21:3 BERKELEY TECHNOLOGY LAW JOURNAL

Pages
1017
to
1214

Summer
2006

Production: Produced by members of the *Berkeley Technology Law Journal* on PC computers. All editing and layout is done using Microsoft Word.

Printer: Joe Christensen, Inc., Lincoln, Nebraska.
Printed in the U.S.A.
The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Library Materials, ANSI Z39.48—1984.

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BERKELEY TECHNOLOGY LAW JOURNAL

VOLUME 21 NUMBER 3 SUMMER 2006

TABLE OF CONTENTS

SYMPOSIUM: CALIFORNIA'S STEM CELL INITIATIVE: CONFRONTING THE LEGAL AND POLICY CHALLENGES

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The *Berkeley Technology Law Journal* (ISSN 1086-3818), a continuation of the *High Technology Law Journal* effective Volume 11, is edited and published four times each year (Spring, Summer, Fall, and Annual Review of Law and Technology) by the students of University of California School of Law, Berkeley (Boalt Hall). Application to Mail at Periodicals Postage Rate is Pending at Berkeley, California, and at additional mailing offices. POSTMASTER: Send address changes to Journal Publications Coordinator, 313 Boalt Hall, Boalt Hall School of Law, University of California, Berkeley, CA 94720-7200.

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Form. The text and citations in the *Journal* conform generally to the UNITED STATES GOVERNMENT PRINTING OFFICE STYLE MANUAL (29th ed. 2000) and to THE BLUEBOOK: A UNIFORM SYSTEM OF CITATION (Columbia Law Review Ass'n et al. eds., 18th ed. 2005). Please cite this issue of the *Berkeley Technology Law Journal* as 21 BERKELEY TECH. L.J. ___ (2006).

BTLJ ONLINE

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

By Sean O'Connor[†]

TABLE OF CONTENTS

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-

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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*, CABLEWORLD, 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?hidenavlink=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 doctrines[16] 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 law[21] 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 underrated 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

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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-2[40] 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

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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]

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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 humans[63] 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 application[64] 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]

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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 phosphotase, 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

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> 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 Patents[73] (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 NCRR 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

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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

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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 chrondocytes) 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-

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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]

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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

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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-

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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

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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 PHS[136] 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

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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.

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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.

COERCION, COMMERCIALIZATION, AND COMMODIFICATION: THE ETHICS OF COMPENSATION FOR EGG DONORS IN STEM CELL RESEARCH

By Radhika Rao[†]

TABLE OF CONTENTS

I. INTRODUCTION

Human embryonic stem cell research (hESCR) involves the extraction of stem cells from human embryos, which are destroyed in the process. The embryos may be obtained in one of three ways: (1) they may be cloned human embryos specifically created for research; (2) they may be research embryos created through in vitro fertilization (IVF); or (3) they may be "spare" embryos left over from infertility treatments that are donated for research.[1] All of these methods entail the use of human eggs at some stage in the process; they may also involve the use of human sperm

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1. *See* NATIONAL RESEARCH COUNCIL & INSTITUTE OF MEDICINE, GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2005) [hereinafter NAS GUIDELINES].

or human cells. How do we protect the individuals who donate these eggs, sperm, cells, or embryos? How do we ensure their consent to the process? Are donors entitled to maintain a certain degree of control over the bodily material they donate, and over the resulting products? Are donors at least entitled to share in the profits generated from such research?

In this Article, I discuss current U.S. guidelines for compensation of egg donors in hESCR. By prohibiting payment, the guidelines attempt to prevent coercion of egg donors and the commodification and commercialization of their bodies. In so doing, the guidelines implicitly invoke the rubric of privacy and reject propertization of the human body. Yet the guidelines fail to limit payment of egg donors in IVF. Moreover, they permit commercialization and commodification of the human body by everyone else engaged in hESCR, except for those who provide eggs and other body parts. Thus, the scientists who conduct hESCR and the companies and universities that fund their research are all free to profit. These inconsistencies and contradictions ultimately undermine the objectives of the U.S. guidelines.

The National Academy of Sciences (NAS) has issued guidelines for hESCR that require "informed consent" and prohibit payment or other "inducements" made to attract donors, beyond reimbursement for their expenses.[2] The California Institute for Regenerative Medicine (CIRM) has recommended that essentially the same restrictions apply to all hESCR funded by the state under Proposition 71.[3] Regulations that proscribe payment to egg donors appear to be quite common and uncontroversial. For example, South Korea has enacted similar laws banning payment to oocyte donors,[4] as have the United Kingdom, Canada, Australia, France, Germany, Israel, and other countries.[5]

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2. *See id.* at 82-89.

3. *See* SCIENTIFIC & MED. ACCOUNTABILITY STANDARDS WORKING GROUP, CIRM, PROPOSED CIRM MES REGULATIONS: ACCEPTABLE RESEARCH MATERIALS § 100007(e)(1)-(3) (proposed Feb. 10, 2006); *see also* INDEPENDENT CITIZENS OVERSIGHT COMMITTEE (ICOC), AGENDA ITEM #16: CONSIDERATION OF ADDITIONAL INTERIM CIRM MEDICAL AND ETHICAL STANDARD REGULATION FOR HUMAN STEM CELL RESEARCH, ICOC MEETING AGENDA (Apr. 16, 2006), *available at* http://www.cirm.ca.gov/meetings/pdf/2006/04/040606_item_16.pdf (considering new § 100085: Use of Fetal Tissue).

4. South Korea banned the sale of human eggs in January 2004. *See* James Brooke, *Korean Leaves Cloning Center in Ethics Furor*, N.Y. TIMES, Nov. 25, 2005, at A1.

5. The United Kingdom permits oocyte donors to be paid no more than £15 plus reasonable expenses. *See* Press Release, Human Fertilisation Embryology Authority, HFEA Confirms UK Position on Payment for Egg Donors (Feb. 25, 2004) (on file with author), *available at* http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-866577E4/

By contrast, the United States lacks uniform legislation regulating the market for human eggs.[6] No federal law limits compensation for egg donors, and only a handful of state statutes address the issue directly. Louisiana is the only state that explicitly prohibits the sale of human oocytes while Virginia is the only state that explicitly authorizes the sale of human oocytes.[7] Several states have enacted statutes that broadly ban the sale of all body parts for valuable consideration without expressly mentioning oocytes, although these laws usually contain exceptions for renewable resources such as blood products and human hair.[8]

While the NAS and CIRM guidelines prohibit payment to egg donors, they appear to be of limited effect. The CIRM guidelines apply only to hESCR that is funded by the state of California under Proposition 71,[9] while the NAS guidelines are purely hortatory. The NAS recommends that the stakeholders in hESCR—funding sources, research institutions, and scientific journals—take action on their own to ensure compliance with the guidelines by imposing appropriate sanctions for violations.[10] The NAS suggests, for example, that funding agencies assess compliance with the guidelines when reviewing grant applications and that scientific journals require evidence of compliance before publishing the results of any

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hfea/hs.xsl/1034.html; HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY, CODE OF PRACTICE 41 (6th ed. 2003), *available at* http://www.phgu.org.uk/newsletter?newsletter_year=2004&newsletter_month=apr. Canada also forbids the sale of human eggs. *See* The Assisted Reproduction Act (Bill C-6), House of Commons, 37th Parl., 3d Sess. (2004) (Can.), *available at* http://www.parl.gc.ca/37/3/parlbus/chambus/house/bills/government/C-6/C-6_3/C-6TOCE.html. For a helpful overview of countries that prohibit oocyte sales, see Alice J. Carlson, Trade in Human Reproductive Biota: Our Quest for Babies, Table 3: International Legal Framework (Dec. 11, 2003) (unpublished M.A. thesis, American University), *available at* http://www.american.edu/TED/reproductive-trade.htm. *See also* Kenneth Baum, *Golden Eggs*: *Towards the Rational Regulation of Oocyte Donation*, 2001 BYU L. REV. 107, 128-29 (2001) (noting guidelines in place for compensating egg donors in England, Israel, and Australia). In March 2004, the European Parliament adopted Directive 2004/23/EC prohibiting the sale of human eggs, while Italy has banned egg donation altogether. *See* Robin Marantz Henig, *On High-Tech Reproduction, Italy Will Practice Abstinence*, N.Y. TIMES, Mar. 2, 2004, at F5.

6. *See* Baum, *supra* note 5, at 123-28.

7. *Id.* at 126.

8. *Id.*

9. CIRM, INTERIM CIRM GRANTS ADMINISTRATION POLICY FOR ACADEMIC AND NON-PROFIT INSTITUTIONS, VERSION 14C, *available at* http://www.cirm.ca.gov/policies/pdf/InterimGAP.pdf (last visited Aug. 21, 2006). The CIRM regulations have the force and effect of law once an agency agrees to them as a condition for receiving funding. *See id.*; CAL. HEALTH & SAFETY CODE § 125290.40(j) (2006).

10. NAS GUIDELINES, *supra* note 1, at 14.

research.[11] As a practical matter, such funding and publication restrictions may achieve virtually the same results as a legal limitation upon hESCR.

Why do these guidelines prohibit payment to egg donors or to those who donate sperm, cells, or embryos? Is it for symbolic reasons—to prevent commodification of the components of human life—or for substantive reasons?

II. TRADITIONAL JUSTIFICATIONS FOR PROHIBITING PAYMENT TO EGG DONORS

A. Why Prohibit Payment for Human Embryos? Personhood vs. Property

The easiest case to make is for prohibiting payment for human embryos. Allowing human embryos to be bought and sold arguably treats them as a form of property. For those who view the embryo as a person, this is as offensive as slavery. Of course, for those who view the embryo as a person, stem cell research itself is the equivalent of murder.

Yet, even for those who do not view an embryo as a full-fledged person, the purchase and sale of embryos could be seen as disrespectful of potential persons. Such attitudes could lead to disrespect for actual persons, just as desecration of dead bodies might breed disrespect for living human beings. Thus, the NAS Report states that one reason to prohibit payment for embryos "might lie in the view that the treatment of the developing human embryo as an entity deserving of respect may be undermined by the introduction of a commercial motive into the solicitation or donation of fetal or embryonic tissue for research purposes."[12]

B. Why Prohibit Payment for Human Eggs? Coercion and Commodification

Allowing human eggs to be bought and sold could be criticized for the very same reason, namely that it treats the sacred components of human life as a form of property, engendering an attitude of disrespect for actual persons. Moreover, egg donation is a risky and painful procedure that requires hormone treatment in order to stimulate the ovaries to release multiple eggs, and involves the extraction of these eggs in a surgical procedure.[13] Thus, prohibitions upon payment may be intended to protect the

11. *Id.*

12. *Id.* at 84.

13. An egg donor must first undergo daily hormone injections for a period of seven to ten days in order to stimulate production of an abnormally large quantity of oocytes. Side effects from these injections may include bloating, abdominal pain, mood swings,

individuals who donate their eggs from possible medical complications, and not just the symbolic value of that which is donated.

Prohibitions upon payment or other "inducements" may be necessary to ensure true consent, protecting donors from being pressured by the possibility of obtaining money or other benefits to agree to something that they would not otherwise choose. An example from South Korea illustrates the kinds of pressure that may be brought to bear upon vulnerable parties in order to obtain eggs and other bodily material. South Korean researcher Dr. Hwang Woo Suk became famous around the world as the first person to successfully clone a human embryo and extract stem cells from the embryo.[14] However, he later became the subject of international controversy when it was revealed that the so-called "donors" of eggs allegedly used to create embryonic stem cell lines were either paid (around $1400 each) or were junior researchers (and even graduate students) in his laboratory.[15] Critics contend that "in the strict hierarchy of a scientific laboratory in a Confucian society like South Korea, junior members often feel great pressure to please their superiors."[16] Dr. Hwang disclaimed any knowledge of the egg donation,[17] but others allege that he pressured his employees to donate eggs, and that he even drove the car that brought one

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and nausea. After the eggs are fully developed, the donor receives an injection of another hormone that prepares the eggs for removal, and the eggs are then removed by means of a long needle that is inserted through the vagina in a minor surgical procedure that requires anesthesia. Risks involved in this process include side-effects from the anesthesia, hemorrhaging, damage to the bowel, bladder, or blood vessels, infection, and ironically even loss of fertility. One of the most serious risks of egg donation is ovarian hyperstimulation syndrome (OHSS), which develops in a very small percentage of egg donors. OHSS is an adverse response to ovulation induction therapy that can cause fluid accumulation in the abdomen and chest, breathing trouble, thrombosis, and kidney failure. In severe cases, OHSS may result in hospitalization and death. There are concerns that the hormone treatments necessary for egg donation may cause ovarian cancer, but there are no conclusive links between the two in humans. *See* AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE, ASSISTED REPRODUCTIVE TECHNOLOGIES: A GUIDE FOR PATIENTS (2003), *available at* http://www.asrm.org/Patients/patientbooklets/ART.pdf; Robert Steinbrook, *Egg Donation and Human Embryonic Stem-Cell Research*, 354 NEW ENG. J. MED. 324, 324-26 (2006); Baum, *supra* note 5, at 118.

14. Suk's claim has recently been called into question by allegations that he falsified data. Nicholas Wade & Choe Sang-Hun, *Researcher Faked Evidence of Human Cloning, Koreans Report*, N.Y. TIMES, Jan. 10, 2006, at A1.

15. Constance Holden, *Korean Cloner Admits Lying About Oocyte Donation*s, 310 SCI. 1402, 1402-03. At least one of the researchers who donated her eggs was Dr. Hwang's Ph.D. student. *Id.*

16. Brooke, *supra* note 4, at A1.

17. Anthony Faiola & Joohee Cho, *S. Korean Stem Cell Expert Apologizes for Ethical Breach*, WASH. POST, Nov. 25, 2005, at A24.

donor to the egg retrieval procedure![18] A blanket prohibition upon payment or other inducements could be intended to shield individuals like the junior researchers in Dr. Hwang's lab from such subtle or not-so-subtle forms of pressure.

The problem with this argument is that it proves too much. If Dr. Hwang actually compelled those who worked in his lab to supply him with eggs for research, clearly their "choice" cannot be said to be voluntary. And if other South Korean women were not adequately informed of the risks involved in egg donation and were paid an unconscionably low price, their treatment might constitute exploitation. Payment to egg donors may be as "coercive" or "exploitative" in the context of IVF as it is in the context of hESCR, yet the purchase and sale of human eggs for IVF is permitted.[19] Indeed, even advertising and market pricing of eggs based upon the donor's appearance and other personal characteristics is allowed. The going rate for eggs in the U.S. ranges from $5,000 to $100,000, depending upon the donor's "qualifications."[20] If compensation can "coerce" women to supply their eggs for hESCR, why does it not "coerce" women to supply their eggs for IVF? And if payment is degrading because it relegates human eggs to the status of objects that can be bought and sold, why does this argument not apply in the IVF context as well? Why allow a market for human eggs in IVP but not in hESCR?

III. JUSTIFICATIONS FOR A MARKET FOR HUMAN EGGS IN IVF BUT NOT IN HESCR

A. Instrumentalization

Perhaps the reason for prohibiting payment to oocyte donors in hESCR but not IVF lies in their very different objectives. Eggs that are purchased for the purpose of IVF will be used to create embryos in the hope that they will ultimately lead to the birth of a child, whereas eggs that are purchased

18. Anita Srikameswaran, *Pitt Panel Castigates Stem Cell Researcher*, PITT. POST-GAZETTE, Feb. 11, 2006, at A1.

19. Although there are no laws limiting payment to egg donors in the context of IVF, the Ethics Committee of the American Society for Reproductive Medicine has recommended that payments above $5,000 to egg donors require justification, and payments that exceed $10,000 should be prohibited. Ethics Committee of the American Society for Reproductive Medicine, *Financial Incentives in Recruitment of Oocyte Donors*, 74 FERTILITY & STERILITY 2, 219 (2000).

20. Gina Kolata, *$50,000 Offered to Tall, Smart Egg Donor*, N.Y. TIMES, Mar. 3, 1999, at A10; *see also* Classified Ad, THE STANFORD DAILY, June 8, 2006, at 19 (offering $100,000 for "attractive, intelligent donor of East Indian decent [sic]"); *id.* at 13 (offering $80,000 to a "special egg donor").

for the purpose of hESCR will be used to create embryos that will ultimately be destroyed in the process of harvesting stem cells. Thus, hESCR may be viewed as treating human eggs (and other bodily materials) in an instrumental way, as a means to other objectives rather than as ends in themselves. Such instrumentalization is a key attribute of property.

But if instrumentalization is the objection, then the problem is not the purchase and sale of human eggs but the *way* in which they will be used. This is an objection to stem cell research itself, which demands the destruction of human embryos in order to extract stem cells.

B. Commercialization

Perhaps the objection is not to instrumentalization alone, but rather to the combination of instrumentalization with commercialization, which is another attribute of property. We may fear that payment for eggs and sperm will commercialize the components of human life—components that should remain intimate and personal, wholly separate from the market. Although IVF also involves the commercialization of eggs and sperm, it fosters the creation of families. In the context of hESCR, however, markets in the raw materials of human life would be for the purpose of creating a commercial product, which might ultimately be patented and produce profits. This may be seen as sliding too far towards treating human beings as objects to be fragmented, manipulated, transformed, and ultimately sold as commodities. Fragmentation, alienation, instrumentalization, and commercialization are the hallmarks of property.[21]

The problem with this objection is that there is no question that everyone else involved in the production of human embryonic stem cells *is* entitled to compensation. The researchers who invest intellectual capital and the companies and universities that invest financial capital will surely share in any profits resulting from human embryonic stem cell research, so why not those who provide the human capital in the form of their own bodies? If the concern is commercialization, why should everyone but the donor possess property rights and profit from hESCR? Such a lopsided rule appears reminiscent of *Moore v. Regents of the University of California*, where altruism was expected of the patient, while profits were anticipated by researchers, the university, and the companies.[22] In *Moore*, the California Supreme Court held that Mr. Moore's spleen cells were not his property, although the cell line created from his spleen cells was the patented property of the researchers who created it and the university and

21. Radhika Rao, *Property, Privacy, and the Human Body*, 80 B.U. L. REV. 359 (2000).

22. *See* Moore v. Regents of Univ. of Cal., 51 Cal. 3d 120 (1990).

company that supported their research.[23] Therefore, if we insist upon altruism from the women who donate eggs for the purpose of stem cell research, shouldn't we likewise limit the profits reaped by the researchers engaged in hESCR and the universities and companies that support their research? Indeed, who would be willing to donate their eggs for free for hESCR, given the knowledge that they could sell the very same eggs for large sums of money for the purpose of fertility treatments, and that everyone else engaged in such research is permitted to profit from their act of altruism?

These justifications appear to be completely incoherent, underscoring the absence of any underlying principle. We deny hESCR donors the right to receive any compensation or even share in the proceeds of such research, while simultaneously allowing IVF egg donors to be paid large sums and permitting everyone else involved in hESCR to profit. Even the reasons offered by the NAS to justify the prohibition on payment to egg donors in the context of hESCR are contradictory. On the one hand, payment to egg donors is criticized as "coercive" because the market value may be "too high," enticing women to consent to a painful and risky procedure with the prospect of financial gain. Thus, the NAS Guidelines state that "[a] major ethical concern is that payments should not be so high as to create an undue influence or offer inducement that could compromise a prospective donor's evaluation of the risks or the voluntariness of her choices."[24] At the same time, payment to egg donors is condemned as a form of "exploitation" because the market value may be "too low," providing a level of compensation that is inadequate to attract anyone to undergo such a procedure except for those who are desperate to make money.[25] Thus the NAS Guidelines also provide that "[o]ther concerns are that payments should not be so low as to recruit disproportionately high numbers of economically disadvantaged persons and that they should compensate participants fairly for their contribution to research."[26]

Such inconsistent attitudes toward payment appear to embody an assumption that egg donations should result from "pure" altruism, rather than self-interest. To the extent that such assumptions are invoked when women are providing material that is intertwined with reproduction, they may stem from deep-seated stereotypes regarding the natural role of women as altruistic and the natural sphere of woman as the family, which should be kept separate from the market. Of course, the NAS Guidelines

23. *Id.* at 141-42.
24. NAS GUIDELINES, *supra* note 1, at 86.
25. *See id.* at 82.
26. *Id.*

provide the appearance of equality by prohibiting payment to men who donate sperm as well as women who donate eggs.[27] However, there is a vast difference between the donation of sperm and the donation of eggs in terms of the invasiveness of the egg retrieval procedure[28] and the serious risks that it entails.[29] This difference is reflected in the huge disparity in price between sperm, which possesses a market value between $50 to $100, and eggs, which may sell for as much as $100,000.[30] Thus, a rule that treats sperm and egg donors the same by denying payment to both exhibits a superficial symmetry that is deeply flawed in substance.

C. Research vs. Therapy

The NAS Guidelines offer another possible justification for a prohibition on payments: "The guidelines . . . are intended to enhance the integrity of privately funded hES cell research both in the public's perception and in actuality by encouraging responsible practices in the conduct of that research."[31] Moreover, the commentary accompanying Recommendation 16—that payment to oocyte donors should not be allowed—provides: "This recommendation is based, in part, on the recognition that payments to oocyte donors raise concerns that might undermine public confidence in the responsible management of hES cell research."[32] Indeed, the commentary accompanying Recommendation 16 makes it clear that this prohibition upon payment is limited to hESCR and should not be extended (as logic and principle would seem to require) to the field of infertility treatments: "The recommendation should not be interpreted as a commentary

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27. *Id.* at 10.

28. While both men and women contribute genetic material to create pre-embryos, women's contribution involves far more 'sweat equity.' Men's donation may be achieved relatively easily and without high-tech intervention. For women, the process is far more arduous. Ellen Waldman, *The Parent Trap: Uncovering the Myth of "Coerced Parenthood" In Frozen Embryo Disputes*, 53 AM. U. L. REV. 1021, 1052-53 (2004).

29. Indeed, the South Korean National Bioethics Committee said that fifteen of the seventy-nine women who donated their eggs to one of the hospitals collecting oocytes for Hwang's research developed ovarian hyperstimulation syndrome, and two were hospitalized. Sei Chong, *Scientific Misconduct: Investigations Document Still More Problems for Stem Cell Researchers*, 311 SCI. 754, 754-55 (2006).

30. *See, e.g.*, THE STANFORD DAILY, *supra* note 20, at 19 (offering $100,000 for "attractive, intelligent donor of East Indian decent [sic]"); *id.* at 13 (offering $80,000 to a "special egg donor" who meets the following criteria: "Caucasian," with a "height approximately 5'9" or taller," and an "S.A.T. score around 1275," who is "athletic" and has "no genetic medical issues"); *see also* Kolata, *supra* note 20, at A10 (offering $50,000 to tall egg donor with S.A.T. score above 1400).

31. NAS GUIDELINES, *supra* note 1, at 1.

32. *Id.* at 87.

on commercial IVF practices, but as a narrow policy position specifically with respect to hES cell research."[33]

These statements suggest that the distinction between hESCR and IVF may lie in the difference between research and therapy, a line that finds support in federal law.[34] Federal law limits "research" upon human subjects, but it does not circumscribe the "practice" of medicine.[35] Thus, research involving human embryonic stem cells is subject to a variety of regulations that do not apply to IVF and other forms of medical therapy that are designed to enhance the well-being of a particular patient and that have a reasonable chance of success.

The federal regulations limiting research on human subjects, however, apply only to research that is conducted by the federal government itself or by research institutions that receive federal funds. But President George W. Bush flatly banned the use of federal funds for human embryonic stem cell research on any cell lines created after August 9, 2001.[36] Thus, the federal law regulating research on human subjects does not apply to most hESCR, which is supported by other sources. Moreover, nothing in the law of research on human subjects prohibits compensation, and research subjects in other contexts typically do receive compensation.[37]

A deeper flaw in this research versus therapy argument is that it blindly follows the letter of the law while flouting the spirit of the human subject's protection. History reveals that human beings may be exposed to

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33. *Id.*

34. *See* Protection of Human Subjects, 45 C.F.R. § 46 (2000).

35. According to the Belmont Report, "the term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals." By contrast, "research" is defined as "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles and statements of relationships)." NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES & GUIDELINES FOR RESEARCH INVOLVING HUMAN SUBJECTS Part A (1979).

36. Press Release, President George W. Bush, President Discusses Stem Cell Research (Aug. 9, 2001), *available at* http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html.

37. *See* FOOD & DRUG ADMINISTRATION, *Payment to Research Subjects*, *in* INFORMATION SHEETS: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS (1998), *available at* http://www.fda.gov/oc/ohrt/irbs/toc4.html#payment; *see also* OFFICE FOR HUMAN RESEARCH PROTECTIONS, *Incentives for Participation*, *in* INSTITUTIONAL REVIEW BOARD GUIDEBOOK ch. 3, sect. G (1993), *available at* http://www.hhs.gov/ohrp/irb/irb_chapter3.htm#e7.

risk and subjected to harm without their knowledge or consent, all in the name of medicine. Federal law limiting research on human subjects protects individual autonomy and prevents individuals from being harmed needlessly or excessively for the benefit of others or society at large. These protections may not be necessary when physicians are engaged in the practice of medicine, which is intended to benefit the patient. Accordingly, IVF is not governed by the law limiting research on human subjects because it involves patients who are receiving treatment for infertility. Yet those who donate eggs to infertile couples are not receiving medical treatment. To the contrary, they are consenting to a regimen of drugs and a surgical procedure that pose great risks to them without any corresponding benefit, for the sole purpose of helping others. If compensation undermines the quality of consent and unduly influences the donor to undergo a risky and painful procedure in the context of hESCR, the same is true for IVF. From the standpoint of the egg donor, the dangers posed by payment would seem to be the same regardless of the destination of the eggs or the use for which they are designed.

Indeed, egg donation for the purpose of hESCR may be regarded as morally superior to egg donation for the purpose of IVF when the risks are weighed against the benefits. Egg donors in IVF undergo a risky and painful procedure in order to satisfy the purely private interests of infertile couples who seek biological children. Egg donors for hESCR, on the other hand, accept these risks in order to advance the public welfare of society by helping to find cures for devastating diseases. Thus, a moral calculus that would exalt egg donation for the purpose of IVF over hESCR is completely upside down. For all these reasons, the prohibition of payment appears to be intended more for political reasons than for substantive ones, to insulate human embryonic stem cell research from the taint of filthy lucre in the eyes of the public, rather than to actually prevent coercion of egg donors or commodification of human life.

D. Property vs. Privacy

In *Property, Privacy, and the Human Body*, I compared property and privacy constructions of the human body and argued that distinctions drawn between "self-ownership and sale of the body to others," are "alien to property law . . . [but are] entirely consistent with the right of privacy."[38] By allowing women only the choice whether or not to donate their eggs while denying them any right to receive compensation or otherwise share in the profits that might result from hESCR, the NAS and

38. Rao, *supra* note 21, at 364, 438.

CIRM regulations invoke the rubric of privacy rather than property. The problem is that privacy protects only the right to consent or refuse consent, but provides no power to control the body part or its use once it has been alienated from the individual. Privacy conceives of the body as a passive entity to be protected from physical interference and alteration, but not mined, manipulated, or exploited for profit. Constructing the body as a form of property, on the other hand, would imply not only freedom from physical invasion, but also freedom to instrumentalize the body by technologically manipulating it or otherwise putting it to productive use. Thus, privacy rights provide meager protection for egg donors in a context in which the body has already been alienated from the person, and is fragmented, instrumentalized, commercialized, and treated as a species of property for everyone else.

BIOETHICS AND STEM CELL BANKING IN CALIFORNIA

By David E. Winickoff†

TABLE OF CONTENTS

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I. INTRODUCTION

Too often, institutionalized bioethics proceeds on the assumption that the existing apparatus of rules is so well fixed that one must only crank new fact patterns through to obtain the correct ethical answer. Holding fast to such a view of bioethics, however, would be to ignore one of the most interesting social aspects of the new life sciences, namely, the way in which new technologies continually confront and unsettle existing dispensations of established bioethical norms.[1] In this regard, recent events in California mark a formative moment for bioethics in the United States.

When voters approved the California Stem Cell Research and Cures Initiative in the November 2004 election, it marked a sea change in the environment for public funding of human embryonic stem cell (hESC) research in the United States.[2] The U.S. government's human embryonic stem cell policy prohibits the use of federal research money to create new hESC lines, and federally funded researchers may not work on any lines created after August 2001.[3] Codified as the California Stem Cell Research

1. *See, e.g.*, David E. Winickoff, *Governing Population Genomics: Law, Bioethics, and Biopolitics in Three Case Studies*, 43 JURIMETRICS J. 187 (2003).

2. Constance Holden, *California's Proposition 71 Launches Stem Cell Gold Rush*, 306 SCI. 1111 (2004).

3. Office for Human Research Protections, Department of Health and Human Services, Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles (Mar. 19, 2002), http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf

and Cures Bond Act, California's program earmarks $3 billion in direct state spending, $6 billion including interest payments, for human embryonic stem cell research and related work over a 10-year period.[4]

Until recently, the question of whether to pursue hESC research has dominated the ethical and political discourse concerning the research. With the passage of the California program, and the development of other state initiatives in its wake,[5] more explicit attention is now devoted to the ethical and political aspects of its implementation. The California Institute for Regenerative Medicine (CIRM) has been given the legal and bioethical mandate to regulate all research funded by the stem cell initiative.[6] The roughly two years since the passage of Proposition 71 have been active ones in the formation of the regulatory regimes that will likely be implemented in California and the rest of the United States.

As the first state seriously grappling with implementing hESC research on a large scale, California will likely exert a strong influence on how stem cell research and its associated technologies are regulated nationwide. At a minimum, any regime of ethical oversight and standards in stem cell research will have to govern three distinct facets of the endeavor: (1) the procurement of the gametes, embryos, and other cells from human donors for the generation of new hESC lines; (2) the conditions under which scientists may derive new hESC lines from these materials; and (3) the manner in which already-derived hESC lines are subsequently used.[7] At least in the United States, systematic thinking in these areas has only recently begun.[8]

("Research on existing human embryonic stem cell lines may be conducted with Federal support if the cell lines meet the U.S. President's criteria which he announced on August 9, 2001[].").

4. *See generally* CAL. HEALTH & SAFETY CODE § 125291.10 (2004).

5. *See, e.g.*, John Wagner, *Maryland Approves Fund to Support Medical Stem Cell Research*, WASH. POST, Mar. 30, 2006, at A1.

6. CAL. HEALTH & SAFETY CODE § 125290.35 (2004).

7. Of course, some of these aspects of regulating stem cell research are already regulated in various ways. *See* discussion of current federal and California regulations *infra* Section II.B.

8. *See, e.g.*, NATIONAL RESEARCH COUNCIL & INSTITUTE OF MEDICINE, GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2005) [hereinafter NAS GUIDELINES]. There are notable exceptions that confront the ethical concerns of the informed consent process. *See, e.g.*, Bernard Lo et al., *Consent from Donors for Embryo and Stem Cell Research*, 301 SCI. 921 (2003); Bernard Lo et al., *A New Era in the Ethics of Human Embryonic Stem Cell Research*, 23 STEM CELLS 1454 (2005); David Magnus & Mildred K. Cho, *Issues in Oocyte Donation for Stem Cell Research*, 308 SCI. 1747, 1747-48 (2005) [hereinafter *Issues in Oocyte Donation*].

As an early adopter and promoter of hESC technologies, California will necessarily become an early and influential adopter of hESC *governance* as well. In establishing a regulatory regime for its stem cell research program, CIRM will have to develop innovative policies that will in turn carry significant normative implications for the rights of research participants, the collective goals of the state, and the interests of research institutions both in the private and public sector. Decisions in these areas will attempt to balance competing substantive and procedural goals, such as experimental freedom, economic and scientific utility, the autonomy of human donors, and public accountability in bioethical decision-making.

California's decisions in this area play upon the increasingly contested normative terrain of biotechnology, and will surely reshape that terrain. In an age of greater commercialization of clinical medicine and biomedical research, traditional relations among research subjects, researchers, taxpayers, corporations, and research institutions have come under increasing strain, whether around the control of biological samples or intellectual property rights,[9] the role of human research subjects in ethical oversight,[10] the growing frustration with the pharmaceutical industry,[11] or the pricing of medical care.[12] Furthermore, the fact that hESC research implicates a fast-evolving ethical frontier—concerning, for example, the manipulation of nascent human life, egg donation for research on a large scale, "immortalized" cell lines that can, in theory, be propagated indefinitely, and new forms of cross-species experimentation—underscores how California will face bioethical and regulatory questions of first impression. The above ob-

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9. *See, e.g.*, Moore v. Regents of the Univ. of Cal., 51 Cal. 3d 120, 129 (1990) (holding a physician must, under informed consent, disclose personal interest unrelated to a patient's health); Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1074-76 (S.D. Fla. 2003) (failing to recognize a property interest in genetic material given to defendants); Wash. Univ. v. Catalona, No. 4:03-CV-01065-SNL, at 49 (E.D. Miss. Mar. 31, 2006) (holding research patients had no proprietary interest in genetic material where it had been donated to the university research program); *see also* Donna M. Gitter, *Ownership of Human Tissue: A Proposal for Federal Recognition of Human Research Participants' Property Rights in Their Biological Material*, 61 WASH. & LEE L. REV. 257 (2004). For a recent journalistic account of this phenomenon, *see* Rebecca Skloot, *Taking the Least of You: The Tissue-Industrial Complex*, N.Y. TIMES MAG., Apr. 16, 2006.

10. *See, e.g.*, JENNY REARDON, RACE TO THE FINISH: IDENTITY AND GOVERNANCE IN AN AGE OF GENOMICS (2005) (detailing the struggles over the Human Genome Diversity Project, especially regarding the contested notion of bioethical expertise and oversight).

11. *See, e.g.*, MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (2004).

12. *See, e.g.*, DANIEL CALLAHAN, WHAT PRICE BETTER HEALTH? HAZARDS OF THE RESEARCH IMPERATIVE (2003).

servations point to the need for a bioethical analysis that can address the emergent stem cell regime in California through the lenses of democratic governance and political economy, not just with a narrow concern for protecting research subjects.

Part II of this Article explores CIRM's regulatory mandate in relation to pre-existing federal and state rules, and compares recently drafted regulations for the ethics and oversight of stem cell research under the California Initiative against an influential set of research guidelines issued by the National Academies in April 2005. Part III argues that this developing regime of ethical oversight suffers from a number of disadvantages from the perspective of governance, especially around the informed consent process, institutionalized ethical review, and egg donation. Part IV outlines my proposal of a new institutional and legal architecture that would address some of these problems through the creation of a centralized stem cell bank with special rules of participatory governance: The California Stem Cell Biorepository. Such an institution could be established in California by requiring that all new hESC lines created with CIRM funds be deposited there. If set up properly, such an institution could help improve the consent process for donors and the system of ethical oversight, as well as remediate problematic power asymmetries established in the currently proposed regime.

II. THE EMERGENT GOVERNANCE REGIME FOR STEM CELL RESEARCH IN CALIFORNIA

Proposition 71 gave the California Institute for Regenerative Medicine full authority for setting the ethical standards that will govern the new stem cell program. As mentioned above, any regime of ethical oversight and standards in stem cell research will have to govern three distinct facets of the endeavor.

First, any regime of ethical oversight for hESC research will have to govern the procurement of the gametes, embryos, and other cells from human donors for the generation of new cell lines. New lines must be derived from human embryos at an early stage of its development called the blastocyst, and there are three major pathways of donation. The first is in vitro fertilization (IVF), which results in so-called "spare" embryos.[13] The

13. IVF involves the extraction of eggs and sperm from potential parents or donors, and the creation of embryos in vitro for subsequent transplant into the potential mother's womb. "Spare embryos," sometimes called "supernumerary embryos," are those embryos created in the IVF clinic that are not actually implanted in the womb. IVF treatment often

second source of embryos could come from the creation of embryos in vitro from egg and sperm specifically for the purpose of deriving new hESC lines. A third source of stem cell lines would involve somatic cell nuclear transfer, also known as cloning.[14] Rules around procurement will help establish the processes and contexts through which donation of gametes, embryos, and adult cells may occur. These rules will also establish rights and duties between researcher and donor with respect to donated materials and the cell lines to which they give rise.

