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The Use of MTAs to Control Commercialization of Stem Cell Diagnostics and Therapeutics

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THE USE OF MTAs TO CONTROL COMMERCIALIZATION OF STEM CELL DIAGNOSTICS AND THERAPEUTICS

By Sean O'Connor[†]

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I. INTRODUCTION

The recent focus on patents as a hindrance to stem cell research may turn out to be a red herring. The real culprits are material transfer agreements (MTAs), which govern the transfer of cell lines and other biological materials.¹ The MTA's primary purpose in life sciences research is to set contractual rights and obligations between parties where one party trans-

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1. See generally John P. Walsh, Charlene Cho & Wesley M. Cohen, *View from the Bench: Patents and Material Transfers*, 309 SCI. 2002 (2005) [hereinafter *View from the Bench*]; John P. Walsh, Charlene Cho & Wesley M. Cohen, Presentation at Madrid CSIC/OECD/OEPM Conference on Research Use of Patented Inventions: Roadblocks to Accessing Biomedical Research Tools (May 18-19, 2006), <http://www.oecd.org/dataoecd/40/12/36816897.pdf> [hereinafter Walsh, Roadblocks].

fers biological materials to the other.² For example, MTAs often focus on the physical handling, use, and distribution of the materials by the recipient, ensuring that the recipient complies with regulations for research involving humans or animals.³ Although these interests are legitimate, evidence indicates that owners of important biological research materials use their non-patent property rights to require recipient consent to arguably onerous MTAs, which include provisions governing intellectual property rights (IPR). When an intended recipient's institution refuses to sign the MTA, the researcher cannot access the biological materials, and in some cases cannot pursue her research.

One must understand the interaction between physical property rights and IPR in MTAs to achieve a proper balance among (1) rewarding innovators, (2) reducing obstacles to next generation innovators, and (3) ensuring that the public receives benefits in exchange for public research funding. Part II works through the details of this interaction by placing life sciences MTAs in the context of a broader technology distribution model that I call the "lease-license model." Part III examines Wisconsin Alumni Research Foundation's (WARF) and WiCell Research Institute's (WiCell) current dominant control of the stem cell research environment as a case study in the power of MTAs to control life sciences research. Part III also discusses some of the important counterbalancing government rights that can be used to provide for relatively unfettered research. Part IV subsequently analyzes the impact that the current WARF/WiCell legal position will have on research funded by the California Institute for Regenerative Medicine (CIRM). In conclusion, Part V suggests legal strategies for moving beyond the current WARF/WiCell controlled research environment.

II. MATERIAL TRANSFER AGREEMENTS AND THE LEASE-LICENSE TECHNOLOGY DISTRIBUTION MODEL

Confusion surrounds MTAs because they frequently convey both physical property rights and IPR licenses.⁴ One must distinguish the physical property rights from whatever IPR the MTA may convey. In some MTAs, the transferor makes explicitly clear that the recipient may need IPR licenses from third parties to use the transferred biological mate-

2. See Uniform Biological Material Transfer Agreement: Discussion of Public Comments Received; Publication of the Final Format of the Agreement, 60 Fed. Reg. 12,771, 12,771 (Mar. 8, 1995) [hereinafter UBMTA].

3. *Id.*

4. See Memorandum of Understanding between WiCell Research Institute, Inc. and Public Health Service, (Sept. 5, 2001), http://stemcells.nih.gov/staticresources/research/registry/MTAs/Wicell_MOU.pdf [hereinafter WiCell MOU].

rials for the recipient's specific research purposes.⁵ Of course, one would assume that the transferor at least implies that the delivery of the biological materials has not violated any IP rights.

Interestingly, MTAs usually do not convey ownership of the biological materials they transfer; rather, they typically lease those materials.⁶ I refrain from using the term "license" here because it will only add to the confusion between the physical property rights grant and any IPR licenses that are included in the MTA. However, my sense is that most institutions refer to the legal conveyances of permission to use the biological materials *qua* physical property as well as *qua* IP as "licenses." This dual "lease-license" model is hardly unique to life sciences MTAs—it is also the underlying model for much of the software industry,⁷ the original Bell telephone service,⁸ commercial test prep materials,⁹ musical scores made available for school performances,¹⁰ many of the original cable television services,¹¹ and even the recent controversial practice of "bag tags" in the seed and agricultural biotechnology industries.¹² Many technology or service providers who use the lease-license model do not even require or expect the return of the physical materials. The recipient may destroy the materials or retain them indefinitely. Restrictions apply, though, to further transfers by the recipient. Thus, few software vendors require that pur-

5. See American Type Culture Collection, Material Transfer Agreement and Order, <http://www.atcc.org/documents/mta/mta.cfm> (last visited Sept. 8, 2003) [hereinafter American Type MTA].

6. See WiCell MOU, *supra* note 4; American Type MTA, *supra* note 5.

7. See Xuan-Thao Nguyen, Robert Gomulkiewicz & Danielle Conway-Jones, Intellectual Property, Software, and Information: Licensing Law and Practice (forthcoming 2006).

8. See Bell System Memorial: Bell System Property—Not For Sale, http://www.bellsystemmemorial.com/bell_system_property.html (last visited Aug. 30, 2006) [hereinafter Bell Property].

9. See, e.g., Bar/Bri Patent Bar Review, Bar/Bri Patent Bar Review Enrollment Form, <http://www.patentbarbri.com/download/pdf/enrollment01.pdf> (last visited Aug. 30, 2006).

10. See, e.g., Music Theater International, FAQ: How to License a Musical, http://www.mtishows.com/faq_licensing.asp (last visited Aug. 30, 2006).

11. See, e.g., Sanjay Talwani, *Industries Battling for the Future of Set-Top Boxes*, TVTECHNOLOGY.COM, Nov. 14, 2001, <http://www.tvtechnology.com/features/news/n-settops1.shtml>; David Connell, *Waiting for Set-Tops: Making Set-Top Boxes Available for Purchase at Retail is Not as Simple as it Sounds – Broadband Content*, CABLE-WORLD, Nov. 27, 2000, available at http://www.findarticles.com/p/articles/mi_m0DIZ/is_48_12/ai_80191763; National Cable and Telecommunications Association, Cable Industry Announces Retail Set-Top Initiative, <http://www.ncta.com/ContentView.aspx?hiddenavlink=true&type=reltyp1&contentId=163> (last visited Aug. 30, 2006).

12. See, e.g., *Monsanto Co. v. McFarling*, 363 F.3d 1336 (Fed. Cir. 2004).

chasers return the CD-ROMs containing the software. Test prep services sometimes require a deposit on materials, which they refund when the user returns the materials to the company. If the consumer fails to return the materials, he simply forfeits the deposit, though the transfer restrictions continue to bind him. Seeds transferred under bag tag licenses are the ultimate example of this practice in that they are, of course, destroyed through the very use for which they were leased-licensed to the farmer.¹³

Like their counterparts in other industries, many distributors of biological materials under MTAs do not require the materials to be returned. This begs the central question of why transferors lease them out rather than sell them. Presumably, one could charge a higher upfront payment for an outright sale than for a lease. Other common lease situations such as auto leases or real estate rentals are likely premised on potentially greater economic returns over time through the continued payments by the lessee/tenant. However, in most of the lease-license models given above, including biological MTAs, ongoing payments are rarely required.¹⁴ Instead, transferors may well be seeking other important legal and business advantages that are forfeited in a sale model. These advantages generally fall into three categories: (1) control of IP rights/ownership; (2) elimination, or at least limitation, of potential liability to third parties who might otherwise obtain the materials from the original recipient; and (3) unlocking extra value for the distributor and its clients through business models that focus on more than just sales of goods. The lease-license model also gives extra business and negotiation leverage to the transferor, since the recipient bears the risk that certain triggering events set out in the contract will terminate the IP license and require the return of all materials, sometimes including derivative materials created by the recipient.

The first category of legal and business advantages of the lease-license model—IPR control—is likely the most important to transferors of materials. The inclusion of strong IPR language in the lease-license agreement—*e.g.*, MTA or end-user license agreement—often causes the public and even the parties to conflate the physical property lease rights and the IPR. Essentially, the transfer agreement often sets up the two strands of rights—physical and IP, or tangible and intangible—to reinforce one another. A version of this reinforcement strategy is examined in more detail

13. This, however, does lead directly to the litigated controversy in bag tag license situations whereby the farmer attempts to (re)use the next generation seeds, if any, which is generally prohibited under bag tag licenses. *See, e.g., id.*

14. Note, however, that the original Bell telephone service and some bag tag licenses are the exceptions in that ongoing payments are/were required for continued use or service.

below as the focus of this Article: the stem cell ownership rights exercised by WARF and its affiliate WiCell.¹⁵ At the abstract level, this reinforcement strategy is best explained by thinking of it first as the physical property lease reinforcing, or even enhancing, the IP license. If the physical property embodying or carrying the IP is sold outright, the transfer arguably invokes first sale/exhaustion doctrines¹⁶ allowing the recipient to transfer, experiment with, disassemble, repair, or modify the physical property. Where the recipient later transfers the property, the original transferor/owner risks that an unknown third party recipient will use the property outside the scope of the original IP license, including to generate unlawful further copies. The original recipient could do these things as well, but at least the transferor knows, to some extent, with whom it dealt. Importantly, the lease-license model cuts off the first sale/exhaustion doctrines for the physical property transferred, thus allowing the transferor to impose a wider range of use restrictions on the recipient.¹⁷ Critical types of desired use restrictions (for the transferor) include prohibitions on reverse engineering—to reduce the risk of loss of trade secrets—and prohibitions or limitations on transfer of the physical property.¹⁸ Less critical, but frequently seen, are use restrictions including prohibitions on uses that might otherwise fall within fair use or research use exemptions in copyright and patent law, respectively. The ultimate goal, then, is to enhance

15. See *infra* Parts III & IV.

16. The “first sale” doctrine in copyright law gives purchasers of lawful copies of a copyrighted work the rights to sell or otherwise transfer the copy, which would otherwise be controlled by the copyright owner under her distribution right established in the Copyright Act. 17 U.S.C. § 109(a) (2000); see also PAUL GOLDSTEIN, GOLDSTEIN ON COPYRIGHT § 1.4.3 (2nd ed. 2002). The doctrine of “patent exhaustion” allows purchasers of objects embodying issued patent claims to similarly sell or transfer the object, as well as to repair the object, even if any of these activities would otherwise infringe the patent owner’s exclusive rights to make, use, sell, or import the patented invention or objects embodying the patented invention. See *Mallinkrodt v. Medi-Part, Inc.*, 976 F.2d 700, 706 (Fed. Cir. 1992). However, one major patent law casebook questions the appropriateness of the term “patent exhaustion” and argues that the doctrine should be called “first sale” in the context of patents. See DONALD CHISUM ET AL., PRINCIPLES OF PATENT LAW 1136-38 (3d ed. 2004).

17. Note that there can be conditioned sales, but the use restrictions that can be enforced in that model may be more limited than those that can be enforced in the lease-license model. See, e.g., *Mallinkrodt*, 976 F.2d 700. Another way to look at this is that the lease-license model allows the transferor to prohibit all of the user rights that might come along with first sale or exhaustion because there is no sale to trigger those doctrines. The conditioned sale model, by contrast, still triggers those doctrines.

