted a referral by the German Supreme Court to the European Court of Justice (ECJ), the judicial organ of the European Union.[25] As E.U. law has supremacy over national law in relation to the Directive, the ECJ's guidance on the scope of application of the specific exclusion on human embryos and embryonic stem cells is expected to ease the legal uncertainty in the national laws and policies of E.U. member states' patent offices.

What is less clear is how the EPO and its examining boards and tribunals will respond in light of the institutional and legal gulf between the European Union and the European Patent Office. The EBA's refusal to refer the question raised in the WARF appeal to the ECJ, citing the absence of a legal basis or procedure in the EPC Treaty or the European Union Treaties for such an action, is illustrative of the depth of the existing institutional and legal divide.[26] Current proposals to create an E.U. Patent, together with a post-grant unified mechanism for enforcement through a hierarchical tribunal system (a "European and E.U. Patent Court", or EEUPC) in the European Union[27] do not directly impact the EPO's autonomy or the powers of its tribunals under the EPC Treaty to examine and grant European

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[19] Council Directive 98/44, 1998 O.J. (L 213) 13 (EC); *see generally* EMBRYONIC STEM CELL PATENTS: EUROPEAN LAW AND ETHICS (Aurora Plomer & Paul Torremans eds., 2009).
[20] Martin Grund et al., *European Court of Justice to Decide the Fate of Patenting Stem Cells in Europe*, 10(5) BIO-SCIENCE L. REV. 193 (2010) (on file with author).
[21] Wisconsin Alumni Research Found., G 2/06, 2009 O.J. EPO 306 (EPO Enlarged Bd. App. 2008), *available at* http://archive.epo.org/epo/pubs/oj009/05_09/05_3069.pdf.
[22] *Id.* at 307.
[23] Eur. Patent No. 1040185 (issued Sept. 4, 2008).
[24] *See* Grund, *supra* note 20.
[25] *Id.*
[26] Initiatives to integrate the EPO within the EU have hitherto been unsuccessful.
[27] The initiative was pursued under the leadership of Sweden, which assumed the EU's six-month presidency on July 1, 2009. *See* Posting of Dugie Standeford to Intellectual Property Watch, http://www.ip-watch.org/weblog/ (Dec. 4, 2009, 23:19:00 GMT).

applications with the same legal effect as if they had been granted by each of the member states, although a degree of cooperation would be required, including possible accession of the European Union to the EPO.[28]

Thus, the controversies surrounding patents on hESCs in Europe point to a complex and deeply fragmented legal map for stakeholders to navigate.[29] Applicants have to weigh the costs of filing and maintaining pending applications at the EPO in an uncertain legal environment against the hitherto restrictive policy on moral exclusions on hESC patents adopted by the EPO boards in the Edinburgh and WARF cases. The additional costs to applicants of the heightened uncertainty attending applications subject to moral exclusions in Europe comes on top of the already higher costs of European patents. According to a former EPO chief economist, it can cost between four and ten times more to get a patent in Europe than in America, Japan, China, or South Korea, depending on how many countries are involved—and this in the case for patents that are not morally contested.[30] Not surprisingly, some applicants in the hESC field have opted to bypass the EPO altogether and/or concurrently file at the EPO and selected national patent offices in Europe to maximize the chances of securing a grant.[31]

IV. CASE STUDY: HEMATOPOIETIC STEM CELLS

Whilst the EPO has yet to clarify whether downstream applications of stem cell lines and cultures from cell lines originally obtained by destruction of a human embryo may be patentable, some applicants have opted to file directly with national patent offices that have clearer, more receptive policies. The U.K. Intellectual Property Office (UKIPO) took a clear lead in 2003 with the publication of a policy interpreting the exclusion in the Directive to extend only to totipotent cells or processes to derive cells from a human embryo.[32] The policy was revised in 2009 in light of the EBA's WARF ruling at the EPO. The updated policy now specifically excludes inventions that, at the date of the filing, could only be obtained through destruction of a human embryo.[33] However, the qualification should not be read as a turnaround in the UKIPO's policy to grant patents on stem cell lines and cultures originally derived from hESCs, as the revised statement notes that the UKIPO will continue to grant patents on embryonic stem cells which fulfil the eligibility criteria. As of August