Second, the governance regime for stem cell research must address the derivation of new hESC lines. Even those who favor hESC research tend to agree that human embryos enjoy some sort of special status and should not be destroyed simply at will, without some specific research justification.[15] The use of somatic cell nuclear transfer to derive new hESC lines is an emerging practice that raises serious ethical questions around the manipulation of early human life. Since the embryos produced through cloning could in theory be used to produce a cloned human being, the use of this technique is more controversial.[16] Many bioethicists and scientists agree that if the use of this technique is to proceed, it should proceed in a regulated fashion.[17]

Third, a regime for stem cell oversight might address how already-derived hESC lines are used, an area that is currently only minimally regulated.[18] A number of highly controversial types of research are possible using human embryonic stem cells. Because of their potential to develop into human nerve and brain cells, embryonic stem cells could be used to

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involves the creation of more embryos than necessary, because some percentage of created embryos will not be viable.

14. Through this method scientists inject genetic material from an adult cell into an egg cell, stimulating it to reproduce. An advantage of somatic cell nuclear transfer is that it may avoid the problem of rejection that is common in stem cell transplantation procedures. *See, e.g.*, NAS GUIDELINES, *supra* note 8, at 13. It should be noted, however, that an efficient human cloning technique is further away than previously imagined in the wake of the discovery that Dr. Hwang's stunning cloning efficiency in South Korea was a fraud. David Cyranoski & Erika Check, *Koreans Admit Disguising Stem-Cell Lines*, 441 NATURE 790 (2006).

15. For a balanced and useful discussion, see Rebecca Dresser, *Stem Cell Research: The Bigger Picture*, 48 PERSP. BIOLOGY & MED. 184, 184-94 (2005).

16. Indeed, Canada, Spain, Switzerland, Taiwan, The Netherlands, and other countries do not allow somatic cell nuclear transfer for the creation of new hESC lines, but they do allow derivation of new lines from spare embryos. Lori Knowles, *A Regulatory Patchwork—Human ES Cell Oversight*, 22 NATURE BIOTECH. 157 (2004).

17. *See* NAS GUIDELINES, *supra* note 8.

18. *See infra* Section II.B and accompanying discussion of current federal and California regulations.

create animals with a significant number of human cells. These so-called chimeras may prove useful for conducting biomedical experiments, but they blur the boundary between human and non-human animals, introducing great complexity into the question of human research subject protections as well as animal experimentation.[19] Furthermore, human donors' rights to limit certain research uses are recognized and documented, and it will be necessary to enforce these limitations either contractually, through regulatory oversight, or through some combination of the two.

A. CIRM's Regulatory Mandate

The California Institute for Regenerative Medicine (CIRM) is governed by a twenty-nine member board, the Independent Citizens' Oversight Committee (ICOC), consisting of representatives of public and private universities, non-profit research centers, patient advocacy groups, and biotechnology firms. To help it execute its $3 billion grant-making authority, the ICOC is advised by three working groups, which include committee members and outside experts. These groups recommend research grants, facilities grants, and ethics standards. Interestingly, the California Stem Cell Initiative established the ICOC's exclusive regulatory authority over "Medical and Scientific Accountability Standards" governing CIRM-funded research.[20] This involves a regulatory exemption for CIRM-funded research from pre-existing or future state laws "dealing with the study and research of pluripotent stem cells and/or progenitor cells, or other vital research opportunities."[21]

This exemption is significant. California had been ahead of most states and even the federal government in adopting certain regulations governing stem cell research. For example, federal human research subject regulations cover all federally funded research and also all research conducted at institutions that have granted the federal research agency "assurances" of compliance,[22] which covers all major universities. This set of regulations—the so-called "Common Rule"—mandates that an institutional review board (IRB) reviews all covered human subject research protocols, and that research subjects provide informed consent.[23] However, the regu-

19. *See* Jamie Shreeve, *The Other Stem-cell Debate*, N.Y. TIMES MAG., Apr. 10, 2005 (discussing the controversy surrounding the creation of human animal hybrids). For a discussion of nascent efforts to ban the creation of certain human chimeras, see Christopher Thomas Scott, *Chimeras in the Crosshairs*, 24 NATURE BIOTECH. 487 (2006).

20. CAL. HEALTH & SAFETY CODE § 125290.35 (2004).

21. *Id.* § 125290.35(a).

22. 45 C.F.R. § 46.103 (1991).

23. *Id.* § 46. For a history of federal regulation in this area, see, e.g., RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT 151-232

lations permit a waiver of consent (as well as of full IRB review) for the research use of biological samples when the identity of the donors is not "readily ascertained" to the researchers.[24] In this case, under federal rules, such donors do not qualify as protected research subjects. In other words, so long as "spare" embryos and gametes donated for research remain sufficiently coded, then federal rules mandating informed consent and institutional review boards for both the derivation and use of stem cell lines do not apply.[25]

State laws in California governing stem cell research go well beyond federal regulations in a number of ways. First, California mandates IRB evaluation of research involving the derivation and use of hESCs, human embryonic germ cells, adult stem cells, and somatic cell nuclear transfer, even where samples and biological materials remain unidentifiable.[26] It also provides for the establishment of a "Human Stem Cell Research Advisory Committee"—a 13-member committee composed of ethicists, lawyers, scientists, and clergy—empowered to generate clear guidelines for the research by January 1, 2005.[27] All research involving derivation and use of stem cells in California would have to be approved by an institutional review board in accordance with the guidelines developed by this committee.[28] These IRBs must report to the California Department of Health on the number of projects reviewed and their status, as well as on unforeseen or adverse events.[29] Finally, California law requires the Department of Health to review IRB reports annually, to reconsider the exist-

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(1986); NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL & POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 97-108 (2001) [hereinafter NBAC, RESEARCH SUBJECTS].

24. *See* U.S. OFFICE FOR HUMAN RESEARCH PROTECTIONS, GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OF BIOLOGICAL SPECIMENS 3-4 (2004), *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.

25. However, it must be noted that this work is not necessarily unregulated by federal agencies in all cases. Absent specific triggers, federal regulation of lab research will not apply. However, if the work is on cell lines aimed at transplantation, it will be regulated by the FDA; if it involves animals, it must be overseen by an Institutional Animal Care and Use Committee (IACUC); and if it involves recombinant DNA work, it must be overseen by an Institutional Biosafety Committee (IBC). Furthermore, the absence of federal IRB jurisdiction in some instances of embryo donation does not necessarily imply an absence of a requirement of consent for use, e.g., through requirements under state common law for property, family, and contract. On the need for regulatory protections for the donors of gametes, embryos, and adult cells in stem cell research, see Bernard Lo et al., *Consent from Donors for Embryo and Stem Cell Research*, *supra* note 8.

26. CAL. HEALTH & SAFETY CODE § 125300 (2002).

27. *Id.* §§ 125118, 125118.5.

28. *Id.* § 125119.

29. *Id.* § 125119.3 (a)-(b).

ing guidelines governing the research, and to report to the California legislature on hESC research activity.[30]

The text of the Initiative declares exemption from all of these regulations in order "to avoid duplication or conflicts in technical standards for scientific and medical research." The only relevant statute that was not pre-empted requires that health providers delivering fertility treatment provide adequate information to allow individuals "to make an informed and voluntary choice regarding the disposition of any human embryos remaining following the fertility treatment," and furnish the clear choices of storing, donating, or discarding unused embryos.[31] The same statute mandates that embryos cannot be donated for research without "written consent," and that a list of statements regarding the terms of donation be conveyed to individual embryo donors.[32]

In addition to exempting CIRM-funded research from most governing statutes in this area, the Initiative text requires CIRM to establish standards for obtaining the informed consent of research participants, reviewing human subjects research, prohibiting excess payment to research donors or participants (while permitting "reimbursement of expenses"), assuring compliance with patient privacy laws, and setting a limit on the extraction of stem cells from blastocysts.[33] The California Stem Cell Research and Cures Bond Act establishes the Scientific and Medical Accountability Standards Working Group[34] to, among other tasks, "recommend to the [Independent Citizens' Oversight Committee] scientific, medical and ethical standards."[35]

The ICOC appointed its Scientific and Medical Accountability Standards Working Group in spring 2005, which met for the first time on July

30. *Id.* § 125119.5 (a)-(b).

31. *Id.* § 125315 (a)-(b).

32. *Id.* § 125315(c). The fact that this statute applies to CIRM-funded research has not been widely appreciated. Under this law, donors of embryos for research in fertility clinics must be told that identifiers associated with the embryos will be removed prior to the derivation of human pluripotent stem cells. Donors will not receive any information about subsequent testing on the embryo or the derived human pluripotent cells. Derived cells or cell lines, with all identifiers removed, may be kept for many years. Donated material may have commercial potential, and donor will not receive financial or any other benefits from any future commercial development. Human pluripotent stem cell research is not intended to provide direct medical benefit to the donor. Early human embryos donated will not be transferred to a woman's uterus, will not survive the human pluripotent stem cell derivation process, and will be handled respectfully. *See id.* § 125315(c)(1)-(7).

33. California Stem Cell Research and Cures Bond Act, CAL. HEALTH & SAFETY CODE § 125290.35(b) (2004).

34. *Id.* § 125290.50(a)(2).

35. *Id.* § 125290.55(b)(1).

6, 2005.[36] The committee adopted a set of interim standards that was based on a new set of guidelines produced in April 2005 by a joint committee of the National Research Council and the Institute of Medicine of the National Academies entitled "Guidelines for Human Embryonic Stem Cell Research" ("NAS Guidelines").[37] The NAS Guidelines focus on the derivation, procurement, banking, and use of hESC lines.[38] Co-chairs of the joint NAS committee issuing the Guidelines have urged institutions engaging in hESC research in the U.S. to adopt the voluntary Guidelines, for fear that the research is proceeding without adequate guidance at the federal level.[39] This report is a far-ranging and useful document that attempts to summarize ethical thinking in the field. It does, however, leave certain important matters unaddressed.

B. Overview and Comparison of CIRM Regulations and NAS Guidelines

The California Office of Administrative Law published CIRM's Draft Medical and Ethical Standards Regulations ("CIRM Regulations") on March 17, 2006, and a public comment period for the proposed regulations concluded on June 29, 2006.[40] Although CIRM did not adopt the NAS Guidelines in their entirety as it had done for its interim guidelines, the institute did use the NAS Guidelines as a framework.[41] The following pages provide an overview and comparison of these two sets of guidelines.

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36. *See* CIRM, Scientific and Medical Accountability Standards Working Group, http://www.cirm.ca.gov/working_group/standards.asp (last visited Aug. 13, 2006).

37. NAS GUIDELINES, *supra* note 8, at vii. The National Academies is an umbrella organization containing the National Academies of Sciences, National Academies of Engineering, Institute of Medicine (IOM), and the National Research Council (NRC). IOM is the pre-eminent academic society of health professionals, established in 1970 "to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health and the public." The NRC was organized in 1916 as the principal body of scientific experts involved in advising the government, the public, and scientific and engineering communities. *Id.* at iii; *see also* The National Academies: About, http://www.nationalacademies.org/about (last visited Aug. 13, 2006).

38. For a concise overview and assessment of the NAS GUIDELINES, see Constance Holden & Gretchen Vogel, *Panel Would Entrust Stem Cell Research to Local Oversight*, 308 SCI. 611 (2005).

39. Jonathan D. Moreno & Richard O. Hynes, *Guidelines for Human Embryonic Stem Cell Research*, 23 NATURE BIOTECH. 793 (2005).

40. These rules will be finalized by fall 2006. For an updated timeline and updated proposed changes, see CIRM, Laws/Regulations, http://www.cirm.ca.gov/laws/ (last visited Aug. 13, 2006).

41. *See* discussion *infra* pp. 1076-82.

1. Categories of Permissibility for Different Types of hESC Research

The NAS Guidelines set out three categories of permissibility for different types of hESC research, including: (a) research that does not require any additional ethical review but requires notification of relevant research ethics committees; (b) research that is permissible only after review by a hESC Oversight Committee—a new body constituted at the research institutions; and (c) research that "should not be conducted at this time."[42] This last category comprises research on any intact human embryo past fourteen days or until formation of the primitive streak begins, and also any research introducing hESCs into non-human primate blastocysts or embryonic stem cells into human blastocysts. The Guidelines also state that no animal into which hESCs have been introduced at any stage of development should be allowed to breed.[43] The CIRM Regulations follow these rules by declaring these same types of research ineligible for funding.[44] Further, both the NAS Guidelines and the CIRM Regulations reaffirm that reproductive cloning should and will not be allowed. Neither set of rules forbids other types of controversial stem cell research, such as the creation of certain kinds of human chimeras.[45]

2. Establishment of hESC Oversight Committees

The NAS Guidelines, which span 131 pages, emphasize procedural matter. They aim to provide for the ethical review of different aspects of hESC research through institutional review boards and the addition of new review entities—local hESC research Oversight Committees (ESCROs)—that fill what is widely perceived as a critical gap in the existing federal rules for the ethical conduct of hESC research.[46] The NAS Guidelines suggest that each research institution should establish an ESCRO "to provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hESC research."[47]

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42. NAS GUIDELINES, *supra* note 8, at 7-8.

43. *Id.* at 8.

44. CAL. CODE REGS. tit. 17 § 100030 (West forthcoming). One minor difference is that CIRM will not fund research involving the introduction of any stem cells (whether embryonic or not) into human embryos. *Id.* § 100030(d).

45. Chimeras are organisms with cells from multiple species. Some leading stem cell researchers see the creation of embryonic chimeras as a promising avenue of research, though it remains controversial. *See* Shreeve, *supra* note 19. For a discussion of nascent efforts to ban the creation of certain human chimeras, see Scott, *supra* note 19.

46. *See* Lo, *A New Era in the Ethics of Human Embryonic Stem Cell Research*, *supra* note 8.

47. NAS GUIDELINES, *supra* note 8, at 82.

They recommend that the ESCRO have "suitable scientific, medical, and ethical expertise to conduct its own review" and "should also include at least one person from the community."[48]

Under the CIRM Regulations, many types of CIRM-funded stem cell research cannot begin without the review and approval in writing of a similar committee, called a Stem Cell Research Oversight Committee (SCRO).[49] In the CIRM Regulations, there is less emphasis on the need for a separate SCRO at each institution, leaving the door open to create centralized review of some sort.[50] Further, for CIRM, the SCRO must include one patient advocate in addition to the one community member required under the NAS rules. But as we will see below, the function of the SCRO mirrors that of the ESCRO under the NAS Guidelines.

3. Rules for Procurement of Gametes, Blastocysts, or Adult Cells for hESC Generation

a) Institutional Review Board Review

The NAS recommends that an IRB, as described in the Federal Regulations at 45 C.F.R. § 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hESC lines,[51] even where no review is mandated under federal human research subjects regulations.[52] Under the CIRM Regulations, any stem cell lines used in CIRM-funded research must be "acceptably derived," which means already approved by a named institution[53] or else derived through a donation process approved by an IRB or equivalent institution.[54]

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48. *Id.* at 46.

49. CAL. CODE REGS. tit. 17 § 100070(a) (West forthcoming).

50. *Id.* § 100060(e) ("[A]n SCRO committee may be convened by an institution, a group of institutions, the CIRM or other state agency.").

51. NAS GUIDELINES, *supra* note 8, at 49.

52. *See supra* note 23 and accompanying text.

53. Under these rules, lines approved by NIH, deposited in the U.K. Stem Cell Bank, U.K. Human Fertilization and Embryology Authority, or derived in accordance with the Canadian Institutes of Health Research Guidelines will be considered "acceptably derived." CAL. CODE REGS. tit. 17 § 100080 (West forthcoming). It is interesting to note that none of these lines, save those coming via the United Kingdom, would have had obligatory IRB oversight over the procurement process. *See* MEDICAL RESEARCH COUNCIL, UNITED KINGDOM, CODE OF PRACTICE FOR THE USE OF HUMAN STEM CELL LINES, VERSION 2, 15 (2005), *available at* http://www.mrc.ac.uk/pdf-public-stem_cell_code_of_practice_june2005.pdf; CANADIAN INSTITUTES OF HEALTH RESEARCH, GUIDELINES FOR HUMAN PLURIPOTENT STEM CELL RESEARCH, JUNE 7, 2005, http://www.cihr-irsc.gc.ca/e/28216.html. CIRM explains these exceptions as follows:

> [T]hese subdivisions are necessary to address the issue of stem cells lines created prior to enactment of Proposition 71 and define the per-

b) Mandated Disclosures in Consent Process

Furthermore, the NAS Guidelines recommend that in all cases of donation for research a number of conditions should be met. Some of the most salient requirements include that consent be obtained from each donor at the time of donation; that where "practicable," the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hESCs not be the same person; that the consent process must contain specific disclosures:

- blastocysts or gametes will be used to derive hESCs for research that may include research on human transplantation;
- whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hESC lines and whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines;
- embryos will be destroyed in the process of deriving hESCs and derived hESCs and/or cell lines might be kept for many years, used in research involving genetic manipulation of the cells or the mixing of human and non-human cells in animal models;
- the possibility that the results of study of the hESCs may have commercial potential, and the donor will not receive financial or any other benefits from any future commercial development; and
- risks involved to the donor.[55]

The CIRM Regulations govern the procurement process of human materials in two major ways, setting up one regime for the procurement process for cell lines not created through CIRM funds, the other for cell lines derived through CIRM funding.

The procurement of stem cell lines derived from donations without CIRM funding get regulated indirectly through Section 100080 defining "acceptable research materials." As stated above, any stem cell lines used

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> missible lines for use in CIRM-funded research. This allows needed flexibility and ensures availability of acceptable stem cell lines for CIRM-funded research ensuring proper standards are adhered to.

Notice of Proposed Regulation Adoption and Initial Statement of Reasons, CAL. CODE REGS. tit. 17, div. 4, ch. 2, at 12 (Mar. 17, 2006) [hereinafter Statement of Reasons], *available at* http://www.cirm.ca.gov/laws/pdf/OalnoticeadoptionOALREVISIONSl.pdf.

54. CAL. CODE REGS. tit. 17 § 100080(e)(4) (West forthcoming).

55. NAS GUIDELINES, *supra* note 8, at 90-91.

in CIRM-funded research must be "acceptably derived," which means already approved by a named institution or else derived through a donation process approved by an IRB or equivalent institution. In lieu of a sister institution's approval, acceptable derivation also requires acquisition through "voluntary and informed consent."[56] This indirect method regulates the procurement process for materials used in the initiative.

Second, if CIRM funds are themselves used to derive new cell lines from gamete, embryo, and adult cell donations, then the SCRO must affirm compliance with specific consent procedures that are in addition to those required by Section 100080(e).[57] For this context, the CIRM Regulations contain disclosure requirements that are substantially similar to the NAS disclosure recommendations,[58] although such disclosure requirements may be "determined by the SCRO or institutional review board to be inapplicable."[59]

Finally, unlike the NAS Guidelines, the CIRM Regulations specify special disclosures that need to be made when CIRM funds pay for deriving new cell lines from donated eggs. This could occur through the donation of extra eggs in the course of IVF treatment, or through the recruitment of donors specifically for stem cell research. The rationale for this distinction in the CIRM Regulations is that egg donation specifically for research is more ethically contested than for treatment of embryo donors in the IVF context or that of sperm and somatic cell donors; egg donors are subjected to greater risks without the prospect of direct benefit.[60] Risks of egg extraction include pain and emotional stress in the short-term, and a small chance of developing ovarian hyperstimulation syndrome, which can be a serious condition.[61] Accordingly, the CIRM Regulations comprise a number of rules specific to this situation, including disclosure of the foreseeable risks of donation, the nature of the physicians' relationship

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56. CAL. CODE REGS. tit. 17 § 100080(e)(1) (West forthcoming).

57. *See id.* § 100090(a) (requiring that donors have given voluntary and informed consent in accordance with Section 100100).

58. *Id.* § 100100(b)(1-9), (c); NAS GUIDELINES, *supra* note 8, at 102.

59. CAL. CODE REGS. tit. 17 § 100100(b).

60. *See Issues in Oocyte Donation*, *supra* note 8, at 1747. A recent meta-study has concluded that large increases in cancer risk due to ovulation induction have not been established, but that some findings based on small numbers suggest slight increased risk associated with fertility drugs in certain situations. *See* Louise A. Brinton et al., *Ovulation Induction and Cancer Risk*, 83 FERTILITY & STERILITY 261, 261-74 (2005).

61. *See* American Society for Reproductive Medicine, *Ovarian Hyperstimulation Syndrome*, 82 FERTILITY & STERILITY (SUPP. 2) S81, S81-S86 (2004); *see also* Abraham Golan et al., *Ovarian Hyperstimulation Syndrome: An Update Review*, 44 OBSTET. GYNECOL. SURV. 430, 430-40 (1989).

to the research, the methods of stem cell line derivation to be used (whether fertilization, somatic cell nuclear transfer, parthenogenesis,[62] or some other method), and the possibility of recontact to gain more information in the future.[63] Effectively, under these recommendations, SCROs would have fairly broad discretion to select their disclosures.

c) Additional Protections for Egg Donors in Procurement Process

The CIRM Regulations feature a number of additional protections for egg donors involved in CIRM-funded cell line derivation. SCROs overseeing derivation must confirm that the following conditions have been met: the donor's fertility treatment has not been compromised; the funded institution has agreed to assume the cost of medical care required as a result of the donation for research; the physician attending the donor and the principal investigator are not the same person (unless approved by the IRB); and the physician performing oocyte retrieval does not have a financial interest in the outcome of the research.[64]

Note however, that these special rules only govern the egg donation process when those eggs will be prospectively collected for use in CIRM-funded research. Recall that research on pre-existing cell lines derived from donated eggs can be used so long as they have been "acceptably derived," that is, derived from reciprocal institutions or assuredly derived after IRB review and informed consent. In other words, CIRM-funded researchers may use lines that have been previously derived from eggs donated specifically for research that were not donated under the more rigorous conditions of Sections 100090(b) and 100100(d).

d) Payment of Donors and for Donated Materials

The CIRM Regulations require that assurances be made to SCROs that no stem cell lines used in CIRM-funded research involved the purchase or sale of gametes, embryos, somatic cells or human tissue,[65] or the compensation of donors beyond "permissible expenses."[66] The Regulations define "permissible expenses" as "necessary and reasonable costs directly incurred as a result of donation or participation in research activities," including but not limited to "costs associated with travel, housing, child

62. Parthogenesis is a form of reproduction in which the ovum develops into a new individual without fertilization.

63. CAL. CODE REGS. tit. 17 § 100100(d) (West forthcoming).

64. *Id.* § 100090(b)(1)-(3).

65. *Id.* § 100080(e)(3).

66. *Id.* § 100080(e)(2).

care, medical care, health insurance and actual lost wages."[67] These rules are based on the NAS Guidelines.[68]

4. Rules for the Derivation of New hESC Lines and Use of Oocytes and Embryos

The CIRM Regulations closely follow the NAS Guidelines regarding the proper oversight of new stem cell line derivations. CIRM-funded research involving derivation of new stem cell lines or the use of human oocytes or embryos in the research may not proceed without SCRO committee review and approval in writing.[69] CIRM-funded researchers must justify the need for new lines and the number of new cell lines needed, and provide special rationale for using somatic cell nuclear transfer.[70] They must provide documentation of compliance with any required review of the proposed research by an IRB and other already mandated reviews,[71] and document how stem cell lines will be characterized, validated, stored, and distributed to ensure donor confidentiality.[72] All of these rules track closely the recommendations of the NAS.[73]

5. Rules Governing the Research Use of hESC Lines

As explained above, federal regulations governing research with human subjects generally do not cover laboratory research with existing hESCs unless the research involves personally identifiable information. The NAS Guidelines state that this research should nevertheless be reviewed by an ESCRO committee, and create a two-tiered system of oversight.[74] For basic in vitro research on pre-existing hESC lines, ESCRO committees should require "notification" of the research, "documentation of the provenance of all hES cell lines," and "evidence of institutional review board approval of the procurement process."[75] The Guidelines provide that all cross-species transplantation and experimentation be subject to ESCRO pre-approval of protocols.[76] The rules for CIRM-funded stem cell research follow the recommendations of the NAS fairly closely here.

67. *Id.* § 100020(h).
68. *See* NAS GUIDELINES, *supra* note 8, at 85-86.
69. CAL. CODE REGS. tit. 17 § 100070(a) (West forthcoming).
70. *Id.* § 100070(a)(1).
71. *Id.* § 100070(a)(3).
72. *Id.* § 100070(a)(4).
73. *See Recommendations 4.1-4.4, 4.6, in* NAS GUIDELINES, *supra* note 8, at 73.
74. *See* NAS GUIDELINES, *supra* note 8, at 105-06.
75. *See Recommendations 6.0-6.2, in* NAS GUIDELINES, *supra* note 8, at 89.
76. *See Recommendations 6.4-6.7, in* NAS GUIDELINES, *supra* note 8, at 54.

Chimeric research requires SCRO review and pre-approval,[77] while in vitro research on pre-existing lines requires written "notification" to the SCRO and "assurances" that all lines have been acceptably derived.[78] Unlike the Guidelines, the CIRM Regulations seem to allow for a waiver of full review by the SCRO committee even where cell lines are identifiable, although such protocols would be subject to IRB review under the federal regulations, and may also trigger the Health Insurance Portability and Accountability Act's consent requirement. The CIRM Regulations would require establishing registries cataloguing all CIRM-funded research and all materials used in the research, with sufficient detail to establish provenance and disposition.[79]

III. ANALYSIS AND CRITIQUE OF CIRM'S CONSENT AND SCRO REGIME

So what can be said about this emergent regime of bioethics for stem cell research in California, other than the fact that it follows many of the rules advocated by the National Academies and departs from others? The CIRM Regulations represent an impressive body of work and a credible adaptation of the prevailing human subjects protection regime in the United States to a novel context. Nevertheless, I wish to make a number of critiques about this regime, some of which could easily be leveled at other wings of the governance system for biomedical research as well.

First, the consent process under the CIRM Regulations breaks with traditional notions of informed consent in ways that must be acknowledged: the regulations exemplify how informed consent has become a mechanism of expropriating commercial rights from altruistic donors over their biological materials in ways that may undermine meaningful choice. Second, in light of existing experience with IRBS and also the unique questions we face with stem cell research, the regime of ethical oversight by the SCROs suffers from a number of disadvantages from the perspective of governance: the proposed system of SCRO review may reproduce many of the well-documented problems with the decentralized institutional review board system, and suffers from a lack of transparency and public accountability with respect to both the public and donors. Third, although recent bioethical commentaries and the emergent rules discussed above have focused due attention to filling critical regulatory gaps, too

77. CAL. CODE REGS. tit. 17 § 100070(b) (West forthcoming).

78. *Id.* § 100070(c).

79. *Id.* § 100120. Registries are also recommended by NAS. *See* NAS GUIDELINES, *supra* note 8, at 53-61.

little attention has been paid to the political economy of egg donation in the hESC context—the patterns of extraction, use, and transfer of eggs in relation to markets, power relations, regulation, and collective action. Rules with respect to financial compensation to donors deserve deeper scrutiny in light of the larger political economy of both human eggs and U.S. biomedical research in the twenty-first century.

A. The Regime of Consent: Autonomy, Open Consent, and Commercial Use

Informed consent is the traditional pillar of the protection of autonomy in research involving human subjects.[80] Articles in the bioethics literature repeatedly state that consent should involve a process of communication, not simply filling out a form.[81] If individual subjects are treated with respect, they will understand the purposes for which their tissue or blood will be used, comprehend the risks and benefits of particular projects, and retain the right to withdraw from the study at any time.[82] The CIRM Regulations raise two large issues regarding informed consent and autonomy. First, the consent process under the CIRM Regulations breaks with these traditional notions of informed consent in ways that must be acknowledged. Second, the CIRM's consent rules are emblematic of how informed consent has become a mechanism of expropriating commercial rights from altruistic donors over their biological materials in ways that may undermine meaningful choice.

The CIRM Regulations provide that the consent process for derivations of new hESC lines using CIRM funds must include a statement to the effect that resulting cell lines may be used for future studies that are

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80. NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE, VOL. 1, 47-49 (1999) [hereinafter NBAC, BIOLOGICAL MATERIALS].

> Put most simply, to be autonomous is to be one's own person, to be directed by considerations, desires, conditions, and characteristics that are not simply imposed externally upon one, but are part of what can somehow be considered one's authentic self. Autonomy in this sense seems an irrefutable value, especially since its opposite—being guided by forces external to the self and which one cannot authentically embrace—seems to mark the height of oppression.

John Christman, *Autonomy in Moral and Political Philosophy*, *in* THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Edward N. Zalta ed., 2003), *available at* http://plato.stanford.edu/archives/fall2003/entries/autonomy-moral; *see also* GERALD DWORKIN, THE THEORY AND PRACTICE OF AUTONOMY (1988).

81. George J. Annas, *Reforming Informed Consent to Genetics Research*, 286 JAMA 2326, 2326 (2001).

82. FADEN & BEAUCHAMP, *supra* note 23, at 151-232.

not predictable at this time.[83] There remains a hotly contested question in bioethics concerning whether human research subjects should be allowed to grant a broad and "open" consent over future and unspecified uses of their bodily materials.[84] A broad waiver of control over the future uses of donor cells cannot protect the donor's autonomy in the way that the traditional mechanism of informed consent was intended. The major virtue of promoting broad consent for unforeseen future uses of biological materials is efficiency: if researchers have to go back to the donor every time a new research project is proposed, the consent process would slow down research and significantly increase transaction costs. But there are also costs in terms of donor autonomy. Open-ended permission makes it difficult for participants to make informed and voluntary decisions throughout their involvement in the research.[85] There may also be costs in terms of participation: donors may be more reluctant to participate if they are not given a clear idea of how exactly their donations will be used.

This issue of the permissibility of open consent was contested on President Clinton's National Bioethics Advisory Commission (NBAC).[86] Some have attempted to balance the interests in efficiency of research and the autonomy of tissue donors by arguing that biobanks' requests for general permission should be allowed only if certain additional safeguards are in place, including provision of information about subsequent contact, clearly stated time limits for the project, an absolute right of withdrawal, disclosure of details about commercial arrangements, and the ethical review of any subsequent research.[87] Except for a provision of information

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83. CAL. CODE REGS. tit. 17 § 100100(b)(3) (West forthcoming).

84. *See* Marshall B. Kapp, *Ethical and Legal Issues in Research Involving Human Subjects: Do You Want a Piece of Me?*, 59 J. CLINICAL PATHOLOGY 335, 336 (2006).

85. *See, e.g.*, Henry T. Greely, *Breaking the Stalemate: A Prospective Regulatory Framework for Unforeseen Research Uses of Human Tissue Samples and Health Information*, 34 WAKE FOREST L. REV. 737, 737-66 (1999) (arguing that because it is impossible for the donor to make an informed choice about the risks and benefits of unspecified future research protocols, such permission should never be called informed consent).

86. A majority of the NBAC members recommended that signed consent to unforeseen research uses of biological samples—"open consent"—may be an acceptable alternative to requiring informed consent for each specific use of the sample. *Recommendation 9*, *in* NBAC, BIOLOGICAL MATERIALS, *supra* note 80, at 64-65. NBAC members Capron and Shapiro rejected the view that patients and donors should be allowed under any circumstances to consent to "any kind of future study." *Id.* at 65.

87. Greely, *supra* note 85, at 764, stakes out this middle position. Still other bioethicists reject "open consent" unless all DNA samples are stripped of all identifiers. *See, e.g.*, George J. Annas, *Privacy Rules for DNA Databanks: Protecting Coded "Future Diaries"*, 270 JAMA 2346, 2347-48 (1993) (suggesting that individuals might not give

regarding recontact of donors,[88] the CIRM Regulations lack many of these safeguards. No time limits must be stated. Instead, a statement that the materials will be "kept for many years" is required.[89] Whereas the NAS Guidelines state that donors "should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation,"[90] the CIRM Regulations require no such disclosure.

Furthermore, neither the NAS Guidelines nor the CIRM Regulations recommend or require the disclosure of details concerning planned commercial uses of derived cell lines. Rather, they both require a general statement that the research may have commercial potential and that donors "will not receive financial or any other benefit from future commercial development."[91] These rules provide researchers, research institutions, and commercial entities broad leeway for appropriating the commercial value of donations and the cell lines to which they give rise. This marks more of a continuity than a departure from existing practice in the use of biological samples in research.[92] Nevertheless, the rules provide donors little awareness of whether or not their materials and derivatives will be controlled by commercial entities.

Even after reading statements like those recommended by CIRM, donors may be misled on this score. Empirical studies in the genomic biobanking area suggest that arrangements between medical centers and for-profit biobanks are often insufficient to keep donors apprised of new research uses for their samples. As a result, when patients agree to donate tissue or blood, they sign away their control and oversight. Patients might disagree with a particular commercial or scientific use of their material, but they have no recognized right to be kept informed about it. A number of well publicized cases have emerged in which participants who thought they were participating in an altruistic endeavor subsequently sued their

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permission if they knew that the data were being used to study possible genetic correlations to conditions such as alcoholism or homosexuality).

88. CAL. CODE REGS. tit. 17 § 100100(b)(2) (West forthcoming).

89. *Id.* § 100100(b)(1).

90. *See Recommendation 3.2*, *in* NAS GUIDELINES, *supra* note 8, at 83.

91. *See Recommendation 3.6(h)*, *in* NAS GUIDELINES, *supra* note 8, at 91; CAL. CODE REGS. tit. 17 § 100100(b)(9) (West forthcoming).

92. This waiver of commercial benefits is by now a standard feature of informed consent forms for research protocols involving donated biological samples. *See* Winickoff, *Governing Population Genomics*, *supra* note 1, at 207-14. Even where there is no informed consent on this score, courts have tended to support a default rule at common law that research donors retain no commercial rights after donation. *See* Moore v. Regents of the Univ. of Cal., 51 Cal. 3d 120, 137-38 (1990). Common practice, however, does not necessarily make it a good one.

research institution when its intellectual property practices led to prohibitively expensive pricing or other commercial behavior.[93]

The drafters of the CIRM Regulations attempted to enhance the degree of choice afforded to materials donors by requiring researchers to offer them the opportunity to express objections to certain types of research. The NAS Guidelines mention the possibility, but not the requirement, that donors be offered the option of agreeing to some forms of hESC research but not others. "For example," the Guidelines state, "donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for [SCNT]. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored."[94] The CIRM Regulations make providing this option to donors a requirement, stating that "researchers *shall* offer donors an opportunity to document their preferences regarding future uses of their donated materials" (emphasis added).[95] However, the CIRM Regulations take pains to point out that "researchers may choose to use materials only from donors who agree to all future uses."[96] Furthermore, no CIRM funds may be used to support research that "violates the documented preferences of donors with regard to their donated materials."[97]

Despite these specific rules on donor limitation, the CIRM rules evince a spirit of compromise but real ambivalence regarding the powers of donors to exert control over cell lines derived from their materials. The rules do not specify the choices that donors should have regarding which types of research. For example, should donors be explicitly given the choice to opt-out their materials from somatic cell nuclear transfer (cloning) derivations and chimeric experiments? Should consent forms have check-boxes next to these "sensitive" techniques, or simply allow for open-ended objections? CIRM rules seem to imagine a regime of blanket disclosure of a

93. While *Moore v. Regents* is the canonical case, there have been other recent cases. For example, when a group of Canavan's patients and their families agreed to participate in research on their disease, they were subsequently shocked to find out that a diagnostic test discovered through their participation had been patented, and that many members of the group were incapable of affording the test at market prices. Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1067 (S.D. Fla. 2003). This case recently settled out of court. *See also* Skloot, *supra* note 9.