18. Note that while patents and copyright still seem to dominate discussion of technology and IP transfers, trade secret protection plays a far larger role in actual practice than generally considered in the literature.

the IPR owner's control of the technology through state contract law. The potential conflict between state contract law and federal IPR law in applications such as the lease-license model has increasingly attracted the attention of commentators.¹⁹

From the opposite direction, the IP, and licenses thereunder, also reinforce claims or leverage with regard to physical property. This is particularly important where others could fairly easily replicate the biological materials without access to the original owner's materials. The doctrines of misuse, especially patent misuse,²⁰ or prohibitions on some tying arrangements under antitrust law²¹ traditionally limited this leverage. Under earlier interpretations of both the patent misuse doctrine and the prohibition on improper tying arrangements under antitrust law, patent owners were generally not allowed to use their patents to force others to buy their version of non-patented staple goods, or perhaps even non-patented non-staple goods.²² The 1952 Patent Act, through Sections 271(c)-(d), restricted patent misuse to those cases where the patentee conditions patent licenses, or sales of patented goods, on the purchase of staple goods from the patentee. These provisions essentially exempt the tying of non-staple goods that are essential to the practice of the patent from the definition of patent misuse.²³ In 1988, Congress amended Section 271(d) of the Patent Act to restrict misuse to cases involving non-patented staple goods where the patentee had market power in the patent or patented goods.²⁴ Courts generally presumed that the patent itself gave the patentee market power for the patent or patented goods.²⁵ Thus, courts frequently found patentees who tied licenses or patented goods to staple goods to have engaged in patent misuse, prohibiting them from enforcing their patent until the misuse was discontinued.²⁶ Accordingly, firms using the lease-license model were effectively restricted from forcing customers to purchase staple

19. See, e.g., Daniel Laster, *The Secret is Out: Patent Law Preempts Mass Market License Terms Barring Reverse Engineering for Interoperability Purposes*, 58 BAYLOR L. REV. 621 (forthcoming 2006).

20. See, e.g., CHISUM, *supra* note 16, at 1084-1104.

21. See *Illinois Tool Works Inc. v. Indep. Ink, Inc.*, 126 S. Ct. 1281, 1284-88 (2006).

22. See *Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176, 187-215 (discussing development of judicial doctrines of patent misuse and contributory infringement with respect to both staple and non-staple goods, and the legislative history of Section 271 of the 1952 Patent Act which substantially limited the extent of the patent misuse doctrine); see also *Illinois Tool*, 126 S. Ct. at 1284-90.

23. *Illinois Tool*, 126 S. Ct. at 1290.

24. *Id.* at 1290-91; CHISUM, *supra* note 16, at 1104.

25. *Illinois Tool*, 126 S. Ct. at 1290.

26. *Id.* at 1288-90; CHISUM, *supra* note 16, at 1084-85, 1103-04.

goods that fell outside the claims of their patents—say, computer mouse pads along with patented software or hardware. However, the recent Supreme Court decision in *Illinois Tool Works Inc. v. Independent Ink, Inc.*²⁷ abrogates the presumption of market power conferred upon a patent owner by the patent grant. Consequently, infringement defendants who want to assert patent misuse or antitrust law as a defense must demonstrate actual market power. Accordingly, patent owners may now be able to impose a wider range of license or use restrictions on potential licensees and purchasers. Yet, even under the earlier interpretations of law, they were almost certainly permitted to specify that they would only grant licenses as a package deal with leases, rentals, or sales of physical embodiments of the patents that the patent owner produced. At the same time, they could bundle other, possibly less desirable, patent licenses together with the sought after licenses, so long as they plausibly asserted that the entire package cost no more than the stand alone desired license would have cost.²⁸

The strategy of refusing to grant IPR licenses except as part of products or services developed and marketed by the IPR owner itself is essentially that of the closed technologist, such as Apple Computer.²⁹ The closed technologist does not license others to bring versions of the technology to the marketplace, but rather directly manufactures, or has others manufacture for its distribution, all of the permitted saleable versions of its products. By contrast, open technologists license out their patents for manufacture and distribution of patented articles, sometimes to companies in some degree of competition with the pioneer technologist. IBM used this model to sell its PC platform.³⁰ An early example of a closed technologist company exerting tight control of IPR and embodying products was that of the original Bell telephone system. Bell highly restricted hardware choices for phone service customers.³¹ Affiliates such as Western Electric supplied the approved hardware to Bell customers,³² and the use of unapproved telephones or other hardware on the Bell phone lines violated the service contract.³³ Of course, the government broke up the Bell

27. 126 S. Ct. 1281.

28. *See Zenith Radio Corp. v. Hazeltine Research, Inc.*, 395 U.S. 100, 133-40 (1969).

29. For a history of Apple Computer and its decisions to neither license out its hardware or software nor produce other parties' technologies as clones, see OWEN W. LINZMAYER, *APPLE CONFIDENTIAL: THE REAL STORY OF APPLE COMPUTER, INC.* 47 (1999).

30. This platform was recently sold off to Lenovo.

31. *See Bell Property*, *supra* note 8.

32. *See id.*

33. *See id.*

system, as part of the original AT&T, as a monopoly in violation of federal antitrust laws in 1984.³⁴

Discussion of the Bell system highlights how the sometimes under-rated distinction between goods and services—as legal categories—can play a critical role in determining rights between parties. So far this Article has addressed either sales of goods—covered by Article 2 of the Uniform Commercial Code (UCC)—or lease-license hybrids—covered by a combination of Article 2A of the UCC (for the lease portion) and the relevant IP law (for the licenses).³⁵ One could characterize the original Bell system as a *service* that provided hardware. Today, what is commonly referred to as “phone service,” that is, the live connection transmitted by a phone line, differs from the historical meaning of the term. Old advertisements for telephone service and the explanatory materials AT&T provided during the break-up explain the difference between its phone service and the package customers could expect from other providers or from AT&T where customers used their own telephones and hardware. It is clear AT&T felt it was providing the phones, wires, maintenance, and even phone books as part of the original service.³⁶ Though AT&T’s old true phone service is gone, hardware based services are still installed in homes to this day in the form of security systems and some cable and satellite television services. Since the technologist provides a service rather than either a sale of goods or a lease-license, neither the UCC nor IP laws seem to directly apply. Instead, common law rules regarding the provision of

34. *See, e.g.*, Bell System Memorial: AT&T Divestiture, http://www.bellsystemmemorial.com/att_divestiture.html (last visited Aug. 30, 2006) [hereinafter Bell Divestiture]. The eventual fate of the Bell System and AT&T raises the related issue that aggressive technologists who leverage their physical and intellectual property off each other too strongly may find themselves targets of antitrust investigations by the Justice Department or Federal Trade Commission. Ultimately, of course, something close to the original AT&T has recently risen phoenix-like from the long smoldering ashes of “Ma Bell” and the “Baby Bells;” the former SBC Communications, itself a product of mergers of former Baby Bells, and the remaining long distance provider shell of the AT&T corporation, merged to form the “new” at&t. *See* at&t, AT&T Fact Sheet: Company Overview: Corporate History, <http://att.sbc.com/gen/investor-relations?pid=5711> (last visited Aug. 30, 2006). Marketing and PR gurus can speculate as to the choice of lower case letters for the acronym—maybe the new at&t is supposed to be more warm and fuzzy or approachable than the perhaps imposing former “AT&T” in capital letters.

35. For a fuller discussion of the relationships among IPR licensing, sales of goods rules in the UCC, and leases under the UCC in technology distribution models, see Nguyen, Gomulkiewicz & Conway-Jones, *supra* note 7.

36. *See generally* Bell System Memorial: Bell System Advertisements, http://www.bellsystemmemorial.com/bellsystem_ads.html (last visited Aug. 30, 2006); Bell Divestiture, *supra* note 34; Bell Property, *supra* note 8.

personal or professional services apply, except where specifically regulated otherwise.³⁷ This common law realm may seem to be even more favorable to the technologist's bid to tightly control its platform technologies.³⁸ In fact, a trend in the software industry has followed the model of application service providers (ASPs), who host software applications on websites that customers can access to use the software.³⁹ In this relatively recent model, the product delivered is purely a service. The provider neither sells nor leases any goods to the customer. Thus, the technology-as-service model may yet persist some time longer. Based on a patented technology or platform, this service model increasingly concerns health care professionals with regard to exclusive control of critical diagnostic procedures. For example, Myriad Genetics, Inc. exclusively provides BRCA-1 and BRCA-2⁴⁰ breast cancer gene diagnostic test services, and Athena Diagnostics, Inc. exclusively provides certain genetic diagnostic test services for Alzheimer's disease and Spinocerebellar Ataxia Type 1 (SCA1) disease.⁴¹ Because other biological materials governed by MTAs already remain the property of the supplier, it would not be a very large step for commercial suppliers to structure distributions of biological materials as a service, rather than to use the lease-license model. If major stem cell line suppliers like WiCell moved in this direction, it would further complicate the research environment.

In the life sciences, the transfer of biological materials among researchers has relied on the lease-license model as much because of the second category of legal and business advantages to transferors—limiting third party access and hence potential liability—as for the IPR control category.⁴² Clearly, regulation is needed for the downstream distribution

37. See Nguyen, Gomulkiewicz & Conway-Jones, *supra* note 7.

38. See *id.*

39. See *id.*

40. See National Institutes of Health, Division of Intramural Research, Questions and Answers, BRCA1 and BRCA2, <http://www.genome.gov/DIR/GMBB/BRCA/questions.html> (last visited Aug. 30, 2006).

41. See, e.g., Debra G.B. Leonard, Gene Patents: A Physician's Perspective, Presentation at the National Academies' Intellectual Property in Genomic and Protein Research and Innovation Project, http://www7.nationalacademies.org/step/Leonard_presentation_October_proteomics.ppt (last visited Aug. 30, 2006). For more information on this Project, see National Academies, Intellectual Property in Genomic and Protein Research and Innovation Project, http://www7.nationalacademies.org/step/STEP_Projects_Proteomics.html (last visited Aug. 30, 2006).

42. Biological material transfers are not considered a service in most cases because the transferor does not retain control over the materials transferred to the recipient and plays no role in producing the outcome that the recipient seeks to produce in the lab. In the technology service examples discussed above, the technology owners still largely

of materials that have the potential to be biohazards if not handled properly. Nonetheless, in part because of the heightened risk associated with potential third party liability for biohazard materials, the negotiation of MTAs has become a difficult and time-consuming process, many times ending with no deal and no materials for the prospective recipient researcher.⁴³ While this may just be a reality that parties have to live with, a number of researchers and institutions in the field believe the real obstacle lies in the lack of a standard form of MTA.⁴⁴ In other industries that use the lease-license distribution model, standard forms—such as end-user license agreements in software—have emerged from the parties themselves.⁴⁵ This had not happened in the life sciences.⁴⁶ Consequently, the Public Health Service (PHS), acting through the National Institutes of Health (NIH), in conjunction with the Association of University Technology Managers (AUTM) and representatives of universities, law firms, and industry, launched an initiative to create a uniform biological MTA (the UBMTA) in the 1990s.⁴⁷

The final model UBMTA, issued in 1995,⁴⁸ consists of a Master Agreement to be adopted by institutions who voluntarily became signatories to the UBMTA initiative, and a shorter Implementing Letter form to be used by and between signatory institutions to record specific biological material transfers.⁴⁹ Although 292 research institutions have signed onto

controlled and maintained the system installed in the home or business. The customer had the relatively narrow—although critical in terms of the ultimate value of the service to the customer—task of, say, dialing a phone number. Of course, in the earliest days of phone service the customer merely picked up the receiver, “rang” for the operator, and requested that a call was placed by the service provider itself.