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[28] *See* Council of the European Union, Conclusions on an Enhanced Patent System in Europe ¶ 44 (2009) (It is envisaged that "[e]nhanced Partnership should fully respect the central role of the European Patent Office in examining and granting European patents. Under the Enhanced Partnership the European Patent Office would be expected to consider but not be obliged to use the work provided by participating offices. The European Patent Office should remain free to carry out further searches. The Enhanced Partnership should not restrict the possibility for applicants to file their application directly at the European Patent Office.").

[29] *See* BRUNO VAN POTTELSBERGHE, LOST PROPERTY: THE EUROPEAN PATENT SYSTEM AND WHY IT DOESN'T WORK 13-17 (2009) (noting that firms are weary of the legal uncertainty and costs of multiple suits in national courts).

[30] *Id.* at 13 (suggesting that a single "Community patent" applying in all twenty-seven countries of the European Union could bring down the cost of obtaining protection by 60%).

[31] *But see* Eur. Patent Office, *Annual Report 2008*, at 2, (2008) *available at* http://www.epo.org/about-us/publications/general-information/annual-reports/2008.html (reporting that an ever-growing number of direct applications filed with the EPO do not claim the priority of an earlier application; more than 20,900 such first filings were recorded in 2008 (2007: 20,200 + 3.3 %), accounting for 14% of the total number of applications received).

[32] Practice Notice, Intellectual Prop. Office, Inventions Involving Human Embryonic Stem Cells (Apr. 2003), http://www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells.htm.

[33] Practice Notice, Intellectual Prop. Office, Inventions Involving Human Embryonic Stem Cells (Feb. 3, 2009), http://www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells-20090203.htm.

2009, a search of patents granted by the United Kingdom on the public database GB esp@cenet showed that fewer than 100 hESC patents had been granted.[34]

A preliminary examination of U.K. patents reveals that at least a third of these originated as international applications under the Patent Cooperation Treaty (PCT) with a priority filing in the United States.[35] An instructive example of the complex global routing and international fate of a potentially dominant patent on hESC cultures is the patent on "Hematopoietic Cells from Human Embryonic Stem Cells" from the U.S. Corporation, Geron.[36] Application PCT/US2002/039091 was filed as an international application with WIPO on December 6, 2002[37] with priority from provisional application US60/338,979, dated February 7, 2001. According to the WIPO database, there are ten corresponding applications in the same family that have entered the national and regional phase, including: Australia, Canada, China, Europe, Great Britain, Italy, Japan, Korea, and the United States.

The original international application WO/2003/050251 is comprised of 36 claims. Claims 1-12 describe a cell population obtained by differentiating primate pluripotent stem cells (pPS) that proliferate in culture, having one or more of the following properties: at least 1% of the cells are CD45 positive, at least 30% are CD34 positive, at least 70% are CD13 positive, or at least 10% are AC133 positive. Claims 13-22 describe a method to differentiate and maintain the pPS cells including hESCs. Claim 25 is to an "erythrocyte, erythroblast, neutrophil, eosinophil, basophil, monocyte, macrophage, megakaryocyte, platelet or lymphocyte, produced by further differentiating the differentiated cell population of claim 1." Claim 26 is to "[a] method of screening a compound for its ability to modulate hemtopoietic cell function." Claim 27 is to "[a] pharmaceutical composition for treatment of the human or animal body comprising the differentiated cell population in claim 1, obtained according to the methods described in claim 13." Claims 28-36 are for uses of the same cell population made by the method of claim 13 in a number of preparations, including: "the preparation of a medicament for reconstitution hematopoietic function in a human" (claim 28), or "preparation of a medicament for genetic therapy of a human" (claim 29), and "a pharmaceutical combination comprising together or in separate containers a first cell population comprising a differentiated cell population according to claim 13, or inactivated undifferentiated pPS cells, formulated to be suitable for human administration; and a second cell population comprising differentiated cells that are MHC compatible" with the first population (claim 31).