94. NAS GUIDELINES, *supra* note 8, at 91.

95. CAL. CODE REGS. tit. 17 § 100100(c) (West forthcoming).

96. *Id.*

97. *Id.* § 100100(b).

large range of types of research, without facilitating donor choice.[98] Although a strong efficiency rationale for framing, indeed constructing, donor autonomy in this way exists, perhaps we really don't believe that donors have a deep claim in determining how the materials derived from their cells are used. However, an argument otherwise will be developed below. Even so, different consent procedures construct, as much as embody, different visions of research participant subjectivity. It should be acknowledged that there were many ways a more autonomous research donor might have been imagined.

B. The Regime of SCROs

Following the model of the NAS Guidelines, the CIRM Regulations attempt to fill gaps in existing research oversight by creating Stem Cell Oversight Committees (SCROs). In a structural sense, this mechanism of research oversight mimics the existing federal institutional review board regime in a number of ways. First, oversight bodies will tend to be localized at the research institution, although the regulations permit institutional sharing. Second, the regulations set minimum standards that local oversight bodies must follow, but not precise standards of review. Third, the system of oversight is enforced through contractual mechanisms tied to research funding. While having such an oversight system is better than having none at all, and is certainly a credible attempt to adapt the existing IRB model to stem cell research oversight, such a system has a number of important shortcomings.

1. Reproducing the Institutional Review Board's Well-Known Problems

Localized IRB oversight has some well-known advantages.[99] However, the proposed system of SCRO review may reproduce many of the well-documented problems with the decentralized institutional review board system, which is widely believed to be inadequate.[100] Many U.S.

98. The level of detail in the regulations would be going beyond what is typical for regulatory language and is more typical of the close details governed at the IRB or SCRO level. Nevertheless, the regulatory-level guidelines do construct the normative frameworks for local review board activities, and it would be highly unlikely for individual review boards to enact consent mechanisms that do more than is required in terms of offering choices to research participants.

99. NBAC, RESEARCH SUBJECTS, *supra* note 23, at 30 (discussing the advantages and disadvantages of a centralized, as opposed to localized, IRB system and noting that localized review helps provide important contact and proximity to those involved in the daily conduct of research).

100. *See, e.g.*, Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANNALS INTERNAL MED. 282,

agencies and professional organizations have already proposed remedies for major problems such as uneven standards, poor enforcement, and the scarcity of IRB resources.[101] Because of these problems, NBAC discussed at length the desirability of centralized accountability and standardization across the IRB system.[102]

Creating yet another ethical review body within the research institutions themselves would also suffer from an emergent problem afflicting institutional review boards in the modern era of academic-industry relations, namely that of institutional conflicts of interest.[103] Institutional conflicts of interest between the SCROs, research donors, and "the public" would be most pronounced in CIRM-funded entities organized as commercial enterprises. Nevertheless, another problem, which the Jesse Gelsinger incident at the University of Pennsylvania has come to symbolize, increasingly abounds, namely that of conflicts at non-profit hospitals, clinics, and other research entities themselves possessing investments or financial interests in the human subjects research being conducted.[104] SCRO members are likely to be department chairs, deans, and mid- and high-level administrators from the research institution itself. Such members would likely appreciate the value of these investments to the institution, and may be influenced by the desire to protect the overall fiscal health of the entity.[105]

282-86 (2004). *See generally* JUNE GIBBS BROWN, INSPECTOR GENERAL, DHHS, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM (1998), *available at* http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf.

101. *See, e.g.*, Emanuel, *supra* note 100; *see also* INSTITUTE OF MEDICINE, PRESERVING PUBLIC TRUST: ACCREDITATION AND HUMAN RESEARCH PARTICIPATION PROGRAMS (2001).

102. NBAC, RESEARCH SUBJECTS, *supra* note 23, at 28-64.

103. *See, e.g.*, Ezekiel J. Emanuel & Daniel Steiner, *Institutional Conflict of Interest*, 332 NEW ENG. J. MED. 262, 262-67 (1995).

104. *See* Mark Barnes & Patrick S. Florencio, *Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future*, 32 SETON HALL L. REV. 525, 547-48 (2002). The 1999 death of 18-year-old Jesse Gelsinger, a research subject in a gene therapy trial for a rare metabolic disorder, caused the government and research institutions to scrutinize the profitable relationships that researchers and their academic institutions have with companies that are financing their research. Gelsinger died in an experiment at the University of Pennsylvania's gene therapy program led by Dr. James Wilson, who founded a company that funded part of the research. The company, Genovo Inc., was later sold to a bigger company and Wilson received a reported $13.5 million in stock. *See also* Robert Gatter, *Walking the Talk of Trust in Human Subjects Research: The Challenge of Regulating Financial Conflicts of Interest*, 52 EMORY L.J. 327, 330-342 (2003).

105. For a discussion of these conflicts in the IRB context, see Barnes, *supra* note 104, at 544-48.

2. Transparency, Accountability, and Trust

The SCRO regime also has a number of shortcomings in terms of transparency and public accountability, problems that may undermine public trust in the oversight system over the long term. As discussed above, hESC research will likely involve procedures—such as somatic cell nuclear transfer, or cloning, as well as mixing human stem cells into non-human organisms to create chimeras—that remain ethically controversial in the public at large. Under the NAS Guidelines and the CIRM Regulations, the local stem cell oversight committee would have the discretion to approve or disapprove of new stem cell line derivations, whichever technique is used, and also chimeric experiments. Many countries currently forbid somatic cell nuclear transfer techniques with human cells.[106] Others, such as the United Kingdom, allow research using these techniques but only after researchers receive a license from a centralized regulatory authority.[107] Although the Independent Citizens' Oversight Committee and the Scientific and Medical Accountability Standards Working Group must both conduct their meetings in public, the work of the SCROs will not be conducted in public. There is a danger that the SCRO system of oversight could create the perception that crucial ethical decisions are being made in the dark backrooms of the very institutions that stand to gain from large CIRM grants. Because the research is occurring on a fast-changing ethical landscape, there is a strong push to proceed quickly in California. Moreover, because the system of assurances involves self-reporting only, the danger of undermining public trust in the proposed stem cell research governance regime is especially high.

Focusing on the composition of membership on ethical oversight committees may engender public representation, accountability, and trust. The CIRM Regulations specify that in addition to having "persons with expertise in, including but not limited to, developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research," the SCRO should also have a public representative from a non-scientific background and also at least one patient advocate. This seems a rather meager nod to public representation. In pointed contrast, the Human Fertilisation and Embryology Authority in the United

106. Shaun D. Pattinson & Timothy Caulfield, *Variations and Voids: the Regulation of Human Cloning Around the World*, 5 BMC MED. ETHICS 1, 1-8 (2004), *available at* http://www.biomedcentral.com/1472-6939/5/9.

107. *See* Knowles, *supra* note 16, at 160.

Kingdom contains a majority of non-physicians and scientists in related areas.[108]

3. Donor Participation in Oversight

As currently imagined, SCROs suffer from a lack of accountability not only with respect to the public at large, but also with respect to the donor group. In the field of biobanking for genetics and other research, both accountability to and representation of the donor group have emerged as important norms and active areas of policy development.[109] Recent controversies involving donor groups, researchers, and commercial entities around ethical decision-making have led to lawsuits and the collapse of projects.[110] Institutional review board decision-making has become less tenable in the absence of donor representation when there are commercial rights at stake, and disparate risks and benefits will be distributed across different constituencies, whether they are commercial interests, research interests, or the participants themselves.[111] The interests of research par-

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108. *See* Human Fertilisation and Embryology Act 1990, Schedules, http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_3.htm#sdiv1 (last visited Aug. 21, 2006). The relevant provision states:

> (3) The following persons are disqualified for being appointed as chairman or deputy chairman of the Authority—
>
> (a) any person who is, or has been, a medical practitioner registered under the [1983 c. 54.] Medical Act 1983 (whether fully, provisionally or with limited registration), or under any repealed enactment from which a provision of that Act is derived,
>
> (b) any person who is, or has been, concerned with keeping or using gametes or embryos outside the body, and
>
> (c) any person who is, or has been, directly concerned with commissioning or funding any research involving such keeping or use, or who has actively participated in any decision to do so.
>
> (4) The Secretary of State shall secure that at least one-third but fewer than half of the other members of the Authority fall within subparagraph (3)(a), (b) or (c) above, and that at least one member falls within each of paragraphs (a) and (b).

Id.

109. *See* REARDON, *supra* note 10; *see also* Winickoff, *Governing Population Genomics*, *supra* note 1, at 196-201 (arguing that the struggles over the Human Genome Diversity Project highlight how expert ethical review can usually be reframed as not just an expert, but also a political space, one requiring political representation of participants especially where group interests—whether financial or cultural—are at stake).

110. *See, e.g.*, REARDON, *supra* note 10; *see also* Eric Niiler, *Collapse of Framingham Data Deal Highlights Lack of Cooperative Model*, 19 NATURE BIOTECH. 103 (2001); Gitter, *supra* note 9.

111. *See* Winickoff, *Governing Population Genomics*, *supra* note 1, at 192-93, 226-28.

ticipant groups are often not commercial. For instance, a number of disease groups have actively constructed their own biobanks in order to steer research to the particular diseases they are interested in.[112]

The controversies over donor accountability and representation in IRB review underscore the ways in which the CIRM Regulations are problematic. Recall that CIRM Regulations recommend ethical review of subsequent research on CIRM-derived cell lines only for the most sensitive of research applications; otherwise mere notification suffices. Furthermore, if researchers in California send cells out to non-CIRM-funded researchers, then any subsequent SCRO oversight would be purely voluntary. No formal legal requirement would exist that research funded outside of CIRM, but on CIRM-derived lines, be subject to any institutional oversight. If donors wish to limit the types of research that can be conducted using their materials, it will be left to researchers' own materials transfer agreements, and no SCRO oversight, to help ensure that these limitations are enforced. But the CIRM Regulations do not make this obligation of researchers related to distributing CIRM-funded cell lines explicit.

This lack of accountability to and representation of the donor group is especially problematic for women who donate eggs, as this group of women will incur a greater proportion of the physical risks involved in this research, as discussed below.[113]

C. The Regime of Property, Power, and Egg Donation

As stated above, both the NAS Guidelines and the CIRM Regulations recommend an altruistic regime of egg donation that compensates donors only for direct expenses. This regime contrasts with that of donation in the IVF context, at least in the United States, where more of an open market prevails in which women can be paid in excess of $5,000 per procedure.[114] Limiting the free market in this context is not unreasonable; inducing egg donors with money would tend to shift disproportionately the health burdens of supplying eggs onto poorer women, resulting in possible economic coercion.[115] However, the donation regime proposed by the NAS Guide-

112. *See id.* at 222-26.

113. *See* discussion *infra* Section III.C.

114. Kenneth Baum, *Golden Eggs: Towards the Rational Regulation of Oocyte Donation*, 2001 B.Y.U. L. REV. 107, 108 (2001). For a recent journalistic account of the emerging market for eggs in the IVF context, see Carlene Hempel, *Golden Eggs*, BOSTON GLOBE MAG., June 25, 2006.

115. There is extensive literature on how to distinguish between a coercive, as opposed to an enticing but ethical offer. In practice, the line may not be clear. *See, e.g.*, Neal Dicker & Christine Grady, *What's the Price of a Research Subject? Approaches to Payment for Research Participation*, 341 NEW ENG. J. MED. 198-203 (1999); Evan G. DeR-

lines—and largely enacted in California—raises at least three ethical problems that have been inadequately addressed by policymakers.[116]

First, there is the problem of what might be called "asymmetrical altruism." Under the NAS Guidelines and the CIRM Regulations, the regime of altruism is deployed asymmetrically with respect to donors and researchers: while altruism is required of donors, it is not required of research institutions or corporations that may profit from the donations. As mentioned before, this asymmetry might be justified by the possibility of coercion raised by payment. But if society is so worried about the possible coerciveness of paying women for eggs, or about the commodification of body parts, why are payments in excess of $5,000 allowed in the IVF context? Although such asymmetry is not new in biomedical research, it is more troublesome in this context where the risk and time-burden of donation is significant, and where the commercial value of the resulting products—new human embryonic cell lines—are likely to be significant.

Second, the NAS Guidelines fail to address compensation of donors who are harmed in the process of donation, and the proposed rules in California do so insufficiently. Existing federal research policies do not require compensation for injured research participants, and the NAS Guidelines are silent about the issue. However, a compensation system is warranted in large-scale programs of state-sponsored egg donation as a matter of fairness. CIRM has moved part of the way towards closing this gap in a set of proposed research standards in which funded institutions would have to agree to "assume the cost of any medical care required as a direct and proximate result of oocyte donation for research."[117] But because some of the health problems that may be associated with egg retrieval do not show up in the short term, such as infertility or ovarian diseases, this provision may prove inadequate.[118] Large state funding programs like California's should make sure that research institutions provide insurance to egg donors that cover both short and long-term risks associated with

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enzo, *Coercion in the Recruitment and Retention of Human Research Subjects, Pharmaceutical Industry Payments to Physician Investigators, and the Moral Courage of the IRB*, 22 IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH 1, 1-5 (2000).

116. This section is based on David E. Winickoff, *Governing Stem Cell Research in California and the USA: Towards a Social Infrastructure*, 24 TRENDS IN BIOTECH. 390 (Sept. 2006).

117. CAL. CODE REGS. tit. 17 § 100080 (West forthcoming).

118. *See, e.g.*, Brinton, *supra* note 60, at 261-74; American Society for Reproductive Medicine, *supra* note 61, at S81-S86; Golan, *supra* note 61, at 430-40.

egg extraction, though more research on these long-term risks will undoubtedly be necessary.[119]

Finally, there is a strong argument to be made from the perspective of procedural justice that altruistic donors should be represented as a group in the regime of ethical oversight, especially where the power to benefit financially from donation is denied to individual donors. Neither the NAS Guidelines nor the proposed CIRM Regulations would allow donors to exercise any collective power in the governance of the research. The NAS Guidelines recommend that local oversight committees include "at least one member of the community," but there is little or no discussion of the collective representation of egg donors in the regime of ethical oversight.[120] But the contributions of charitable egg donors to public hESC projects arguably give rise to special duties of political accountability and representation to this group of women, which might mean donor representation both on ethics committees and committees setting funding priorities. These committees are charged with weighing collective scientific benefits of particular forms of research against potential harms to this group of donors, who arguably should be represented in this process as a matter of legitimacy. Research participants on the whole are not usually represented on ethics review committees in other contexts, but this does not necessarily justify the practice from a political theory point of view. Further, the claim of representation for the donor group in the egg donation context is arguably greater than in other forms of research participation. The significance of the donor group in the hESC research context, the denial of financial compensation, and the historic neglect of women's health issues in research[121] all suggest how a more participatory form of governance may be appropriate, useful, and fair.

IV. THE CALIFORNIA STEM CELL BIOREPOSITORY (CSCB)

This Part explores my proposal for stem cell policy that would strengthen hESC research governance in important ways: the construction of a centralized public stem cell bank in California, to be linked up with

119. Compensating for long-term risks associated with egg donation, however, does raise the problem of uncertainty in causation, a well-known problem in toxic tort litigation. Clearly, more data and study is needed in this area before claims could be adjudicated fairly and efficiently.

120. NAS GUIDELINES, *supra* note 8, at 55. However, note that later in the report, the recommendation is for the ESCROS to "include representatives of the public," indicating that one might not be sufficient. *Id.* at 100.

121. *See generally* SUSAN SHERWIN, NO LONGER PATIENT: FEMINIST ETHICS AND HEALTH CARE (1992).

national and international networks of similar banks in the future, with particular structures designed to render policies more transparent, accountable, and effective. The NAS Guidelines set out a number of standards for the banking of hESC lines, and commend efforts that have begun to encourage the sharing and dissemination of cell lines and other research materials.[122] These recommendations suggest that each cell line repository establish uniform guidelines for quality control, standardized consent and IRB procedures, tracking procedures, privacy assurances, and consistent rules for deposits and withdrawals. They also develop a committee for policy and oversight.[123] Nascent efforts to build such facilities have begun in both the United Kingdom and Wisconsin with some success,[124] and the NAS Guidelines focus on the U.K. Stem Cell Bank.[125] However, whereas the centralized stem cell bank plays a crucial role in the governance architecture in the U.K., it seems to play a much smaller governance role within the NAS's imagined regulatory regime. Furthermore, the idea of centralized banking of stem cell lines, though perceived as a probable eventuality by CIRM, has not been discussed as a feature of stem cell governance.

The ways in which the stem cell bank could be an efficient and effective vehicle for better governance over stem cell research in California deserve exploration. Indeed, the U.K. model might be adapted to the California context and extended in a way that actually addresses existing shortcomings in the regulatory regimes discussed above.

A. The Role of Stem Cell Banks in Governance: The U.K. Model

Concerned with research involving both embryonic and adult stem cells, the U.K. Stem Cell Bank is a repository aiming to facilitate the sharing of well-characterized and high-quality cell lines with the clinical and research communities in order to support research and the development of

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122. NAS GUIDELINES, *supra* note 8, at 76-79.

123. *See Recommendations 22-23*, *in* NAS GUIDELINES, *supra* note 8, at 128-29.

124. *See* STEERING COMMITTEE FOR THE UK STEM CELL BANK AND FOR THE USE OF STEM CELL LINES, FIRST ANNUAL REPORT FROM THE UK STEM CELL BANK (2004), *available at* http://www.mrc.ac.uk/pdf-stemcell_steer_comm_annrep.pdf; Associated Press, *Wisconsin Group to Run Stem Cell Bank: Federal Program Will Store and Distribute Cells for Research*, Oct. 4, 2005. The federally-funded stem cell bank in Wisconsin is limited to storing and distributing lines approved under Bush's policy, a fact that has hampered the bank's importance. Harvard University, for instance, now distributes far more batches of cell lines than this national bank. Rob Waters & John Laureman, *Harvard Stem Cells Favored Over Those Produced With U.S. Funds*, BLOOMBERG.COM, July 13, 2006, http://www.bloomberg.com/apps/news?pid=20601103&sid=aeyb8GOm8Md8&refer=us.

125. NAS GUIDELINES, *supra* note 8, at 76.

new therapies to treat serious disease.[126] Funded by the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council pursuant to recommendations made by a House of Lords Select Committee, the U.K. Stem Cell Bank (UKSCB) plays a central role in the governance regime for stem cell research in the United Kingdom. The UKSCB's institutional structure and practices help demonstrate that stem cell banks may be useful for ethical oversight and governance in stem cell research.

1. Institutional History

Exactly how the UKSCB became a crucial site of research governance in the U.K. deserves review. In the early 1980s, the United Kingdom worked as a pioneer in the area of new reproductive technologies. The U.K. made new scientific and clinical advancements in the field, but also discussed relevant legal and ethical issues related to such research with the publication of the *Warnock Report* in 1985.[127] The Human Fertilisation and Embryology Act of 1990, passed on recommendations made in the *Warnock* report, created a licensing body for research involving embryos know as the Human Fertilisation and Embryology Authority (HFEA). The governing policy of the Act attempts to promote open and effective regulation of embryo research, delineating that the HFEA should license work only if it is necessary in relation to approved statutory purposes, and that research on embryos should not run beyond fourteen days.[128] Acceptable goals for the research originally included either promoting the advancement in the treatment of fertility, increasing knowledge about disease or miscarriages, developing more effective techniques for contraception, or developing methods for detecting gene or chromosome abnormalities.[129]

Advances in stem cell research throughout the 1990s prompted HFEA officials to revisit regulations and consider whether licenses for stem cell research could be issued under the 1990 Act's originally stated purposes. In 2001, the HFEA released new regulations that added new purposes to embryo research in order to facilitate work on stem cells. These new purposes included increasing knowledge about embryo development or serious disease and its treatment.[130] With the release of the regulations, con-

126. CODE OF PRACTICE, *supra* note 53.

127. *See* Matthew Herder, *The UK Model: Setting a Standard for Embryonic Stem Cell Research?*, 10 HEALTH L. REV. 14, 14-24 (2001).

128. Roger Brownsword, *Stem Cells, Superman, and the Report of the Select Committee*, 65 MOD. L. REV. 568, 571 (2002).

129. Human Fertilisation and Embryology Act 1990, *supra* note 108.

130. *Id.*; Brownsword, *supra* note 128, at 572.

cerns were raised as to whether cloned human embryos produced by somatic cell nuclear transfer fell within the definition of embryo in the Act and would therefore not be subject to the new HFEA provisions.[131]

In response to this concern, the House of Lords agreed to appoint a committee "to consider and report on the issues connected with human cloning and stem cell research arising from the Human Fertilisation and Embryology (Research Purposes) Regulations."[132] The House of Lords Select Committee addressed a number of central issues, including the potential benefits of stem cell research, alternatives to research on human embryos, the moral status of the early embryo, distinctions among categories of embryos (surplus embryos left over from IVF treatment, embryos created by IVF, and embryos created via CNR), commercial involvement, and the possible need for the regulation of stem cell lines derived from embryos.[133]

The House of Lords Select Committee decided that the government should continue to engage in stem cell research in order to understand scientific developments within the field and recommended that the Department of Health and the MRC establish a centralized stem cell bank to provide scientists access to high quality stem cell lines. Furthermore, the committee recommended that a steering committee establish rules governing withdrawals from and deposits in the bank.[134] The following Section discusses the governance structure of the UKSCB.

2. Institutional Governance

The UKSCB Steering Committee oversees the bank's operations and governance. A non-statutory body that meets three times per year and reports annually to the MRC, the Steering Committee ensures that the research associated with the UKSCB is carried out in a transparent and ethical manner. Lord Naren Patel currently heads the Steering Committee, and membership of the committee includes experts in science, ethics, theology, and medicine, regulatory and funding agency representatives, and public lay persons.[135] The Steering Committee is responsible for developing a code of practice for the UKSCB and the use of stem cell lines, reviewing on a case by case basis applications to deposit or access embryonic and

131. HOUSE OF LORDS SELECT COMM. FOR STEM CELL RESEARCH, STEM CELL RESEARCH-REPORT (2002). In the U.K., somatic cell nuclear *transfer* is usually called somatic cell nuclear *replacement*, or CNR.

132. *Id.* at ch. 1, § 1.15.

133. *Id.* at ch. 1, § 1.19.

134. *Id.* at Summary of Conclusions, § xxvi.

135. CODE OF PRACTICE, *supra* note 53, at 10.

adult stem cell lines, ensuring that strategies are in place to manage risk and issues reported by the Bank Management and User and Clinical Liaison Committees, reporting annually to the MRC, and annually briefing Health and Science Ministers on stem cell research.[136] The UKSCB has a number of other important committees involved in the active management and governance of the repository.[137]

Researchers who wish to derive new hESC lines must first obtain a license from the HFEA, a prerequisite for the UKSCB to accept new lines from researchers for banking. The Steering Committee must review that the cell lines have been ethically sourced, with fully informed donor consent,[138] and that the lines present a valuable resource to the research community. Bank researchers are requested to complete an application form in

136. Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines, http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-government_spending_review_initiatives/strategy-stem_cells/strategy-stem_cell_governance/public-stemcell_governance_steering.htm (last visited Aug. 13, 2006).

137. A "User and Clinical Liaison Committee," for example, includes stem cell researchers and clinicians from academia and the industry. This group provides a forum for discussion and consultation on issues relating to oversight of stem cell research and therapy development in the UKSCB. A "Bank Management Committee" meets every six months and directly oversees the UKSCB; it monitors operational issues related to the UKSCB and assists in developing longer term management strategy. The committee is chaired by the NIBSC Director and membership includes stem cell experts from the UKSCB and external experts, professionals, lay members, and funding agency representatives. The committee receives annual reports from UKSCB and reports them formally to the Steering Committee. Currently, the Management Committee has established a number of subgroups that meet more regularly to support day to day functioning of the UKSCB and address specific issues. These include separate working groups to manage public relations, to involve stem cell biologists in providing advice on characterization procedures for the UKSCB, to review proposed procedures for safety testing and potential sources of cell contamination, and to establish appropriate processes and procedures enabling "quick and appropriate response in the event of an adverse discovery relating to a donor or a cell line." *See* STEERING COMMITTEE, FIRST ANNUAL REPORT, *supra* note 124.

138. Patients making embryo donations must be provided with comprehensive information such that it allows a free and informed decision. Written information and consent forms must be reviewed by a Local Ethics Committee, and for research involving embryos, HFEA approval is also required. The HFEA and the Steering Committee for the UKSCB have developed a list of criteria that must be presented to donors in information leaflets: only a few stem cell lines will be successfully derived from embryos; stem cell lines may be used in various research projects and donors may not restrict research conducted on such lines; cell lines may be used for future treatment purposes; embryos will be coded and researchers will not have access to donors' identifying information; and the decision to donate is voluntary and will not affect donors' treatment in any way. CODE OF PRACTICE, *supra* note 53, at 15-16.

order to aid the Steering Committee. The depositor and the UKSCB must sign a "Materials Deposition Agreement" in order to make stem cell lines available to requestors on terms of access negotiated by depositor and requestor in the Material Use License.[139] Depositors remain closely involved in the deposition process through a Project Team. The Project Team, composed of Bank staff and scientists and technicians from the depositor's institution or laboratory, is responsible for the transfer of stem cell lines, along with techniques and skills, to the UKSCB. In addition, the depositor is requested to test cell lines and provide comments on their consistency, a process that gives requestors confidence in the cell lines.[140]

Researchers wishing to access stem cell lines from the UKSCB must meet HFEA requirements for stem cell research. More specifically, researchers requesting the use of banked lines must provide assurances that the experiments are likely to increase knowledge about embryo development or serious disease, and basic research must underpin these aforementioned aims or lead to the development of cell-based therapies for clinical trials.[141] It is expected that proposals for research be subjected to peer review; evidence of this process must be presented to the Steering Committee. Institutional review board (called the Research Ethics Committee in the U.K.) approval must be obtained as part of the HFEA research license process, for research involving human tissues and for clinical trials of all stem cell derived products. The Steering Committee does not require IRB approval for research involving established embryonic stem cell lines.[142]

B. Adapting the U.K. Model to California to Address Governance

Drawing from the new UKSCB, the proposed California Stem Cell Biorepository (CSCB) would offer a vital resource to support this research (both academic and commercial), while establishing governance mechanisms useful for protecting the covenant between donors and the scientific community.[143] The CSCB would be a new non-profit foundation that is funded by and works closely with CIRM, but which is governed independently by a Steering Committee for Public Policy and a Board of Trustees composed of individuals free of conflicts of interest. Members of this body might include directors of CIRM and the ICOC, donor representatives, state senators, and rotating public ombudspeople. The leading features of this institution would be: (1) a centralized biorepository for the

139. *Id.* at 13.
140. STEERING COMMITTEE, FIRST ANNUAL REPORT, *supra* note 124.
141. CODE OF PRACTICE, *supra* note 53, at 13-14.
142. *Id.* at 13.
143. *See* NAS GUIDELINES, *supra* note 8.

characterization, standardization, propagation, and distribution (at cost) of new hESC lines developed under CIRM funding; (2) a Centralized Embryonic Stem Cell Research Oversight Committee (CESCRO) that will consider all research protocols requesting CIRM funds, and also any research protocols requesting materials from the biorepository; and (3) a donor advisory group with procedural rights in the development of CSCB policy and ethics review.

In California, a centralized stem cell bank should be built by requiring that all new hESC lines created with CIRM funds be deposited there. Additionally, to achieve greater coverage over all stem cell research in the state, the legislature should mandate that all stem cell research that is conducted in the state be on cell lines that have either been banked at or approved through reciprocity by the CSCB.[144]

At the bank's physical repository, staff should have the task of propagating the cell lines, keeping a coded cell line registry, and handling distribution to researchers who seek access, freeing many scientists from administrative burden. Centralized banking is also likely to expedite standardization, quality control, and uniform characterization of cell lines,[145] as well as the management of genetic diversity in the archive of therapeutic materials for people with divergent haplotypes.[146] Operational costs should be shared by funding agencies and research institutions themselves, which will save the expense of developing separate banking and distribution facilities. Eventually, such a public stem cell bank in California should be linked into a larger network of hESC banks in the United States and abroad, including the UKSCB.

Previous authors have discussed thoroughly the scientific advantages to centralized banking. Centrally banking and cataloguing new stem cell lines and material-based research tools, and making these widely available for research at cost, would maximize scientific and therapeutic value of CIRM funds. In Recommendation 23, the NAS Guidelines propose a se-

144. This latter policy could be challenged on the basis of rights of contract and freedom of association. However, the state's sovereign police powers and regulatory power over health would likely overcome these claims.

145. *See* Ali H. Brivanlou et al., *Setting Standards for Human Embryonic Stem Cells*, 300 SCI. 913, 916 (2003).

146. *See* Ruth Faden et al., *Public Stem Cell Banks: Considerations of Justice in Stem Cell Therapy*, 23 HASTINGS CENTER REP. 13, 19-20 (2003). Stem cell therapies will involve transplanting tissues derived from stem cells, or the stem cells themselves. Since patient immune systems will try to eliminate cells with foreign antigens, matches will have to be found. Since the relevant antigens tend to correlate with race, the authors argue there are important racial justice issues inherent in the management of cell line diversity. *Id.*

ries of best practices for any lab or institution planning to bank stem cell lines. These include: (a) creating a committee for policy and oversight purposes and creation of clear and standardized protocols for banking and withdrawals; (b) establishing documentation requirements for investigators and sites that deposit cell lines; (c) establishing a secure system for protecting the privacy of donors when materials retain codes or identifiable information; and (d) setting out clear criteria for the distribution of cell lines, including evidence of approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution. Establishing the CSCB would accomplish these goals efficiently. The CSCB would also promote access to high-quality materials and thereby of stem cell therapies, and reduce the burden on individual labs to distribute cell lines, allowing them to focus on their laboratory work. Finally, centralization would facilitate the creation of a centralized and searchable database and registry for eventual therapeutic use.

The new insight in this Article is that the CSCB would help address some of the inadequacies in the governance regime for stem cell research addressed above. First, as a threshold matter, maintaining a public hESC repository in California would reduce the number of egg donors required to support an expanded program of research. Because of the significant risks of donating, such a policy has distinct ethical advantages over maintaining decentralized stem cell banks at each research institution. Since hESC lines can be perpetuated *ad infinitum*, or at least for a period of many years, a central bank could generate a ready hESC supply with fewer cell lines. To the extent that fewer academic researchers would be forced to derive their own cell lines from egg donations, this would reduce the number of donors. If researchers were to allow non-restrictive licensing of the materials, either through voluntary or mandatory rules, then this advantage of a central repository would be enhanced. Finding a way to minimize the number of women undergoing egg extraction for research alone would translate into an ethical imperative to do so.

Second, standardization afforded by the centralization of ethical review would bring more effective review of new hESC research in California, and would help avoid institutional conflicts of interest, both real and perceived. The group of researchers engaging in this line of work at each particular institution is small enough such that well-documented conflicts of interest problems with IRBs would be exacerbated. Attaching a centralized ethics review board to the stem cell bank would facilitate the maintenance of independence crucial for the ethical review body's legitimacy and efficacy. Furthermore, the ethics review body at the bank could maintain a regular dialogue with the ethics policy makers on the Steering

Committee, which would be designed to interface with scientists and the public on complex issues as they arise. This system would mean that non-CIRM-funded researchers would have to apply to the CSCB for access to lines developed from CIRM funds, bringing needed oversight to this work that the CIRM Regulations leave uncovered.[147]

Third, there are strong reasons for centralizing banking and ethical review from the perspective of administrative efficiency. Although some arguments for keeping ethical review on the local institutional level exist,[148] centralized review would be more efficient and less expensive than the use of localized SCROs. It also may be unrealistic to imagine that each institution would be able to find the necessary scientists, personnel, and members of the public with sufficient expertise. One of the main advantages of centralizing a repository of new stem cell lines and other donated materials for research is that the additional ethical oversight required to do this research could be centralized, standardized, and overseen in a publicly accountable institution.

Fourth, from the perspective of transparency and public accountability, this proposal has significant advantages. This system would avoid the perception that crucial ethical decisions are being made in the backrooms of the very institutions that stand to gain from large CIRM grants. This centralized review panel would have the independence necessary to achieve public confidence, would make the ethical review more transparent, and would ultimately lead to a more legitimate policymaking process at the level of the Steering Committee. It would create a nodal point for public engagement, education, and deliberation where one is lacking. It would create a better forum for an iterative communication process between the Centralized Embryonic Stem Cell Research Oversight Committee and the Steering Committee in a way that would position the California initiative to deal with new ethical questions and particular controversies as they emerge.

Fifth, the CSCB as proposed would address the dearth of representation of the donor community in the governance of stem cell research by enhancing the membership of donor representatives and lay people on the Steering Committee, Board of Trustees, and CESCRO. Alternatively, the institutional structure of public stem cell banks could be used to develop a participatory role for the donor group. As discussed above, in the field of biobanking for population genomics, new norms of participation in research governance by donor communities have emerged. These norms

147. *See* discussion *supra* Section III.B.3.

148. *See* NBAC, RESEARCH SUBJECTS, *supra* note 23, at 111-31.

should apply in the stem cell biobanking context, where the physical and emotional investment of donors and the privacy risks are arguably more significant, especially for egg donors. Important and vexing ethical issues relevant to the donor group will likely arise, including those surrounding the retention and management of coded identities, and the possible recontact of donors in the future.

The central banking institution could house an egg donor group to advise and interact with the bank's central ethics committee, empowering donors to participate in deliberations over costs and benefits of the hESC research under review. Representatives could be selected in a similar way as shareholder representatives on corporate boards, or alumni representatives on university corporate committees. In this way, the ethics committee's duty to promote beneficence could be brought into line with the altruistic expectations of the donor group. This arrangement would foster more representative governance and a more meaningful dialogue among key partners in the collective endeavor of hESC research.

Sixth, the collective organization of research donors entailed by these features could help mitigate the problem of "open consent" in two ways. First, through direct representation on repository committees, donors as a group would enjoy greater control over the future uses of their samples, giving donors a voice in decision making over uses of their materials that were "unforeseen" at the time of donation. If a particularly controversial use emerged, representatives of the donor community could contact donors for a sense vote on whether such research should be permitted. A stronger way of addressing the loss of autonomy entailed by open consent would be to allow donors whose materials resulted in useful cell lines to retain a right of refusal to participate in new research projects. Through a repository website, donors could be kept apprised of research protocols requesting cells from the repository. New requests for cells would be posted on the website, giving donors notice to opt out. Donors could be given a window of time to opt out of particular projects, such as one month, after the posting of the new protocol on the web. This mechanism has been proposed before, in the context of tissue donation in genomics research, as middle ground between open consent and informed consent for each new research project.[149]

Seventh, a centralized repository would make characterization of the overall genetic coverage of the new stem cell lines easier, facilitating important distributive justice and ethnic equality goals. Developing stem cell

149. David E. Winickoff & Richard N. Winickoff, *The Charitable Trust as a Model for Genomic Biobanks*, 349 NEW ENG. J. MED. 1180, 1183 (2003).

therapies will necessitate finding genetic matches among diverse genotypes, and some predict that patients may require ethnic-specific lines for transplant.[150] Centralized banking could help guide CIRM as it sets targets for funding the creation of new hESC lines, enhancing CIRM's capacity to develop and track a diverse archive.