43. See *View from the Bench*, *supra* note 1; Walsh, *Roadblocks*, *supra* note 1.

44. See UBMTA, *supra* note 2, at 12771.

45. See Nguyen, Gomulkiewicz & Conway-Jones, *supra* note 7.

46. Whereas other industries that have adopted lease-license models have firms providing one-to-many products, in the life sciences research field the owners of biological materials are not usually involved in one-to-many distributions. Rather, in many cases there may only be one or a handful of distributions of the materials. Further, outside of commercial firms like the American Type Culture Center (ATCC), few if any of the non-commercial research entities that own useful biological materials, such as universities, make a business out of marketing and distributing those materials. Accordingly, where it might be cost effective for firms in one-to-many commercial distribution models such as the software industry to develop and deploy, and customers to accept, mass market licenses that may cost a good deal in upfront legal fees, this kind of approach is harder to justify in the one-to-one or one-to-few world of biological MTAs.

47. See UBMTA, *supra* note 2, at 12771.

48. *Id.*

49. See AUTM, Resources, http://www.autm.net/aboutTT/aboutTT_umbta.cfm (last visited Aug. 30, 2006).

the UBMTA initiative to date,⁵⁰ it does not seem to have had a broad streamlining effect on biological material transfers in the research community. Part of this may be because the initiative was directed only towards the public and non-profit sectors, although PHS suggested that for-profit organizations might “choose to adopt this agreement as well.”⁵¹ Yet, even in the recommended target signatory audience of public and non-profit organizations, PHS did not require organizations to sign the Master UBMTA Agreement as a condition of further PHS funding.⁵² Further, even among signatories, the UBMTA “would not be mandatory” so that organizations could “retain the option to handle specific material with unusual commercial or research value on a customized basis.”⁵³ Accordingly, the allowance of too many exceptions squandered the potential value of a truly uniform MTA. Nonetheless, as discussed further below, the UBMTA seems to have served as the template for a Memorandum of Understanding (MOU) between WiCell and PHS. This MOU paved the way for both effective use of a government license to WARF’s stem cell patents underlying WiCell’s IPR position and reasonable access to WiCell stem cell lines in the federally funded research community.⁵⁴

III. THE CURRENT WICELL CONTROLLED STEM CELL RESEARCH LICENSING REGIME

The story behind WARF’s and WiCell’s current control of the stem cell research environment provides an excellent case study in the power of MTAs to control life sciences research. In 1998, Dr. James A. Thomson at the University of Wisconsin-Madison (“Wisconsin”) achieved an amazing breakthrough in stem cell research when he cultured immortal human embryonic stem cells (hESCs).⁵⁵ While he had earlier cultured an immortal line of primate embryonic stem cells,⁵⁶ creating the human cell line was his ultimate objective. As Thomson continued his pioneering research in this area, WARF, as the external technology transfer office (TTO) of Wis-

50. See AUTM, Resources: Signatories to the March 8, 1995 Master UBMTA Agreement, http://www.autm.net/aboutTT/aboutTT_umbtaSigs.cfm (last visited Aug. 30, 2006).

51. See UMBTA, *supra* note 2, at 12771.

52. *Id.*

53. *Id.*

54. See *infra* Part III.

55. See James A. Thomson et al., *Embryonic Stem Cells Derived from Human Blastocysts*, 282 SCI. 1145, 1145-47 (1998); Gretchen Vogel, *Breakthrough of the Year: Capturing the Promise of Youth*, 286 SCI. 2238 (1999).

56. See U.S. Patent No. 5,843,780 (filed Jan. 18, 1996).

consin, worked to secure patent protection for the subject matter of his invention disclosures. Equally important, WARF also sought to protect and exploit the actual hESC lines as physical property using the lease-license model described above.⁵⁷ In fact, WARF quite effectively used the two strands of rights in a lease-license model—physical property and IPR—to reinforce each other and give WARF, through WiCell, its dominant position in the stem cell research environment. Presumably under a version of the common university faculty policy that requires assignment of patents and physical materials arising from university-based research, Thomson assigned WARF his rights in both a sequence of patents covering stem cells (“WARF/Thomson Patents”) and in physical property rights to the hESC lines themselves.⁵⁸

The crux of his first and second patented inventions was the ability to create stable, embryonic stem cell lines that could continually and indefinitely generate new embryonic stem cells. The cells would not begin differentiation into particularized cells for specific tissues of the adult organism, nor would the cells undergo significant genetic mutations. The claims of the patents are directed both to stem cells as compositions of matter and to the process for creating cultures of such stem cells. The first patent, U.S. Patent No. 5,843,780 issued in 1998 (“the ’780 Patent”), was directed to primate embryonic stem cells.⁵⁹

57. See *supra* Part II.

58. See *id.*; U.S. Patent No. 6,200,806 (filed June 26, 1998); U.S. Patent No. 7,005,252 (filed Mar. 9, 2000); WiCell MOU, *supra* note 4.

59. Because the exact claims of the patent are critical for those who seek to understand its scope and validity, I reproduce them here *in toto*:

We claim:

1. A purified preparation of primate embryonic stem cells which (i) is capable of proliferation in an in vitro culture for over one year, (ii) maintains a karyotype in which all the chromosomes characteristic of the primate species are present and not noticeably altered through prolonged culture, (iii) maintains the potential to differentiate into derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) will not differentiate when cultured on a fibroblast feeder layer.

2. The preparation of claim 1 wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. A purified preparation of primate embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-3 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have karyotypes which includes the presence of all of the chromosomes characteristic of the primate species and in which none of the chromosomes are noticeably altered.

The upshot of the research resulting in the '780 Patent was that Thomson and Wisconsin were now able to produce relatively large quantities of stable primate embryonic stem cells. Researchers could then perform experiments on those cells, directing them to differentiate into specific tissues in a controlled manner. Thomson's breakthrough, therefore, achieved the critical first step on the path to the holy grail of stem cell research: to be able to generate any tissue of the body at will to replace diseased or destroyed tissue in specific patients. Ideally, researchers would create such tissues from stem cells whose genetic materials were identical to, or derived from, the patient's own genome. This genetic matching would minimize the risk that the patient's immune system would recognize the new tissue as dangerous foreign cells and destroy them.⁶⁰

4. The preparation of claim 3 wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. The preparation of claim 3 wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. The preparation of claim 3 wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. The preparation of claim 3 wherein the cells remain euploid for more than one year of continuous culture.

8. The preparation of claim 3 wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

9. A method of isolating a primate embryonic stem cell line, comprising the steps of:

- (a) isolating a primate blastocyst;
- (b) isolating cells from the inner cell mass of the blastocyst of (a);
- (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;
- (d) dissociating the mass into dissociated cells;
- (e) replacing the dissociated cells on embryonic feeder cells;
- (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and
- (g) culturing the cells of the selected colonies.

10. A method as claimed in claim 9 further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. A cell line developed by the method of step 9.

'780 Patent.

60. This patient customization step is the province of so-called therapeutic cloning research that seeks to predictably generate stable blastocysts using somatic cell nuclear transfer processes to combine a specific patient's genetic materials with a donor egg. The blastocysts can then be used to obtain embryonic stem cells containing the patient's genetic material, and thus to generate differentiated tissues/cells to replace the patient's diseased or destroyed tissues without triggering a dangerous immune response.

It remains to be seen whether the '780 Patent directed to "primate embryonic stem cells" covers hESCs as well. At one level it should, because humans are primates. But, if so, why did WARF pursue the next patent in its stem cell patents sequence—U.S. Patent No. 6,200,806 ("the '806 Patent"), issued on March 13, 2001—with essentially identical claims to the '780 Patent, but instead directed to "pluripotent human embryonic stem cells"?⁶¹ In fact, the '806 Patent even uses the same title—"Primate Embryonic Stem Cells"—as the '780 Patent. Further, nearly all of the background descriptive material in the '806 Patent is the same as that in the '780 Patent.

Two arguments suggest that the '780 Patent may not cover hESCs. First, while the "Summary of Invention" and "Description of the Invention" sections of the '780 Patent do not determine the scope of the patent's claims, they do indicate that a significant part of the invention's utility comes from allowing researchers to "generat[e] transgenic non-human primates for models of specific human genetic diseases."⁶² It is standard practice to use animal experiments to explore possible outcomes of treatment regimens in humans by analogy. Thus, WARF may have been concerned that courts would interpret the '780 Patent to cover only non-human primate embryonic stem cells because the patent never mentions any activities directly involving hESCs. Second, WARF may have worried that the U.S. Patent and Trademark Office's (USPTO) stated policy of not issuing patents on humans⁶³ could lead courts to interpret the '780 Patent as covering only non-human primate embryonic stem cells. As just noted, the proposed utility of the invention in the '780 Patent appears to be that researchers could use the patented stem cells to create actual transgenic primates with certain desirable disease traits. This use may have cut too close to a patent on humans if a court interpreted the scope of the claims to cover hESCs.

While these concerns reach the same outcome—omission of hESCs from the interpretation of the scope of the claims—the two issues are quite different. The first simply interprets the claims to omit hESCs because they do not appear to be included, regardless of whether hESCs are prohibited subject matter in the utility application of the patent, under law or USPTO policy. Thus, this interpretation is based on a scenario where a court would deem that WARF did not intend to include hESCs in the patent claims. The second interprets the claims to omit hESCs—even if the

61. '806 Patent at col. 21.

62. '780 Patent at col. 6.

63. 1077 OFFICIAL GAZETTE OF THE U.S. PATENT AND TRADEMARK OFFICE 24 (1987).

court would find that WARF did intend to include them—because such inclusion would be void as illegal or against USPTO policy. The court's only other option, in this second scenario, would be to invalidate any patent claims that appear to include hESCs in the problematic utility application of experimental transgenic primates (assuming these claims are found to represent a prohibited patent on humans).

The '806 Patent may remedy these potential shortcomings in several ways. First, the patent changes the title of the invention description section from "Description of the Invention" to "Detailed Description of the Preferred Embodiments." As well, the patent slightly modifies the text to make it clear that the utility of creating diseased transgenic primates is limited to the two "preferred embodiments," or best mode, of the embryonic stem cell lines described for common marmoset and rhesus monkeys respectively. Further, the '806 Patent attempts to quell any concerns over whether the demonstrated science at the time of the original patent application⁶⁴ allowed claims specifically for hESC lines, even though no line fitting the parameters of the claims appears to have existed when the application was filed. The patent relies on scientific arguments based on drawing analogies between (1) the actual research done on embryonic stem cells in both common marmosets and rhesus monkeys and (2) the postulated ability to reach the same outcomes with hESCs.⁶⁵

64. *See infra* note 65.