As of December 2009, the WIPO database shows that the original PCT application resulted in a myriad of amendments upon entering the national phase at a number of patent offices, with outcomes fluctuating between success following amendments to the original application in the United Kingdom (2004) and Australia (2008), to final rejection by the USPTO (2009). The application is still pending at other offices.

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[34] *See* Aurora Plomer, *Towards Systemic Legal Conflict: Article 6(2)(c) of the Biotech Directive*, *in* EMBRYONIC STEM CELL PATENTS: EUROPEAN LAW AND ETHICS, *supra* note 19, at 174.

[35] In their analysis of the economics of the European Patent System, Guellec and Van Pottelsberghe point out that most applicants commonly start with a national application which provides the legal priority date. Under the Paris Convention (1883), the applicant has one year from the priority date to extend the application to other countries or regions. This period may be extended to 30months if the applicant chooses to file an international application with the World Intellectual Property Office (WIPO) under the Patent Cooperation Treaty (PCT) signed in 1970. In 2008, PCT applications accounted for 57% of the applications received at the EPO for the grant of a European patent. *See* EUR. PATENT OFFICE, ANNUAL REPORT 2008 2 (2008), *available at* http://www.epo.org/about-us/publications/general-information/annual-reports/2008.html.

[36] Therapeutic applications of hESCs and hematopoietic cells in particular are to some degree speculative at this point in time, but include, for instance, the use of hematopoietic hESCs as an alternative to bone marrow transplants in the treatment of leukemia. *See* Maria H. Ledran et al., *Efficient Hematopoietic Differentiation of Human hES Cells on Stromal Cells Derived from Hematopoietic Niches*, 3(1) CELL STEM CELL 85 (2008).

[37] Int'l Pub. No. WO/2003/050251 (June 19, 2003).

A. *The United States: Patent Failure*

In the United States, the prosecution history shows that U.S. application 10/313,196, claiming benefit to U.S. provisional 60/338,979, resulted in a final rejection on October 25, 2005 on grounds of obviousness, lack of written description, and a failure to comply with the enablement requirement.[38] Geron abandoned the application on December 11, 2006. Another application, U.S. patent number 10/862,625, is a continuation-in-part of 10/313,196, which is a continuation of PCT/US02/39091 claiming the same priority. This application also was rejected twice for lack of enablement and written description (a new matter rejection), with a final rejection dated July 21, 2009 following several requests for amendments.[39]

The amended claims that are the subject of the final rejection were filed on October 4, 2009 and encompass a cell culture comprising any differentiation factors or combination thereof and two populations of cells: 1) undifferentiated hES cells and 2) cells expressing CD45 and either CD19, CD3, CD14, or CD13 without foreign stromal cell support. The examiner's rejection states that, "Whereas the nature of the invention is a cell culture of differentiated hematopoietic cells lacking any exogenous non-human additions such as serum or foreign stromal cells, the skilled artisan would find the claimed invention unpredictable as recently amended."[40] Specifically, the examiner rejected the applicant's submission that the findings in the Chadwick paper[41] demonstrate that the claimed invention is enabled and would guide the skilled artisan to generate a cell culture comprising two populations of cells as claimed without foreign stromal cell support.[42] According to the examiner, the culture conditions described in Chadwick are different than those described in the specification; neither do the methods taught in Chadwick result in the claimed invention. Further, the examiner stated, "If hES cells are to be maintained and cultured in a feeder-free environment and with no xenogenic components, the art continues to teach that specific culture conditions and factors are needed to maintain hES cell pluripotency and still provide capacity of hES cells to differentiate."[43]

Following the final rejection dated July 21, 2009, Geron filed a request for continued examination and submitted further amendments in September 2009. These further amendments were also rejected on grounds of obviousness and lack of enablement in a final rejection dated June 24, 2010. The examiner found that the expression of CD45 in human in hematopoeitic cells cultured with BMP-4 would have been obvious when combining the teachings of Johannson and Thomson. [44]