In sum, if set up properly, such institutions could help improve the consent process for donors and the system of ethical oversight. Overall, they would help correct the power asymmetries towards egg donors established in the currently proposed regime. This idea of using stem cell banks to drive governance should not replace the development of binding regulations subjecting human embryonic stem cell research to institutional review board oversight and other controls. However, in a political climate in which the federal government is unlikely to create a new national regulatory architecture for stem cell research, state government and charitable funders could achieve better governance for hESC research through an infrastructure of public stem cell banks. In California, such an institution, if governed transparently and according to the best scientific and ethical thinking, could set a high standard both for the science and the ethical oversight of stem cell research.

V. CONCLUSION

The California Stem Cell Initiative has enormous potential to advance basic science and clinical therapy for a wide range of diseases, but achieving these goals will require careful ethical planning. The NAS Guidelines are a useful starting point for addressing the complex ethical issues involved in conducting embryonic stem cell research, and leaders at CIRM have adapted these recommendations to the California context in credible ways. However, these guidelines should only be a starting point for California, where much more robust structures are imaginable because of the research program's centralization and public character.

While it would be easier for California to simply adapt and apply existing consent and IRB structures onto the field of stem cell research, California would lose an opportunity to innovate and lead not just in biotechnology, but also in bioethics. Taking a cue from the United Kingdom, centralized stem cell banking in California would bring general gains in efficiency while creating a pragmatic opportunity to construct an ethical and legal architecture for long-term public return. This vision of stem cell banking would provide useful flexibility in the face of a fast-evolving

150. Faden, *supra* note 146, at 21-23.

ethical frontier, and help build trust between scientific institutions and society. Such a collaborative vision of biotechnological governance would be economically feasible, socially preferable, and scientifically advantageous.

DOLLARS FOR GENES: REVENUE GENERATION BY THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

By Richard J. Gilbert[†]

TABLE OF CONTENTS

I. INTRODUCTION

Human embryonic stem cell research promises potential breakthrough therapies for diseases such as Alzheimer's and Parkinson's, spinal cord injuries, cancer, HIV/AIDS, multiple sclerosis, heart disease, and mental

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health disorders.[1] In November 2004 California voters passed Proposition 71. The initiative created the California Institute for Regenerative Medicine (CIRM) and authorized the state to issue up to $3 billion in general obligation bonds to fund human embryonic stem cell research and provide overhead for the Institute.[2] In addition to the potential for stem cell research to improve lives, some supporters of Proposition 71 also promised large royalty income from the licensing of new technologies that would result from CIRM-funded research.[3] A study prepared by Laurence Baker, Professor of Health Research and Policy at Stanford University, and Bruce Deal of Analysis Group ("Baker-Deal study") predicted that the state would earn from $537 million to $1.1 billion in royalties from research funded by Proposition 71.[4]

This Article derives a much lower estimate of likely licensing income from CIRM-funded research and development ("R&D"). My methodology refines the approach in the Baker-Deal study and also forecasts future licensing income based on an evaluation of historical licensing income from sponsored research at universities, hospitals, and research institutes. My best estimate of licensing income comprises only a few percent of expenditures on human embryonic stem cell research. California's share of this licensing income is likely to be less than one percent of R&D expenditures in current dollars. The allocation of these relatively small revenues is less important than the greater objective of disseminating CIRM-funded stem cell technology quickly and widely. While investments in stem cell research will generate some financial return for the state of California, the primary benefit from these investments will be progress toward improved

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1. *See* California Secretary of State, *Text of Proposed Laws – Proposition 71*, *in* CALIFORNIA OFFICIAL VOTER INFORMATION GUIDE 147 (2004), *available at* http://www.cirm.ca.gov/prop71/pdf/prop71.pdf [hereinafter *Proposition 71*]; Alliance for Stem Cell Research, Stem Cell Facts – Diseases and Injuries, http://www.allianceforstemcellresearch.org/page.php?id=126 (last visited June 14, 2006).

2. The bond authorization is subject to a $350 million annual limit. California Secretary of State, *Proposition 71 – Title and Summary*, *in* CALIFORNIA OFFICIAL VOTER INFORMATION GUIDE 68-73 (2004), *available at* http://www.ss.ca.gov/elections/bp_nov04/prop_71_entire.pdf.

3. Alan D. Cherrington, Carolyn Aldige & Joan Samuelson, *Argument in Favor of Proposition 71*, *in* CALIFORNIA OFFICIAL VOTER INFORMATION GUIDE 72 (2004), *available at* http://www.ss.ca.gov/elections/bp_nov04/prop_71_entire.pdf ("By making California a leader in stem cell research and giving our State an opportunity to share in royalties from the research, [Proposition] 71 will generate thousands of new jobs and millions in new state revenues.").

4. LAURENCE BAKER & BRUCE DEAL, ANALYSIS GROUP, INC., ECONOMIC IMPACT ANALYSIS: PROPOSITION 71, CALIFORNIA STEM CELL RESEARCH AND CURES INITIATIVE (2004).

therapies for the treatment of major chronic and acute diseases. To be more precise, if income generation were the sole justification for stem cell research funding (which of course it is not), the state would be better off investing in its own municipal bonds.

In Part II, I describe two approaches to estimate potential CIRM royalty income, one based on expected future revenues and the other on extrapolation from actual licensing income earned from sponsored research at universities, hospitals, and research institutions. Taking the value of time into account, I show that both approaches predict present value licensing income that is a small fraction of the present value of CIRM R&D expenditures. I discuss different factors that limit the ability to generate licensing income in Part III, including uncertainty, distant payoffs, the need for additional investments, and unequal bargaining power. Part IV examines the revenue-generating potential for alternative licensing arrangements that rely on fixed fees, running royalties, and equity sharing. Historically, running royalties have been the main generator of license income for universities, hospitals, and research institutions, accounting for about eighty percent of total income. This Part describes why other arrangements, such as relying mainly on fixed fees, may appear attractive in theory yet under-perform relative to licenses that emphasize running royalties. This Part also considers equity participation by CIRM in licensee businesses. Equity sharing is a potentially rewarding path to commercialize CIRM technologies, and it should play a role in CIRM's overall technology transfer program. However, there is not much evidence that increased equity sharing would lead to significantly more licensing income than running royalties. Part V concludes.

II. ROYALTY INCOME

This Part reviews the estimate of future CIRM licensing income prepared by Laurence Baker and Bruce Deal and describes another approach based on actual past license revenues and R&D expenditures. Both approaches project that CIRM license income will be a small fraction of R&D expenditures after taking account of delays between expenditures and income and allowing for the time cost of money.

The Baker-Deal study uses a "prospective" approach to estimate royalty income from CIRM-funded research. This method estimates the likely number of major new therapies that will be introduced using technologies developed with CIRM research support and the expected revenues from these new therapies, and applies a royalty rate to estimate licensing income. An alternative approach is "retrospective," based on actual royalty

generation by research funded by universities, hospitals, and research institutes. Both approaches have merit as a means of estimating likely royalty income.[5] The time cost of revenues is a major issue, because it takes years to apply basic stem cell research to produce useful therapies and many more years for those therapies to wind their way through the U.S. Food and Drug Administration approval process. Nevertheless, CIRM may be able to generate some revenue over an earlier time frame by licensing technologies used as research tools to develop new therapies.[6] Another possible way for CIRM to accelerate income is to negotiate equity in companies that license its technologies and to profit from equity sales that capitalize the future value of stem cell research.

A. The Baker-Deal Methodology

The Baker-Deal study estimates that research funding by CIRM suffices to develop, in expected terms, 3.4 major new therapies, based on historical costs adjusted for inflation in the cost of health care R&D. The report projects $3 billion in revenues from a major biotechnology therapy.[7] In their base case the authors assume that the state will earn a royalty of two percent of sales of CIRM-funded therapies. This gives a nominal return of $60 million per major therapy and total royalty revenue of about $204 million for the estimated 3.4 therapies developed from CIRM-funded research. The authors assume a gap of ten years between the funding point and the start of royalties. The authors then inflate future royalty streams by an expected health care inflation rate of 4.2 percent to account for expected increases in the cost of drug therapies. Inflation increases the cumulative royalties to $537 million in their base case and $1.1 billion in their high estimate, which assumes a royalty rate of four percent of sales.

The obvious problem with this calculation is that a dollar of revenue earned ten years in the future does not have the same value to the state as a

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5. Neither approach is inherently superior. Future revenues in the prospective approach are speculative. Past performance in the retrospective approach need not be indicative of future returns.

6. The history of licensing revenues from the Cohen-Boyer patents suggests that the potential to earn revenues quickly is limited. Only about ten percent of the $254 million in revenues from Cohen-Boyer licenses was collected from up-front payments and R&D licenses. The remaining ninety percent came from product sales. *See* Maryann Feldman, Alessandra Colaianni & Kang Liu, *Commercializing Cohen-Boyer 1980-1997*, at 23 (DRUID Working Paper No. 05-21, 2005), *available at* http://www.druid.dk/wp/pdf_files/05-21.pdf.

7. The revenue figure is based on a forecast of the revenue potential for eighteen biotechnology therapy approvals in 2004, adjusted for inflation. BAKER & DEAL, *supra* note 4, at 81.

dollar of revenue earned in the present. The study accounts for inflation in health care costs, but does not discount future revenue flows. In their defense, the authors report only projected revenue flows, not the value of these revenues. A correct value calculation should discount future revenue flows by the time value of money. While reasonable people may disagree over the appropriate choice of a discount rate, a number at the low end of the range is the rate of interest paid by ten-year treasury bonds. Treasury bonds are exempt from state taxes, but not federal tax. Investments by a state should count federal taxes as a cost, but not state taxes, as they are returned to the state coffers. The interest rate for treasuries, also called the yield, is consistent with these financial flows.[8]

In June 2006, the ten-year treasury bond yielded about 5.0 percent.[9] Discounting the estimated royalty flows in the Baker-Deal study base case by this rate reduces the value of these royalties from $537 million to about $189 million in current dollars, or about thirty-five percent of the royalty revenue reported in the study. The study's high estimate assumes that the state would earn a royalty of four percent of sales, which corresponds to a present value royalty income of about $379 million from the state's $3 billion research investment. Taking into account the value of time, the study's estimated royalty income does not come close to paying back the state's investment in R&D, let alone earn a positive return on that R&D.[10]

Applying the interest rate on treasury bonds reduces the estimated royalties in the Baker-Deal study by about sixty-five percent. A higher discount rate, which is arguably appropriate to account for the high risk of stem cell R&D, would result in still lower present value royalty income. The state's actual payout of licensing income would be less than the discounted numbers indicate, because CIRM plans to assign a share of royalty income to grantee organizations and inventors. The grantee organiza-

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8. One could make an argument for discounting future revenues using the much higher rate of return on private investment, which is the opportunity cost of using state funds. There is a large literature on the appropriate discount rate. *See, e.g.*, Peter G. Warr & Brian D. Wright, *The Isolation Paradox and the Discount Rate for Benefit-Cost Analysis*, 96 Q.J. ECON. 129 (1981).

9. Bankrate.com, Treasury Bill Interest Rates and Treasury Note Interest Rates, http://www.bankrate.com/brm/ratewatch/treasury.asp (last visited June 21, 2006) (indicating that the yield for ten-year constant maturity treasury bonds was 5.05% on June 21, 2006).

10. Discounting the expected flow of CIRM R&D expenditures does not change the conclusion that the expected present value of CIRM royalty income is a small fraction of the present value of R&D expenditures, even assuming the study's high estimate for expected royalties. The present value of R&D expenditures is about $2.4 billion assuming annual expenditures of $300 million per year and a five percent discount rate.

tions' normal policies for externally funded R&D govern how much inventors may accumulate. This is a sensible policy. It ensures that inventors have the same financial incentives to work on CIRM-funded research projects as they do for other projects and does not unduly discourage research entities from accepting CIRM grants.[11] The current CIRM intellectual property policy requires no payment of licensing revenues to the state of California unless total royalties earned by grantee organizations, net of payments to inventors, exceed a threshold of $500,000, adjusted for inflation. For royalties that exceed the threshold, the policy specifies that the grantee organization pay twenty-five percent of its share remaining after payments to inventors to the state of California.[12] As an example, the University of California's current policy permits inventors to retain thirty-five percent of net licensing income from their discoveries.[13] For royalties from inventions funded by CIRM, twenty-five percent of the remainder, or about one-sixth of total revenues, would go to the state. If other funding sources were used in the creation of a CIRM-funded patented invention, the state's return would be proportionate to the share of research support provided by CIRM. The CIRM sharing rule (one quarter to the state after deducting thirty-five percent for the inventor's share, assuming the therapies predicted in the Baker-Deal study exceed the CIRM threshold) would reduce the state's share of estimated royalty income to about $31 million in the Baker-Deal study base case and $62 million in the study's high estimate.

These estimates of royalty income to the state are only a few percent of the total investment in stem cell research that will be funded by CIRM. Under these scenarios, the state's financial return from royalty income for research funded by CIRM will be extremely modest. The state of California will not earn a profit from royalties on stem cell technologies funded

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11. *See* Roger G. Noll, *The Painful Implementation of California's Stem Cell Research Program*, STANFORD INST. FOR ECON. POL'Y RES. POL'Y BRIEF, October 2005; Roger G. Noll, *The Politics and Economics of Implementing State-Sponsored Embryonic Stem-Cell Research* 36-37 (Stanford Inst. for Econ. Pol'y Res. Discussion Paper 04-28, June 2005).

12. CIRM, INTELLECTUAL PROPERTY POLICIES FOR NON-PROFIT ORGANIZATIONS 19 (2006), *available at* http://www.cirm.ca.gov/policies/pdf/IPPNPO.pdf [hereinafter IPPNPO].

13. OFFICE OF THE PRESIDENT, UNIVERSITY OF CALIFORNIA TECHNOLOGY TRANSFER PROGRAM, ANNUAL REPORT, FISCAL YEAR 2004 13 (2004) [hereinafter U.C. TECHNOLOGY TRANSFER ANNUAL REPORT 2004]. License revenue sharing policies vary substantially among universities. Part of the variation is the result of an accounting artifact; revenues may be assigned to a laboratory, yet be under the control of the inventor. *See* Saul Lach & Mark Schankerman, *Incentives and Invention in Universities* 6 (Nat'l Bureau of Econ. Research, Working Paper No. 9727, 2003).

by CIRM, nor will royalties return a significant fraction of CIRM expenditures to the state.

B. A Retrospective Approach

An alternative approach to estimate likely royalty income from CIRM investments requires one to extrapolate from royalties actually earned by universities, hospitals, and research institutes on their past R&D investments. This estimate is retrospective because it is based on returns to historical R&D expenditures rather than likely future returns to expenditures by CIRM. Most CIRM grantees will be associated with universities, hospitals, and research institutes. Hence, licensing revenues from these organizations, particularly hospitals and health-related research institutes, provide an appropriate baseline to estimate revenues from CIRM licenses.[14]

As a reference point, Table 1 shows licensing income from sponsored research at universities and research institutes surveyed by the Association of University Technology Managers (AUTM) for fiscal years 2003 and 2004. For fiscal year 2003, AUTM reported net licensing income of $867 million and total research expenditures of $34.8 billion. Net licensing income equals gross license income less license income paid to others and legal fees expended, plus legal fees reimbursed. The corresponding figures for fiscal year 2004 are net licensing income of $925 million and total research expenditures of $37.2 billion. For both fiscal years, licensing income averaged about 2.5 percent of research expenditures.[15]

Licensing income earned by U.S. hospitals and research institutes surveyed by AUTM was a considerably larger fraction of sponsored research expenditures in FY 2003 and 2004. In fiscal year 2003, these hospitals and research institutes earned licensing income of about $292 million and had total research expenditures of about $3.7 billion. For fiscal year 2004 the corresponding figures are licensing income of $314 million and revenues of about $4.1 billion. Licensing income was 7.9% of sponsored research expenditures at hospitals and research institutes surveyed by AUTM in FY 2003 and 7.7% of sponsored research expenditures in FY 2004.

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14. California universities, hospitals, and non-profit research institutes received the first round of CIRM grants. Press Release, CIRM, ICOC approves first stem cell grants in California (Sept. 9, 2005), *available at* http://www.cirm.ca.gov/pressreleases/2005/09/09-09-05_ii.asp.

15. AUTM, AUTM LICENSING SURVEY: FISCAL YEAR 2003 50 (2003); AUTM, AUTM U.S. LICENSING SURVEY: FISCAL YEAR 2004 56 (2004).

Table 1
AUTM Licensing Survey: FY 2003 and 2004

	U.S. Universities		U.S. Hospitals and Research Institutes	
	FY 2003	FY 2004	FY 2003	FY 2004
Sponsored Research Expenditures ($ millions)	34,827	37,162	3,699	4,082
Net Licensing Income ($ millions)	867	925	292	314
Net Licensing Income as Percent of Research Expenditures	2.5%	2.5%	7.9%	7.7%

The licensing income reported in Table 1 is net of legal fees, but not of other administrative costs associated with running a technology transfer program. Data on overhead costs are available for the University of California's technology transfer program. For fiscal years 2000 through 2004, the University of California system-wide Office of Technology Transfer incurred operating expenses, other than legal and other direct expenses, equal to about fifteen percent of total licensing revenues.[16] Deducting fifteen percent for operating expenses reduces the net licensing income in Table 1 to about 2.1% of research expenditures for all university research and 6.6% of research expenditures for U.S. hospitals and research institutes.

Licensing income earned by U.S. hospitals and research institutes, rather than income earned by universities, arguably better represents the income that the California Institute of Regenerative Medicine will earn. Independent survey research by Castillo, Parker, and Zilberman provides more evidence that medical product and process licenses are likely to command higher royalty percentages than other licenses. Respondents to a survey of thirty-six universities reported royalties of 6.3 to 9.4 percent of sales for medical products, compared to an average royalty of 3.9 percent

16. U.C. TECHNOLOGY TRANSFER ANNUAL REPORT 2004, *supra* note 13, at 16 (showing in exhibit 26 that total licensing revenues include a one-time $200 million legal settlement related to its human growth hormone invention and that including this amount reduces the share of operating expenses to about ten percent of total licensing revenues).

of sales for agricultural products and 6.3 percent for engineering products.[17]

The higher royalties earned on health care technologies reflect the large share of research and development expenses in the medical products sector. In 2001, R&D expenses were 7.8 percent of net sales for pharmaceuticals and medicines and at least 9.0 percent of net sales for medical equipment and supplies,[18] compared to an average for all industry of 4.1 percent.[19] The greater importance of R&D in these industries allows a licensor of new technology to bargain for a larger fraction of net sales relative to royalty percentages in many other industries. The value of a technology to a potential licensee is the amount that the technology saves in product development costs or the additional value that the technology allows the licensee to offer its customers. If R&D costs average only four percent of product revenues, a potential licensee in a competitive market will not be willing to pay a royalty of more than four percent to license an R&D technology unless the technology offers an increase in value that the licensee can capture with a higher price. Competition caps the royalty that the licensee can offer. A licensee could offer more in a market where it has more pricing discretion, although it would not pay a royalty that exceeds its own cost of investing in R&D to develop an alternative technology or the cost of licensing an alternative technology from another source.

The numbers in Table 1 compare *current* royalty income to *current* research expenditures. However, current royalty income is the payoff for research expenditures that occurred many years in the past. Research discoveries take years to evolve into potentially useful products. Regulatory approval adds several more years before companies can market potentially useful drugs and therapeutics. A more accurate estimate of the benefits of R&D would compare R&D investments to expected future payoffs adjusted for the time value of money. Detailed estimates depend on a number of assumptions, including the lag between R&D investment and the launch of commercial products, assumed rates of inflation in health care costs and prices, real discount rates, and the time profile of royalty revenues and licensing expenses.

A partial correction for the temporal effects of R&D and the receipt of royalty income uses the royalty income in Table 1, adjusted for operating

17. Federico Castillo, Doug Parker & David Zilberman, The Performance of Offices of Technology Transfer (1999) (unpublished manuscript, on file with Department of Agricultural and Resource Economics, University of California, Berkeley).

18. NATIONAL SCIENCE FOUNDATION, SCIENCE & ENGINEERING INDICATORS 2004, tbl. A-20 (2004) (omitting federal funding for R&D in this figure).

19. *Id.* at tbl. A-19.

expenses, as a proxy for royalties that will occur in the future as a result of the R&D expenditures shown in the table. This calls for discounting royalties by a real, inflation-adjusted discount rate to account for both increases in health care costs and the time value of money. Assuming a lag of eight years between R&D expenditures and the receipt of income and a real discount rate of five percent, the ratio of royalty income to R&D falls to about 4.5 percent.

The state's actual licensing income will comprise a much smaller fraction of its R&D expenditures. Following the revenue sharing policies currently adopted by CIRM and assuming the University of California policy that assigns thirty-five percent of license revenues to the inventor, the state will receive about one-sixth of total royalty revenues (twenty-five percent of revenues remaining after deducting an inventor share of thirty-five percent). These policies reduce my estimate of the state's licensing revenues to less than one percent of CIRM-funded expenditures on stem cell R&D, one sixth of the estimate of total rate of return on research investment, which is 4.5 percent.

This estimated return implicitly assumes that all CIRM-funded R&D projects will exceed the CIRM threshold for paying royalties to the state. In fact, few technologies generate revenues that exceed the CIRM threshold, although those that do account for a high share of total licensing income. After deducting an inventor share of thirty-five percent, the CIRM threshold is a total royalty income of about $770,000. In fiscal year 2004, the University of California at San Francisco, a major hospital and healthcare research institution in the University of California system, generated net royalty income of $18.2 million from 298 active licensing agreements, an average of $61,084 per agreement.[20] Assuming that a license produces revenues for ten years, the average license revenue would not exceed the CIRM threshold after deducting the inventor's share. The CIRM royalty threshold would have a much smaller impact on the state's share of revenues from the most successful inventions, which account for a very large share of licensing income. While the University of California system had almost one thousand active licenses in fiscal year 2004, the twenty-five licenses with the largest royalty income accounted for almost eighty percent of all royalties.[21] All of these licenses earned cumulative royalties in excess of $770,000.[22] Reducing my estimate of royalty income paid to the

20. U.C. TECHNOLOGY TRANSFER ANNUAL REPORT 2004, *supra* note 13, at 17.

21. *Id.* at 8, 10.

22. University of California Technology Transfer Program Annual Reports for Fiscal Years 2000-2004 confirm that total royalties exceeded the $770,000 threshold for all of the top twenty-five royalty-earning technologies in FY 2004.

state of California by twenty percent to account for technology royalties that do not exceed the CIRM threshold lowers my estimate of the ratio of royalty income to R&D spending to about 0.60 percent in present value terms, which is consistent with the low return I estimate using the Baker-Deal methodology adjusted for the time value of money. Royalty income from CIRM-funded projects will not return a significant fraction of expenditures to the state, and certainly will not generate a significant financial return on the state's investment.

C. Extreme Outcomes and Extreme Expectations

It is not out of the realm of possibility for research expenditures to produce very high royalty returns. In 1998, Florida State University earned royalties from technology licenses that totaled $46.6 million. The entire Florida State University research budget in that year was $112 million, so royalty income at Florida State was 41.6 percent of research expenditures.[23] These extraordinary results are due to research at Florida State University that was instrumental for synthesis of the drug Taxol, a treatment for ovarian, breast, lung, and testicular cancer. Approved by the FDA for initial marketing at the end of 1992,[24] by 2001 Taxol had become the best-selling cancer drug in history.[25] Florida State University earned $67 million in royalty revenues in 2000, roughly 4.2 percent of product sales, nearly all of which was royalties from its technology to synthesize Taxol.[26]

Royalty income from stem cell technologies would more than pay for the cost of R&D if CIRM could reliably turn out patents such as the Florida State University patent for the synthesis of Taxol.[27] Of course, the Taxol patent is an outlier among outliers, a celebrity patent in the world of university technology transfer. Furthermore, taking the time value of money into account, it would require more than fifteen patents as lucrative as Taxol for CIRM to earn a market rate of return on its R&D expenditures solely from licensing income.[28] This is implausible given that the

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23. Rebecca Zacks, *The TR University Research Scorecard 2000*, TECH. REV., Jan 11, 2002, at 4.

24. U.S. GENERAL ACCOUNTING OFFICE, GAO-03-829, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL 11 (2003).

25. *Id.* at 1.

26. *Id.* at 13 (reporting that ninety-eight percent of the licensing income earned by Florida State University in 2000 was from the license for its Taxol synthesis patent).

27. The National Institutes of Health provided Florida State University with a $2 million grant to subsidize its Taxol synthesis research.

28. Suppose that a blockbuster patent, such as Florida State's Taxol patent, generates $60 million in royalties per year for ten years. Assuming that revenues begin eight

annual research budget of CIRM, about $350 million per year for ten years, is only about ten percent of 2003 expenditures on academic R&D in the health sciences in California.[29]

Forecasting is risky. Research funded by CIRM could lead to technologies that have as much or more commercial success as the Cohen-Boyer technology or other blockbuster patents such as Florida State's patent on Taxol. However, if we have to forecast, it is safer to rely on historical average returns for a large sample of R&D investments, rather than extrapolating from Taxol or gene-splicing technologies to all CIRM-funded R&D.

D. Low Royalty Income Is Not All Bad

There is an upside to my estimate that the state is not likely to earn a substantial return on its investment in stem cell R&D solely from royalty income generated by licenses for its discoveries. Significant royalty income could put CIRM at risk of losing tax-exempt status for its bond funding.[30] The loss of tax-exempt status would have an immediate adverse impact on the cost of financing R&D by CIRM. In the fall of 2005, then-California State Treasurer Philip Angelides estimated a difference of seventy-five basis points in interest costs between long term taxable and tax-exempt general obligation California state bonds; the spread would be higher in a higher-interest rate environment.[31] The 0.75% difference exceeds my estimate of the royalty income that CIRM is likely to earn from its stem cell research. If the receipt of royalty income places CIRM at risk of losing tax-exempt status, the state would be better off abandoning any claim to royalty income.[32] This also would have the additional, albeit

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years after R&D expenditures and applying a ten percent discount rate gives a total present value of about $200 million. Fifteen times this number is still less than the CIRM R&D budget.

29. Expenditures on academic R&D in California were $5.36 billion in 2003, of which fifty-eight percent was in the health sciences. National Science Foundation, Science and Engineering State Profiles: 2003-04, http://www.nsf.gov/statistics/nsf06314/ (last visited June 19, 2006); *see also* Noll, *The Painful Implementation of California's Stem Cell Research Program*, *supra* note 11; Noll, *The Politics and Economics of Implementing State-Sponsored Embryonic Stem-Cell Research*, *supra* note 11, at 34.

30. Whether royalty income would negate tax-exempt status is not clear. *See, e.g.*, Letter from Then-California State Treasurer Philip Angelides to CIRM President Zack Hall (Oct. 26, 2005), *available at* http://www.etopiamedia.net/empnn/pdfs/angelides-hall1.pdf (noting that "the use of state bond financing to fund stem cell research is a new frontier in federal tax law").

31. *Id.*

32. The Proposition 71 charter that created CIRM specifies that the Independent Citizens' Oversight Committee (ICOC) shall establish standards that allow the State of

small, advantage of promoting the development and dissemination of stem cell therapies by eliminating a small royalty tax on users of CIRM-developed technologies.[33]

III. WHY IS LICENSING INCOME SO LOW?

Historically, non-financial corporations in the U.S. have earned rates of return on their capital investments in excess of ten percent per annum.[34] This means that an investment of $100 in physical capital earns, on average, in excess of $10 every year for the foreseeable future. Some estimates of average rates of return on investments in R&D are much larger.[35] Yet, royalties on sponsored R&D have averaged only two to eight percent of the cost of these investments and much less when adjusted to account for the long delays between R&D expenditures and the receipt of royalty income. What explains the fact that, historically, universities and research laboratories have captured only a small fraction of revenues related to their R&D? There are many explanations, several of which I explore below.

A. Highly Uncertain Value of R&D

While some research, such as that leading to Taxol or to the discovery of recombinant DNA techniques, has been extremely valuable, these are distant outliers. Most R&D discoveries generate no royalty income. The distribution of royalty income from R&D programs is highly skewed. Only four of the thirty-two university hospitals and research institutes surveyed by the Association of University Technology Managers earned total revenues from technology licensing that exceeded $40 million in 2004.

California to benefit from the patents, royalties, and licenses that result from the activities of CIRM. *Proposition 71*, *supra* note 1, § 5, ch. 3, art. 1. *See also* IPPNPO, *supra* note 12 (describing its current policies with respect to patents, royalties, and licenses). My recommendation could run afoul of this requirement, although the quantitative impact would be small in present value terms.

33. A running royalty increases the marginal cost of using the licensed technology or selling a product made with the licensed technology.

34. *See, e.g.*, Eugene F. Fama & Kenneth R. French, *The Corporate Cost of Capital and the Return on Corporate Investment*, 54 J. FIN. 1939 (1999). The authors also estimate a real rate of return on the book cost of investment equal to about 7.5% over the period 1950–1996 and a nominal rate of return, which includes inflation, of about 13%. *Id*. at 1955.

35. *See, e.g.*, Zvi Griliches, *R&D and Productivity: Econometric Results and Measurement Issues*, *in* HANDBOOK OF ECONOMICS OF INNOVATION AND TECHNOLOGICAL CHANGE 53-89 (Paul Stoneman ed., 1995); Edwin Mansfield, John Rapoport, Anthony Romeo, Samuel Wagner & George Beardsley, *Social and Private Rates of Return from Industrial Innovations*, 91 Q.J. ECON. 221 (1977).

Three-quarters of the hospitals and research institutes in the AUTM survey earned total revenues less than $6 million from technology licensing in 2004. The median total income from technology licenses in 2004 was in the range of $2 to 3 million; that is, half of the university hospitals and research institutes in the survey earned less than $2 to 3 million in total royalty income from technology licenses in 2004.[36] The fact is that most basic research would earn little or no licensing income even if the research institution could bargain for a larger share its value.

Table 2 shows the top five sources of licensing revenues earned by the University of California (U.C.) system for the years 1996, 2000, and 2004. The table also shows the total licensing revenue for the U.C. system in each year and the fraction of total licensing revenue earned by the license with the largest revenues. A single technology, the Hepatitis-B vaccine, accounted for more than forty percent of U.C. licensing revenues in 1996 and for more than a third of all U.C. licensing revenues over these years.

36. AUTM U.S. LICENSING SUVEY: FISCAL YEAR 2004, *supra* note 15, at 25.

Table 2
Licensing Revenues Earned by the University of California System ($000's)[37]

FY 1996	Hepatitis-B Vaccine (1979,1981)	$25,412
	Process for splicing genes (1974)	$12,662
	Human Growth Hormone (1977)	$5,292
	Nicotine Patch (1984)	$1,576
	Radiographic Media (1979)	$1,214
	Total Licensing Revenues	$63,204
	Largest as Percent of Total	40.2%
FY 2000	Hepatitis-B vaccine (1979,1981)	$26,462
	Treatment-Intracranial Aneurysms (1989)	$5,671
	Human Growth Hormone (1977)	$2,890
	Process for splicing genes (1974)	$2,785
	Camarosa strawberry (1992)	$2,266
	Total Licensing Revenues	$67,765
	Largest as Percent of Total	39.0%
FY 2004	Hepatitis-B vaccine (1979,1981)	$18,910
	Treatment-Intracranial Aneurysms (1989)	$7,896
	Energy Transfer Primers (1994)	$3,513
	Interstitial Cystitis Therapy (1980)	$3,469
	Camarosa strawberry (1992)	$3,222
	Total Licensing Revenues	$79,265
	Largest as Percent of Total	23.9%

Other university licensing programs also illustrate the importance of single blockbuster discoveries. Revenues from licenses for the Cohen-Boyer patent for gene splicing accounted for roughly half of the technology licensing revenues earned by Stanford University over the life of the patent.[38] More than half of the licensing revenues earned by Harvard University in fiscal year 2004 came from licenses for the Cardiolite, a tool for diagnosing coronary artery disease. Harvard had 554 active licenses in fis-

37. OFFICE OF THE PRESIDENT, UNIVERSITY OF CALIFORNIA TECHNOLOGY TRANSFER PROGRAM, ANNUAL REPORTS, FISCAL YEARS 1996, 2000 & 2004 (1996, 2000, 2004).

38. The Cohen-Boyer patent, which expired in 1997, earned licensing revenues of about $255 million on worldwide product sales of over $35 billion. *See* Feldman et al., *supra* note 6, at 23.

cal year 2004, only two of which generated income of more than $1 million, while fifty-eight percent produced income of less than $10,000.[39] The University of California at San Francisco, a major hospital and research institution, reported that about ninety-eight percent of disclosed inventions earn less than $100,000 per year in licensing income and about eighty percent earn less than $10,000 per year.[40]

The highly skewed distribution of licensing royalty income for university hospitals and research institutes suggests that licensees have to bear the risk that most of the technologies they license will be dry holes. The very few gushers have to compensate for expenditures by licensees that generate little or no return.[41] For this reason, licensees are unlikely to be willing to share a large fraction of the revenues from licensed technologies with the licensor. Doing so would sap the licensee of the economic returns generated by the occasional technology that has very substantial value.[42]

B. Distant Payoffs

New drug development requires a sequence of discovery, preclinical development and testing in assays and animals, clinical testing on humans, and regulatory approval. Each of these steps incurs delays and risk of failure. Clinical testing typically begins with small-scale tests on volunteers, then moves to larger-scale tests on targeted populations, and finally to larger-scale tests that are designed to establish efficacy and identify undesirable side-effects.[43] It is only after a drug manufacturer completes these clinical tests that it may submit a new drug application (NDA) or a bio-

39. HARVARD UNIVERSITY OFFICE FOR TECHNOLOGY AND TRADEMARK LICENSING, ANNUAL REPORT FISCAL YEAR 2004 5 (2004), *available at* http://www.techtransfer.harvard.edu/files/OTD_AR2004.pdf.

40. UNIVERSITY OF CALIFORNIA, SAN FRANCISCO OFFICE OF TECHNOLOGY MANAGEMENT, THE OTM GUIDE TO INTELLECTUAL PROPERTY MANAGEMENT 5 (2003), *available at* http://www.otm.ucsf.edu/docs/otmIPMgmt.asp#Patenting.

41. These expenditures include additional R&D costs and the costs of clinical trials, as well as product development and marketing. *See* Henry G. Grabowski & John Vernon, *Returns to R&D on New Drug Introductions in the 1980s*, 13 J. HEALTH ECON. 383, 399 (1994). In their study of the returns to pharmaceutical R&D, Grabowski and Vernon observe that if the top-selling drug were excluded from the cohort introduced between 1980 and 1984, the remaining drugs would fail to break even on average.

42. Cochrane observes that when the distribution of returns is highly skewed, variance contributes to the expected value of returns as well as to risk. Variance is a problem for a licensee because it implies that a small set of licenses has a high probability of earning little or no return. *See* John H. Cochrane, *The Risk and Reward of Venture Capital*, 75 J. FIN. ECON. 3, 5 (2005).

43. Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 156 (2003).

logical license application (BLA) to the U.S. Food and Drug Administration.[44]

Mansfield traced the lag between the publication of academic research results and the first commercial introduction of new products and processes based on those results. He surveyed a sample of innovations in several industries during the time periods 1975-1985 and 1986-1994. For "Drugs and Medical Products," Mansfield reports lags that range from 6.2 to 10.3 years, depending on the time period of the survey and on whether the academic research was necessary or only a very substantial aid for the development of the new drug or medical product.[45]

DiMasi, Hansen, and Grabowski estimated a mean time between the start of clinical testing and submission to the FDA of a NDA or new BLA equal to 72.1 months.[46] At the time of their study, the mean time required for FDA approval was 18.2 months, resulting in a total lag from the start of clinical testing to marketing approval of a new drug equal to about 7.5 years.[47] This is within the range of estimates by Mansfield, but understates the lag from basic R&D to marketing approval for a new drug because considerable R&D is necessary before clinical testing.[48]

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44. "A biologic product is any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries. Biologic products are a subset of 'drug products' distinguished by their manufacturing processes, biological process vs. chemical process. In general, the term 'drugs' includes biologic products." Federal Drug Administration, Glossary of Terms, http://www.fda.gov/cder/drugsatfda/glossary.htm#B (last visited May 7, 2006).