65. In particular, the argument is stated in the following excerpt from the patent:

There are approximately 200 primate species in the world. The most fundamental division that divides higher primates is between Old World and New World species. The evolutionary distance between the rhesus monkey and the common marmoset is far greater than the evolutionary distance between humans and rhesus monkeys. Because it is here demonstrated that it is possible to isolate ES cell lines from a representative species of both the Old World and New World group using similar conditions, the techniques described below may be used successfully in deriving ES cell lines in other higher primates as well. Given the close distance between rhesus macaques and humans, and the fact that feeder-dependent human EC cell lines can be grown in conditions similar to those that support primate ES cell lines, the same growth conditions will allow the isolation and growth of human ES cells. In addition, human ES cell lines will be permanent cell lines that will also be distinguished from all other permanent human cell lines by their normal karyotype and the expression of the same combination of cell surface markers (alkaline phosphatase, preferably SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81) that characterize other primate ES cell lines. A normal karyotype and the expression of this combination of cell surface markers will be defining properties of true human ES cell

Even though some or all of the foregoing reasoning explains WARF's motives in filing for the '806 Patent, it does not explain why the USPTO allowed two heavily overlapping patents to issue. Either it is an accidental incidence of double patenting, which could raise validity questions for the patents, or the USPTO believed that the claims of the '780 Patent did not extend to hESCs even though humans would normally be considered a species in the genus of primates. If the latter interpretation is correct, there are strong ramifications for the scope of the federal government's rights and license to the WARF hESC technology. As indicated in the '780 Patent, the Thomson research leading to the claimed invention in that patent was at least partially funded by an NIH grant.⁶⁶ This means that the invention falls under the provisions of the Bayh-Dole Act of 1980 ("Bayh-Dole"),⁶⁷ which provides the government with some rights in the technology. First, Bayh-Dole gives a mandatory non-exclusive license granted back to the government.⁶⁸ Second, the Act enables the government, upon certain triggering events, to exercise march-in rights which allow it to grant licenses under the patent to third parties against the wishes of the patent owner (essentially a kind of compulsory license).⁶⁹ The '806 Patent

lines, regardless of the method used for their isolation and regardless of their tissue of origin.

'806 Patent at col. 6-7. What is curious about this approach for the '806 Patent is that Thomson formally announced that he had actually created a hESC line in a November 1998 publication in *Science*. See Thomson, *supra* note 55, at 1145-47. The timing of this article presumably means that he had the line in his possession earlier than the publication date. Yet the application for the '806 Patent—as a division of the earlier 1995 application and continuation-in-part of the 1996 application as discussed below—was not filed until June 26, 1998. Why, then, was there no mention of Thomson's ability to actually culture the hESC line covered in the patent? Instead, the patent relies on the scientific analogy argument reproduced above. There is, of course, a prohibition in patent law on introducing new subject matter into an application after the filing date that one is tracing priority back to—and WARF may well have wanted to get the 1995 or 1996 parent application dates for priority with regard to the '806 Patent—but mention of the actual hESC line would not have been introducing new subject matter. Rather, it would have been simply showing further refinement of the existing subject matter. Perhaps the timing was not connected and WARF filed the application for the '806 Patent without realizing that Thomson was just about to successfully create the hESC line. Ultimately, an examination of the prosecution history of both the '780 Patent and the '806 Patent might yield some answers to all of these questions. Other practitioners and scholars are indeed already analyzing the WARF stem cell patents for infirmities or limitations. See, e.g., Kenneth S. Taymor, Christopher Thomas Scott & Henry T. Greely, *The Paths Around Stem Cell Intellectual Property*, 24 NATURE BIOTECH. 411 (2006).

66. '780 Patent at col. 1.

67. See 35 U.S.C. §§ 200-11 (2000).

68. *Id.* § 202(c)(4).

69. *Id.* § 203.

and the most recently issued patent in WARF's stem cell patent sequence, U.S. Patent No. 7,005,252 ("the '252 Patent") issued on February 28, 2006, either leave the required "Statement Regarding Federally Funded Research" section of the patents blank or list "not applicable." Accordingly, WARF must be claiming that no federal funds were used in the research leading to the patents and the government licenses and rights under Bayh-Dole therefore do not exist for these patents. In the case of the '252 Patent, claiming the absence of federal funding is plausible because the patent issued directly from an application filed on March 9, 2000, and the scope of the claims and invention is clearly different from that of the '780 Patent and the '806 Patent, even though the newest patent still deals with hESC subject matter. But the '806 Patent issued as both a continuation-in-part (CIP) of the same parent application, U.S. Patent Application Serial No. 08/376,327 filed on January 20, 1995 and now abandoned ("the '327 Application"), that led to the '780 Patent (also as a CIP) and as a division of an application filed on January 18, 1996. So, even if the 1996 application introduced material outside of the scope of the '327 Application, there is still common subject matter arising from the '327 Application. Further, because the description of the invention, including the research relied on to justify the patentability of the inventions, is essentially the same in both patents, it is hard to believe that the NIH grant covered research only leading to one and not the other. It is difficult to imagine what research was not relied on in the '806 Patent but was still used in the '780 Patent.

This hair-splitting analysis is not merely academic: as mentioned above, the question of whether federal funding was used to invent the subject matter covered by specific patents directly determines whether the government has the licenses and rights mandated under Bayh-Dole. To some extent, the concerns raised here are moot because of the arrangement that PHS has worked out with WARF and WiCell, as discussed below. Yet, these concerns are still relevant as a practical matter because WARF and WiCell appear to have been playing hardball, even within the context of the PHS arrangement. Further, a failure by WARF to duly record government rights in the '806 Patent could open the patent up to challenges by either the government or infringement defendants in any suits brought by WARF to enforce the patent.

The federal funding analysis is also quite important to Geron Corporation ("Geron"), which also funded much of Thomson's research at Wisconsin and took a license from WARF to any patents that might issue un-

der the '327 Application ("the 1996 Geron License").⁷⁰ This initial license was styled as a "Standard Non-exclusive License Agreement" by the parties.⁷¹ It stipulated that the license granted was non-exclusive in the License section of the agreement.⁷² In actuality, though, Geron was also granted a renewable one-year period of exclusivity for the Licensed Patents⁷³ (defined as the '327 Application, any foreign equivalents, CIPs until January 1, 1998, and continuations and reexaminations).⁷⁴ In addition, Geron was granted an option to obtain "non-exclusive licenses" to any further inventions developed by Thomson by January 1, 1998.⁷⁵ Nevertheless, if Geron did exercise this option, then any new patents licensed under the option would be added to the definition of "Licensed Patents" and would thus presumably be subject to the period of exclusivity so long as Geron continued to renew it.⁷⁶ The 1996 Geron License also contemplates that federal funding may have been involved in Thomson's research leading to the '327 Application, which would mean that Geron's exclusivity under the agreement would be limited by U.S. Government rights under Bayh-Dole.⁷⁷ Accordingly, the 1996 Geron License carves out a limitation to allow for these potential government rights and licenses.⁷⁸ However, the relevant clause also states that, "In the event there is assertion by the Government of such rights, Geron may be entitled to modification of the royalty and license fee provisions of the Agreement."⁷⁹ Thus, the answer to the question of whether federal funding was involved in the research leading to the '327 Application and in any follow-on applications would have significant impact on WARF and Geron's license arrangement. Unfortunately, I am unable to determine the scope of the only-federal funding explicitly tied to any of Thomson's hESC work during this period—NIH NCCR Grant No. RR00167—because I have not been able to obtain a copy.⁸⁰ Thus, we can only be certain that federal funding was used somewhere during the research that led to the '780 Patent. As discussed above,

70. See Geron Corp., Standard Nonexclusive License Agreement (Agreement No. 95-0208) (Form S-1), at Ex. 10.11 (June 12, 1996) [hereinafter 1996 Geron License].

71. *Id.*

72. *Id.* § 2(A).

73. *Id.* § 2(C).

74. *Id.* at app., item A.

75. *Id.* § 2(D).

76. *Id.*

77. See 35 U.S.C. §§ 200-11 (2000).

78. See 1996 Geron License, *supra* note 70.

79. *Id.*

80. I could not find the grant in any of the publicly accessible databases where other NIH grants are posted.

because the '327 Application is the only application that led to the '780 Patent other than the CIP application for the '780 Patent itself, which seemed to add no new subject matter to that introduced by the '327 Application, one could infer that the NIH grant covered the research that led to the '327 Application. If this is the case, though, as discussed above Bayh-Dole should subject the '806 Patent to U.S. Government rights because it is derived in part from the '327 Application. In fact, because Geron's licenses and options covered patents issuing from the '327 Application, if the NIH grant covered the research leading to the '327 Application, Bayh-Dole would subject all of the patents that Geron had some claim to under the agreement to U.S. Government rights.

Although it is somewhat suspicious that the 1996 Geron License includes a nominally non-exclusive license coupled with a "period of exclusivity," it is not necessarily nefarious. There may have been good reasons for not granting an exclusive license outright—from satisfying Bayh-Dole's own stated preference for non-exclusive licenses for federally funded patents to the parties' legitimate desire to reach an agreement that would lower Geron's license costs. In support of the latter, consider that an outright exclusive license normally fetches higher upfront license fees and royalty rates than a non-exclusive license. Accordingly, Geron and WARF may have reached a compromise wherein Geron was granted a less expensive non-exclusive license coupled with an option for exclusivity. Presumably, Geron would have paid some additional amount for this option, but the overall price tag on the deal may have still been lower than if Geron sought an exclusive license. This kind of compromise arrangement, if true, is simply good, creative license negotiations.⁸¹ Keep in mind that at the time of this original license, there was no issued patent on Thomson's research and he had not yet successfully cultured the hESC line. At that stage, WARF could only offer a license to a patent application on what I often call "cool science:" research results that are of significant interest to the research community and science buffs, but that are nowhere near a commercialized product. The technology transfer license game often involves this kind of angling by outside companies. They want to get in early enough on emerging research that leverage in the license negotiation rests more with the company than with the TTO, but not so early that the company bleeds itself dry with payments to TTOs and universities for cool science that is too far away from commercialization to satisfy investors.

81. Anecdotally, I have heard that technology transfer licenses—and IP licenses generally—are increasingly using options to brook disagreements in potential license terms that threaten to scuttle the deal entirely. I think this is a desirable development.

Overall, given the record available, I think both parties played their respective hands well.