B. *The United Kingdom and Australia: Patent Success*

By contrast, in 2006, the UKIPO granted two patents originating in the same international application. These two patents were Patent GB2399572, "Hematopoietic Cells from Human Embryonic Stem Cells" (June 7, 2006), and Patent GB2412379, "Use of Undifferentiated Embryonic Stem Cells to Induce Immune Tolerance and Improve Allograft

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[38] U.S. Pat. & Trademark Office, U.S. Dep't of Commerce [USPTO], Application No. 10/313,196, Office Action Communication, at 2-5 (Oct. 25, 2005); *see generally* 35 U.S.C. §§ 102(b), 103(a) (2010).
[39] USPTO, Application No. 10/862,625, Office Action Communication, at 5 (July 21, 2009) [Final Rejection of July 21, 2009].
[40] *Id.* at 4.
[41] Kristin Chadwick et al., *Cytokines and BMP-4 Promote Hematopoietic Differentiation of Human Embryonic Stem Cells*, 102(3) BLOOD 906 (2003).
[42] Final Rejection of July 21, 2009, *supra* note 39, at 6.
[43] *Id.* at 7.
[44] USPTO, Application No. 10/862,625, Office Action Communication, at 5 (June 24, 2010).

Tolerance" (March 29, 2006).[45] The U.K. patent applications consist of twenty-nine and fourteen claims, respectively.

The claims in GB2399572 are to cell populations of differentiated hematopoietic cells "wherein at least 5% of the cells in the population are both CD34 positive and CD45 positive, and a second population of undifferentiated cells from the same human pluripotent stem (PS) cell line from which the first population was differentiated . . . free of allogeneic stromal or feeder cells" (claims 1, 3), and the methods of culturing the differentiating cells (claims 9-17) are substantially similar to those in the amended U.S. application rejected for lack of disclosure and enablement by the USPTO. The U.K. patent includes in claims 20-29 the use of the cells in therapeutic applications for treating anemia, immune deficiency, or cancer, and/or pharmaceutical combinations based on the cell populations described in the claims.

The second U.K. patent, GB2412379, is for a pharmaceutical combination "comprising together or in separate containers a first cell population comprising undifferentiated pPS cells, formulated to be suitable for human administration; and a second cell population comprising differentiated cells that are MHC compatible with the first cell population" (claim 1), inter-alia, inhibiting inflammatory response (claim 2) or rendering the individual immunotolerant (claim 3).

Notwithstanding the USPTO's concerns about disclosure and enablement, Australia followed the United Kingdom. In 2008, the Australian Patent Office issued two patents identical to the GB patents issued in 2006. Patent application 2002366603 "Hematopoietic Cells from Human Embryonic Stem Cells" was granted on October 2, 2008. A divisional application 2008243182 with the same title was granted on December 4, 2008. A comparison of the international search report (ISR) issued by WIPO on June 19, 2003 with the USPTO examiner's office actions shows that the USPTO search identified prior art not identified in the ISR by WIPO, which the U.S. examiner judged to make obvious some of the claims based on the prior art. Furthermore, in response to the U.S. examiner's request for disclosure, Geron cited prior art published in 2008 and 2009.

It is, of course, recognized that the patent laws and legal precedents stemming from court decisions differ among countries. Furthermore, the claims in the various applications may have varied. Nonetheless, this study shows that prosecution of international applications with the same priority has produced different results. The claims are allowed in some countries, but rejected in others. I next explore the reasons for the variance and possible avenues by which to tackle them.

V. THE FUTURE OF STEM CELL PATENTS: CHALLENGES AHEAD

National variances in the fate of international applications essentially can be traced to either: a) differences in the quality of the searches on prior art carried out by different patent offices, or b) differences in the scope and/or application of the substantive patenting criteria of novelty, non-obviousness, and utility. In emerging fields of science, a combination of the two factors is probably responsible. Quality depends on the competence of the patent examiners, as well as the resources and materials available to them, while the scope and application of substantive patenting criteria reflect national laws and policies.[46] Current research points to three major barriers to addressing this dual challenge in future years.

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[45] The U.K. applications were granted over six months after the final rejection of U.S. application 10/313,196 on October 25, 2005. Geron filed an appeal of USPTO's rejection on March 24, 2006, just three days before the date of the U.K. grant, but abandoned the appeal on December 11, 2006.