45. Edwin Mansfield, *Academic Research and Industrial Innovation: An Update of Empirical Findings*, 26 RES. POL'Y 773, 775-76 (1998).

46. DiMasi, *supra* note 43, at 164.

47. In recent years the FDA has reduced the average lag for new drug approvals. The approval time for a new molecular entity (NME) fell from about two years in the early 1990s to about one year in 1999, but then increased to over fifteen months in 2000. A NME is medication containing an active substance that has never before been approved for marketing in any form in the United States. FDA, FDA's Drug Review and Approval Times, http://www.fda.gov/cder/reports/reviewtimes/default.htm (last visited May 7, 2006). Approval times for NMEs could be somewhat longer than approval times for NDAs, which may be based on familiar chemical compounds. New drugs made with stem cell technologies are likely to be NMEs and hence have longer approval times than for NDAs. However, the approval time could be as low as six months if classified as a priority new drug application.

48. *See also* James D. Adams, *Fundamental Stocks of Knowledge and Productivity Growth*, 98 J. POL. ECON. 673 (1990) (reporting a twenty-year lag between publication of research results and its peak effect on industrial productivity).

With private discount rates in the range of 10-15% per year, delay between R&D expenditures and commercial products causes a very large reduction in the financial value of that R&D.[49] Consider the following optimistic scenario for an illustration of the effects of discounting. Suppose a CIRM program costs $100 million and, after a ten year delay for product development, testing, and regulatory approval, leads to a drug that earns $200 million per year for ten years, for a total of $2 billion. The nominal payoff from CIRM R&D is impressive. The R&D program earns $20 in revenue from each dollar of R&D. But accounting for the time value of money with a 15% discount rate makes the R&D investment much less attractive. First, the present value of the revenues from the drug falls by almost half from $2 billion to about $1.15 billion. Second, the ten-year delay between R&D and the commercial product further reduces the ultimate payoff from $1.15 billion to about $285 million. The R&D program still turns a tidy profit, but now the payoff falls from $20 in nominal revenue for each dollar of R&D expenditure to less than $3 in present value revenue for each dollar of R&D expenditure.

The time value of money takes a devastating toll on the payoff from basic research and development. The risk that any products that might emerge from basic R&D may fail to win regulatory approval or encounter market obstacles further reduces the benefits from R&D.

The lags between R&D on stem cell technologies and revenues from products that use these technologies are likely to be on the high side of these estimates. Any new therapeutic products based on research in regenerative medicine will require extensive testing and will face regulatory hurdles and likely legal challenges that will impose long delays to commercial product introduction. Research and development tools developed at CIRM may earn royalty streams with a shorter delay. However, the value of these tools will be limited by the long delays between the use of the tools and the generation of revenues from approved products that are designed, developed, or produced using these tools.

C. Need for Large Additional Investments

Most technologies licensed by universities are at an early stage of development and there is no reason to believe that technologies developed by CIRM will be any different.[50] The commercialization of a new thera-

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49. The private discount rate should reflect the private return on investment, which Fama and French estimate to be about thirteen percent in nominal terms. *See* Fama & French, *supra* note 34.

50. In a survey of technology transfer offices of sixty-two major universities, Thursby et al. found that a majority of the technologies licensed by these offices were at

peutic treatment typically requires expenditures of many millions of dollars in development, testing, and approvals, and millions more to market the new treatment. A prospective drug manufacturer first must submit an investigational new drug application (IND), which demonstrates results of pre-clinical testing in laboratory animals. Based on the IND, the FDA decides whether it is reasonably safe to move forward with testing the drug on humans.

Clinical trials on humans proceed in three stages. Phase 1 studies are small-scale treatments usually conducted on healthy volunteers. If results from Phase 1 studies are acceptable, Phase 2 trials begin with subjects ranging from a few dozen to about 300. Phase 2 trials are designed to assess clinical efficacy of the therapy, as well as to continue Phase 1 assessments in a larger group of volunteers and patients. Phase 3 studies begin if Phase 2 shows evidence of effectiveness without unacceptable side effects. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3000 people.[51] It is only after these clinical tests are completed that a drug manufacturer submits a NDA or BLA to the FDA. On average, drug development costs increase dramatically in each clinical phase prior to FDA approval.[52] DiMasi et al. estimate that the average cost of developing a drug to the point of marketing approval was $802 million for a sample of sixty-eight drugs first tested in humans between 1983 and 1994.[53]

Given the nascent state of most technologies developed in universities and other basic research institutes, the large investments necessary to transfer these technologies into useful products, and the high risks of failure, it is not surprising that licensees are unwilling to commit to large upfront payments or to share a high percentage of the value of successful products with their licensors.

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an early stage of development and about half were only a proof of concept when they were licensed. Jerry G. Thursby, Richard Jensen & Marie C. Thursby, *Objectives, Characteristics and Outcomes of University Licensing: A Survey of Major U.S. Universities*, 26 J. TECH. TRANSFER 59, 59, 62 (2001).

51. Michelle Meadows, *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, FDA CONSUMER, July-Aug. 2002, *available at* http://www.fda.gov/fdac/features/2002/402_drug.html.

52. DiMasi, *supra* note 43, at 171.

53. *Id.* at 151.

D. Bargaining Power

Another possible reason for small royalty shares is that technology transfer managers have little bargaining power or simply are not effective bargainers. Bargaining power is a function of a party's threat point: the value the party can earn by walking away from an agreement. For technology managers this threat point may be quite low in many circumstances. Thursby et al. note that while multiple potential licensees often examine a technology, it is much less frequent for multiple companies to become involved in license negotiations.[54] A technology manager's threat is to license the technology to another company, but that threat is absent if there is only one serious potential licensee. The licensee's threat is to license a substitute technology from another source or develop the technology in-house, both of which may be viable alternatives. For many technologies the licensee will have the upper hand in the licensing negotiations.

IV. LICENSING STRATEGIES TO INCREASE RETURNS

Historically, U.S. universities, hospitals, and research institutions have earned only a small return on their R&D expenditures from licensing the outputs of their research. The previous Part discussed some of the reasons why licensing income has been only a small fraction of R&D expenditures for most universities, hospitals, and research institutions. In this Part, I consider various approaches to technology licenses, namely fixed fees, running royalties, and equity sharing. Each approach has certain benefits as a means for the licensor to obtain value from the licensed technology. I show that a licensing strategy that emphasizes fixed fees is attractive in theory, but is unlikely to perform better than a running royalty in actual licensing situations. Equity sharing is attractive in some respects, in part because isolated examples have produced stunning returns. I argue, though, that equity sharing is not likely to dominate running royalties as a way to capture value for most CIRM technologies.

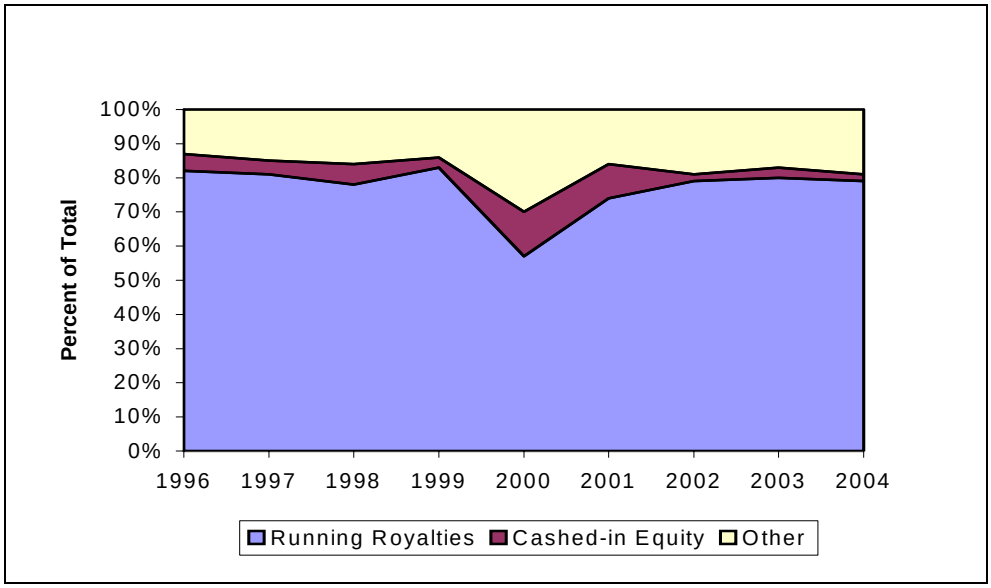
Licenses come in different forms. A license can specify a fixed fee, a running royalty, a share of equity in the assets of the licensee, or require payments that are conditional on meeting certain thresholds such as use of the licensed technology in commercial production of goods or services. In a paid-up or pure fixed-fee license, the licensee makes a one-time payment for the right to use or sell the licensed technology. Running royalties are

54. Thursby, Jensen & Thursby, *supra* note 50, at 63. (observing that it is unusual for a technology to attract multiple bidders, due to uncertainty and the need for additional investment).

payments that vary with sales of products made using the licensed technology, usually calculated as a percentage of gross sales or a per unit fee. These license terms are not mutually exclusive. Licenses can combine fixed fees and running royalties, and in addition may include some equity ownership.

Figure 1 shows the distribution of revenues earned by all university technology licenses over the period FY 1996 through FY 2004. Running royalties account for by far the largest share of university licensing revenues, averaging seventy-seven percent of license income over this period. The other two categories in Figure 1 are cashed-in equity, which is the amount collected from sales of equity holdings in technology licenses, and "other," which includes fixed fees as well as other sources of license income such as litigation settlements.[55]

Figure 1
Licensing Revenue Shares by Type of License



Source: AUTM Licensing Survey, FY 1996-2004 (all respondents)

55. These figures are not directly comparable if the lags between R&D expenditures and the receipt of income differ for royalties and equity payouts. It is not obvious, though, that lags differ significantly. Furthermore, adjusting for lags is unlikely to change the conclusion that running royalties are the dominant source of licensing income.

Running royalties are close to eighty percent of the total in every year from FY 1996-2004 except for FY 2000. This fraction holds at a more disaggregated level for hospitals and research institutes as well as for total university licensing reported by AUTM. FY 2000 was unusual because the University of California recorded a $200 million settlement of an infringement suit involving its human growth hormone patent, which is included in the "other" category for that year.[56] Leaving out FY 2000, the "other" category, which includes fixed fees, accounted for only about sixteen percent of university licensing revenues over the period 1996-2004.

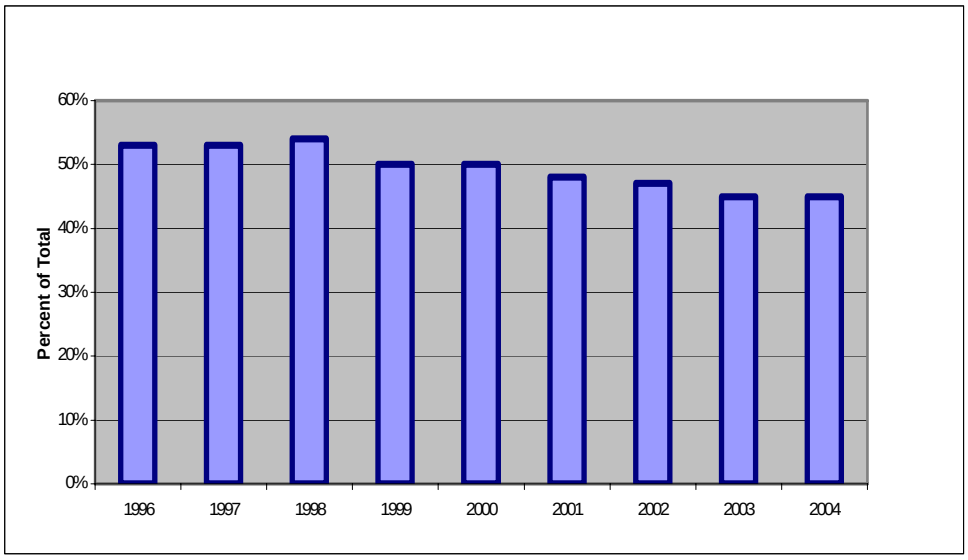
This result may appear odd, at least to economists. Under some conditions, an exclusive license with a fixed fee and no running royalty is a good way for a licensor to recover the value of licensed intellectual property. With no running royalty, or a running royalty equal to the marginal cost of transferring the technology, a single licensee can earn a monopoly profit as the sole supplier of the licensed technology, which the licensor can extract with a fixed fee. A running royalty that exceeds the marginal cost of transferring the technology imposes an artificial cost on the licensee and reduces the total available profit for the licensor.[57] Thus, in theory and with a number of implicit assumptions, a license with a fully paid-up royalty and with little or no running royalty would extract the maximum profit from a licensed technology.

This argument has not had much traction for managers of university technology transfer offices. Fixed fees represent a small share of licensing revenues, with the lion's share coming from running royalties. Furthermore, less than half of university licenses are exclusive and the share of licenses that are exclusive has fallen over the past several years (Figure 2).

56. OFFICE OF THE PRESIDENT, UNIVERSITY OF CALIFORNIA TECHNOLOGY TRANSFER PROGRAM, ANNUAL REPORT, FISCAL YEAR 2001 20 (2001).

57. *See, e.g.*, Patrick Rey & Jean Tirole, *A Primer on Foreclosure*, *in* 3 HANDBOOK OF INDUSTRIAL ORGANIZATION 21, 40 (Mark Armstrong & Robert Porter eds., forthcoming), *available at* http://venus.unive.it/roson/papers/primer20030716.pdf (last visited June 21, 2006).

Figure 2
Share of University Technology Licenses that are Exclusive[58]



Are university technology managers missing an opportunity to earn more from licenses, or is the simple economics story too simple? What lessons can we learn from university technology managers that might apply to licensing by the California Institute for Regenerative Medicine? The argument that an exclusive license with a fixed fee and with little or no running royalty is a good way for a licensor to recover the value of licensed intellectual property is indeed too simple. It omits many considerations in real-world licensing that affect the potential for licensing income, including uncertainty, moral hazard, diseconomies of scale, and different profit opportunities for licensees.

A. Uncertainty

A fixed fee burdens the licensee with the risk associated with the new technology. As demonstrated above, most technology licenses generate little or no income, not because the royalty rate is low, but because most technologies do not realize significant commercial value. Reflecting this risk, the demand for licenses from potential licensees is often quite low. In a survey of university licenses granted from 1991-1995, only twenty-two

58. AUTM, AUTM LICENSING SURVEYS: FISCAL YEARS 1996-2004 (1996-2004).

percent had more than one bidder.[59] The uncomfortable fact is that most exclusive university licenses are exclusive because only one potential licensee was willing to pay for the right to use the technology, not because the university technology transfer manager limited the license to a single licensee.

University technology managers typically are not flush with bids for exclusive licenses. The University of California at San Francisco Office of Technology Management notes that not all patented life science technology is licensable, affording value to a commercial developer, for several reasons. The technology often requires more research and development to attract commercial interest. As well, the market for the technology is frequently undeveloped and inadequate. The patent claims may be too narrow or difficult to enforce. The technology may not sufficiently differ from other technologies. Furthermore, there may be no economical method to manufacture products deriving from the technology.[60]

An exclusive license also creates uncertainty for the licensor. The licensor faces the risk that the chosen licensee is not the best entity to develop the commercial potential of the licensed technology. The licensor could protect against licensee underperformance by including minimum payments, contingent payments, and termination provisions, although these terms are typically difficult to negotiate. Furthermore, even a licensee that performs well may choose not to develop the commercial potential of the licensed technology in every application.[61]

B. Moral Hazard

Moral hazard exists when the structure of a license fails to offer incentives for efficient investment in the licensed technology. A common theme expressed both by university technology transfer managers and by those people who have studied technology transfer is that new technologies licensed by universities and research institutes typically require a great deal more research and development to become commercially useful.[62] Often

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59. Richard Jensen & Marie Thursby, *Proofs and Prototypes for Sale: The Licensing of University Inventions*, 91 AM. ECON. REV. 240, 245 (2001).

60. UNIVERSITY OF CALIFORNIA SAN FRANCISCO OFFICE OF TECHNOLOGY MANAGEMENT, *supra* note 40, at 4.

61. Gregory Graff. et al. offer the example of an exclusive license to Monsanto for genetic engineering of plants, which Monsanto chose not to exploit for some minor crops. *See* Gregory Graff., Amir Heiman & David Zilberman, *University Research and Offices of Technology Transfer*, 45 CAL. MGMT. REV. 88, 114 n.22 (2002).

62. *See, e.g.*, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO OFFICE OF TECHNOLOGY MANAGEMENT, *supra* note 40, at 4; Gregory Graff. et al., *supra* note 61, at 92-93; Jensen & Thursby, *supra* note 59.

the inventor of the technology has the intellectual ability, and sometimes the entrepreneurial capacity, to contribute to this additional research and development. A paid-up license, though, offers no pecuniary incentive for the inventor to invest in the technology after the license has been negotiated, because the inventor's compensation does not depend on its commercial performance. With a running royalty the inventor's compensation depends on the commercial performance of the technology. This compensation model motivates the inventor to participate in a technology's development after negotiating the license.[63] Alternatively, an equity share also offers the inventor an incentive to increase the value of the equity by participating in the development of the licensed intellectual property.[64]

C. A Single Licensee Can't Do It All

An exclusive fixed fee license presumes that the exclusive licensee can satisfy all of the demand for products made with the licensed technology in a cost-efficient manner. But the exclusive licensee cannot efficiently supply all of the demand for products if it incurs diminishing returns to scale or faces other constraints that limit its ability to exploit the full potential of the licensed technology, including limits on its ability to explore creative applications for the new technology. The technology licensor could permit the licensee to sublicense others, and extract some of the value of the sublicenses with the fixed fee. However, this requires that the licensee identify the appropriate sub-licensees and that the licensor, the original licensee, and the sub-licensees negotiate terms for sharing profits. This is a complex undertaking with the potential to sacrifice potential economic surplus. Furthermore, there is little assurance that the licensor would be able to capture a high share of the remaining surplus, particularly with limited competition among potential licensees for the rights to an exclusive license.

An alternative is to license the technology non-exclusively to all takers with a running royalty and low or no upfront fees. This strategy limits the profit that the licensor can extract from each licensee, but royalties from a large number of licensees can more than compensate for a high fixed fee from an exclusive licensee. The licensing history of the Cohen-Boyer patent for recombinant DNA is a case in point. Patented in 1980, the Cohen-Boyer technology for inserting genes in cells was the foundation for the

63. *See* Jensen & Thursby, *supra* note 59, at 248 (arguing that development requires a positive royalty rate when the contract terms specify a royalty and/or fixed fee).

64. There may be a dilution effect that reduces inventor incentives if the value of equity depends on activities that are unrelated to the licensed technology. *See id.* at 251 n.26.

biotechnology revolution. The patent was licensed non-exclusively, in part out of concern that one company could not explore all of the possible applications of the technology and in part because potential licensees feared that they would be excluded if the patent were licensed to a single company.[65] A total of 468 companies ultimately licensed the Cohen-Boyer technology and paid a total of $254 million during the patent's term, ninety percent of which was from running royalties.[66] Adoption of the Cohen-Boyer technology would probably not have been as pervasive with an exclusive license, and an exclusive license would also probably not have generated as much revenue for its licensors.

D. Not All Licensees Are Alike

Suppose that efficient exploitation of a technology requires more than one licensee. If the licensor knew exactly what each potential licensee could earn from using the licensed technology, it is possible that the licensor could design a unique contract for each licensee that would extract a large share of each licensee's profit and limit competition among licensees. However, the informational requirements of such a contract would be enormous, particularly for new technologies whose potential profitable applications are largely unknown. An alternative approach is to design a one-size-fits-all contract that most potential licensees would accept. A well-designed standard contract can increase the ability of the licensor to profit from the technology.

The optimal standard license would not be a single fixed fee, because a single fixed fee would not extract all of the available profit from each licensee. If the licensor wants to set a single fixed fee and license all firms that can efficiently produce goods or services using the licensed technology, the fixed fee would have to be the smallest fee that any licensee would be willing to pay. This would fail to extract all of the profits available from licensees that could earn more using the licensed technology. A standard license that extracts more of the available profit combines a fixed fee with a running royalty. The fixed fee can be set low enough to make the license attractive to licensees with modest profit expectations, while the running royalty can collect revenues from licensees that have large business opportunities.[67] Indeed, a mix of fixed fees and running royalties

65. Feldman, *supra* note 6, at 5-6.

66. *Id.* at 20, 23.

67. *E.g.*, Walter Y. Oi, *A Disney Land Dilemma: Two-Part Tariffs for a Mickey Mouse Monopoly*, 85 Q.J. ECON. 77 (1971); Richard Schmalense, *Monopolistic Two-Part Pricing Arrangements*, 12 BELL J. ECON. 445 (1981).

is a common feature of most technology licenses, although running royalties account for most of the revenues.[68]

E. Equity Participation

Licenses that include an equity stake in the licensee account for only a few percent of all licenses negotiated by universities, hospitals, and research institutes surveyed by AUTM over the past several years (Figure 1). This is surprising given that many potential licensees are short on cash. The option value of cashing in an equity stake is a tempting alternative to the expectation of meager royalties. Equity sharing can be an attractive way to realize the value of new technology when it is appropriate to grant an exclusive license to a firm whose business model is focused on the new technology, as in a new startup venture. A startup with a focus on the new technology avoids a dilution of effort and interest that could happen if the licensee is a large diversified company.[69]

Although equity sharing can be an attractive alternative to royalty-based licenses, the benefits should derive from better risk sharing and alignment of incentives for the licensor and the licensee. There is no reason why the expected value of an equity share should exceed the expected present value of a royalty stream unless the equity contract itself promotes investments that increase the value of the licensed technology. If the licensor and the licensee agree that a license would generate $1 million in royalties, the licensee should not be willing to give up more than $1 million in expected equity value, and the licensor should not be willing to accept less than that amount. Whether the payment to the licensor is based on revenues produced by the licensed technology or the equity value of the licensee is irrelevant in this example.[70]

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68. Jensen & Thursby, *supra* note 59, at 245.

69. Equity sharing, which often goes hand-in-hand with exclusive licensing, could conflict with the CIRM goal to negotiate non-exclusive licenses to CIRM-funded intellectual property whenever possible. *See* IPPNPO, *supra* note 12, at 17.

70. Equity participation can be a last resort to obtain value from a cash-starved licensee. Bray and Lee report that "When [a university executive] asked one licensing manager why he had taken equity so many times he shrugged and said it was all he could get." Michael J. Bray & James N. Lee, *University Revenues from Technology Transfer: Licensing Fees vs. Equity Positions*, 15 J. BUS. VENTURING 385, 388 (2000); *see also* AUTM, AUTM U.S. LICENSING SURVEY: FISCAL YEAR 2004, *supra* note 15, at 30 (demonstrating that equity is often the only currency that startup companies have to offer licensor institutions as upfront consideration).

There are examples of spectacular equity rewards, such as Stanford University's $336 million sale of its equity share in Google,[71] which may not have been equaled with a royalty-based license.[72] On the other hand, there are also examples of licenses that have produced spectacular royalties, such as the $254 million in royalty income from the Cohen-Boyer technology. It is not obvious that a negotiated share of equity in a Cohen-Boyer licensee would have generated an equally large return.

Equity participation is an appealing technology transfer alternative when it increases the *total value* of the licensed technology by better aligning the incentives of the licensor and the licensee. If an inventor has an equity share in the licensee, the inventor may have greater motivation to work with the licensee to develop the commercial potential of the technology. A license with running royalties also offers an incentive for the inventor to work with the licensee to produce greater revenues. Equity participation can be more effective by offering rewards for work outside the boundaries of the licensed product or process. Licensed technologies can benefit from continued inputs of knowledge and creativity from the original inventors as well as feedback from the licensees to the inventors. An equity stake can provide a platform for these critical communications that is superior to the incentives that flow from a product or license.[73]

Equity sharing can create value relative to a royalty license in other ways. Equity offers some diversification benefit by assigning the licensor a share of the value of an entity rather than a share of revenues from a product or process. Equity may simplify negotiations in the event of contingencies that were not anticipated in a royalty license. For example, a licensee could have a technology opportunity that competes with the licensed technology. The allocation of effort between the licensed technology and the alternative would be a concern to a licensor with a royalty

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71. *Google Stock Turns into Windfall for Stanford University*, S.F. CHRON., Dec. 1, 2005.

72. It is conceivable that Stanford would have earned even more if it had negotiated a royalty license with Google. Google earned $3.2 billion in revenues in 2004 and $6.1 billion in 2005. Google Investor Relations, http://investor.google.com/fin_data.html (last visited July 9, 2006). Had Stanford negotiated a license with a royalty equal to two percent of Google's sales, it would have earned $64 million in 2004 and $122 million in 2005. Stanford's equity payout corresponds to only a few years worth of royalties at these levels.

73. Interviews with university technology managers suggest that equity participation changes the university from being a potential adversary of the licensee to a concerned partner. Bray & Lee, *supra* note 70, at 389; *see also* Maryann Feldman, Irwin Feller, Janet Bercovitz & Richard Burton, *Equity and the Technology Transfer Strategies of American Research Universities*, 48 MGMT. SCI. 105, 106 (2002).

contract, though less of a concern to a licensor with an equity share in the company because equity could increase with development of either technology.[74] Equity sharing can mitigate other potentially costly conflicts that might arise, such as over rights to new technologies that are developed using the licensed technology. An equity license can also realize value from the licensed technology before the technology generates significant revenue flows through the sale of equity in an initial public offering or acquisition.[75]

The pecuniary incentive for post-license cooperation comes from the prospect of increased royalties, which means that the contract has to be back-loaded to emphasize running royalties rather than up-front fees. But a running royalty increases a licensee's marginal production cost, which can interfere with the dissemination of the technology and reduce its ultimate value. This risk is particularly severe when production requires many licenses, each with a running royalty, and the total stack of royalties adds to the licensee's marginal cost.[76] An equity participation license does not add to the licensee's marginal cost and can avoid the distortion imposed by a running royalty.

Despite some attractive features, there are negatives to equity participation. Many technologies are not likely candidates for an equity license. If a technology offers only an incremental value to an on-going concern, a royalty license is a better way to measure its incremental contribution. Equity participation is attractive to a startup if the licensed technology has clear commercial potential and the licensee can build a firm around it.[77] Larger licensee companies offer greater diversification benefits for sponsors of new technologies, but also dilute the incentives for the licensor to develop the technology because the efforts make only a small contribution to the total value of a large company.

In many respects equity sharing is the ultimate exclusive license. The choice of equity as the path to commercialize a technology discourages broad dissemination of the technology to other licensees, which are poten-

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74. Feldman et al. note the example of an equity share for an artificial heart technology where the licensee was working on a competing technology. Equity minimized the conflicts that could have been serious with a royalty contract. Feldman et al., *supra* note 73, at 112.

75. Bray & Lee, *supra* note 70, at 389.

76. *See, e.g.*, Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard-Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY (Adam Jaffe, Joshua Lerner & Scott Stern eds., 2001); Richard Gilbert, *Antitrust for Patent Pools: A Century of Policy Evolution*, 2004 STAN. TECH. L. REV. 3, ¶¶ 25-26 (2004), *available at* http://stlr.stanford.edu/STLR/Articles/04_STLR_3/article_pdf.pdf.

77. Bray & Lee, *supra* note 70, at 388.

tial sources of competition that can reduce the value of the equity stake. The licensor with an equity stake in a single company may be reluctant to explore other partners to commercialize the licensed technologies, and the licensee may be equally reluctant to consider sub-licensing the technology to others. Equity participation can make it difficult to terminate an underperforming licensee because it would require admission that the equity stake is worthless.

An equity license, with its focus on a single licensee, may contradict the objective of broad dissemination of technologies developed by CIRM. In addition, an equity license may interfere with the potential health benefits from stem cell technologies, which should be the primary objective of CIRM. Exclusivity is not necessarily bad, because it can encourage investment to commercialize the technology. All the same, CIRM has to ensure that the benefits of exclusivity do not come at the expense of broader dissemination.[78]

Equity licenses pose other challenges for CIRM. Equity magnifies the risk inherent in technology transfer, with the prospect of very large rewards offset by the much larger probability of no return. With equity sharing, the licensor acts much as a venture capitalist. Successful venture capitalists are highly skilled at identifying the potential winners. If CIRM intends to make equity sharing a major component of its licensing program, it should develop venture capital expertise in-house or acquire it from others. In the latter case, a significant fraction of the reward for picking attractive equity sharing opportunities will go to those with the expertise to choose them.[79] Furthermore, equity participation can expose the licensor to liability for product defects, or more generally sully the licensor's reputation as a research institution serving the public good if products sold by the equity partner harm patients or the environment.[80] Equity can become a trap for the licensor if the need for additional investments to commercialize the technology lures the licensor into making expenditures that generate little or no financial returns.

Actual financial returns to equity licensing by universities, hospitals, and research institutes have been mixed compared to royalty licenses. Bray and Lee report that the average value of equity sold in sixteen uni-

78. *See* IPPNPO, *supra* note 12, at 17, 23, 36 (describing concerns about exclusive licenses).

79. Choosing the right licensee is also an issue for an exclusive royalty-based license. A difference is that equity participation may presume more active involvement by the licensor and hence the need to match the capabilities of the licensor, the licensee, and the licensed technology.

80. *See* Feldman et al., *supra* note 73, at 107.

versity spin-off companies in 1996 was $1,384,242, while the average annual income of a royalty license was only $63,832 in the same year. These numbers, though, are not directly comparable. The equity number includes only successful equity licenses. If half the equity deals fail, this reduces the average realized value to $692,121. Excluding a few of the highest equity sales drops the average value of equity sold to only $279,443.[81] Equity is the capitalized value of the contract, while royalties represent income in one year. If a license generates $60,000 in royalty income for ten years and the discount rate is ten percent, the capitalized value of the royalty income is over $400,000. Furthermore, the comparison is potentially misleading because many licenses that generate royalty income would not have been suitable candidates for an equity share.[82]

Equity is not becoming a preferred method to realize technology value for universities, hospitals, and research institutes. Although the number of licenses reported by AUTM that include an equity share has more than doubled since 1996,[83] the share of licenses with equity and startups with equity has not increased dramatically from 1996 to 2004 (Figure 3). Furthermore, with the exception of fiscal years 2000 and 2001, which offered unusually favorable conditions to realize equity values, the share of licensing income from cashed-in equity has been in the low single digits and has been falling since 1996 (Figure 4). However, it is likely that FY 2005 will be a notable exception to this trend with Stanford's sale of Google stock.[84]

Equity sharing is a potentially rewarding path to commercialize CIRM technologies and it should play a role in its overall technology transfer program. However, other than Stanford's sale of Google stock, there is not much evidence that, compared to licenses with running royalties, increased equity sharing would significantly change historical patterns of

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81. Other studies have shown that estimated equity returns from new ventures are very sensitive to adjustments for failures. In one study, eliminating failed projects reduced the average rate of return for venture capital from about 700% to 59%. The high average that remains after adjusting for failures reflects the small probability of earning an extremely large return, combined with the much larger probability of a more modest return. *See* John H. Cochrane, *The Risk and Reward of Venture Capital*, 75 J. FIN. ECON. 3, 5, 30 (2005); *see also* Peng Chen, Gary Baierl & Paul D. Kaplan, *Venture Capital and Its Role in Strategic Asset Allocation*, 28 J. PORTFOLIO MGMT. 83 (2002).

82. University policies typically limit their maximum equity share to about ten percent. *See* Jensen & Thursby, *supra* note 59, at 250.

83. AUTM, AUTM U.S. LICENSING SURVEY: FISCAL YEAR 2004, *supra* note 15, at 29.

84. The share of licensing income from cashed-in equity should increase dramatically in FY 2005 after recording Stanford's $336 million share of Google stock. This figure dwarfs total cashed-in equity sales of $29 million in FY 2004. *Id.* at 26.

licensing income from research by universities, hospitals, and research institutes.

Figure 3
Share of Licenses with Equity

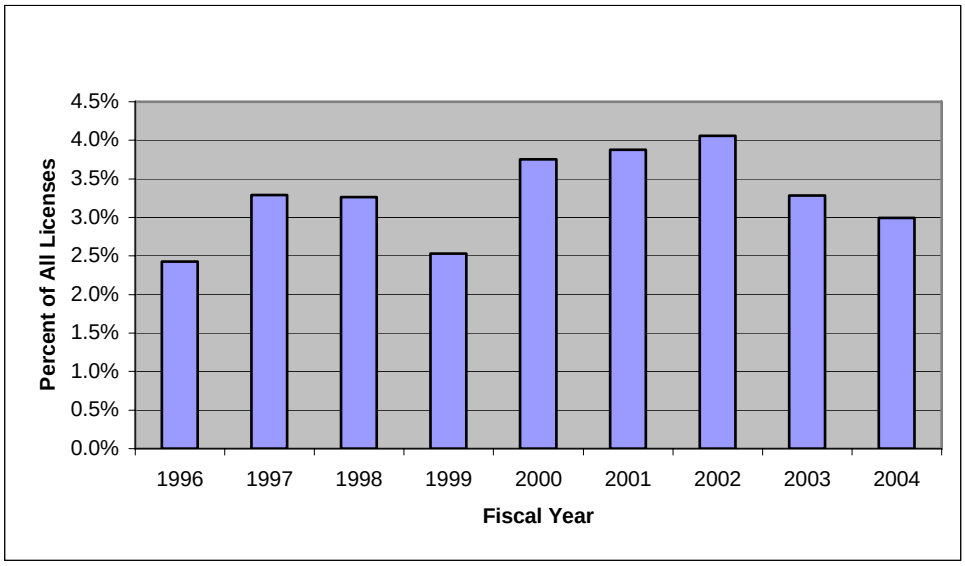
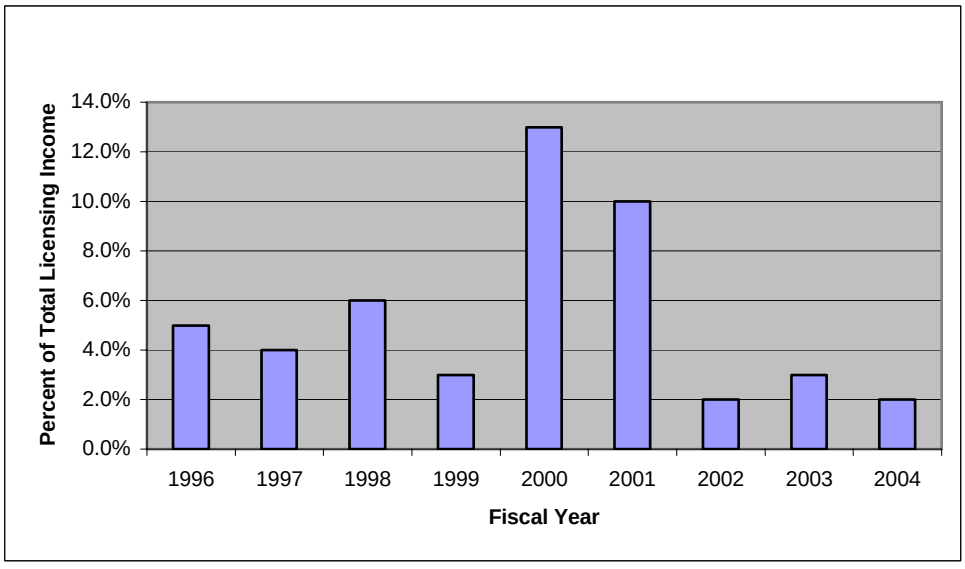


Figure 4
Share of Licensing Revenue from Cashed in Equity



V. CONCLUSIONS

The approach that CIRM will pursue to collect revenues from the licensing of intellectual property created with CIRM R&D support is yet another source of controversy in the brief history of this institute.[85] A main conclusion of this Article is that this particular controversy is a tempest in a teapot. The present value of licensing revenues is unlikely to be a source of income that will substantially offset the cost of R&D by CIRM, taking into account the likely long lag between R&D funding and the realization of commercial therapies made possible with CIRM support. This conclusion applies only to licensing income and does not diminish the prospect that research funded by CIRM will lead to important health benefits.[86]

I take two different paths to reach my conclusion about likely royalty income from CIRM-supported R&D. One approach follows the analysis performed in the Baker-Deal study, which forecasts the likely number of major therapies that CIRM support will produce and the revenues from these therapies. The Baker-Deal study estimates that the state will earn royalties from research funded by CIRM that will total either $537 million or $1.1 billion, depending on the royalty rate. The study, however, does not account for the time cost of revenues that occur far in the future. Applying a discount rate corresponding to the interest rate on ten-year treasury bonds reduces the present value of revenues from CIRM-funded R&D predicted in the Baker-Deal study by sixty-five percent. Under the current CIRM policy for revenue sharing, the state will receive only about one-sixth of these revenues (twenty-five percent of licensing revenues remaining after deducting thirty-five percent for the inventor's share). This leaves the state with about $31 million in the base case of the Baker-Deal study and $62 million in their high estimate, very small fractions of the more than $3 billion in R&D funding for CIRM.