Although Geron received a number of favorable provisions in the 1996 Geron License, one provision is quite unfavorable—the inclusion of the January 1, 1998, date for emergent CIPs on the '327 Application as part of the definition of Licensed Patents. Geron and WARF agreed to amendments of this agreement in March 1997 and March 1998. I have been unable to track down the text of these amendments because Geron has not included them in their required Securities and Exchange Commission (SEC) filings (despite having included the redacted text of the original license in its initial public offering (IPO) filing with the SEC). One can therefore infer that the amendments were not particularly important.⁸² Assuming the definition of Licensed Patents remained the same through January 1998, the '806 Patent, containing possibly the only claims covering hESCs, would not qualify as a Licensed Patent because it was filed as a CIP on the '327 Application on June 26, 1998. Tough luck for Geron, if true.⁸³

It is likely that Geron found itself without exclusivity to the '806 Patent, as a new license was negotiated and executed between WARF and Geron in May 1999, effective as of April 23, 1999 (“the 1999 Geron License”).⁸⁴ In the alternative, Geron could have desired to flip the agreement into an outright exclusive license arrangement based upon the twin

82. I am unaware of any publicly available sources for the licenses between Geron and WARF other than Geron's required filings with the SEC for both its IPO, under the Securities Act of 1933, 15 U.S.C. §§ 77a-77aa (2000), and as a reporting company, as defined under the Securities Exchange Act of 1934, 15 U.S.C. §§ 78a-78mm (2000). However, these requirements mandate only certain initial and periodic disclosures, including agreements or contracts that are “material” to the reporting company. Geron must have considered the 1996 Geron License material because it included the agreement as an exhibit to its Form S-1, filed on June 12, 1996, as part of its IPO. However, Geron must not have considered the 1997 and 1998 amendments to the 1996 Geron License material, even though they were mentioned in a subsequent 1999 license that supersedes the 1996 Geron License (included as a material agreement in a later SEC filing), because these amendments were not themselves included in any of Geron's SEC filings. Significant amendments to a material contract would seem to me to be material, themselves. Thus, assuming that Geron did not violate any securities laws through its selective disclosure of these agreements and amendments, the contents of these amendments presumably were not significant enough to be deemed material.

83. One could speculate as to filing date decisions by WARF, but, again I have found no evidence of underhanded activities by either WARF or Geron in any of the stem cell patents issues, despite the apparent unpopularity of WARF in this matter.

84. Geron Corp., License Agreement (Form 10-Q), at Ex. 10.1 (Nov. 15, 1999) [hereinafter 1999 Geron License].

events of issuance of the '780 Patent and announcement of Thomson's creation of a viable hESC line in 1998. In any event, the 1999 Geron License is indeed a straightforward exclusive license agreement for both "Therapeutic Products"⁸⁵ and "Diagnostic Products"⁸⁶ worldwide.⁸⁷ The "Licensed Patents" in the agreement expressly include the '780 Patent, and, presumably, the application for the '806 Patent.⁸⁸ The 1999 Geron License also provides a worldwide exclusive license to the Licensed Patents for "Research Products,"⁸⁹ which are essentially research tools.⁹⁰ These two exclusive license grants are limited to the "Licensed Field," which includes only "(i) Research Products, (ii) Therapeutic Products and (iii) Diagnostic Products developed from and/or incorporating the Materials as precursors to [certain enumerated cell types] as well as [the same

85. Defined as:

products or services other than Diagnostic Products that (i) are used in the treatment of disease in humans, and (ii) employ, are in any way produced by the practice of, are identified or arise out of any research involving the inventions claimed in the Licensed Patents or that would otherwise constitute infringement of any claims on the Licensed Patents.

Id. at app. A, item C.

86. Defined as:

products or services that (i) are used in the diagnosis, prognosis, screening or detection of disease in humans, and (ii) employ, are in any way produced by the practice of, are identified using or arise out of any research involving the inventions claimed in the Licensed Patents or that would otherwise constitute infringement of any claims of the Licensed Patents.

Id. at app. A, item D.

87. *Id.* § 2(A)(i).

88. *Id.* at app. A, item A; *Id.* at app. B (listing the '780 Patent but also including two other patent applications, titled "Primate Embryonic Stem Cells" and "Primate Embryonic Stem Cells With [. . .] Genes" (bracketed material in title redacted by Geron in the SEC filing) respectively, but whose application numbers and other identifying information have been redacted by Geron in the SEC filing).

89. Defined as:

products or services that (i) are used in research as research tools which would infringe the claims of patented technology owned by Geron or which Geron has a right or license to use other than the Licensed Patents, and (ii) which employ, are in any way produced by the practice of, are identified using or arise out of any research involving the inventions claimed in the Licensed Patents or that would otherwise constitute infringement of any claims of the Licensed Patents. Research Products specifically excludes the Materials.

Id. at app. A, item E. Materials are defined as "the primate, including human, embryonic stem cells claimed in the Licensed Patents." *Id.* at app. A, item H.

90. *Id.* § 2(A)(ii).

enumerated cell types].”⁹¹ Materials are defined as “the primate, including human, embryonic stem cells claimed in the Licensed Patents.”⁹² Finally, the 1999 Geron License also provides a worldwide non-exclusive license to the Licensed Patents for Geron to use in its internal research programs.⁹³

There is no doubt about it—this is a strong license for Geron. In essence, it allows the company to lock down the entire worldwide commercialization of stem cell therapies and diagnostics,⁹⁴ with the latter only limited to cell types enumerated in the agreement. Even the cell type limitation for diagnostics is not as strict as it sounds, because Geron also has a first option to negotiate exclusive licenses to new cell types that it identifies. Furthermore, if the parties cannot negotiate the new exclusive license, then WARF may not offer a license to those new cell types to any other party on terms more favorable than those offered to Geron in the option exercise negotiation.⁹⁵ As a final extra kicker, Geron has a right to sublicense its licenses under the agreement.⁹⁶

WARF has achieved a good deal as well. It has had the opportunity to evaluate Geron as a commercializing entity for WARF’s patents since 1996 and, presumably, has been pleased with Geron’s progress.⁹⁷ TTOs

91. *Id.* at app. A, item I. The bracketed material was redacted by Geron in the SEC filing. An interesting postscript in the scope of the license grant occurred in 2001. WARF apparently came under public pressure to increase access to its patented stem cell technologies and sued Geron to recover some of the exclusive rights granted to Geron. Antonio Regalado & David P. Hamilton, *How a University’s Patents May Limit Stem-Cell Research*, WALL ST. J., July 18, 2006, at B1, B5. The parties settled the lawsuit out of court by limiting Geron’s exclusive rights to nerve, heart, and pancreatic cells. *Id.*

92. 1999 Geron License, *supra* note 84, at app. A, item H.

93. *Id.* § 2(A)(iii).

94. It allows this to the extent that the ’780 Patent and ’806 Patent continue to be interpreted as covering all current possible hESCs and their production and that foreign patent filings by WARF are successful.

95. *Id.* § 2(C).

96. *Id.* § 2(B).

97. Indeed, Geron recently made three announcements. First, it has data supporting important progress in its first-in-class hESC therapies. *See* Press Release, Geron Corp., Geron Presents New Data that Document Progress in Development of Therapeutic Products from Human Embryonic Stem Cells (July 5, 2006), *available at* <http://www.geron.com/pressview.asp?id=765>. Second, it published preclinical data showing the safety and utility (efficacy) of its hESC therapy for spinal cord injury. *See* Press Release, Geron Corp., Geron Announces Publication of Study Results Supporting Safety and Utility of Human Embryonic Stem Cell-Derived Therapeutic Product for Treatment of Spinal Cord Injury (July 19, 2006), *available at* <http://www.geron.com/pressview.asp?id=769>. Third, it commenced preclinical safety and efficacy studies for three cell types derived from hESCs (hepatocytes, osteoblasts, and chondrocytes) for the treatment of liver failure and

are required to place two bets when considering commercializing faculty research: first, that the research, and its related technology, will ultimately result in successful products in the marketplace; and second, that the outside organization the TTO selects to undertake the commercialization process as licensee of the technology will successfully execute a good commercialization plan. This process resembles weighing the relative importance of the technology versus the management team in a startup company. Anecdotally, in the venture capital (VC) community, VCs would rather fund a good, experienced management team with mediocre technology than a good technology with a mediocre management team.⁹⁸ WARF also obtained a grant-back non-exclusive license to any enhancement or improvement patents Geron develops under the agreement.⁹⁹ Yet, it is the compensation provisions of the 1999 Geron License that really shine for WARF. The provisions continue the arrangement from the 1996 Geron License wherein Geron reimbursed portions of WARF's costs for prosecuting the patents both domestically and abroad.¹⁰⁰ As well, WARF secured presumably decent royalty rates, including minimum annual royalties and milestone payments.¹⁰¹ Finally, WARF negotiated for generous upfront payments from Geron. These payments initially comprised a combination of cash, 100,000 stock options to Geron stock, and 20,000 shares of Geron common stock.¹⁰²

The value of the equity portion of the upfront payment became much easier to calculate when the parties amended the agreement in October 1999 to flip the stock option portion of the equity payment into actual shares of Geron common stock.¹⁰³ The net result was a flat upfront equity payment of 92,000 shares of Geron common stock, most critically with a specific requirement that Geron file a registration statement with the SEC by October 8, 1999, to register such shares for unrestricted public trad-

musculoskeletal disorders including osteoarthritis, bone fractures, and osteoporosis. *See* Press Release, Geron Corp., University of Edinburgh Form Collaboration for Development of Three Cell Types Derived From Human Embryonic Stem Cells (Aug. 7, 2006), available at <http://www.geron.com/pressview.asp?id=773>.

98. This may be because of the other conventional wisdom in the high tech community that the best technology in an emerging market/industry does not always win out in the race for public acceptance and market share.

99. 1999 Geron License, *supra* note 84, § 2(D).

100. *Id.* § 4(C).

101. *Id.* § 4(D)-(E). The actual royalty rates, minimum annual royalty payments, and milestone payments have been redacted from Geron's SEC filing.

102. *Id.* § 4(A). The cash payment amount has been redacted from Geron's SEC filing.

103. Geron Corp., Amendment to License Agreement (Form 10-Q), at § 1 (Nov. 15, 1999).

ing.¹⁰⁴ On the date that this amendment became effective, Geron's common stock was trading on Nasdaq at around \$10 per share, thus the value of the equity payment to WARF was approximately \$920,000. Not bad, especially considering that there was a cash upfront payment as well. Additionally, in early 2000, Geron's common stock peaked at nearly \$80 per share, making WARF's stake worth approximately \$7.3M, assuming that WARF had not already sold part of it.¹⁰⁵

Those people who are unhappy with Geron's exclusive license can take some comfort in the fact that the 1999 Geron License includes termination provisions tied to the usual triggers, such as failure to meet milestones specified in the agreement or make royalty and other contractual payments.¹⁰⁶ Further, and most relevant for the discussion below, the agreement also contains the government rights clause included in the 1996 Geron License, outlined above.¹⁰⁷ Thus, to the extent that any of the Licensed Patents arose from federally funded research—as did the '780 Patent and arguably the '806 Patent as well—the U.S. Government has a non-exclusive license to practice those patents for government purposes. Technically, this means that Geron cannot have an exclusive license to any such patents, despite the exclusive grant language in the 1999 Geron License. Of course this is a standard issue in technology transfer licenses, especially in the life sciences, where Bayh-Dole covers many university patents because of the extent of federal funding of university life sciences research. So, few sophisticated licensees will feel duped by having executed an agreement specifying an exclusive license, only to have the grant cut back later in the document by a clause noting the possibility of a government non-exclusive license. Nonetheless, the possibility of a government non-exclusive license does impact the value of the otherwise truly exclusive license to the licensee. For this reason, the 1999 Geron License, like the 1996 Geron License, reduces royalty rates and license fees in the event that the government asserts a license.¹⁰⁸

104. Under federal securities laws, unregistered shares are not freely tradable on national stock exchanges. This limits the liquidity of such shares, and hence also reduces their value because resale of the shares involves a more cumbersome process than working through a broker-dealer affiliated with a national stock exchange such as the New York Stock Exchange.