[46] *See* Tomoko Miyamoto, *International Treaties and Patent Law Harmonization: Today and Beyond*, *in* PATENT LAW & THEORY 154 (Toshiko Takenaka ed., 2009); *see also*, EUR. PATENT OFFICE, SCENARIOS FOR THE FUTURE, *supra* note 6, at 17.

Identifying prior art in rapidly developing fields of science and technology poses considerable challenges for patent examiners who face limited resources and time constraints with respect to accessing all relevant publications, including conference presentations and articles in journals.[47] In a pilot project run by New York Law School in cooperation with the USPTO and patent applicants, patent examiners reported relying on prior art submitted by a group of self-appointed reviewers in more than 25% of applications it handled.[48] The project shows that public/expert input into the examining process has the potential to enhance the quality of patents granted; but cultural, legal, and technical barriers must be removed before we can secure engagement from scientists in the stem cell field.

Cultural barriers include scientists' sense of alienation from the patent system and their (mistaken) belief that they are safe from litigation.[49] Technical barriers include the limited functionality of public patent information databases,[50] the lack of timeliness of published information,[51] and the presumed knowledge of the patent system required to access and understand data. In the United Kingdom, the Gowers Review of Intellectual Property recommended in 2006 that "[t]he Patent Office . . . make the publication of inventions which are available for use more accessible. An easily accessible, open standards database should be provided that people can draw upon to identify inventions in the public domain. The inventions should be grouped by subject, with a brief description of the invention so that they can be easily identified. This should link to esp@cenet patent entries for maximum transparency."[52] Legal challenges include the need for adaptation of patent standards and legal categories devised for an industrial era driven by the steam engine to today's world where innovation is driven by knowledge economies and research is increasingly reliant on bioinformatics or focused on the "logic" of biology.[53]

As dramatic shifts occur in the organization, methodology, and production of science, the patent system struggles to keep abreast of developments at the technological edge.[54] With increased reliance on software technologies in the specification of claims, the legal boundaries of patenting standards of novelty/obviousness and utility/industrial application are

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[47] *See* CTR. FOR PATENT INNOVATIONS, PEER-TO-PATENT SECOND ANNIVERSARY REPORT 4 (2009), *available at* http://dotank.nyls.edu/communitypatent/CPI_P2P_YearTwo_hi.pdf (describing how the volume of patent applications worldwide continues to increase substantially; consequently, patent examiners at the USPTO have roughly twenty hours to examine an application and draft office actions).

[48] *Id.* at 5.

[49] Zhen Lei et al., *Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research*, 27 NATURE BIOTECHNOLOGY 36 (2009).

[50] *E.g.*, Abstracts are not searchable in the esp@cenet database.

[51] *See* Helene Dernis, *Nowcasting Patent Indicators* 5 (Directorate for Science, Tech., & Indus., Working Paper No. 2007/3, 2007), *available at* http://www.oecd.org/dataoecd/0/20/39485567.pdf (explaining that "[t]imeliness is a major drawback . . . which can not easily be circumvented"); *see also* Wim van der Eijk, Eur. Patent Office, PCT Backbone of the Global System: In Need of Support, Presentation at the World Intellectual Property Organization Global Symposium of Intellectual Property Authorities – Developing Global Intellectual Property Infrastructure for Promoting Science, New Technologies and Innovation Worldwide (Sept. 17, 2009), *available at* http://www.wipo.int/export/sites/www/meetings/en/2009/sym_ip_auth/presentations/wim_van_der_eijk.ppt (noting substantial lack of compliance with PCT Rule 42 on publication of ISRs).

[52] ANDREW GOWERS, GOWERS REVIEW OF INTELLECTUAL PROPERTY 90 (2006), *available at* http://www.official-documents.gov.uk/document/other/0118404830/0118404830.pdf

[53] *See* JAMES SHREEVE, THE GENOME WAR (2004).