A second approach I use to estimate likely future royalty income from CIRM-supported R&D relies on actual royalty income collected by U.S. universities, hospitals, and non-profit research institutes surveyed by the Association of University Technology Managers. CIRM will not perform research itself, but will contract with entities, most of which will be uni-

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85. *See, e.g.*, Michelle Chen, *Stem-Cell Research Blasted From New Angle*, THE NEW STANDARD, May 8, 2006, *available at* http://www.genetics-and-society.org/news disp.asp?id=1000.

86. Another possible benefit, which I do not address in this Article, is increased economic activity in the state of California from the activities of CIRM. While these benefits may be important, they are unlikely to be large given that R&D funding by CIRM is a small fraction of total academic R&D expenditures in California. *See* sources cited *supra* note 29.

versities, hospitals, and non-profit research institutes engaged in biomedical research. For this reason the licensing revenue performance of the organizations surveyed by AUTM, particularly hospitals and non-profit research institutes, is a good model to estimate the likely revenues from licenses for technology generated with R&D support from CIRM.

Over the past several years, the hospitals and research institutes surveyed by AUTM earned licensing revenues equal to about 6.6 percent of their current R&D expenditures net of operating expenses. After correcting for the lag between R&D expenditures and receipt of royalty income and applying a time cost to future income, I estimate a return on R&D for these entities in current dollars equal to about 4.5 percent of R&D expenditures. Adjusting this number to account for CIRM's revenue sharing policies reduces the state's return in current dollars to about 0.60 percent of R&D expenditures.

Although I estimate that the state of California will earn little in technology licensing royalties from CIRM-funded research, I do not regard this conclusion as particularly bad news for the state. My analysis does not undermine the value of the potentially enormous health benefits from therapies made possible by advances in human embryonic stem cell science. This is the true measure of value from the state's support of CIRM. Furthermore, the low expected royalty income to the state reduces the risk that royalty income will jeopardize tax-exempt status for the bonds that pay for CIRM. Tax-exempt status reduces the cost of CIRM funding by more than the state is likely to earn in royalty income. There is little to gain, and much to lose, from struggles over policies to distribute royalty income for CIRM-funded research. There is a potential conflict between the goal of advancing stem cell science and achieving an attractive financial rate of return on California's investment. Bad policies could undermine CIRM's research program by distorting incentives for inventors to work on CIRM-funded projects. The controversy over the allocation of royalties from CIRM-funded research is a distraction from the main benefits from CIRM R&D support, which are the therapies that research funded by CIRM will help to create.

I have also considered ways by which CIRM may increase its licensing income. Central among these alternatives is a greater reliance on equity sharing. Taking equity in licensees of CIRM-supported technologies has a number of attractive features, but is unlikely to produce a major increase in expected licensing revenues compared to licenses that specify running royalties and up-front fees. Stanford University's $336 million sale of Google stock is indeed impressive, but a running royalty could have produced as much income from Google's large and growing revenue

base. Equity sharing has the potential for large rewards, but the risks are great. CIRM or its grantees would have to gain expertise as venture capitalist, or purchase this expertise, if CIRM is to rely heavily on equity sharing to realize monetary benefits from technology transfer.

While CIRM investments in human embryonic stem cell research will generate some financial return for the state of California, the primary benefit from these investments will be progress toward improved therapies for the treatment of major chronic and acute diseases. The justification for the state's investment in CIRM is the promise of better health, not the promise of financial reward.

DESIGNING AN EFFECTIVE PROGRAM OF STATE-SPONSORED HUMAN EMBRYONIC STEM CELL RESEARCH

By Roger G. Noll†

TABLE OF CONTENTS

I. INTRODUCTION

Research on human genetics and cell biology periodically has given rise to intense, polarized debates about whether such research should be permitted and, if so, whether it should be financed by government. From the eugenics movement early in the 20th Century,[1] through the debate in

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1. DANIEL J. KEVLES, IN THE NAME OF EUGENICS (1985).

the 1970s over recombinant DNA research,[2] to the attempts by Presidents William J. Clinton and George W. Bush to define the federal role in research on human embryonic stem cells (hESC), political leaders have found themselves torn between the enormous potential human benefits that might flow from increasing knowledge about human genetics and the intense beliefs of some that such research is immoral.

In the wake of federal restrictions on hESC research, California as well as some other states are considering or have established programs to support this research. This Article reviews the current state of federal and state policies, including the difficulties states have encountered in setting up their own programs, with special attention given to the problems encountered in setting up the California Institute for Regenerative Medicine (CIRM).

California's initiative to create CIRM, which sponsors hESC research within the state, was significantly delayed by a series of political and legal battles over the structure, procedures and policies of CIRM, including its policies regarding intellectual property rights emanating from its grants. CIRM's problems reflect the underlying political and economic environment that any state faces in creating a successful stem cell research program. To be efficiently implemented, all government-supported research projects that have commercial potential must overcome the danger of "pork barrel" effects and the political problem of accommodating confidential peer review. In addition, some problems associated with this program arise from its particular characteristics: its narrow scope, which is an example of "earmarking" government research expenditures; the bitter public controversy over the legitimacy of stem cell research; and unrealistic perceptions that political leaders and the public maintain about the short-run therapeutic advances and financial payoffs from this research. This Article explores these problems and discusses the extent to which the structure of CIRM is likely to lead to an effective response to them.

The federal government operates under two policies that restrict hESC research. First, the Dickey Amendment, which has been added as a rider to appropriations bills annually since 1995,[3] bars the use of federal funds for any activity that destroys or endangers embryos or that creates embryos for research purposes. It also prevents the use of federal funds to extract stem cells from embryos, but does not prohibit research on stem cells that

2. *See generally* Roger G. Noll & Paul A. Thomas, *The Economic Implications of Regulation by Expertise: The Case of Recombinant DNA Research*, *in* RESEARCH WITH RECOMBINANT DNA (1977).

3. Pub. L. No. 104-99, § 128 (renewed each year in appropriations bills).

were extracted using funds from other sources. Second, President Bush directed federal agencies in 2001 to prohibit the use of federal funds to support hESC research except on stem cell lines that were developed before the directive was issued.[4] Because of contamination and other problems with these lines, the federal policy is widely regarded as having severely inhibited the most promising hESC research projects.[5] The President's policy directive not only has dubious legal status, but it also does not make clear exactly what is and is not banned. Consequently, organizations that receive federal research grants have been forced to develop their own interpretations of the directive with essentially no assistance from the federal government. The President's policy directive is controversial even among Republicans in Congress. In May 2005, the Castle-Degette Bill, which would allow federal funds to be used on new stem cell lines, passed in the House of Representatives by a vote of 238-194.[6] Introduced in the Senate as the Specter-Harkins Bill, it then passed in July 2006 but was vetoed by the President.[7]

Meanwhile, over thirty states have enacted, have failed to enact, or currently are considering legislation related to hESC research.[8] Although California's program is the largest—designed to spend about $300 million annually for ten years—five other states have established state-sponsored hESC research programs: Connecticut ($10 million per year for ten years), Illinois (the governor allocated $10 million for stem cell research from the

4. Press Release, President Discusses Stem Cell Research, The White House (Aug. 1, 2001), http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html.

5. *See Exploring the Promise of Embryonic Stem Cell Research: Hearing Before the S. Special Comm. on Aging*, 109th Cong. (2005).

6. *See* U.S. Congressman Mike Castle, *Castle-Degette Legislation H.R. 810 Passes the U.S. House! Final Vote: 238 to 194*, May 24, 2005, http://www.house.gov/castle/Castle%20DeGette%20ESCR.html.

7. *See* U.S. Senate Legislation & Records Home, Vote Summary, http://www.senate.gov/legislative/LIS/roll_call_lists/roll_call_vote_cfm.cfm?congress=109&session=2&vote=00206 (last visited Aug. 25, 2006) (concerning Senate passage); Sheryl Gay Stolberg, *First Bush Veto Maintains Limits on Stem Cell Use*, N.Y. TIMES, July 20, 2006, *available at* http://www.nytimes.com/2006/07/20/washington/20bush.html?ex=1155009600&en=035c3f389da0659e&ei=5070 (concerning the veto and unsuccessful override attempt).

8. The discussion of state legislation for and against stem cell research was compiled from the following websites: GRC State Stem Cell Research News and Alerts, What's New in State Stem Cell Legislation and Funding, http://grassrootsconnection.com/state_stem_cell_resources.htm (last visited Aug. 25, 2006); National Conference of State Legislatures, State Embryonic and Fetal Research Laws, http://www.ncsl.org/programs/health/genetics/embfet.htm (last visited Aug. 25, 2006); National Conference of State Legislatures, Genetics Legislation Database, http://www.ncsl.org/programs/health/genetics/geneticsDB.cfm (last visited Aug. 25, 2006).

state's portion of the settlement of the tobacco litigation, with a larger appropriation pending as of June 2006), Maryland (authorization passed but appropriation pending), New Jersey ($8.5 million and $14.5 million for the past two years, with further appropriation pending), and Ohio (research institution established in 2003 with $19.5 million in one-time state funding). Several other states are considering programs, including proposals in New York and Pennsylvania to spend $100 million annually. Smaller programs are being considered by state legislatures in Delaware, Florida, and Texas. Meanwhile, New York Mayor Michael Bloomberg donated $100 million of his own money to support stem cell research at Johns Hopkins University.[9]

On the other side, Indiana, Louisiana, and South Dakota have passed legislation banning hESC research, and Kentucky, Mississippi, and Missouri are considering such legislation. Arizona, Missouri, Nebraska, and Virginia have laws banning the expenditure of state funds on hESC research, although Missouri faces a ballot initiative to overturn that legislation.

The purposes for enacting state-sponsored hESC research programs are diverse. Most obvious is a philosophical disagreement with the President. Another motive is the practical objective of seeking effective treatments for several important and heretofore incurable diseases. These programs also create an opportunity for a state to gain strategic advantage for its higher education and biotech industries, to obtain royalties from patents arising from the research, and to reduce state spending on medical care.

California's experience shows that setting up an effective research program is difficult. While spending money is easy, spending money without causing a political backlash is difficult. Several problems stand in the way of establishing an effective program, but this Article focuses on four that are especially important: (1) uncertainties about federal policy and politics; (2) difficulties of using government research programs to attract industry; (3) organizational challenges in creating a merit-based method of providing financing through government agencies; and (4) difficulties concerning the assignment of the intellectual property rights arising from state-sponsored research. These problems are not insurmountable, but state governments have little or no experience in dealing with them, and as a result they may be prone to make mistakes.

The remainder of this Article discusses the underlying economics and politics that shape states' responses to these issues, and then examines

9. *See* Sara Kugler, New York Mayor Donates $100 Million to Johns Hopkins, WTOP (Feb 2, 2006), http://www.wtopnews.com/?nid=25&sid=688013.

how California has dealt with these issues. This Article has three main conclusions. First, to avoid inefficiencies arising from the politicization of grants, agencies that implement research programs must base their decisions on merits as determined by competitive peer review. The California program is well designed in this regard. Second, intense political polarization over the legitimacy of hESC research inevitably slows implementation and increases the costs of these programs, as exemplified by CIRM. Third, in designing an intellectual property regime for hESC research programs, some political leaders have vastly overestimated the potential revenue from licensing research results, and as a result have proposed licensing rules that may undermine the viability of the research program. California is no exception. State legislators have proposed rules for licensing patents from CIRM's projects that make grants from CIRM substantially less attractive to leading research institutions than grants from the federal government and private foundations. Because state-sponsored hESC research programs will account for a small fraction of all biomedical genetics research, states cannot realistically expect to receive substantially more favorable licensing arrangements than those available from other sources.

II. THE ECONOMICS AND POLITICS OF R&D PROGRAMS

California's hESC program will support basic research in genetics, but it also has a practical orientation that plausibly will lead to commercial development. This Part summarizes three key economic and political factors that are likely to affect adversely the performance of an hESC research and development ("R&D") program. The first factor is the salience and controversial nature of stem cell research among the general population, which creates a political environment in which the program and its implementing agency are constantly subjected to intense scrutiny and criticism irrespective of how the policy evolves. The second factor is that the policy instruments for increasing a society's overall investment in research inevitably have undesirable effects that can offset the benefits of the program. Third, the political process creates additional impediments to effectively managing R&D programs that have substantial and immediate commercial significance.

A. Salience and Polarization

Government research programs rarely achieve high political salience, and so rarely are created and sustained because they enjoy widespread grassroots support. As a result, neither the federal government nor any state has ever had a coherent technology policy. Instead, technology policy is a fragmented mish-mash of largely unrelated programs, nearly all of

which generate little interest outside of the communities that are directly involved with them.

The most important exception to the lack of salience of technology policy pertains to defense-related R&D during the Cold War. From the late 1940s to the late 1980s, fear of military confrontation with the Soviet Union created a durable base of political support for large expenditures on R&D that was related to national defense. In the late 1980s, as the Soviet Union collapsed, support for defense-related R&D waned. As a result, real federal R&D expenditures declined in every field of R&D except biological sciences, and the federal government's share in U.S. R&D subsequently fell roughly by half.[10]

Another area of relatively high political salience in the United States is health care. The high salience of health has sustained substantial federal expenditures on research in biomedical sciences. hESC research is a type of practically significant basic research in biological sciences that derives support from the widespread beliefs that science is useful in creating more effective treatments for illnesses and that the government bears some responsibility for the effectiveness of the health care system.

An important difference between hESC research and most other research in biological sciences is opposition among a significant minority of the population. Various public opinion polls, stating the issue in different ways, report significant numbers of respondents who favor hESC research between 55 and 60 percent, with a few as low as 50 percent or as high as 70 percent. The fraction of respondents who oppose hESC research hovers around 20 to 25 percent, and an additional 10 to 15 percent oppose government funding of this research.[11]

The controversy about hESC research is intensely polarizing politics: a clear majority that supports stem cell research is pitted against a large minority that wants to stop this research. Intense polarization creates a circumstance in which battles are never won because losers do not accept defeat, as exemplified by the continuing political battles over abortion, school prayer, evolution versus creationism in school curricula, and flag burning decades after court decisions appeared to have resolved the core constitutional issues about them. The rise of programs to support hESC

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10. *See generally* Linda R. Cohen & Roger G. Noll, *Research and Development after the Cold War*, *in* COMMERCIALIZING HIGH TECHNOLOGY: EAST AND WEST (Judith B. Sedatis ed., 1997); Roger G. Noll, *Federal R&D in the Antiterrorist Era*, *in* INNOVATION POLICY AND THE ECONOMY 3, (Adam B. Jaffe, Josh Lerner & Scott Stern eds., 2003).

11. For a summary of these polls, see Polling Report.com, Origin of Human Life, http://www.pollingreport.com/science.htm (last visited Aug. 25, 2006).

research in a few states, the reaction of its opponents to use numerous legal and political means to stop it, and the inability of most states and Congress thus far to speak definitively on the matter all illustrate the extent of political polarization and the paralysis that it creates.

B. The "Public Good" Rationale for Government R&D

The product of research is information, which is a public good in that once knowledge has been obtained by one person, the costs of discovering the information need not be repeated in order for a second person to gain access to it.[12] By contrast, ordinary economic goods are rivalrous. For example, if one person consumes a hamburger, a second person cannot consume it also. Unlike hamburgers, information is difficult to privatize. Even in the presence of strong intellectual property (IP) rights, creating and exploiting new knowledge enables others to draw inferences about the knowledge and how they might use it without violating its IP rights.

These features of new knowledge lead to socially inefficient under-investment in creating fundamental new information. As well, the same features can lead to socially inefficient over-investment in "copy-cat" R&D. This sort of research seeks to "invent around" the original discoverer's intellectual property rights by creating the closest thing to a copy that differs sufficiently to avoid infringing those rights.[13]

The presence of these inefficiencies creates a policy dilemma for officials in that the policies that might ameliorate investment inefficiencies also create other costs that can offset these benefits. Both subsidies and IP rights increase an innovator's net financial reward from R&D and thereby reduce under-investment in research. Subsidies reduce the expected financial reward that is necessary to make R&D privately profitable. IP rights reduce competition from copies or unauthorized use, thereby enabling rights holders to charge more for innovations. Both subsidies and strong IP

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12. *See generally* Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY 609-25 (1962). For a comprehensive survey of the field, see Paula E. Stephen, *The Economics of Science*, 34 J. ECON. LITERATURE 1199-1235 (1996).

13. *See* Charles I. Jones & John Williams, *Too Much of a Good Thing? The Economics of Investment in R&D*, 5 J. ECON. GROWTH 65, 80 (2000); Edwin Mansfield, Mark Schwartz & Samuel Wagner, *Imitation Costs and Patents: An Empirical Study*, 91 ECON. J. 907-18 (1981); Nancy Galini & Suzanne Scotchmer, *Intellectual Property: When Is It the Best Incentive System?*, *in* 2 INNOVATION POLICY AND THE ECONOMY 63-65 (Adam Jaffe, Joshua Lerner & Scott Stern eds., 2002).

rights also can reduce wasteful copy-cat R&D by increasing its cost if decisions to subsidize R&D or to grant IP protection are based on novelty.[14]

The dilemma arises because both policies also create costs that can offset their innovative benefits. IP protection reduces the likelihood that inventions will be maximally exploited to produce economically useful products.[15] If someone seeks to make use of the information arising from an innovator's R&D, the act of applying the new information imposes no costs on the original innovator. And, because no costs are imposed when an idea finds a new use, the socially efficient price of using information—that is, the price that maximizes the social benefits that new knowledge creates—is zero. However, if the price of using knowledge is zero, the creator of the knowledge may not be able to recover the cost of creating it. By allowing the creator to charge for (or to deny) the use of new knowledge, IP policy reduces the social benefits that can be derived from the discovery.

Strong IP protection also can inhibit innovation for technologies in which innovations are sequential—that is, some useful applications of one piece of knowledge depend upon the creation of other knowledge.[16] For example, a British report on patent policy examined the use of genetic information to create effective new malaria drugs.[17] Over thirty plausibly valid patents apply to genetic information that might be used to create a malaria vaccine. An innovator must obtain a license for all of these patents before introducing a malaria vaccine. According to the Commission, "although the malaria vaccine is unlikely to be of significant commercial value, holders of intermediate patents often put an unrealistically high value on their technologies."[18] The need to obtain all of these licenses on reasonable terms is a substantial barrier to entry.

Both IP policy and subsidy programs also have significant implementation costs. One cost arises from the process of evaluating the novelty of the creator's idea, as in determining whether an innovation deserves a patent or whether a grant proposal is meritorious. Another is the cost of en-

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14. Galini & Scotchmer, *supra* note 13, at 53-62 (analyzing the relative merits of IP, *ex ante* grants, and *ex post* prizes as means to encourage private R&D).

15. For a thorough analysis of the advantages and disadvantages of intellectual property, see FRANÇOIS LÉVÊQUE & YANN MÉNIÈRE, THE ECONOMICS OF PATENTS AND COPYRIGHTS (2004), *available at* http://www.bepress.com/leveque/.

16. For a more thorough discussion of cumulative innovation, see Galini & Scotchmer, *supra* note 13, at 65-69.

17. COMMISSION ON INTELLECTUAL PROPERTY RIGHTS, INTEGRATING INTELLECTUAL PROPERTY RIGHTS AND DEVELOPMENT POLICY, 2001-02, at 143-44, *available at* http://www.iprcommission.org/graphic/documents/final_report.htm.

18. *Id.* at 144.

forcement. For IP, enforcement costs arise from using courts to penalize infringers. For grants, enforcement costs arise from complex accounting rules that assure accountability in spending public funds.[19]

Whether the benefits of stronger IP rights offset the costs is an empirical question that turns on, among other things, the responsiveness of innovative efforts to prospective financial rewards. IP protection is most likely to produce net social benefits if: (1) innovative effort is highly sensitive to financial rewards; (2) multiple complementary but independent innovations are not likely to be needed to create a valuable commercial product; (3) the nature and scope of IP rights are relatively transparent, thereby minimizing the need for costly litigation to resolve disputes; and (4) the social payoff for innovation is high.

For innovators who are motivated solely by the profitability of commercial applications, subsidies and intellectual property protection are substitutes because they both increase the financial incentive to undertake R&D. The profitability of an R&D project is the difference between the net revenue derived from commercializing the results and the cost of the project. The expected profitability of a project is increased by either lowering its cost with a subsidy or strengthening the intellectual property right in the output that is derived from the R&D project.

In academic research, the goals of scholars may attenuate the substitutability between subsidies and intellectual property.[20] If the main goal of scholars is career advancement within the academic community, scholars lack a strong incentive to disseminate the product of their research to those outside of academe who would find commercial uses for it. If subsidies are the only policy for promoting scholarly research, researchers will seek to win as many grants as possible, will focus their energy on research productivity, and will not pursue commercial exploitation of their research outputs. Only if scholars do seek financial reward will granting them IP rights in their research output encourage commercial uses of scholarly research.

Until fairly recently, government programs to subsidize R&D typically did not have a coherent, parallel policy about intellectual property that was derived from subsidized projects. Prior to 1980, each federal agency that

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19. For a description and analysis of these accounting rules, see Roger G. Noll & William P. Rogerson, *The Economics of University Indirect Cost Reimbursement in Federal Research Grants*, *in* CHALLENGES TO RESEARCH UNIVERSITIES 105-46 (Roger G. Noll ed., 1998).

20. For a detailed discussion of the economics of academic research that contains the analytical basis for the argument of this paragraph, see Richard R. Nelson, *The Simple Economics of Basic Scientific Research*, 67 J. POL ECON. 297-306 (1959).

subsidized R&D developed its own rules regarding IP rights arising from its sponsored research. Some agencies required that research results be the property of the government. This practice was common in defense research. Other agencies required that researchers place research outputs in the public domain, while still others insisted that the researcher grant IP rights to the government. Publications were a major exception. Researchers who wrote books and articles and private publishers of scholarly books and journals could profit from publications that were derived from federally financed research.

The old system drew three criticisms.[21] First, the patchwork of procedures among agencies increased the complexity of managing IP from federal research. Second, policies created an artificial distinction between patents and copyrights, which became more important with the rise of academic computer science. Third, universities and research institutions were thought to lack an incentive to find commercial applications of their research.

In 1980, the federal government passed the Bayh-Dole Act to solve these problems.[22] Bayh-Dole allows recipients of federal grants to obtain IP rights from work supported from federal funds in return for facilitating commercial uses of these rights. Giving IP rights to scholars and their employers creates the opportunity for financial gain if discoveries are commercialized, and thereby could cause research to find wider commercial application. But giving scholars a commercial interest in their discoveries also could deflect attention from more important (and even more commercially significant) fundamental discoveries that cannot be protected by intellectual property. For example, scholars can receive patents for creating new chemicals or discovering new genomic information, but not for characterizing a naturally occurring chemical or discovering a new physical property of matter. If financial gain motivates basic research, allowing researchers to have IP rights could shift research in favor of the former.

Notwithstanding all of these arguments, the Bayh-Dole Act has not had much of an effect on universities. First, the Act has not caused a change in the allocation of research among science and engineering disci-

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21. For a more detailed discussion of the nature and problems of pre-1980 federal IP policies, see Jerry G. Thursby & Marie C. Thursby, *University Licensing Under Bayh-Dole: What Are the Issues and Evidence?*, May 2003, http://opensource.mit.edu/papers/Thursby.pdf.

22. The next three paragraphs are derived from a comprehensive evaluation of the Bayh-Dole Act: DAVID C. MOWERY, RICHARD R. NELSON, BHAVEN SAMPAT & ARVIDS ZIEDONIS, IVORY TOWER AND INDUSTRIAL INNOVATION: U.S. UNIVERSITY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOLE ACT (2004).

plines and, within disciplines, research priorities among fields of research. The most important factor affecting the allocation of faculty across research areas is the federal budget for basic research.[23] Second, although the Act created a new financial incentive to find commercial applications of university research, it has had no significant effect on the extent to which universities commercialize research outputs. In most industries, patents and licenses are not regarded as important in the innovative process.[24] Publications, conferences, consultancies, student employment, and informal contacts with faculty account for most technology transfer, with patents and licenses being relatively unimportant.[25] Third, while over 200 universities have technology transfer offices,[26] in most cases these offices have had little impact. Technology transfer offices in leading research universities have licensed hundreds of patents that are a major source of income. In 2004, eighteen universities received more than $22.5 million from licenses, and three received more than $65 million; however, among all universities with licensing offices, median licensing income is around $750,000.[27] The precise costs of these offices are not reported, but the median number of FTE employees is four and the median expenditure for legal fees (not including the costs of infringement suits) is around $500,000.[28] Considering that universities typically share licensing income with faculty, it is likely that most universities experience a net loss from their technology transfer offices.

C. Political Impediments

The organization of electoral systems, legislatures, and the bureaucracy can introduce inefficiencies into the design and implementation of an R&D program. The design of political institutions creates incentives that work against focusing R&D policy on inducing socially desirable but privately unprofitable R&D. By definition, an efficient R&D policy should not be much concerned about projects that researchers would undertake

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23. Linda R. Cohen & Roger G. Noll, *Universities, Constituencies, and the Role of the States*, *in* CHALLENGES TO RESEARCH UNIVERSITIES 40-46 (Roger G. Noll ed., 1998).

24. Richard C. Levin, Alvin K. Klevorick, Richard R. Nelson & Sidney G. Winter, *Appropriating the Returns from Industrial Research and Development*, *in* 3 BROOKINGS PAPERS ON ECON. ACTIVITY 793-98 (1987).

25. Wesley M. Cohen, Richard Florida, Lucien Randazzese & John Walsh, *Industry and the Academy: Uneasy Partners in the Cause of Technological Advance*, *in* CHALLENGES TO RESEARCH UNIVERSITIES 178-82 (Roger G. Noll ed., 1998).

26. AUTM U.S. LICENSING SURVEY: FY 2004 13 (2005), http://www.autm.net/events/File/FY04%20Licensing%20Survey/04AUTM-USLicSrvy-public.pdf.

27. *Id.* at 25.

28. *Id.* at 13, 21.

anyway, regardless of government policies, but instead should focus on projects that researchers otherwise would not pursue. In short, policy ought to be evaluated on the basis of the incremental innovation it creates, not the fraction of all innovations that are subsidized. Unfortunately, the government is not likely to be inclined to orient R&D policy in this way for three reasons: the political intolerance for failed projects, the influence of distributive politics (the "pork barrel") on project selection, and the short time horizon of government due to the frequency of elections.

1. Optimal Failure

One political impediment to efficient government R&D arises because an optimally designed R&D program is likely to support many failures. Whether an R&D program will succeed in producing useful innovations is inherently uncertain, which is perceived as a cost to private innovators. Hence, the failure rate will be higher among borderline projects that government policy hopes to induce. A program that has a high incidence of failure is vulnerable to attack on the grounds that it is inefficient, and supporters of such a program face a difficult task in convincing constituents that a program is effective. Hence, both elected officials who support an R&D program and civil servants who implement it have an incentive to support some projects for which the probability of commercial success is high and that are likely to be privately supported regardless of policy. Precisely this phenomenon has arisen in the federal Small Business Innovation Research (SBIR) program, where SBIR grants for R&D in small firms have had no statistically significant effect on R&D effort or employment among firms that receive grants.[29]

2. Pork Barrel

Another political source of inefficiency in R&D programs arises because elected officials are rewarded for bringing government expenditures to their constituency, even when projects have little intrinsic merit. Public R&D subsidies are prone to pork barrel incentives that arise from a systematic attempt to reward the constituencies of elected officials who support the program.[30] An example of the prosaic pork barrel in R&D is the use of "earmarking" expenditures for specific projects in appropriations

29. For a more comprehensive analysis of these points concerning the SBIR program, see Scott J. Wallsten, *The Effects of Government-Industry R&D Programs on Private R&D: The Case of the Small Business Innovation Research Program*, 31 RAND J. ECON. 674-92 (2000).

30. *See* THE TECHNOLOGY PORK BARREL (Linda R. Cohen & Roger G. Noll eds., 1991) (containing several examples of large-scale commercial R&D projects that yielded negative net benefits but nonetheless persisted because of their pork barrel effects).

bills. Earmarks represent the alternative to selecting R&D projects from among competing proposals on the basis of their merits, including both technical novelty and potential societal impact, as assessed by people with technical expertise in the proposed line of research.

A special problem in R&D is that the same political forces also create an incentive for elected officials to keep the economic exploitation of new knowledge within the jurisdictions that support its creation. Examples are the Cooperative Research and Development Agreements (CRADAs) that were initiated after the passage of the Stevenson-Wydler Act in 1986. This Act allows federal government research organizations to undertake joint R&D projects with private partners in which the private partners obtain commercialization rights to the research results.[31] CRADA rules limit eligibility for these programs to U.S. firms.

Another consequence of the incentive to deliver political benefits is the incentive to avoid harming organized interests. R&D programs risk loss of political support if they "pick winners"—that is, among competing applicants, pick a few entities to receive subsidies while rejecting others. If the latter outnumber the former, the net effect on the political support for the program is likely to be negative. For example, the federal programs in communications satellites and photovoltaic energy were prematurely terminated not because they were failures, but because their success threatened some large, politically influential firms.[32]

3. Impatience

The third distorting effect of political institutions arises from frequent elections.[33] The electoral cycle creates an artificially short time horizon for subsidy programs. Elected officials are motivated to seek political benefits within the time horizon of the electoral cycle. Typically, commercial R&D projects have a very long gestation period, in some cases twenty years or more. Consequently, elected officials who create a new R&D program are unlikely to be able to claim credit for its results, which typically accrue

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31. *See* Linda R. Cohen & Roger G. Noll, *Feasibility of Effective Public-Private R&D Collaboration: The Case of Cooperative R&D Agreements*, 2 INT'L J. ECON. OF BUS. 223-40 (1995) (discussing the rise and fall of the CRADA program).

32. Linda R. Cohen & Roger G. Noll, *The Applications Technology Satellite Program*, *in* THE TECHNOLOGY PORK BARREL, *supra* note 30, at 149-78; William Pegram, *The Photovoltaics Commercialization Program*, *in* THE TECHNOLOGY PORK BARREL, *supra* note 30, at 77-96.

33. For a complete discussion of the effect of election cycles on the time horizon of elected officials and R&D policies, see Linda R. Cohen & Roger G. Noll, *The Political Discount Rate* (Stanford Inst. for Econ. Policy Research, Discussion Paper No. 209, 1990).

after their political career is over. A short political time horizon biases projects with very long-term payoffs, which works against supporting long-term R&D projects.

III. APPLICATIONS TO HESC RESEARCH

The potential impediments to effective R&D laid out in the preceding Part apply to hESC research in four ways. First, political polarization creates uncertainty and costly delay in implementing the program. Second, political pressures sacrifice merit in favor of pork barrel spending as a criterion for support. Third, the political process favors projects with short-term commercial payoff at the expense of more fundamental, long-term projects with much larger expected future payoffs. Fourth, the quest for geographic economic advantage can lead to an inefficient bidding war across jurisdictions.

A. Political Controversy and Policy Uncertainty

As discussed in Section II.A, hESC research is an intensely polarized policy issue. Continuing political controversy causes uncertainty in the durability of hESC policy over the long investment horizon of a research program, and in so doing increases the risks faced by organizations that receive grants from the program. Uncertainty arises because agencies that support hESC research and organizations that undertake it are likely to experience continuing challenges to their procedures and decisions. Ongoing challenges to the program create legal costs and highly bureaucratized procedures to assure accountability. These challenges come from many sources. One is litigation that seemingly expresses concerns about program design, but that in practice is intended to delay, minimize or even prevent hESC research from taking place. Another is continuing political pressure to seek legislation or to pass initiatives that limit, redirect or destroy the program.

1. Litigation

In California, two lawsuits were filed soon after Proposition 71 passed to prevent CIRM from making any grants.[34] These lawsuits claimed that Proposition 71, the initiative measure that created California's stem cell program and CIRM, unconstitutionally delegates spending authority to a body that is not adequately controlled by elected officials. The cases were

34. People's Advocate v. Indep. Citizens' Oversight Comm., No. HG05 206766 (Cal. Super. Ct. May 12, 2006), *available at* http://www.cirm.ca.gov/pressreleases/pdf/2006/04-21-06.pdf.

consolidated, and plaintiffs lost at trial,[35] but the appeals process is still under way. A victory for the plaintiffs would kill CIRM by eliminating its process for making grants, but such an outcome always has been regarded as unlikely.

In June 2006, another lawsuit was filed to prevent CIRM from making grants to the University of California on the grounds of conflict of interest arising from the fact that CIRM's governing body includes nine members who are University of California employees.[36] While focused on the University of California, the complaint raises the same general issues about the structure of CIRM that were raised in the previous case, and so is likely to suffer the same fate.

Despite the dubious legal merits of these challenges, they have imposed substantial costs and delays on the California program. Until the litigation is resolved CIRM is unable to sell bonds to finance its grants, and meanwhile much of the early effort of CIRM's leadership has been devoted to fighting these lawsuits and seeking other sources of funds to enable it to launch a much smaller grant program.[37] Thus, as of this writing, litigation already has delayed full operation of the program for fifteen months, and a reasonable expectation is that the delay will be two years or even more.

2. Political Resistance to Peer Review

Some elected officials, especially those who are unfamiliar with research programs, are wary of making grants through a competitive process in which decisions are based on peer review. Reflecting this wariness, the California state legislature is considering a State Constitutional Amendment (SCA 13) to require open public records and meetings in making grants.[38] The amendment is a work in progress, so its ultimate form, if it passes, is uncertain. Its history, though, sheds light on the political envi-

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35. *See* Press Release, California Institute for Regeneration Medicine, Court Upholds Constitutionality of Stem Cell Program; Judge Sabrow Declares Proposition 71 Constitutional in Its Entirety (Apr. 22, 2006), *available at* http://www.findarticles.com/p/articles/mi_m0EIN/is_2006_April_22/ai_n16131786.