105. At the close of business on Tuesday, Aug. 22, 2006, Geron's common stock traded at \$6.21 per share (Nasdaq trading symbol: GERN). Hopefully WARF has already diversified its portfolio by selling off some of the Geron shares at an earlier date (and higher value).

106. 1999 Geron License, *supra* note 84, § 7.

107. *Id.* § 14.

108. *Id.*

This time period must have been quite busy for stem cell related projects at WARF. As it was prosecuting the '806 Patent with the USPTO and negotiating with Geron to amend the 1999 Geron License, it was also creating WiCell as a not-for-profit, wholly owned subsidiary for further research, training, and distribution of the newly cultivated Thomson hESC lines.¹⁰⁹ WiCell claims it was necessary to move hESC research off-campus while it sorted through the ethical, legal, and social implications of the “federal funding prohibition,”¹¹⁰ likely referring to the NIH moratorium on funding hESC research.¹¹¹ Ironically, the moratorium itself seems to have been put in place largely *as a response* to Thomson’s cultivation of the hESC line.¹¹² I have heard that WARF’s and Wisconsin’s interest in moving the research off campus was actually to keep new inventions from falling under Bayh-Dole. The truth is likely somewhere in between: faced with the sudden prospect of greatly diminished funding for hESC research while NIH sorted things out, Wisconsin and WARF may have intended to keep new hESC completely outside of federal funding in order to avoid government claims to new inventions under Bayh-Dole. The amount of new federal funding for the research would not justify giving up those rights. However, the argument that Wisconsin and WARF wanted to keep cultivation of actual hESC lines outside of federal funding to cut off government rights is off-key in one specific regard: Bayh-Dole only governs patents that arise under federally funded research—not physical property, or even, for that matter, other forms of IP such as copyrights or trade secrets.¹¹³

Regardless of WARF’s true motivations for the creation of WiCell, the net result was that WiCell now controlled the valuable Thomson hESC line for distribution under MTAs. Further, WiCell held a sub-licensable license from WARF for the Thomson stem cell patents and presumably for any relevant new patents or applications arising from Thomson’s ongoing work. Though WiCell’s stated mandate is to “share widely” the Thomson

109. PowerPoint Presentation, WiCell Research Institute, Inc., Special Cells Create Special Opportunities and Special Problems (on file with author) [hereinafter WiCell PowerPoint].

110. *Id.*

111. See Sean M. O’Connor, *Intellectual Property Rights and Stem Cell Research: Who Owns the Medical Breakthroughs?*, 39 NEW ENG. L. REV. 665, 671 (2005).

112. See *id.* at 670-71.

113. Although, even where a federal funding recipient deems some new proprietary item or process a trade secret, it may still fall under government rights if it is nonetheless patentable subject matter and hence a subject invention under Bayh-Dole. In other words, the federal funding recipient cannot elect to protect something as a trade secret just to evade U.S. government rights in a patentable invention.

hESCs,¹¹⁴ commentators assert that WiCell has failed to do this.¹¹⁵ In WiCell's defense, the 1999 Geron License restricts what third party activities WARF, and therefore WiCell, can license or sublicense. Yet, if a particular third party activity cannot be licensed or sublicensed appropriately without violating the terms of the 1999 Geron License, WiCell likely cannot deliver Thomson hESCs to that third party. Even if its license from WARF permitted this, the transfer would be of little use to the recipient if it could not legally use the cells without infringing WARF's patents.¹¹⁶

Outside of the 1999 Geron License (which does not specify that Geron use Thomson cultured hESCs) and the PHS funded researchers operating under the WiCell-PHS MOU,¹¹⁷ WARF and WiCell appear to have undertaken a lease-license model for distributing the Thomson hESC technology platform to industry researchers.¹¹⁸ In other words, the only available license to the Thomson patents for industry researchers is a combination license and MTA which, while permitting the licensee to obtain some hESCs from third party suppliers, contemplates that the licensee will also receive hESCs from WiCell.¹¹⁹ At the same time, no hESCs have been distributed by WiCell without a sublicense to the patents.¹²⁰ In the early days following Thomson's announcement of the cultivation of his hESC line, the conditions for WARF's mutually reinforcing physical property and IP rights were pretty good: no one else was publicly in possession of such a cell line, generating substantial leverage for WARF and WiCell. Further in their favor, the '780 Patent arguably covered hESCs, and the hESC-specific '806 Patent was already being prosecuted.

Nonetheless, in 2001, WiCell's position of leverage received a tremendous boost from two sources. First, although NIH resolved its concerns about hESC research and issued hESC research guidelines and solicitation of funding proposals in 2000, President Bush announced on Au-

114. WiCell PowerPoint, *supra* note 109.

115. *See, e.g.*, Taymor, Scott & Greely, *supra* note 65.

116. Still, many suspect that university researchers are in fact routinely infringing third party patents in their research based either on ignorance of the patents or misguided belief that the patents simply do not apply to them legally or morally. *See generally View from the Bench, supra* note 1; Walsh, Roadblocks, *supra* note 1.

117. *See* text accompanying notes 135-46.

118. *See* WiCell Research Institute, Inc., Form of Industry Research License and Material Transfer Agreement (on file with author).

119. *See* 1999 Geron License, *supra* note 84.

120. Some concrete evidence of this exists in the 1999 Geron License where WARF permits Geron to sublicense the patents only to collaborators in Geron's internal research program that do not require hESCs. If the collaborator does require them, they must come from WARF under a negotiated MTA. *Id.* § 2(A)(iii).

gust 9, 2001, that no federal funding would go to any researchers working with hESCs derived from cell lines created after that date.¹²¹ Somewhere between Thomson's 1998 announcement of what was supposed to be the first immortal hESC line and August 2001, a number of new hESC lines had apparently been created. There were so many, in fact, that President Bush claimed there would be plenty of sources of hESCs for federally funded researchers to work from even while complying with his order.¹²² One wonders whether anyone licensed these lines under the '780 Patent, or whether, again, WARF believed that the '780 Patent covered only non-human primate embryonic stem cells and not hESCs. At any rate, the number of viable hESC lines quickly dropped in the months after the Bush Order, and the NIH Human Embryonic Stem Cell Registry ("the Registry") ultimately listed only twenty-two approved hESC lines.¹²³ Many of the original estimated sixty hESC lines at the time of the Bush Order either turned out not to exist, failed to continue producing new cells, failed to remain stable in an undifferentiated state, or were tainted by non-human cultures or feeder cells intended to sustain them.¹²⁴ Further, even among the twenty-two hESC lines finally certified in the Registry, many are owned by a single entity, meaning that only seven distinct organizations control all of the approved lines. One of these entities—MizMedi Hospital in South Korea—is currently "on hold" in the wake of the stem cell crisis in that country.¹²⁵ Thus, currently there are only six sources of viable, approved hESCs in the world, with only three—WiCell, BresaGen in Georgia, and University of California, San Francisco—based in the United States.¹²⁶ Clearly, this dramatically increases the value of WiCell's lines.

The second major event for WARF and WiCell in 2001 was the March 13 issuance of the '806 Patent, unmistakably directed to hESCs. At that point, regardless of the interpretation of the scope of the '780 Patent's claims, WARF had established clear patent control over hESCs, which has

121. See O'Connor, *supra* note 111, at 671-73.

122. See *id.* at 672. The Administration estimated that sixty hESC lines were available at the time of the Order. *Id.*

123. See *id.* at 689.

124. See, e.g., Press Release, Salk Inst. for Biological Studies, Press Releases: Current Human Embryonic Stem Cell Lines Contaminated with Potentially Dangerous Non-Human Molecule, UCSD/Salk Team Finds, Jan. 24, 2005, available at <http://www.salk.edu/news/releases/details.php?id=115> [hereinafter Stem Cell Lines Contaminated].

125. See Nat'l Insts. of Health, NIH Human Embryonic Stem Cell Registry, <http://stemcells.nih.gov/research/registry> (last visited Aug. 30, 2006) [hereinafter NIH Registry].

126. *Id.*

yet to be openly challenged.¹²⁷ Even providers other than WiCell of Registry-approved hESC lines are likely subject to WARF's patent rights. Those researchers who use hESCs from other sources need a license from WARF or WiCell.

With these two developments in 2001, WARF and WiCell solidified their position as the dominant force in hESC research, owing much of their success to their highly effective lease-license model. It is hard to overestimate the strength of WARF's and WiCell's position in the field—a realization that has slowly been dawning on many players in the field, including the forces behind Proposition 71 and the California Institute of Regenerative Medicine (CIRM). Unless someone finds a way to successfully challenge or design around the '780 Patent and the '804 Patent, WARF and WiCell own the field. Further, even if someone finds a way around the patents, unless a future President rescinds the Bush Order, or a subsequent Congress passes legislation that will not be vetoed by the President in office at that time,¹²⁸ researchers are still stuck with seven or fewer suppliers of hESCs approved for federally funded research.¹²⁹ This realization has led to state, federal, and local funding initiatives.¹³⁰ At any rate, the current hESC environment provides an excellent case study in the stickiness of effective technology lease-license models based on mutually reinforcing physical property and IP rights. It reveals that finding a way around one set of rights simply drives the researcher headlong into the other set of rights. Accordingly, a researcher must work around both sets of rights, which is a far more difficult challenge than evading only one set. Yet, all is not lost for the non-commercial hESC researcher who wants to work with hESCs without signing an agreement (at least directly) with WARF/WiCell. As evidenced by the government rights listed in the '780 Patent and potentially included in the '806 Patent, outlined above, the

127. The Wall Street Journal, however, reported that the Foundation for Taxpayer and Consumer Rights, based in Santa Monica, California, has petitioned the USPTO to reexamine the WARF/Thomson Patents. See Regalado & Hamilton, *supra* note 91, at B1, B5. Even so, there is no indication of this on the Foundation's stem cell project web pages. See The Foundation for Taxpayer & Consumer Rights, Stem Cell Research: Who Will Benefit?, <http://www.consumerwatchdog.org/healthcare/StemCell> (last visited Aug. 24, 2006).

128. After the current Congress' inability to override President Bush's veto of the Stem Cell Enhancement Act, H.R. 810, 109th Cong. (2006), it is unlikely that any new law will be enacted to effectively override the Bush Order with President Bush still in office.

129. Even these approved lines may in fact be contaminated and unusable for human therapeutics. See Stem Cell Lines Contaminated, *supra* note 124.

130. See O'Connor, *supra* note 111, at 674-81.

critical right mandated under Bayh-Dole is the non-exclusive license back to the government required in funding agreements.¹³¹ I cannot stress enough that what I will call the 202(c)(4) license (after its section in the U.S. Code) is *completely different* from the march-in rights that the funding agency can exercise only if the funding recipient has failed to commercialize the patent or otherwise triggered one of the specific bases for march-in rights.¹³² March-in rights are a bit of a red herring. Although they have received the lion's share of media attention as the key government right to federally funded patented inventions, the government has yet to exercise them, and has only contemplated doing so a handful of times.¹³³ On the other hand, the 202(c)(4) license requires no triggering event to become effective. Every federal funding agreement executed after Bayh-Dole took effect must include a provision giving the government a non-transferable non-exclusive license. Thus, the government already has a non-exclusive license to a patent as soon as it arises from federally funded research.¹³⁴ This is effectively no different from the licenses and options that Geron received as part of its funding of Thomson's research. In the Thomson case, so long as the federal funding was obtained under a funding agreement executed after Bayh-Dole, the 202(c)(4) license must have been included as part of that agreement. As a result, the government may practice, or have practiced on its behalf, for government purposes, any patented technologies arising from that federal funding.¹³⁵

Although it is still unclear when the funding agreement was executed, and whether the federal funding covered the research leading to the '806 Patent, WARF, WiCell, and PHS¹³⁶ appear to agree that the 202(c)(4) li-

131. 35 U.S.C. § 202(c)(4) (2000).