[54] *See* Rochelle Dreyfuss, *Pathological Patenting: The PTO as Cause or Cure*, 104 MICH. L. REV. 1559 (2006) (tracing the origin of the breakdown to institutional failures to keep the patent system abreast of new technologies).

becoming increasingly blurred, as are the boundaries between copyright and patents. The fear is that the patent system is heading for "the perfect storm."[55]

Despite major investments at the USPTO,[56] UKIPO,[57] and WIPO[58] over the past decade, the global public patent information infrastructure is struggling to meet the needs of scientists, industry, and the public.[59] Against this background, calls for wide-scale treaty reform and international harmonization of standards seem arguably premature.[60] A more realistic strategy is for the PCT system to aim to more effectively meet the Treaty's goal of "deliver[ing] results which meet the needs of applicants, Offices and third parties in all Contracting States . . . without limiting the freedom of Contracting States to prescribe, interpret and apply substantive conditions of patentability and without seeking substantive patent law harmonization or harmonization of national search and examination procedures."[61] There is clearly scope for patent offices to share their work and take advantage of searches done by other offices to improve quality and identification of prior art. But measures to achieve greater harmonization of patenting standards of novelty, non-obviousness, and utility presume a degree of consensus on the rationale and economic value of intellectual property rights, when the reality points to differences in national and regional policies. Unravelling global patent trends in emerging fields of science thus poses formidable challenges. Stem cell patents are but the tip of an iceberg.

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[55] *See* Arti K. Rai & James Boyle, *Synthetic Biology: Caught Between Property Rights, The Public Domain, and The Commons*, 5(3) PLOS BIOLOGY e58 (2007), http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.0050058.

[56] *See* Press Release, U.S. Dep't of Commerce, Commerce Department Announces New Open Government Initiatives (Dec. 9, 2009), *available at* http://www.commerce.gov/news/press-releases/2009/12/09/commerce-department-announces-new-open-government-initiatives (announcing initiative to expand the online availability of information on past patent grants and applications).

[57] *See* Practice Notice, Intellectual Prop. Office, Electronic Publication of Patent Documents (2010), http://www.ipo.gov.uk/types/patent/p-os/p-find/p-find-publication/p-find-publication-notice.htm (noting that from April 1, 2010, the IPO will be utilising its online publication server as its official publication means for all published, granted, and corrected patent publication documents).

[58] *See* Press Release, WIPO, WIPO Symposium to Address Operational Deficiencies in Global IP Systems (Aug. 28, 2009), *available at* http://www.wipo.int/pressroom/en/articles/2009/article_0031.html ("A new WIPO strategic goal seeks to create a more robust and coherent global IP infrastructure by supporting efforts to upgrade technical capabilities of offices and by fostering greater collaboration and more focused coordination of activities by IP offices. There is great scope to facilitate the flow of technological information by, for example, upgrading databases and introducing best practices into the operations of IP offices to ensure that the system keeps pace in practical terms with the evolving needs of the user community.").

[59] This was illustrated at the WIPO Global Symposium for Intellectual Property Authorities in Geneva, Switzerland on September 17-18, 2009. *See* Press Release, WIPO, WIPO Symposium Concludes Global Patent Application Blacklogs Unsustainable (Sept. 18, 2009), *available at* http://www.wipo.int/pressroom/en/articles/2009/article_0035.html ("WIPO Director General Francis Gurry referred to recently published data that showed that the global backlog in unprocessed patent applications around the world in 2007 was a staggering 4.2 million. These backlogs have grown on average at a rate of 8.7% over the past five years.").

[60] Jerome H. Reichman & Keith H. Maskus, *The Globalization of Private Knowledge Goods and the Privatization of Global Public Goods*, 7 J. INT'L ECON. L. 279 (2004), *reprinted in* INTERNATIONAL PUBLIC GOODS AND TRANSFER OF TECHNOLOGY UNDER A GLOBALIZED INTELLECTUAL PROPERTY REGIME 3 (Keith E. Maskus & Jerome H. Reichman eds., 2005).

[61] WIPO, Patent Cooperation Treaty Working Group, *Second Session, Geneva, May 4 to 8, 2009, Summary by the Chair*, ¶ 5, WIPO Doc. PCT/WG/2/13 (May 8, 2009).