36. *See* Joint Complaint for Declaratory Injunction Relief, Nat'l Tax Limitation Found. v. Westley (June 23, 2006), *available at* http://www.lldf.org/Prop71.fu.Complaint-Rev3.pdf.

37. For documentation of the effects of the lawsuits on CIRM's activities, revenues, and expenditures, see CIRM Home Page, http://www.cirm.ca.gov (last visited Aug. 25, 2006).

38. For progress of the bill, see California State Senate, Official California Legislative Information, http://info.sen.ca.gov/cgi-bin/postquery?bill_number=sca_13&sess=CUR&house=B&site=sen (last visited Aug. 25, 2006).

ronment in which a state constructs a basic research program. The original version of the bill would have required open records and open meetings for all aspects of the CIRM grant-making process, preventing blind peer review of research projects. The bill has been watered down, preserving blind peer review, but imposing the following requirements:

> [A]ny working or advisory group that is charged with reviewing and recommending medical research projects for funding shall produce a written summary that shall be a public record of the reasons for recommending or not recommending any project for funding as well as how each project recommended for funding will benefit residents of California. The working or advisory group shall hold an open session to allow public comment on its decision prior to submitting any recommendation to the [Independent Citizens' Oversight Committee].[39]

The parallel is to require that grant proposals to the National Science Foundation (NSF) be subjected to public reviews of recommendations by referees and decisions by the NSF disciplinary panels, and that scientific researchers and disciplinary panels predict the ultimate societal benefits to be derived from each research project. Obviously, these requirements would substantially lengthen the delay and cost in making grants, increase the difficulty in finding scholars who are willing to referee proposals and serve on advisory groups, and generate a substantial volume of useless paperwork as basic researchers project plausible uses for their work decades in the future.[40]

The response of the California legislature to the passage of Proposition 71 illustrates both a short-term and a long-term problem for constructing state analogues to the basic science agencies of the federal government. The short-run problem is the absence of experience and knowledge concerning basic research, and the properties of an effective process for deciding which projects to pursue. Presumably this problem will diminish as states gain more experience with such programs, but in the interim it can make these programs far less efficient—and far less attractive as sources of funds for top researchers—than need be the case. The long-term problem is that in controversial areas, like hESC research, opponents of the

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39. S.C.A. 13 § 8(c)(2), 2005 S., Reg. Sess. (Cal. 2005), *available at* http://info.sen.ca.gov/pub/bill/sen/sb_0001-0050/sca_13_bill_20050531_amended_sen.html (last visited Aug. 25, 2006). The Independent Citizens' Oversight Committee (ICOC) is the governing body of CIRM. The role and composition of the ICOC are discussed in Section III.B.

40. For an apocryphal perspective on this onerous process, see Roger G. Noll, *Einstein's Interoffice Memo*, 309 SCI. 1441, 1490-91 (2005).

research are given the opportunity to forge alliances with proponents who rigidly adhere to the principle that all government decisions ought to be transparent but that have the effect of undermining the effectiveness of the program.

3. Federal Policy Uncertainty

The constraints on hESC research imposed by the federal government are another source of uncertainty for state-sponsored programs. While President Bush issued a public statement prohibiting granting agencies from spending federal funds on any unauthorized hESC research, the legal requirements emanating from the President's statement remain unclear. Federal agencies have interpreted the President's statement as requiring the development of accounting procedures to carry it out. Like other rules regarding expenditure of federal funds, the penalty for a violation is Draconian, involving repayment of the grants that somehow were used for hESC research and loss of eligibility for future federal support. Thus, potential recipients of grants from both the federal government and state agencies that sponsor this research need to be virtually certain that their system satisfies all subsequent authoritative federal auditors that the President's directive has been respected. Otherwise, the potential risk of accepting state hESC grants is huge compared to the likely benefit of financial support from them.

How potential recipients of hESC research grants answer these questions is important not only to institutions undertaking research, but also to a state that is supporting hESC research. If a research institution is found to violate the federal rules, its punishment is very likely to be financially devastating and to undermine its ability to perform state-supported projects, which in turn would thwart its ability to serve as an economic magnet for biotechnology firms in the state.

Unfortunately, the practical meaning of the federal directive is far from clear, and the federal agencies that support research that is most likely to have common inputs with hESC research have, understandably, been reluctant to stick their necks out by issuing clarifying regulations. The National Institutes of Health (NIH), the main federal sponsor of biomedical research and thus by far the most important entity for implementing the President's ban, has stated: "Scientists who receive federal funds and study both federally fundable and non-federally fundable human embryonic stem cells must charge research costs for study of non-federal

lines only to non-federal sources of funding."[41] While all agree that direct expenditures on prohibited hESC research cannot come from federal funds, other issues about potential indirect support remain unresolved. According to the same guideline: "Federal policy is clear that no federal funding may be used, either directly or indirectly, to support human embryonic stem cell research outside the criteria established by the President on August 9, 2001," and goes on to state that indirect costs should be divided between federal projects and prohibited stem cell research projects according to the principles of OMB Circular A-21.[42] But these instructions are far from definitive.

Most importantly, the legal status of the President's directive is unclear. Notably, the President has not issued an Executive Order on the matter, forcing agencies to attempt to implement a vague policy that was set forth in a speech, not a carefully crafted legal document that has gone through the standard vetting process among relevant federal officials. Because the directive is not an Executive Order, it was not published in the Federal Register. Thus, the outcome of an attempt by the federal government to enforce the directive is far from clear. Moreover, the President's directive covers all federal expenditures, not just NIH grants, so that while NIH auditors probably are limited to enforcing the directive as it was embellished by the NIH, other agencies are not so constrained, and have not issued guidelines that set forth their interpretation of the directive. In particular, agencies that support students directly through fellowships, work-study grants, and student loans have been silent.

A few examples convey the importance of the gray areas and, therefore, the uncertainties facing potential recipients of state grants. Can a student who holds an NSF graduate fellowship or a government-guaranteed student loan work in a lab that undertakes prohibited hESC research, or would this represent the expenditure of federal funds in support of prohibited research? If a university buys equipment with federal funds, can this equipment be used on prohibited hESC research as well if it is not fully utilized on federally-supported projects? Can such equipment be used for prohibited hESC research after the grant has expired, full title to the equipment has passed to the university, and the equipment has been fully

41. National Institutes of Health, Stem Cell Information Frequently Asked Questions, http://stemcells.nih.gov/info/faqs.asp (last visited Aug. 25, 2006) (addressing how to assure that federal funds are not spent on prohibited stem cell research).

42. *Id.* For the Circular A-21 text, see Office of Management and Budget, Circular A-21: Revised 5/10/04, http://www.whitehouse.gov/omb/circulars/a021/a21_2004.html (setting forth the basic policies and procedures that recipients of federal grants must use to determine the reimbursable costs of federally sponsored research).

depreciated? If universities use indirect cost recovery from federal projects to finance seed grants, as many do, are projects involving prohibited hESC research eligible for these grants? Can administrative personnel who supervise expenditures from federal grants also oversee expenditures on hESC research if any part of their salaries is included in the entity's indirect cost rate? If a journal publishes an article reporting the results of prohibited research, can the costs of the university library in subscribing to that journal be part of the indirect cost pool for federal grants? Can a building be used partly for federally funded research and partly for hESC projects if the university incorporates a portion of the building, but not all, in its indirect cost pool?

Circular A-21 states that accounting procedures for separating costs between federal and non-federal projects must assure that federal projects do not cross-subsidize other activities. NIH has adopted the same principles for segregating costs between allowed and prohibited research. But creating accounting safeguards against cross-subsidization is not the same as creating safeguards to guarantee that no federal funds are used even indirectly for prohibited projects. The principles behind A-21 are that the federal government should not pay more than the stand-alone costs of a project and that joint costs of multiple projects can be allocated among federal and non-federal funds. For example, federal auditors do not care if a scholar uses a computer that was purchased from a federal grant to read e-mail, to surf the internet, or to work on other research projects as long as the federally-financed work is undertaken as promised. The President's directive seems to say that a scholar could not use this computer to write a paper on prohibited hESC research. And, while students with NSF fellowships can work on research projects that are not paid for by the federal government, the President's directive seems to ban them from working in a lab that conducts prohibited hESC research.

The optimal response of a research institution to all of these unresolved issues is not necessarily to be as safe as possible from federal reprisal. Complete separation of state-sponsored hESC research from all other activities at the university—the kind of "walling off" that arises in firms that engage in government contracting in order to avoid running afoul of procurement rules[43]—is quite costly because it prevents a research institu-

43. *See, e.g.*, OFFICE OF THE UNDERSECRETARY OF DEFENSE FOR ACQUISITION, REPORT OF THE DEFENSE SCIENCE BOARD TASK FORCE ON DEFENSE ACQUISITION REFORM 3 (1993) (suggesting that a major problem in defense procurement has been the tendency of private firms completely to separate work for the government from other commercial work, thereby preventing synergies among product lines as well as economies of scale in production).

tion from capturing economies of scale and scope, and because it creates barriers to information sharing and intellectual synergies among closely related research projects. Thus, both research institutions and state governments may prefer to take some risks about how the federal directive ultimately will be interpreted in order to make their research programs more efficient.

States probably should be more willing to take such risks than individual institutions for three reasons. First, a state that successfully takes more risks will obtain more research output per dollar spent, and thereby be more likely to achieve both the scientific and economic objectives of the state program. Because the state, but not research institutions, values the economic spillover effect of the research program, it will place more value on accepting risks. Second, the state is not likely to view some federal funds at stake in undertaking state-sponsored hESC work as having the same economic spillover benefits as hESC research. If so, the state will place less significance in the continuation of this support than will the institutions that receive this support, and be more willing to risk losing it. Third, the state presumably will support projects in a portfolio of institutions, not all of which are likely to be found to be out of compliance—especially at the same time. This portfolio effect will cause the state to perceive the average risk per project to be lower than the risk of a state-supported project that a research institution perceives.

For these reasons, tension may develop between the protocols that the state recommends for complying with federal rules and the protocols research institutions prefer. Likewise, less prestigious institutions are likely to be less risk averse than more prestigious institutions simply because they have less to lose. If so, they can develop a cost advantage over more prestigious competitors, causing a relatively larger share of grant money to flow to projects with a lower probability of success.

The Bush Administration is not likely to resolve the ambiguity in federal rules. Likewise, the attempt by Congress to change the President's policies was vetoed, and Congress is not likely to pass further legislation that limits and/or clarifies the President's ban. Consequently, the clarification of the federal directive most likely will emerge from court cases in which either opponents of hESC research file *qui tam* lawsuits against research institutions or research institutions appeal decisions by aggressive federal auditors.

Compounding the uncertainty of federal policy is the strong possibility that the President's ban will not survive the Bush presidency. Many politicians, including early Republican candidates for the 2008 Presidential nomination Bill Frist, Rudy Giuliani, John McCain, and Mitt Romney, fa-

vor lifting the President's ban, indicating that they support at least some limited role for hESC research in federal R&D policy.[44] Because a speech created the current federal ban, the next President can equally easily dismantle it. The odds favor lifting the federal ban early in 2009.

If states and research institutions believe that the ban will be lifted, their incentives regarding state-sponsored research are affected. If the NIH begins to treat hESC as just another research tool, NIH immediately will become the dominant player in this research. With a $30 billion annual budget, NIH quickly can dwarf the spending of all state programs, relegating the latter to relatively unimportant fringe programs. State political leaders, then, can ignore the issue and thereby avoid compromising themselves to the polarized politics of hESC research. At the same time, if states and research institutions could quickly implement a research program, they would get a head start on research centers in states without a program. The empirical issue is whether the leading researchers in the field are likely to locate in states with active programs to obtain a two- to three-year head start in hESC research.

B. Pork Barrel

As discussed in Section II.C.2, all policies are in danger of being seriously distorted by the forces of distributive politics. Programs are especially susceptible to pork barrel spending if they involve authorizations or appropriations bills that fund specific activities. In the research budget, specific projects for which funding arises from a provision in legislation are called earmarks. Both federal research agencies and the President's annual budget frequently criticize the tendency of Congress to bypass peer review and competitive bidding as the means for making research grants or selecting among proposals for new research facilities.[45]

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44. Frist and McCain voted for the Specter-Harkins Bill, and Giuliani supports stem cell research. *See Potential Presidential Candidates' Plans for Cancer Research*, DES MOINES REGISTER, July 30, 2006, at 15A, *available at* http://desmoinesregister.com/apps/pbcs.dll/article?AID=/20060730/NEWS09/607300355/1056. Romney supports hESC research, but opposes cloning to create new stem cell lines. *See* Scott S. Greenberger & Frank Phillips, *Romney Draws Fire on Stem Cells: Opposes the Use of Cloned Embryos*, BOSTON GLOBE, Feb. 11, 2005, at A1, *available at* http://www.boston.com/news/local/articles/2005/02/11/romney_draws_fire_on_stem_cells/. George Pataki has not taken a clear position, while Senators Allen, Brownback and Hegel voted against the bill to lift the ban.

45. *See, e.g.*, OFFICE OF MANAGEMENT AND BUDGET, ANALYTICAL PERSPECTIVES: BUDGET OF THE UNITED STATES GOVERNMENT, FISCAL YEAR 2006 63 (2005), *available at* http://www.whitehouse.gov/omb/budget/fy2006/pdf/spec.pdf.

Despite the presence of earmarks in research appropriation bills, the R&D budget has been less distorted by distributive politics than many other areas of federal spending. Estimated R&D spending through earmarks in the 2005 federal budget was $2.1 billion out of over $130 billion, or less than two percent.[46] The best examples of pork come from construction projects—federal buildings, rivers and harbors projects, sewage treatment plants, transportation infrastructure, and military bases. Projects to support end-stage commercial development also have been distorted by distributive politics. Examples of projects that were continued far longer than they should have been, largely for pork barrel reasons, were the Supersonic Transport/National Aerospace Plane, the breeder reactor, and the space shuttle.[47]

The design of a research program affects the extent to which it is influenced by distributive politics. To minimize pork barrel effects, the first important design requirement is that projects be selected by the agency, not by the legislature. The second important design requirement is that the enabling legislation requires peer review by experts as a mandatory part of the project selection process. The third important design requirement is that the ultimate selection of projects be made by people who do not have strong connections to any particular group that is a candidate to receive funds.

The agency that best exemplifies a design that minimizes the influence of distributive politics is the National Science Foundation (NSF). Though on occasion facilities expenditures by NSF are earmarked, nearly all of the NSF's budget is authorized and appropriated according to broad categories of research. Proposals are then subject to peer review, and project selection goes through specialized expert panels, the NSF professionalized bureaucracy, and the National Science Board. The primary distributive influence in this process is the community of scientific researchers. While some have claimed that this process is biased in favor of established researchers and research institutions, it is difficult to imagine any other method for awarding a large number of grants on the basis of merit.

The NIH is designed in a similar fashion to the NSF, with one major exception. Unlike the NSF, NIH-sponsored government laboratories, rather than university researchers, undertake a significant share of the re-

46. *Id.* at 61, 63.

47. *See* Jeffrey S. Banks, *The Space Shuttle*, *in* THE TECHNOLOGY PORK BARREL, *supra* note 30, at 179-216; Linda R. Cohen & Roger G. Noll, *The Clinch River Breeder Reactor*, *in* THE TECHNOLOGY PORK BARREL, *supra* note 30, at 217-58; Susan A. Edelman, *The American Supersonic Transport*, *in* THE TECHNOLOGY PORK BARREL, *supra* note 30, at 97-148.

search that is supported from the NIH budget. Likewise, the Department of Defense, the Department of Energy, and the National Aeronautics and Space Administration, which along with NIH and NSF are the most important supporters of federal research, also spend a substantial portion of their budgets in their own research laboratories. The advantage of in-house research is that administrators can more easily direct R&D into specific activities that are high priority for the agency but not necessarily high priority for external institutions. The disadvantages are, first, that internal research is less likely to be closely linked to commercial application (as compared to business R&D) or education (as compared to university R&D), and second, that funding decisions are influenced by the desire to keep the agency's labs financially healthy.

NIH also has another manifestation of distributive politics: the National Institute for Alternative Medicine (NIAM). NIAM is a form of earmark: elected political officials have set aside part of the NIH budget for research that, by scientific consensus, has no serious prospect for creating important new fundamental knowledge or significant therapeutic advances.

The structure of the California Institute for Regenerative Medicine (CIRM) as created by Proposition 71 provides an interesting and largely unprecedented example of an agency that was constructed to be influenced by the practical significance of research, but protected against pork barrel influences.[48] At first glance, CIRM appears to be especially susceptible to the influence of distributive politics, partly because its goal is to develop commercial products and partly because CIRM was created by a ballot initiative. Because initiatives are costly, well-organized interests are the primary source of ballot measures. These sponsors are likely to take advantage of a policy vacuum from a slow-to-respond legislature to place measures on the ballot that, from the perspective of a majority of the voters, are better than the status quo, but still far from the policies that centrist voters would prefer and would vote for if given the opportunity.[49] Plausibly some beneficiaries of the program—biotechnology firms, university researchers in biological sciences, and venture capitalists who specialize in

48. *See* California Secretary of State, *Text of Proposed Laws – Proposition 71*, *in* CALIFORNIA OFFICIAL VOTER INFORMATION GUIDE 147 (2004), *available at* http://www.cirm.ca.gov/prop71/pdf/prop71.pdf [hereinafter *Proposition 71*].

49. *See* Thomas Romer & Howard Rosenthal, *Bureaucrats versus Voters: On the Political Economy of Resource Allocation by Direct Democracy*, 93 Q. J. ECON. 563-87 (1979); *see generally* ELIZABETH R. GERBER, THE POPULIST PARADOX: INTEREST GROUP INFLUENCE AND THE PROMISE OF DIRECT LEGISLATION (1999).

biotechnology—were the forces behind the proposition and designed CIRM as a program to enrich themselves. In reality, this did not occur.

Proposition 71 was written by real estate developer Robert Klein, who had no direct stake in the program other than as an advocate of hESC research. Financial support for the proposition was broadly based, and did not include significant contributions from researchers.[50] Some California biotechnology and venture capital (VC) firms donated to the campaign for Proposition 71, but of these only people from the VC firm Kleiner Perkins were among the largest donors. Likewise, among disease advocacy groups only the Juvenile Diabetes Fund was a large contributor. Some major donors, including two who contributed over $1 million each, were from outside California, and therefore could not receive direct financial payoffs from the program.

Proposition 71 created CIRM's administrative framework. CIRM was designed to enable industry and disease advocacy organizations to be influential but not dominant.[51] The governing board, the Independent Citizens' Oversight Committee (ICOC), has twenty-nine members who are selected to represent a variety of constituencies: nine from universities (five of whom are from UC campuses with a medical school), four from other research institutions, ten from patient/disease advocacy organizations, four from commercial life sciences enterprises, and two (the chair and vice chair) without portfolio. The distribution of these members among interests is diffused to avoid significant political influence by anyone. The chancellors of the five UC campuses with medical schools designate who will represent them on the ICOC. The Governor, Lieutenant Governor, Controller, and Treasurer (all elected offices) each appoint one person from a university, a research institute, and a life sciences company, and two people from a disease advocacy organization. The Speaker of the Assembly picks the representative for mental health, and the President Pro Tempore of the Senate picks the AIDS advocate. The twenty-seven ICOC members so selected then pick the chair and vice chair. The initial appointees to the ICOC included twelve representatives from universities. The remaining members were divided among industry, research institutes, foundations, and patient advocacy organizations. A few disease advocates

50. *See* Roger G. Noll, *The Politics and Economics of Implementing State-Sponsored Embryonic Stem Cell Research*, *in* STATES AND STEM CELLS 39 (Aaron D. Levine ed., 2005), *available at* http://region.princeton.edu/media/pub/pub_xtra_19.pdf (containing details about the contributors to the Proposition 71 campaign).

51. The number, qualifications, and selection process of members of the ICOC are set forth in chapter 3, article 1, section 125290.20 of Proposition 71. *See Proposition 71*, *supra* note 48.

were from either business or academe, but most were from disease advocacy organizations.

Beneath the ICOC are three working groups: one for reviewing grant proposals (Scientific and Medical Research Funding), one for reviewing facilities proposals (Scientific and Medical Research Facilities), and one for standards (Scientific and Medical Accountability Standards). About a third of the membership of each is from the ICOC, and each includes the ICOC Chair and representatives of disease advocacy groups. The working groups "are purely advisory and have no final decisionmaking [sic] authority . . ."[52] Final decisions about grants and standards are made by the ICOC using majority-rule voting.

The Scientific and Medical Research Funding Working Group has twenty-three members, including seven disease advocates from the ICOC and fifteen scientists who are "nationally recognized in the field of stem cell research."[53] Only the fifteen scientists are involved in evaluating the scientific merit of proposals.[54] The same procedures for peer review and technical assessment are applied to basic research, therapy development, and clinical trials.[55]

The Scientific and Medical Research Facilities Working Group has eleven members, six of whom are also members of the Research Funding Working Group and four of whom are "real estate specialists" who must not have any financial interest in the construction of any facility that is funded by CIRM.[56] Since Proposition 71 does not spell out clear procedures for making decisions about facilities grants, it remains to be seen whether these grants will be decided on the basis of peer review and merit. The facilities projects are limited to non-profit institutions, i.e., universities and research institutes. The basis for evaluating facilities proposals is not as clearly spelled out or structured as the procedures for research grants.

The structure of the ICOC presents one way to deal with the dilemma of expertise versus self-interest. Barring all people with a self-interest in hESC research would sacrifice expertise in allocating resources. CIRM attempts to resolve this by having a very large decision-making body representing many interests, some of which are likely to conflict on at least some issues, to dilute the ability of any one group to control allocations in

52. *Id.* § 125290.50(e)(3).
53. *Id.* § 125290.60(a)(2).
54. *Id.* § 125290.60(c)(1).
55. *Id.*
56. *Id.* § 125290.65(a)(2).

a self-serving manner. An interesting distinction between CIRM and federal research agencies is that, while it is structured to give academic scientists a great deal of influence, it also gives disease advocates direct participation in evaluating proposals and making grants.

Unlike other institutions, CIRM will not undertake research in-house. By contrast, the New Jersey hESC program establishes a new state research institution, jointly operated by two state universities, to undertake the research.[57] The New Jersey structure likely will be more responsive to legislative priorities, for better or for worse, because the entity that undertakes the research is government-owned. Federal laboratories, even if they are managed by universities, often are more responsive to legislative priorities than other university funded research facilities and other independent research organizations.

C. Short-Term Payoffs

Another problem facing state sponsored hESC programs is that R&D projects with potential commercial applications may be over emphasized at the expense of more fundamental, long-term projects with larger expected payoffs. As discussed in Section II.C.3, the necessity to seek reelection causes elected officials to seek short-term results for which they can claim credit to their constituents at the next election. The short time horizon of elected officials favors projects promising near-term commercial payoffs. The largest immediate benefit would arise from subsidies for the last stages of commercialization rather than fundamental research. An example is to underwrite clinical trials of new therapies derived from hESC research, with the idea that somebody else (perhaps in another state) will pay for the fundamental research that leads to the treatment that will be tested in the clinical trials.

CIRM overcomes this problem by removing the legislature and the governor from the appropriation of funds for CIRM and decisions about the allocation of the research budget. The only mechanism for political influence is through the appointment of members to the ICOC, but because membership is dominated by representatives of research organizations and disease advocacy groups, elected officials are not likely to have much influence over their appointees should they press for less promising projects with more immediate payoffs.

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57. *See* State of New Jersey Commission on Science & Technology, Stem Cell Institute, http://www.state.nj.us/scitech/stemcell/institute (last visited Aug. 25, 2006).

D. The Quest for Geographic Advantage

State government officials, because they represent citizens and businesses within a state, have a political incentive to design programs so that as much of the benefit of the program as possible accrues within the state. The desire to design state programs to obtain an advantage over other states is a form of distributive politics because its political purpose, like pork barrel expenditures, is to deliver benefits to constituents. In one way, the quest for geographic advantage can be more conducive to inefficiency than standard pork barrel influences. State funded pork barrel projects create some losers within a state (entities that do not receive grants and contracts), and partially counteract the political benefit of delivering uneconomic projects to favored constituents. Those harmed by the pursuit of geographic advantage are mostly residents of other states, who are not part of the constituency of a state's elected officials.

The quest for geographic advantage can lead to either greater subsidies or more IP rights than are necessary to induce socially optimal R&D. State R&D expenditures that give a state an economic advantage over other states deliver both political and economic benefits. The economic benefits are the new knowledge and products emanating from the program, and the redistribution of wealth from other states. The program has no effective political cost because prospective grant applicants who are denied support for worthy projects are firms and citizens of other states. This problem is likely to be more severe among states than in the federal government. The federal government is much larger than any state, and the system of geographic representation in Congress prevents one state's congressional delegation from gaining an economic advantage for their state by channeling expenditures to it. While nations engage in international competition for research-intensive industries, this competition is less of a factor in federal decisions than interstate competition is likely to be in state programs. The U.S. is substantially more dominant in world R&D than any state is in national R&D, so that the U.S. has less to gain or lose in the relocation of industry from changes in its R&D budget. Moreover, international agreements limiting subsidization as an instrument for biasing the flow of trade constrains the federal government, but not individual states.

If the federal ban on hESC research does not survive the Bush Administration, the opportunities for a state to obtain geographic advantage by initiating its own program will be circumscribed. While the California program is at a scale that might have conferred such an advantage, litigation against CIRM has delayed the program. If a significant number of CIRM projects cannot begin until, say, summer 2007, and federal support

begins in summer 2009, the ability of CIRM to create a substantial first-in advantage for California is certainly limited.

IV. THE INTELLECTUAL PROPERTY REGIME

As discussed in Section II.B., IP policy allocates the commercial benefits of the results of R&D, and so can be used to create incentives for researchers to undertake projects with commercial potential and then proactively seek to transfer these results to commercial interests. Because states historically have not been extensively involved in supporting R&D with a commercial objective, they currently are in a position similar to that of the federal government before the passage of Bayh-Dole. States currently have no coherent policy regarding IP derived from state-sponsored research. Consequently, states that have enacted or are considering enacting a stem cell research program also must design an associated IP policy.

This section examines the development of IP policy in California, where both CIRM and political leaders have embarked on a process of developing a state IP regime that differs in important ways from federal IP policies under Bayh-Dole and CRADA. Even if federal IP policy is not optimal, creating state IP policies that conflict with federal policy is not a good idea for two reasons. First, a different state IP regime will generate substantial administrative costs for organizations that receive support from both state and federal sources. Second, California's proposed IP program is smaller than the federal program and less generous to grant recipients. Consequently, these proposals, if adopted, would discourage the best researchers from accepting grants from CIRM rather than federal agencies. This section explains the basis for these conclusions.

CIRM announced its policies regarding intellectual property rights in the results of research that it sponsors in non-profit institutions in February 2006.[58] These policies were provisional, and could be amended on the basis of public comment submitted in July 2006.[59] The proposed policy requires that grant recipients give twenty-five percent of royalty incomes in excess of $500,000 from intellectual property that is derived from CIRM projects.[60] This proposal differs from the federal program created by

58. CIRM, INTELLECTUAL PROPERTY POLICY FOR NON-PROFIT ORGANIZATIONS (2006), http://www.cirm.ca.gov/policies/pdf/IPPNPO.pdf [hereinafter IPPNPO] (approved by the Indep. Citizens' Oversight Comm. Feb. 10, 2006).

59. *See* Meeting Agenda, IP Task Force Subcommittee of the Independent Citizens' Oversight Committee to the California Institute for Regenerative Medicine (July 14, 2006), http://www.cirm.ca.gov/meetings/2006/07/07-14-06.asp.

60. *See* IPPNPO, *supra* note 58, at 19.

Bayh-Dole, which involves no sharing with the federal government. Policies regarding for-profit grant recipients will be announced later.

The appropriate IP regime for CIRM has been the subject of intense public scrutiny and political debate over the extent to which the state should design an IP regime that enables it to recapture its expenditures on CIRM. The state can seek to recoup its expenditures on CIRM either directly through licensing the IP from CIRM's projects or indirectly by requiring firms that produce commercial products from CIRM projects to sell these products at discounted prices in California.

The pressure for local advantage and short-term payoffs can distort a state's policies regarding IP arising out of the research that it sponsors. Advocates of hESC research sought public support by claiming that it will generate therapeutic benefits to the public and financial payoffs to the state. These claims may have created unrealistic expectations about the immediate economic and financial benefits to a state that are likely to arise from IP that is derived from hESC research.

As discussed in Section II.B, the principle policy of the federal government regarding IP rights from federally sponsored research is the Bayh-Dole Act of 1980. Although Bayh-Dole generally has not had much of an effect on the commercialization of university research, it has caused several leading universities to establish technology transfer offices that generate substantial income for the universities from the research results of their faculty. Nevertheless, even among the successes, university revenue from licensing is much smaller than research expenditures. For example, in 2000, the University of California system spent almost $2 billion on research but received only $74 million in licensing income.[61] Nationally, in 2003, the last year for which data are available, all colleges and universities received about $1 billion in licensing income, but spent over $40 billion on research, $20 billion of which went to biological and medical research.[62] These facts should give pause to state officials who see a potential financial bonanza in the IP arising from state-sponsored hESC research. Judging from recent royalty data, the licensing income from patents derived from stem cell research is likely to be a small fraction—less

61. For a summary of the revenues from the most effective university licensing programs, see Herb Brody, *The TR University Research Scorecard: Patenting and Licensing at U.S. Universities is Going Strong. Biotech in Particular Gets High Marks*, 104 TECH R. 81 (2001), *available at* http://www.technologyreview.com/articles/01/09/scorecard0901.asp.

62. NATIONAL SCIENCE BOARD, 2 SCIENCE AND ENGINEERING INDICATORS 2006 5-55 tbl.5-28, A4-4 tbl.4-3, A5-6 tbl.5-5 (2006), *available at* http://www.nsf.gov/statistics/seind06/pdfstart.htm.

than five percent—of the costs of that research. Moreover, because these projects are likely to have a long gestation period, the revenue from licensing is not likely to be substantial for many years.

State universities risk political backlash against successful commercial ventures that arise from their research. One potential form of backlash could arise from a belief that neither universities nor the state should seek to charge state businesses to use the product of research that was funded partly by taxes that were paid by those same businesses. Another possible backlash could arise from the view that, regardless of revenues, state universities should never sell rights to their IP to entities outside the state. Still another potential backlash could occur from those who believe that generating revenues from IP is a fine idea, but that the state, not the university, should be the beneficiary.

In California, some state political officials believe that hESC research is potentially a huge source of revenue, and favor assigning all or part of the IP rights to research supported by CIRM to the state. For example, the original version of the proposed constitutional amendment that the California legislature is debating sets forth an objective for California to recover from royalties all of the expenditures it has made through CIRM.[63] Others have proposed that CIRM keep some of the royalties to fund further research after the money from the bond issue has been spent.[64] Because CIRM has funds for a ten-year program, these proposals assume that after ten years royalties will be large enough to recover or replace an average annual expenditure of $300 million. These beliefs likely will prove to be unrealistic, even if the state were to capture all of the royalties. Moreover, even if such revenues were feasible, it would be bad policy to try to capture them.

Allocating the royalties to CIRM to finance more research after the bond funds are spent creates an earmarking opportunity ripe with the problems associated with earmarks discussed in Section II.C. Legislating a particular use of a designated component of state revenue is a permanent earmark. The optimal amount of state support for hESC research, or indeed any area of research, bears little relation to whether the research un-

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63. *See* S.C.A. 13, 2005 S., Reg. Sess. (Cal. 2005), *available at* http://info.sen.ca.gov/pub/bill/sen/sb_0001-0050/sca_13_bill_20050531_amended_sen.html. The most recent mark-up deleted this and other provisions regarding the state's rights to IP from CIRM. *See* S.C.A. 13 (June 8, 2005), *available at* http://info.sen.ca.gov/pub/bill/sen/sb_0001-0050/sca_13_bill_20050608_amended_sen.html.

64 For a summary and analysis of proposals for CIRM's IP policy, see CAL. COUNCIL ON SCI. & TECH., INTELLECTUAL PROPERTY INTERIM REPORT 33-35 (Aug. 2005), *available at* http://www.ccst.us/ccst/pubs/ip/ip%20interim.pdf.

dertaken in the first few years generates a bonanza of royalty income. The amount of state-sponsored hESC research a decade hence should be based on the opportunities for useful research and the availability of grants from other sources that are available at that time. hESC research could be highly successful and could generate enormous royalties, but opportunities for further useful research might not be as promising as research in other areas a decade hence. If so, the state should not create a financial incentive for researchers to continue to plow a field with low productivity. Likewise, the U.S. is three presidential administrations away from the day that CIRM funds run out, and the ban against federal support for hESC research is unlikely to remain in place through all three. If a future administration relaxes the rules regarding federal hESC research, the case for state support will be weaker. Thus, if the state lays claim to any royalty income, it would be better not to earmark it.

The proposal that royalties ought to be used to recover the initial cost of CIRM or finance CIRM in the future would create another problem that would undermine its success. If the state seeks to capture the equivalent of $300 million annually in royalties from CIRM projects, most likely all royalties would have to go to the state. If all royalties go to the state, institutions that receive grants have no financial incentive to commercialize the IP that arises from CIRM grants, especially given that they can profit from IP rights derived from other research. Thus, implementing this goal likely will require that either CIRM or another state agency actually assumes responsibility for acquiring the IP rights and then licensing them. Because the state does not have the connections to or knowledge of the biotechnology industry that are possessed by research institutions, this approach likely will be less effective in actually producing either commercial products or royalties.

If grant recipients are the best institutions for licensing the IP that their research produces, they must be compensated for that effort. In fact, the advantage of making these institutions responsible for technology transfer is that they already have in place a set of institutions and internal procedures for implementing the system of research exploitation that was created by Bayh-Dole. Because Bayh-Dole is in place, research institutions and individual researchers anticipate that they, not the state, will be the beneficiaries of IP rights. As a result, if states claim a substantial fraction of the royalties from innovations arising from CIRM projects, they will create a disincentive for the best researchers to seek research support from CIRM grants instead of federal or private sponsors. The proposed CIRM policy runs the risk of making the best researchers reluctant to give up some of their potential royalties by taking CIRM grants.

Still another problem is that the advances for which IP is sought cannot usually be traced to a specific research grant, but instead are the product of many projects from many sources over a long period of time. If all rights are assigned to the research institution, tracking down all of the sponsors that were involved in creating it is not a problem. But if the state claims rights to revenues from IP arising from CIRM-sponsored projects, research institutions face the considerable problem of separating the independent sources of an innovation among sponsors. Because this can be very difficult, even impossible, to accomplish, a policy to pay some royalties to the state will create still another disincentive to accept CIRM grants.

Universities and research institutes can incorporate state-supported hESC research into technology transfer systems they already have in place with relative ease. However, by doing so they could run afoul of the ban on using federal funds for supporting hESC research. Because the cost of technology transfer offices is paid out of royalty income from federally sponsored research projects, the federal government might decide that these offices cannot be used to commercialize IP rights from state-sponsored hESC research.

Notwithstanding this problem, states should not attempt to differentiate hESC research from other biomedical research with respect to IP rights. Doing so will bias decisions of both researchers and their organizations about what kinds of research to pursue, and will create additional implementation costs for the program. The most reasonable solution is to mimic the policies of the federal government and to allow universities to combine their federal and state IP commercialization activities. State-sponsored hESC research is not a good vehicle for waging a battle against the form and spirit of Bayh-Dole, even if such a battle is warranted.

V. CONCLUSION

States have entered the business of sponsoring hESC research because of the current political controversy over hESC research. Some are jumping into a domain of policy in which they have little direct experience—financing basic research in universities and other independent research centers, and perhaps commercialization projects (therapy development and clinical trials) involving for-profit entities. This area of policy is difficult to implement efficiently and is all the more difficult because these research programs are narrowly focused and highly controversial.