132. See 35 U.S.C. § 203 (2000).

133. See O'Connor, *supra* note 111, at 700-07.

134. See Sean M. O'Connor, Presentation at Madrid CSIC/OECD/OEPM Conference on Research Use of Patented Inventions: Public-Private Partnerships and De Facto Research Use Exemptions: Case Study of the Thomson Stem Cell Patents (May 18-19, 2006), <http://www.oecd.org/dataoecd/40/25/36817472.pdf>.

135. Note that even though Bayh-Dole was passed in 1980, much research leading to currently patented inventions was funded before Bayh-Dole's passage. Even though many federal funding agreements before Bayh-Dole contained the non-exclusive license grant back to the government, not all did. See O'Connor, *supra* note 111, at 681-87. Thus, evidence of federal funding for, and thus government rights in, any particular patent must be examined to determine exactly when the funding agreement was executed and whether it contained a license clause if executed before Bayh-Dole's passage in 1980. This issue has arisen in the recent high-profile litigation involving John Madey and Duke University. See *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002).

136. PHS is the parent agency of NIH, which funded the research noted in at least the '780 Patent.

cense is in place for both the '780 and '806 Patents. Effective September 5, 2001—thus after both the Bush Order and the issuance of the '806 Patent—WiCell and PHS entered into a Memorandum of Understanding (MOU). This MOU confirmed PHS's non-exclusive license to the '780 Patent and '806 Patent, as well as to the patent application that led to the '252 Patent (deemed the "Wisconsin Patent Rights").¹³⁷ Furthermore, the MOU stipulated that PHS has no ownership rights in the actual hESC lines (deemed the "Wisconsin Materials").¹³⁸

The WiCell-PHS MOU is fascinating because it undertakes to clearly authorize PHS contractors, who are none other than regular PHS extramural researchers at universities and other research institutions, to practice the WARF/Thomson Patents directly under PHS's license rights. At the same time, it can be confusing that the WiCell-PHS MOU does not specifically use the term "license" nor reference the 202(c)(4) license by name. One scholar at the "California's Stem Cell Initiative" Conference at Boalt Hall responded to a question about what led to the execution of the WiCell-PHS MOU by explaining that PHS pressured WiCell into giving a license to the WARF/Thomson Patents under threat of march-in rights. Yet, nothing in the record indicates that such pressure existed.¹³⁹ Moreover, there is no mention of a license in the subsequent conditions, except

137. See WiCell MOU, *supra* note 4. The application for the '252 Patent was U.S. Patent Application No. 09/522,030 (filed March 9, 2000).

138. See *id.* at recital cl. 5.

139. Further, there was no justification for why march-in rights could have been exercised in 2001 when the WiCell-PHS MOU was executed. A threat of march-in rights by a federal agency is not really credible unless the funding recipient has failed to take reasonable steps to commercialize the invention or otherwise triggered one of the specific bases for march-in rights. Ultimately, if WiCell was bullied into giving a license that did not already exist, why is there no license grant in the WiCell-PHS MOU? The relevant language simply states that "The Parties agree that Wisconsin Patent Rights are to be made available without cost for use in the PHS biomedical research program subject to the following conditions . . ." See WiCell MOU, *supra* note 4, § 1. Finally, the recitals to the WiCell-PHS MOU explain that "W[hereas] PHS funded primate research studies at the University of Wisconsin-Madison that led to certain discoveries claimed in Wisconsin Patent Rights. . .[,] the Government has certain use and other rights to the intellectual property comprising the Wisconsin Patent Rights granted by law and regulation . . ." *Id.* at recital cl. 4. This clearly indicates that the parties agreed that PHS' funding was conditioned on a license back to the government of any patents arising under that funding ("the Government has certain use and other rights to the intellectual property"), exactly as occurs with the 202(c)(4) license. If the rights contemplated in this recital were march-in rights, the language would have had to either include mention of a completed march-in rights proceeding (which has most certainly *not* occurred with regard to the WARF/Thomson Patents), or that government IP use rights would be contingent upon the successful exercise of march-in rights after a formal proceeding.

for a license granted to third party suppliers of hESCs solely for providing the hESCs to PHS researchers.¹⁴⁰ This confirms that no new license was needed, because the 202(c)(4) license was already in place. The third party license grant in the MOU also confirms that once the '806 Patent issued, all of the third party approved hESC providers were arguably infringing WARF's patents.

Under the terms of the WiCell-PHS MOU, a PHS researcher need only submit a completed version of the "Sample Simple Letter Agreement for the Transfer of Materials to PHS Scientists and PHS Contractors" ("the Simple Letter Agreement") that was included as part of the WiCell-PHS MOU.¹⁴¹ The Simple Letter Agreement is a basic form of standard life sciences MTA. In combination, the master WiCell-PHS MOU document and the Simple Letter Agreement for recording specific transfers of materials are similar to the Master UBMTA and its Implementing Letter form, described above in Part I. No license grant is included in the Simple Letter Agreement. This further reinforces the conclusion that PHS and WiCell must be operating under the 202(c)(4) license, as no other license has been explicitly granted or would have arisen by operation of law or regulation.

Finally, the WiCell-PHS MOU underscores the lease-license model used by WiCell. It clearly states in the master document and the Simple Letter Agreement that "Wisconsin Materials are the property of WiCell and are being made available to investigators in the PHS research community as a service by WiCell." The document also clarifies that "[o]wnership of Wisconsin Materials shall remain with WiCell."¹⁴² Finally, the MOU includes further restrictions on the use of Wisconsin Materials, in part to reinforce WARF's exclusive IP license to the therapeutic and diagnostic fields (by prohibiting PHS contractors from using Wisconsin Materials in these fields and limiting all uses to teaching and non-commercial research purposes), and in part to provide the liability limiting function discussed in Part I above.¹⁴³

In the end, the WiCell-PHS MOU is perhaps most intriguing because it clearly demonstrates that a government agency can make good use of the often-overlooked 202(c)(4) license. This is especially important in the

140. *Id.* § 1(c).

141. *Id.* at 8-9.

142. *Id.* § 2(a). It is unclear whether the inclusion of the term "service" is meant in the sense we used it above—e.g., personal or professional services—or whether it is used in the sense of a public benefit or moral duty. If the former, WiCell is claiming a service-license model that has even more implications for the legal rights of PHS and its researchers as set forth in Part II. *See supra* Part II.

143. WiCell MOU, *supra* note 4, § 2.

hESC context because it shows that there are effective counterbalancing government rights that give researchers access to federally funded inventions even where patents and exclusive licenses otherwise have locked down the field. Indeed, outside of this PHS research license bubble or zone, WiCell and WARF are widely believed to have been very tight with granting licenses, even for research purposes. Of course, the Bush Order itself limits this PHS research bubble/zone. At the same time, though, WiCell has made it clear that it intends to make its hESCs and appropriate sublicenses to the WARF/Thomson Patents widely available to non-commercial researchers outside of the PHS research bubble/zone through an MOU and Simple Letter Agreement format similar to the WiCell-PHS MOU arrangement.¹⁴⁴ Moreover, it has a separate MTA for industry research, which it claims to be willing to use in “nearly all fields.”¹⁴⁵ Needless to say, the terms of the 1999 Geron License must limit this aspect of its program. Nonetheless, WiCell successfully bid to become the host for the National Stem Cell Bank established by NIH.¹⁴⁶ It thus committed to attempt to collect all twenty-two approved stem cell lines and make them available to all researchers for \$500 per line, apparently including a license to the WARF/Thomson Patents.¹⁴⁷

IV. WHERE DOES CIRM FUNDED RESEARCH FIT IN?

One of the most unhappy places in the country with regard to WiCell’s domination of the hESC terrain is California, and particularly, CIRM. In 2004, the Bush Order of 2001 appeared to be the primary obstacle for California’s strong hESC research community.¹⁴⁸ In order to sidestep the federal funding restrictions, Californians sought to finance research themselves through Proposition 71.¹⁴⁹ It turned out, though, that the WARF/Thomson Patents—already issued before Proposition 71 appeared on the ballot—were the real problem. California and the new CIRM were unprepared for this. Further, because Proposition 71 and CIRM were in-

144. WiCell Research Institute, Inc., FAQs About WiCell’s Policies on the Use of its hESC Lines, http://www.wicell.org/uploads/media/NIH_FAQs.pdf (last visited Aug. 30, 2006) [hereinafter WiCell hESC Lines].

145. See WiCell PowerPoint, *supra* note 109; WiCell hESC Lines, *supra* note 144.

146. See WiCell hESC Lines, *supra* note 144.

147. See *id.* WiCell makes it clear that hESCs obtained from other providers may require a separate license to the WARF/Thomson Patents, leading one to infer that such a license is included when one obtains the hESCs from WiCell. See *id.* Again, it is not clear how this squares with the 1999 Geron License or with the strong sentiment in the hESC research community that WiCell is holding up research by being stingy with licenses.

148. See O’Connor, *supra* note 111 at 675-79.

149. See *id.*

tended to fund exactly the kinds of research that would *not* be funded by NIH under the Bush Order, CIRM was and is still boxed out of co-funding research with NIH that would bring California CIRM funded researchers within the PHS research license zone, outlined at the end of Part II above. While Proposition 71 does not prohibit such co-funding situations, it steers CIRM grants towards hESC research that would not otherwise receive timely funding.¹⁵⁰

CIRM now faces two basic avenues of pursuit. First, it can fund researchers to work “earlier” in, or alternatively to, the current chain of hESC research in order to avoid infringing the WARF/Thomson Patents, while at the same time designing around those patents to create pluripotent human stem cell lines that do not infringe the patent. Second, it can help researchers pursue a *de facto* research-use exemption, possibly available to states and their agencies under the doctrine of sovereign immunity. Along the former avenue, Kenneth Taymor, Christopher Thomas Scott, and Henry Greely of the Stanford University Program on Stem Cells in Society discuss some promising approaches in a recent article in *Nature Biotechnology*.¹⁵¹ Along the latter avenue, I will be examining this mechanism more completely in a future article, and so I will only briefly describe it here.

Beginning from the premise that CIRM is truly a state agency, rather than an independent legal entity, CIRM can arguably practice patents without the owner’s authorization under the doctrine of sovereign immunity. This works because under federal law prospective plaintiffs cannot use the federal courts to sue individual states.¹⁵² At the same time, patent infringement suits are limited to federal courts because they arise under federal law.¹⁵³ Therefore, patent owners cannot sue states for infringement. While this doctrine has been upheld by the Supreme Court,¹⁵⁴ it has prompted some unsuccessful bills in Congress. Thus, to the extent that a state and/or its agencies begin relying on this doctrine as a routine matter, we could expect to see attempts at Congressional legislation overriding this doctrine. Nevertheless, because it is rooted in constitutional law, the courts can overturn any such legislation as unconstitutional. The more practical question is whether a state or its agencies could immunize contractors under this doctrine by arguing that the contractors have been au-

150. *See id.* at 675.

151. Taymor, Scott & Greely, *supra* note 65.

152. *See Fla. Prepaid Postsecondary Educ. Expense Bd. v. Coll. Sav. Bank*, 527 U.S. 627, 635, 647 (1999).

153. 28 U.S.C. § 1338(a) (2000).

154. *See Fla. Prepaid*, 527 U.S. at 635, 647.

thorized to produce certain goods or services on behalf of the state government or agency. If so, CIRM would be able to authorize grant recipients to perform their work on behalf of the State of California. This would be similar to the way PHS authorizes extramural researchers performing hESC research under PHS grants to act on behalf of PHS, thus bringing them directly under the 202(c)(4) government license.

If CIRM cannot successfully pursue any of these avenues, it will be stuck with whatever license terms it can negotiate with WARF and/or WiCell, at least until the patent terms run out for the '780 Patent and '806 Patent. WiCell's license terms for non-commercial research are not that onerous. In fact, because WiCell won the grant to host the first NIH National Stem Cell Bank, it is now obligated to make at least the hESC lines even more readily available. Currently, it will provide hESC lines to any researcher engaged in non-commercial research at a U.S. academic institution or not-for-profit research organization for \$500 whether or not that researcher is working under an NIH grant.¹⁵⁵ However, WiCell is reported to have told CIRM that it considers CIRM's plans to take 25% of the revenue from patenting discoveries made by CIRM-funded entities as a commercial use of the WARF/Thomson Patents, entitling WARF and WiCell to "a cut of [CIRM's] take."¹⁵⁶ CIRM has responded that such a claim is "unprecedented," though the parties appear to remain at an impasse.¹⁵⁷ WiCell's argument may be a non-starter at any rate; directed to CIRM itself, it could only be enforced through a patent infringement action from which CIRM, as a California State agency, would receive immunity under the doctrine of sovereign immunity. Further, CIRM's practice of funding research and receiving a return on that funding investment would in no way constitute the making, using, selling, or importing of the WARF/Thomson Patents or any products embodying those patents. Thus, there would be no patent infringement by CIRM. Alternatively, if WiCell sought to impute the potentially patent infringing activities of CIRM funding recipients to CIRM, CIRM again could authorize its funding recipients to perform their research on behalf of CIRM as state contractors—but then, such contractors are likely equally immune under sovereign immunity as agents of the state.

155. See WiCell Research Institute, Inc., National Stem Cell Bank, *available at* http://www.wicell.org/index.php?option=com_oscommerce&Itemid=192 (last visited Aug. 30, 2006); WiCell Research Institute, Inc., FAQs for Requesting Stem Cells, http://www.wicell.org/index.php?option=com_content&task=blogcategory&id=124&Itemid=197 (last visited Aug. 20, 2006).

156. See Regalado & Hamilton, *supra* note 91, at B1, B5.

157. *Id.*

Finally, if it is really a commercialization license issue that creates hurdles to CIRM's plans, based on WiCell's own linkage of the commercialization license with the path to clinical trials, I would suggest the unorthodox and potentially risky strategy of using the non-commercial licenses as far as they will go and then relying on the Supreme Court's recent broad interpretation of the Hatch-Waxman regulatory review research-use exemption under 35 U.S.C. § 271(e) in *Merck v. Integra*.¹⁵⁸ This would allow researchers to seamlessly move from easy-to-obtain non-commercial licenses to a full blown commercialization research and development ("R&D") phase without having to negotiate with WARF or WiCell for the more challenging commercialization licenses. This strategy is viable because the non-commercial license explicitly allows licensees to patent any new inventions that come out of the non-commercial research performed under the license. Yet, once the beginnings of a promising new therapeutic, diagnostic, or research tool arose in the non-commercial setting, the academic or not-for-profit research institution would then be able to patent the new invention and license it out to industry to commercialize. The licensee could then commence the translational R&D phase to transform the early stage patented invention into a potential therapeutic, diagnostic, or research tool product. Simultaneously, the licensee could begin preliminary toxicology screenings in animals, dosing experiments, or any of the other activities that the Supreme Court has identified as "on the path to" FDA approval, and hence covered by the 271(e) regulatory review research use exemption.¹⁵⁹ While many view the Supreme Court's interpretation of the scope of the 271(e) exemption as far too broad, it currently

158. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

159. *See id.* at __; *see also* Sean M. O'Connor, *Summary: Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. __ (2005), 12 CASRIP NEWSLETTER (2005), available at <http://www.law.washington.edu/Casrip/Newsletter/Vol12/newsv12i1US1.html>. Arguably, WARF could respond by first attempting to distinguish the commercializing entity's uses of the WARF/Thomson Patents that fall within one of the activities listed by the Supreme Court as nearing FDA approval and then claiming infringement—and damages or injunctive relief—on all the rest of the uses. However, I think this would be a messy proposition, and courts might find the different uses inseparable or simply covered under the 271(e) regulatory review research use exemption. If the uncertainty is high enough, it could cause WARF to reconsider whether to bring such a suit in the first place, especially considering that a patent infringement lawsuit would open the WARF/Thomson Patents to validity challenges by the defense. The best outcome would be that WARF revisits its commercialization license policy and finds a way to be as reasonable as possible, without violating its agreements with Geron. That way, it could license the patents to the potential infringers, thereby reinforcing the presumed validity of those patents and receiving a negotiated enforceable royalty stream from whatever stem cell products finally reach the marketplace.

appears to be the law of the land. CIRM and the California stem cell research and commercialization industry should use this fact to their advantage. Such high profile use of the strategy proposed herein may push Congress to amend 271(e), assuming that enough members of Congress believe that the Supreme Court interpreted the current language of 271(e) too broadly. Until Congress does so, though, the strategy proposed herein maps a perfectly legal path around the allegedly onerous and largely unavailable WiCell commercialization licenses.¹⁶⁰

V. CONCLUSION: LOOKING BEYOND THE THOMSON PATENTS

I am confident that CIRM will find a path around the obstacles surrounding the WARF/Thomson Patents. As argued above, though, patents do not necessarily pose the greatest hurdles to research over time. Physical property rights, as controlled and enforced through MTAs, are often the most difficult to overcome. As discussed above, primarily state contract law governs MTAs and other mechanisms for controlling or enforcing physical property rights. In the case of human biological materials, states have established constitutional, statutory, and/or case law that may limit the downstream use of materials, depending on the type of informed consent or other permission given by the original donor.

The absence to date of any significant donor issues in the approved hESC lines should not make us complacent.¹⁶¹ With only twenty-two lines total, all developed by only seven research organizations, we may not have the kind of volume and long term experience with hESC lines necessary for donor issues to emerge. As CIRM continues to promulgate rules and regulations for hESC research programs in California, it would do well to consider planning for and implementing a comprehensive chain-of-title type of system for biological materials from donation through inclusion in commercialized products. With materials passing through many different organizations, this is undoubtedly an incredibly attenuated chain, but it reflects the nature of MTAs. Allowing different parties with very different goals to control the materials at different times creates a substantial risk that a downstream party will use the materials in a manner inconsistent

160. Of course, if the numerous interpretations of the *Merck* Court's holding finding a broad reading of 271(e) are incorrect, then the strategy proposed herein may be vulnerable to legal challenges in court.

161. Only one donor seems to have exercised any rights that would effectively retract an approved hESC line. See NIH Registry, *supra* note 125 (noting that the Sahlgrenska 3 cell line formerly offered by Cellartis AB has been withdrawn by its donor).

with the donor's consent. This will hold especially true if and when the patent obstacles are overcome, which would trigger a race to obtain large quantities of donor materials, such as oocytes.

Other presenters and articles in the "California's Stem Cell Initiative" Conference have greater expertise in the legal and ethical issues involved in informed consent, so I will not attempt to recapitulate those issues here. Instead, I will conclude by focusing on the consent issue most directly linked with commercialization: the consent form's statement of proposed use of materials. For example, Advanced Cell Therapies (ACT) has already begun actively soliciting donors to supply oocytes. It uses an informed consent form that includes an explicit waiver of any donor rights in commercial benefits arising from research.¹⁶² The form focuses, though, on the use of the materials for scientific research as opposed to the eventual product R&D that leads to a saleable product. Further, many human biological materials are collected in university or non-profit settings that align with the public's general sense of what constitutes scientific research—that is, relatively impartial, objective research into natural principles and mechanisms with no direct profit motive. Prospective donors might feel quite differently about giving biological materials to a for-profit entity that expressly plans to use the materials for profitable products or services. Still, is the disclosure of potential commercialization in the context of a waiver of donor rights in commercial benefits enough to trigger a meaningful understanding in donors that their materials can be transferred to a for-profit corporation for commercialization? In other words, the standard informed consent forms may play on the public's general unfamiliarity with how the chain of commercialization works. Put yet another way, will women being asked to donate oocytes, an unpleasant and risky procedure, be more inclined to do so when they are told the eggs will be used for potentially life-saving medical research than if they are told the eggs will be used to develop profitable products for a private corporation? I do not intend to denigrate the role that for-profit entities play in the commercialization chain. Rather, I wish to ensure that *all* entities in the commercialization chain—non-profit and for-profit alike—accurately manage expectations.

Therefore, I propose that CIRM establish a system to monitor, guide, and control the entire commercialization rights chain. The first stage would consist of consent forms and other documentation for the original oocyte donation to research units. The second stage would be MTAs and

162. Advanced Cell Therapies, Form of Consent to Participate in a Study Involving Egg Donation for Stem Cell Research, at 6 (on file with author).

other documentation used to transfer the materials, or their derivatives, to applied or translational R&D units. The third and final stage would be MTAs and other documentation used to transfer the materials to manufacturing, distribution, and sales units, as applicable. This list is not meant to be exclusive—other transfers may be required for specific commercialization efforts. It is, however, a proposal for a comprehensive title chain for the materials. Admittedly, this new layer of monitoring could devolve into a clunky bureaucracy that slows down or even sometimes prevents the timely collection and transfer of valuable biological materials. However, given modern inventory tracking systems and CIRM's willingness to focus on implementing an effective system, the biological materials title chain should not slow down the research or commercialization processes. In fact, an efficient tracking system could very well speed up research and commercialization by allowing faster location and routing of needed materials.

The biological materials title chain will not perform its desired function unless donors receive realistic and accurate disclosures in their informed consent forms. While I do not advocate unnecessarily scaring off donors, we generally go too far in suggesting an overly-romantic view of donations to medical science for the benefit of humanity. At one level, this depiction may well be true. Yet at another, it may seem manipulative to donors who do not realize that their biological materials will wind up in the hands of a for-profit corporation intending to make a fair bit of profit off of the materials, albeit in a highly derivate form. In sum, donors require more disclosure about the commercialization process for hESC therapies, diagnostics, and research tools. Through disclosure, we will avoid problematic backlashes by donors who are willing to undergo pain and inconvenience so long as it is for a cause they understand and support.