States embarking on these programs should not try to be very innovative in creating agencies and policies to make grants and oversee IP rights.

These programs will not succeed if they ask grant recipients to act differently than they are required to act by other, much larger sources of funds. As an illustration, Stanford University receives as much revenue in a year as CIRM is likely to spend on external grants over a decade. Thus, CIRM cannot expect to have much leverage over either Stanford or the entities that support it. Any attempt to change the way that California research organizations do business with an annual expenditure of only $300 million is doomed to failure.

Nevertheless, in the short term, CIRM's program will substantially increase expenditures on stem cell research not only in California but in the entire nation. As long as the program is not regarded as a source of substantial financial risks and administrative costs to research organizations, CIRM could jump-start this area of research and shorten the wait for the new knowledge and therapeutic applications from hESC research by a few years. In so doing, it could give California's research universities and medical research centers a head-start in this research, thereby enabling them to maintain, if not enhance, their international leadership in biomedical research. Thus, California will maximize the benefits to society and the state by making CIRM's IP and accountability policies parallel those applying to federal grants, thereby minimizing the disincentives to California research organizations from participating in the program. CIRM is reasonably well designed to carry out an effective R&D program with decisions about grants made mostly on the merits. If the state wants the program to succeed, it should not impose further restrictions on the agency.

PUBLIC ACCESS TO PUBLIC SCIENCE: RECOMMENDATIONS FOR THE CALIFORNIA STEM CELL INSTITUTE'S POLICIES REGARDING GRANTEE-PRODUCED JOURNAL ARTICLES

By Michael B. Eisen & Andy Gass[†]

TABLE OF CONTENTS

I. INTRODUCTION

While the public's attention has been focused on a number of high-profile controversies presented by the prospect of a taxpayer-funded institute for stem cell research, several more arcane—but nevertheless noteworthy—matters have largely escaped the notice of the community activist groups, the town-hall meeting attendees, and the reporters covering the California Institute for Regenerative Medicine (CIRM). One such question is who will own the rights to the peer reviewed journal articles written by CIRM-funded researchers—an open issue the resolution of which will

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substantially determine how accessible those articles will be online for other scientists, the media, students, and the justifiably curious public.

In this brief Article, we argue that in the context of stem cell research, a policy arena rife with seemingly intractable disputes that implicate deeply held and conflicting moral intuitions, one of the few questions that has a relatively straightforward answer is whether policymakers should require that publications arising from CIRM-funded research be freely accessible online. They undoubtedly should. The benefits of a well-crafted plan in this area would be tremendous, and the downside would be trivial. The primary argument against such a policy—that scientists would decline to apply for CIRM funding if it came with an "open access" requirement—is simply implausible.

Why should CIRM require that articles produced by its funded investigators be free online? Within three or four years, researchers will complete the first round of projects funded by the institute. While we all hope that this early work will itself produce powerful new treatments for diseases from diabetes to Parkinson's, such rapid progress is unlikely to occur. Rather than generating cures initially, CIRM-funded projects will be generating *knowledge* about the basic biology of stem cells—how they behave in the lab and in the clinic—and about prospective applications that do and do not show promise.

The voters who passed Proposition 71 to launch and fund the stem cell institute, eager to see the highly touted potential of stem cell research fulfilled and interested to know if their first billion dollars was well spent, will probably scrutinize these projects more closely than is typical for experimental results on the cutting edge of biomedicine. Certainly, science journalists in the popular media will report on the gist of the discoveries in the broad brushstrokes that they must necessarily use. But if taxpayers want more detail—if teachers want to assign papers for their students to read; if family members of people with potentially curable diseases want to keep themselves abreast of the latest progress in the lab; if entrepreneurs want to learn about the particular methods state-funded scientists used; or if researchers at California institutions of higher education with less-than-generous library budgets simply want to read the articles—they will be out of luck. Insofar as the prevailing practices of the scientific community are allowed to persist, the sole tangible product of this scientific research *specifically mandated by the public itself* will be too expensive for most of the public to access—and for no particularly good reason.

II. SCIENTIFIC PUBLISHING: BACKGROUND AND OVERVIEW

Scientific projects are not finished when the last experiment is done. They are complete only when the results are available for others to scrutinize and build upon in their own research. Scientists conduct this communication and correspondence with their colleagues by publishing papers—replete with details of the methods used, the results obtained, and the conclusions reached—in peer reviewed journals. Journals have been the lifeblood of the scientific community since the 17th century when the Royal Society in London began publishing accounts of experiments and lectures for far-flung members and interested laymen who could not attend the regular meetings.

There are now thousands of scientific journals. It is not hyperbole to suggest that their collective contents are one of humanity's greatest creations—the accumulated ideas and discoveries of tens of thousands of scientists, living and dead, who have dedicated themselves to figuring out how the world works. Today, virtually all of these publications are online by subscription. Consequently, anyone who logs onto the computer network at a major American university has instant access to the latest discoveries in fields ranging from quantum mechanics to astrophysics to, indeed, stem cell biology.

Outside of research institutions, though, access to the scientific literature is extremely limited. Universities are prohibited, by contract with publishers, from allowing unaffiliated users to have online access to journals paid for through academic library budgets. And while individuals may subscribe to a publication or two in a given field, such limited access is rarely enough to carry out even the most basic research project, which invariably requires reading papers from multiple sources. Personal subscriptions to scientific journals are substantially cheaper than institutional subscriptions, but they remain relatively pricey. To select an example more or less at random of a journal that might publish the results of research in cell biology, it costs a single reader $335 for a year's worth of *Leukemia Research*.[1] And while articles are frequently available on a pay-per-download basis, those fees quickly add up as well. It costs $30 to buy a single article from *Leukemia Research*;[2] the fees for papers in similar journals typically range up to fifty dollars.[3]

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1. Elsevier.com, Leukemia Research Order Page, http://www.elsevier.com/wps/find/journalorderform.cws_home/583/journalorderform2 (last visited July 24, 2006).

2. Sciencedirect.com, Access Online Article, http://www.sciencedirect.com/science/journal/01452126 (last visited Aug. 25, 2006) (follow "Volume 30, Issue 9" hy-

How can, and why do, publishers of scientific journals erect barriers to prevent the public from accessing their contents? The answer lies in the curious fact that the only permanent record of the scientific process is owned and controlled not by the scientific community or the public that largely funds its work, but rather by the publishers of scientific periodicals. These publishers first require as a condition of publication that authors transfer the copyrights in their works and then wield those rights to charge scientists and their institutions steep fees to access their journals.[4]

While this state of affairs may seem sensible from the publishers' perspective, the relatively singular system by which scientific research papers come into being renders the prevailing model of disseminating scientific knowledge decidedly disadvantageous for the institutions that produce the work and then buy it back. Consider the relative contributions of different groups to the production of a finished scientific paper. There are the scientists, who do the experiments and submit their work for publication with no expectation of remuneration. Then there are the volunteer peer reviewers—other scientists—who carefully pore over the details of the paper to make sure the methods are sound, the data valid, and the conclusions warranted by the results. Finally there are the sponsors, usually the government or other public institutions, who pay for the research and the salaries of the experimenters. The publisher does something too: it manages the editing and peer review process, oversees production, and posts the completed articles on the web. But to reward this modest contribution to the process with permanent control of the finished product is at best suboptimal from the perspective of most of the other stakeholders and at worst simply absurd.[5]

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perlink; then follow "Full-Text + Links" hyperlink under the article *Facing mortality: A qualitative in-depth interview study on illness perception, lay theories and coping strategies of adult patients with acute leukemia 1 week after diagnosis*).

3. Rick Weiss, *A Fight for Free Access to Medical Research*, WASH. POST, Aug. 5, 2003, at A1.

4. In 2002-03, for example, the University of California ("UC") paid $8 million for online access *just to scientific journals published by Reed-Elsevier*—a figure that represented fully one-sixth of UC's materials budget that year. *See* UC BERKELEY LIBRARY – COLLECTIONS MANAGEMENT, ELSEVIER CASE STUDY (2005), http://www.lib.berkeley.edu/Collections/elsevier_case_study.html. For more on the shockingly high costs of scientific journals, see generally Daniel Greenstein, *Not So Quiet on a Western Front*, NATURE WEB FOCUS (2004), http://www.nature.com/nature/focus/accessdebate/23.html; Rick Weiss, *A Fight for Free Access to Medical Research*, *supra* note 3.

5. One might, for example, compare the publisher to a midwife. Midwives play an important role in the birth of a child—just as publishers play an important role in the final step of the scientific process. But no midwife would claim that his or her contribution should be rewarded with ownership of the baby. Yet, in a sense, this is precisely what

Why have scientists and their institutions allowed such a system to develop and persist? Until recently, the cheapest and most efficient way to distribute scientific knowledge was to deliver printed journals through the mail, and the costs of publishing a scientific journal arose mostly in producing and distributing printed pages. Since these costs naturally scaled with the number of readers, a subscription-based business model, in which publishers charged for each copy they distributed, made good economic sense. The system was reasonably efficient and fair to readers, to boot. To capitalize on their front-end investments in paper, printing, and postage, journals requested that scientists grant them the exclusive right to publish their work. Scientists, who were unable to publish and distribute works on their own, were happy to comply.

With the rise of the internet, though, the trade-offs embodied in this arrangement no longer benefit the producers and users of scientific articles to the same degree. Today, the internet provides the cheapest and most useful way to distribute published scientific work. The intrinsic costs of the online publishing process arise principally from producing the initial peer reviewed, edited, and formatted copy of each work. With printing costs eliminated and distribution infinitesimally cheap, the costs of publication are now largely independent of the number of readers.

Despite this fundamental pragmatic change, most scientific publishers continue to charge individuals and institutions for the right to access the papers they have published. Setting aside for a moment the question of whether this system remains desirable, there is no question that its prevalence is a vestige of a time when the economics of the publishing process were very different than they are today.

It hardly seems radical to suggest that, if the stakeholders in science were to devise *de novo* a system to pay for the peer review and online publication of research papers, they might very well not opt for one in which the final product was accessible only to people or institutions willing to pay annual or per-download fees. Subscription charges and other access fees are now, in some respects, an obstacle to the optimal use of scientific knowledge. They inhibit scientific and medical progress by curtailing the free flow of information upon which research depends; they prevent the development of creative new ways to sort through and use the information contained in the literature; and they deny the public access to the treasury of scientific knowledge it has paid trillions of dollars to create. Insofar, then, as there exists a way to publish scientific research articles of equally

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happens in scientific publishing; it's as if midwives claimed ownership of babies and charged parents an annual fee to visit their child.

high quality, sustainability, and *without* fees for access, that alternative system inherently offers numerous advantages over the traditional one.

III. SCIENTIFIC PUBLISHING: ALTERNATIVE TRENDS AND RECENT DEVELOPMENTS

Over sixty percent of internet users have searched for medical information online—more than have downloaded music or than look for salacious images of movie stars.[6] But while a Google search for any disease or symptom returns a bevy of information, ranging from the useful and informative to the dangerous and quackish, it rarely turns up the careful, peer reviewed studies published in major medical journals that contain the most up-to-date and useful medical knowledge available. Are web users seeking health tips really looking for technical, jargon-heavy articles? Undoubtedly, many are not. But some online searchers surely are, particularly those with a personal interest in solving a serious medical problem. And others conceivably *would be* interested in finding primary literature if they had any reason to believe such reliable information was available—which for or the most part, they currently do not.

The bodies that fund scientific research are gradually becoming aware that this lack of public access is a problem and are slowly—very slowly—devising solutions. The National Institutes of Health (NIH), for example, promulgated a policy in 2005 requesting that scientists who received research grants from the agency's $28 billion budget submit their resulting journal articles to an online, free-to-access library called PubMed Central.[7] However, because compliance is not mandatory, and because individual scientists typically have minimal or indirect incentives from self-interest to make their own articles free online, authors' participation in the NIH

6. SUSANNAH FOX & DEBORAH FALLOWS, PEW INTERNET & AMERICAN LIFE PROJECT, INTERNET HEALTH RESOURCES 1 (2003), http://www.pewinternet.org/pdfs/pip_health_report_july_2003.pdf (finding that over sixty percent of internet users have searched for medical information online); MARY MADDEN & LEE RAINE, PEW INTERNET & AMERICAN LIFE PROJECT, TECHNOLOGY & MEDIA USE (2005), http://www.pewinternet.org/PPF/r/153/report_display.asp (finding that about twenty-seven percent of internet users have downloaded music or video files); DEBORAH FALLOWS, PEW INTERNET & AMERICAN LIFE PROJECT, SEARCH ENGINE USERS 5 (2005), http://www.pewinternet.org/pdfs/PIP_Searchengine_users.pdf (finding that "Entertainment or recreation" and "Sex or pornography" both rank below "Health or sciences" among subject matter categories of popular searches).

7. PubMed Central, which contains the full texts of scientific papers, is distinct from PubMed, which contains the abstracts of scientific papers.

program has been negligible.[8] The Wellcome Trust, the United Kingdom's largest private funder of biomedical research, has gone a step further. Beginning on October 1, 2006, all journal articles resulting from the £400 million that the charity disperses annually in research grants will be deposited in PubMed Central.[9] And at the time of this writing, bipartisan legislation is pending in the U.S. Senate that would, if enacted, impose a similar mandate on virtually all scientists funded by the American government.[10]

Faced with the prospect of funder-imposed requirements that journal articles be made free online, scientific publishers have divided into two camps. The first group embraces the change and has begun to adopt business models that are consistent with providing unfettered access to journal contents. Those models typically entail an upfront fee, paid from researchers' grants or from centralized pools of money that funders have made available, to cover the publisher's costs of overseeing peer review and preparing accepted articles for publication.[11] The Wellcome Trust has estimated that such fees, if paid for all the journal articles its grantees produce, would amount to between one and two percent of the cost of conducting the research reported in the papers.[12]

The second camp of publishers, by contrast, has resisted calls to make the scientific literature free online. The principal grounds for their obstruction have been purely financial. Journals like *Science* have suggested that funding agencies simply would not be willing to pay upfront what it costs

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8. NATIONAL INSTITUTES OF HEALTH, REPORT ON THE NIH PUBLIC ACCESS POLICY (2006), http://publicaccess.nih.gov/Final_Report_20060201.pdf. It is worth noting, however, that support is high among prominent scientists for mandatory deposition of NIH-funded articles in PubMed Central. *See, e.g.*, Open Letter from 25 Nobel Laureates to the U.S. Congress (Aug. 26, 2004), http://www.fas.org/sgp/news/2004/08/nobel082604.pdf (advocating a requirement that taxpayer-funded research articles be made freely available to the public).

9. *See* Wellcome.ac.uk, Open and Unrestricted Access to the Outputs of Published Research, http://www.wellcome.ac.uk/node3302.html (last visited Aug. 3, 2006).

10. *See* The Federal Research Public Access Act of 2006, S. 2695, 109th Cong. § 2 (2006); Rick Weiss, *Bill Seeks Access to Tax-Funded Research*, WASH. POST, May 3, 2006, at A21.

11. *See, e.g.*, Nicholas R. Cozzarelli, *An Open Access Option for PNAS*, *in* 101 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 8509 (2004), *available at* http://www.pnas.org/cgi/content/full/101/23/8509 (describing the policy of *Proceedings of the National Academy of Sciences*). New journals relying on this business model have also sprung up, including the six published by the non-profit organization the Public Library of Science and the dozens published by the for-profit BioMed Central.

12. Andy Gass, *Paying to Free Science: Costs of Publication as Costs of Research*, 31 SERIALS REV. 103, 105 (2005), *available at* http://www.plos.org/downloads/PLoS_CHE.pdf.

to publish a research article in a selective forum.[13] Independent estimates, however, indicate that such claims of economic impracticality tend to be wildly exaggerated.[14]

An alternative reason for resistance has been a more overtly misguided concern over potential misuses of articles to which publishers hold only some, rather than all, rights. The *New England Journal of Medicine* ("*NEJM*"), for example, has cautioned of the following danger: if a funder of research prohibits its grantees from transferring the full rights to their articles to *NEJM*, then the paltry non-exclusive rights the journal would acquire would effectively "allow third parties to selectively use the materials in scholarly articles for commercial gain."[15] Not only does *NEJM's* concern betray a profound misunderstanding of copyright law—which bestows a thin layer of protection on technical works and which allows fair uses of portions of copyrighted research articles—but it fails to support the asserted conclusion (that copyrights must always be transferred in full) even on its own terms. *NEJM*, along with every other publisher of biomedical journals, routinely publishes articles whose exclusive rights it does not hold: articles written by scientists not merely *funded* by NIH, but *employed* there, whose works automatically enter the public domain by virtue of 17 U.S.C. § 105.[16] To date, there has not been a single report of misleading or inappropriate use of any article produced by researchers in the two dozen NIH institutes and centers, despite the fact that all such articles are wholly unprotected by copyright.[17]

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13. *See* Lila Guterman, *The Promise and Peril of Open Access*, 50 CHRON. HIGHER EDUC. A10 (2004), *available at* http://chronicle.com/weekly/v50/i21/21a01001.htm (including an estimate by the American Association for the Advancement of Science that it would have to charge $10,000 per paper to make its articles free online and maintain the revenue it derives from subscriptions).

14. WELLCOME TRUST, COSTS AND BUSINESS MODELS IN SCIENTIFIC RESEARCH PUBLISHING 3 (2004), *available at* http://www.wellcome.ac.uk/assets/wtd003184.pdf (finding that the per-article cost to publish in a high quality, subscription-based scientific journal is around $2750).

15. Jeffrey M. Drazen & Gregory D. Curfman, *Public Access to Biomedical Research*, 351 NEW ENG. J. MED. 1343 (2004), *available at* http://content.nejm.org/cgi/content/full/351/13/1343.

16. "Copyright protection under this title is not available for any work of the United States Government . . . ." 17 U.S.C. § 105 (2000).

17. It also bears mention that scientific journals whose entire contents are governed by permissive Creative Commons licenses, such as those published by the Public Library of Science, have reported no ill effects of such liberal copyright terms in their concededly brief histories of operation. *See* Andy Gass, Helen Doyle & Rebecca Kennison, *Whose Copy? Whose Rights?*, 2 PUB. LIBR. SCI. BIOL. 0877 (2004), *available at* http://biology.plosjournals.org/archive/1545-7885/2/7/pdf/10.1371_journal.pbio.0020228-S.pdf (de-

Discussions of funder-imposed public access requirements often overlook the significance of the copyright-transfer exception that publishers routinely make for NIH intramural researchers. That exception demonstrates, however, that virtually all journals are willing to publish good science, regardless of whether the authors of an article are for some reason prohibited from assigning rights in the work to their publisher.

IV. CONCLUSION

A. Policy Recommendations

The research institute funded by the California stem cell initiative is, if nothing else, a grand experiment in direct public support for biomedical research. Its successes and failures will impact not only stem cell research but also the broader relationship between science and the public. In order to ensure that the public is fully informed about the results of CIRM-funded research, and in order to share as widely as possible the benefits of the knowledge that such research produces, CIRM should adopt the following policies regarding the journal articles that result from its grantees' investigations:

1. Like works produced by NIH intramural researchers, the articles should not be protected by copyright. They should instead be dedicated to the public domain, by rule, in order to allow the public to make creative use of the works in databases, for patient advocacy purposes, in educational settings, and for other projects.

2. As a condition of accepting CIRM funds, grantees should be required to deposit with PubMed Central either the final manuscripts or the published versions of all articles that result from their CIRM-funded work for posting in PubMed Central immediately upon publication in the journals in which they appear.

3. CIRM should make available a standing fund from which grantees can draw money to pay the reasonable costs of publication in open access journals which request such fees.

B. Final Comments

At the "California's Stem Cell Initiative" Conference at Boalt Hall that spawned this Article and the other works in this volume, several knowl-

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scribing the Public Library of Science's experience with and reasons for using the Creative Commons Attribution License).

edgeable and influential legal scholars expressed the concern that imposing conditions such as these on grants would cause scientists to turn elsewhere for funds to do stem cell research with fewer strings attached. In other words, some scholars posited that requiring open access to CIRM-funded journal articles would scare off the best scientists. Little empirical data is available regarding the influence of grantor result-sharing requirements on scientists' willingness to accept funds burdened with such conditions.

However, the fear that scientists might be driven away strikes us as baseless. Few scientists are concerned that their funders require them to be too *open* with the results of their work (although undoubtedly some scientists refuse grants that would require them *not* to publicize some findings). Furthermore, even for those researchers who might, all else being equal, object to our proposed conditions, the sad reality is that funds for stem cell research, at least in this country, are relatively hard to come by. In other words, a qualified scientist would not likely turn down a CIRM grant because the articles she produced would enter the public domain and be made free online.

How would scientific journals react to this proposed policy? If their treatment of NIH intramural authors is any indication, then the journals would accept CIRM-funded authors with open arms, despite the scientists' inability to transfer rights in their articles to their publishers. In the event that some journals did object and refused to publish CIRM-funded articles, those journals would be the only stakeholders to suffer. The public would still have access to the identical scientific paper, but published in a CIRM-friendly journal (such as the many peer reviewed open access venues which thrive on the front-end payment model described above). The institutions that evaluate the work of scientist-authors, for the purposes of tenure, promotion, and future grants, would be aware that some journals do not publish CIRM-funded work and would adapt their metrics of evaluation accordingly. Certainly, the publication that refused the article would suffer for excluding an otherwise worthy contribution to the scientific literature for reasons unrelated to its intellectual merit. At the end of the day, as between the bottom line of a subscription-based journal publisher and the public's interest in access to scientific information, the CIRM policymakers should choose to support the latter.

HARNESSING AND SHARING THE BENEFITS OF STATE-SPONSORED RESEARCH: INTELLECTUAL PROPERTY RIGHTS AND DATA SHARING IN CALIFORNIA'S STEM CELL INITIATIVE

By Rebecca S. Eisenberg & Arti K. Rai†

TABLE OF CONTENTS

I. INTRODUCTION

The considerable attention that the California Institute for Regenerative Medicine (CIRM) and its Independent Citizens' Oversight Committee (ICOC) have already devoted to framing their intellectual property (IP)

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policies[1] is a sure sign of the growing salience of IP in biomedical research. In its Intellectual Property Policy for Non-Profit Organizations (IPPNPO), CIRM has endorsed a "core principle" to "encourage broad dissemination of CIRM-funded intellectual property of all types beyond practices commonly used in 2005 to promote scientific progress."[2] At the same time, CIRM has acknowledged competing interests that might limit such sharing, such as bringing scientific advances to the public through commercialization and providing a financial benefit to the State of California through revenue sharing.[3] Indeed, the text of Proposition 71, the initiative that created CIRM, explicitly sets forth these conflicting interests.[4]

When it comes to balancing interests, the devil is in the details. The IPPNPO is richly detailed with respect to patenting, licensing, and the exchange of research materials. For these matters, the policy generally follows evolving standards of "best practices" for federally-funded research, as articulated in reports from the National Institutes of Health (NIH).[5] For data sharing, however, while it states CIRM's general expectations, the IPPNPO barely touches upon the details.[6]

In recent years, data sharing has been a recurring focus of struggle within the biomedical research community as improvements in informa-

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1. *See* CIRM, INTELLECTUAL PROPERTY POLICY FOR NON-PROFIT ORGANIZATIONS (2006), *available at* http://www.cirm.ca.gov/policies/pdf/ippnpo.pdf [hereinafter IPPNPO]; *see also* CALIFORNIA COUNCIL ON SCIENCE & TECHNOLOGY, POLICY FRAMEWORK FOR INTELLECTUAL PROPERTY DERIVED FROM STEM CELL RESEARCH IN CALIFORNIA: INTERIM REPORT TO THE CALIFORNIA LEGISLATURE, GOVERNOR OF THE STATE OF CALIFORNIA, CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (2005), *available at* http://www.ccst.us/ccst/pubs/ip/ip%20interim.pdf.

2. IPPNPO, *supra* note 1, at 25.

3. *Id.* at 4-5.

4. California Secretary of State, *Text of Proposed Laws – Proposition 71*, *in* CALIFORNIA OFFICIAL VOTER INFORMATION GUIDE 147 (2004), *available at* http://www.cirm.ca.gov/prop71/pdf/prop71.pdf [hereinafter *Proposition 71*].

5. *See, e.g.*, Principles and Guidelines for Recipients of NIH Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources, 64 Fed. Reg. 72,090 (Dec. 23, 1999), *available at* http://ott.od.nih.gov/pdfs/64FR72090.pdf (cited with approval in IPPNPO, *supra* note 1, at 12).

6. The IPPNPO embraces the lofty aspirations for data sharing set forth in a series of recent reports from the National Research Council. *See, e.g.*, NAT'L RESEARCH COUNCIL, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (2006), *available at* http://newton.nap.edu/catalog/11487.html#toc; NAT'L RESEARCH COUNCIL, SHARING PUBLICATION-RELATED DATA AND MATERIALS: RESPONSIBILITIES OF AUTHORSHIP IN THE LIFE SCIENCES (2003), *available at* http://newton.nap.edu/catalog/10613.html#toc (cited in IPPNPO, *supra* note 1, at 26-27) [hereinafter SHARING DATA & MATERIALS].

tion technology and digital networks have expanded the ways in which data can be produced, disseminated, and used.[7] Electronic archives aggregate data from multiple sources, making it simpler and easier to share data.[8] Such sharing and aggregation facilitate observations that would otherwise be impossible, but data disclosure poses a dilemma for scientists. Data have long been scientists' stock in trade, lending credibility to their claims while highlighting new questions that merit future research funding. Some disclosure is necessary in order to claim these benefits, but data disclosure may also benefit one's research competitors. Scientists who share their data promptly and freely may find themselves at a competitive disadvantage relative to free riders in the race to make future observations and thereby earn further recognition and funding. The possibility of commercial gain further raises the competitive stakes. As information technology has advanced, and as commercial interests in biomedical research have grown, this dilemma has become more pronounced.

The role of statutory IP law in data sharing has been limited. Data per se are generally considered ineligible for either copyright or patent protection.[9] As a consequence, the Bayh-Dole Act,[10] which gives recipients of federal funding broad discretion to seek patent rights in the results of their federally-sponsored research, does not directly address the dissemination of unpatentable data.[11] Meanwhile, the scientific community has sought to clarify its data sharing norms and to determine how to implement them.[12]

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7. *See, e.g.*, SHARING DATA & MATERIALS, *supra* note 6. *See generally* NAT'L RESEARCH COUNCIL, BITS OF POWER: ISSUES IN GLOBAL ACCESS TO SCIENTIFIC DATA (1997), *available at* http://newton.nap.edu/catalog/5504.html#toc.

8. Of course, integration of data from sources that use different formats can be a problem. But software tools, such as BioPerl in the case of the genomic data produced by the Human Genome Project, can help to address the problem. *See* Colin Crossman & Arti Rai, A Brief History of BioPerl (working paper, on file with authors).

9. For a review of the limits on copyright protection of data with citations to the relevant cases and literature, see J.H. Reichman & Paul F. Uhlir, *A Contractually Reconstructed Research Commons for Scientific Data in a Highly Protectionist Intellectual Property Environment*, 66 LAW & CONTEMP. PROBS. 315, 336-41 (2003). For a review of the limits on patent protection of data, see U.S. Patent & Trademark Office, *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*, 1300 OFFICIAL GAZETTE OF THE U.S. PATENT & TRADEMARK OFFICE 4 (2005), *available at* http://www.uspto.gov/go/og/2005/week47/patgupa.htm.

10. Act of Dec. 12, 1980, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. §§ 200-212 (1994)).

11. Although *sui generis* database protection has been enacted in Europe, Council Directive 96/9 of 11 March 1996 on the Legal Protection of Databases, 1996 O.J. (L 77) 20, and proposed in the U.S., it has not yet been passed into law in the U.S. For a review of U.S. database protection proposals from the perspective of the scientific community, see J.H. Reichman & Paul F. Uhlir, *Database Protection at the Crossroads: Recent De-*

One important focus of debate has been the extent of data disclosure that should accompany scientific publication.[13] Although disclosure of research results is the essence of publication, scientific print journals typically reveal data only in summary form. This format provides authors substantial control over access to the underlying raw data. In an earlier era, such summary disclosures may have been necessary as a practical matter, given scarcities of space in print media. Now, however, with the growth of computer networks and information technology, a researcher can easily make vast data sets available over the internet at minimal cost. Yet, a recent survey found that less than half of the most frequently cited journals in the life sciences and medicine had policies requiring deposit of data associated with published articles.[14]

Debate within the scientific community over the disclosure obligations of publishing scientists reached a fevered pitch with the publication of an article in the prestigious *Science* magazine announcing the completion of the human genome sequence by scientists at the private firm Celera.[15] Although Celera made its sequence data available free of charge from its own website, access was restricted along certain dimensions, including quantitative limitations on the amount of data that could be downloaded, a prohibition on redistribution, and additional limitations on commercial users.[16]

The National Research Council of the elite National Academy of Sciences[17] entered into the debate by forming a Committee on Responsibilities of Authorship in the Biological Sciences to examine the topic of sharing published data and materials. The Committee issued a report that called upon authors to include in their publications or otherwise make freely available "the data, algorithms, or other information that is central or integral to the publication—that is, whatever is necessary to support the

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velopments and Their Impact on Science and Technology, 14 BERKELEY TECH. L.J. 793 (1999).

12. *See, e.g.*, NAT'L RESEARCH COUNCIL, FINDING THE PATH: ISSUES OF ACCESS TO RESEARCH RESOURCES (1999), *available at* http://newton.nap.edu/catalog/9629.html#toc [hereinafter FINDING THE PATH]; SHARING DATA & MATERIALS, *supra* note 6.

13. *See, e.g.*, FINDING THE PATH, *supra* note 12; SHARING DATA & MATERIALS, *supra* note 6.

14. SHARING DATA & MATERIALS, *supra* note 6, at 33 tbl.2-1.

15. J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCI. 1304 (2001).

16. Science Online, Accessing the Celera Human Genome Sequence Data, http://www.sciencemag.org/feature/data/announcement/gsp.dtl (last visited July 6, 2006).

17. Membership in the National Academy of Sciences is restricted to those scientists who have made highly significant contributions in their fields.

major claims of the paper and would enable one skilled in the art to verify or replicate the claims."[18] The report further indicated that authors should provide data "in a form on which other scientists can build with subsequent research."[19] In this regard, it specifically condemned the terms of access to the Celera human genome sequence data as "not consistent with the principles laid out in this report," noting that it permitted only "static access" for purposes of validation and not "dynamic access" for use in further research.[20]

Another important focus of debate has been the timing of data disclosure. The traditional trigger for data sharing in academic research is publication of research results. Large data sets, though, may not be ripe for publication in a prestigious journal until long after they are generated. Thus, research projects that aim to create large data sets over an extended period of time have presented special challenges for the implementation of data sharing norms.

In the genomics context, a series of international collaborative research efforts to create community resources for widespread use have prescribed data sharing policies that call for disclosure prior to publication.[21] In addition to facilitating prompt access to data for use in subsequent research, some of these efforts have also aimed to defeat corresponding patents, including patents on downstream inventions resulting from the data.[22] Within genomics, public research sponsors like NIH and the U.K.'s Wellcome Trust have applied normative pressure to achieve widespread data dissemination.

Outside the context of genomics, NIH has sought to use its leverage as a research sponsor to guide the data sharing practices of its grantees.[23] In recent years NIH has required researchers applying for more than

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18. SHARING DATA & MATERIALS, *supra* note 6, at 5.

19. *Id.* at 34.

20. *Id.* at 48 box 3-2.

21. *See, e.g.*, The Human Genome Program of the U.S. Department of Energy Office of Science, Summary of Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing—Bermuda (Feb. 25-28, 1996), http://www.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml#1; WELLCOME TRUST, SHARING DATA FROM LARGE-SCALE BIOLOGICAL RESEARCH PROJECTS: A SYSTEM OF TRIPARTITE RESPONSIBILITY (2003), *available at* http://www.wellcome.ac.uk/assets/wtd003207.pdf [hereinafter TRIPARTITE RESPONSIBILITY].

22. *See* International HapMap Project, Genotype Access Registration, http://www.hapmap.org/cgi-perl/registration (last visited July 6, 2006).

23. *See* NIH, NOTICE NOT-OD-03-032, FINAL NIH STATEMENT ON SHARING RESEARCH DATA (2003), *available at* http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html [hereinafter NIH STATEMENT].

$500,000 in funding to submit a plan for data sharing.[24] NIH cites a compelling list of arguments in support of such sharing, including reinforcing open scientific inquiry, facilitating new research, encouraging diversity of analysis and opinions, enabling the exploration of topics not envisioned by the original investigators, and permitting the creation of new data sets that combine data from different sources. The policy stops short of mandating data sharing, however, acknowledging the competing interest of "protecting confidential and proprietary data."[25]

While these international and federal initiatives provide useful benchmarks for CIRM to consider in formulating its own approach to data sharing, they do not constrain CIRM. In the patent context, the pervasive influence of the Bayh-Dole Act on publicly-sponsored research institutions is likely to constrain even a relatively large state-sponsored research initiative such as CIRM. These institutions actively seek and already hold many patents on stem cell technology.[26] By contrast, intellectual property rights for data are less clearly defined and institutional practices are less standardized. Given the variability in approaches to data sharing within the biomedical research community, CIRM may be well-positioned by virtue of the scale of its operation and the scarcity of federal funding for stem cell research to take a leadership role in setting the terms for data sharing in this context.

This Article discusses data sharing in California's stem cell initiative against the background of other data sharing efforts and in light of the competing interests that CIRM is directed to balance.[27] We begin by considering how IP law affects data sharing. We then assess the strategic considerations that guide the IP and data policies and strategies of federal, state, and private research sponsors. With this background, we discuss four specific sets of issues that public sponsors of data-rich research, including CIRM, are likely to confront: (1) how to motivate researchers to contribute data; (2) who should have access to the data and on what condi-

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24. NIH, NIH DATA SHARING POLICY AND IMPLEMENTATION GUIDANCE (2003), *available at* http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm [hereinafter NIH DATA SHARING POLICY].

25. *Id.*

26. The most significant university patents are held by the Wisconsin Alumni Research Foundation (WARF). WARF holds broad patents on both embryonic stem cell lines in general and human embryonic stem cell lines in particular.

27. For purposes of this Article's analysis, we take these interests as a given. Thus, we do not evaluate, for example, whether CIRM's interest in providing financial benefit to the State of California is appropriate. Rather, we confine our analysis to possible conflict between the various CIRM interests.

tions; (3) what data get deposited and when; and (4) how to establish database architecture and curate and maintain the database.

II. THE ROLE OF INTELLECTUAL PROPERTY LAW IN DATA SHARING

Neither copyright nor patent law offers federal statutory protection for data as such. Indeed, both copyright law and patent law treat the informational content of writings and inventions as a spillover benefit for the public, while limiting the exclusionary rights of creators to something else: an original expression in the case of copyright,[28] and a product or process in the case of patent.[29]

On one reading, the failure to protect information under either patent or copyright law suggests that information gets no respect. This is the sense that emerges from reading copyright cases like *Feist Publications, Inc. v. Rural Telephone Services Co.*,[30] in which the Supreme Court re-

28. *Cf.* Feist Publ'ns, Inc. v. Rural Tel. Serv. Co., 499 U.S. 340 (1991) (holding that an alphabetized list of names and phone numbers lacked the minimum originality necessary for copyright protection, even though considerable effort may have gone into creating it).

29. Patentable subject matter is limited by statute to any new and useful process, machine, manufacture, or composition of matter, 35 U.S.C. § 101 (2000), all generally understood to be distinct from data or information. The subject matter boundaries of the patent system have been diminishing in recent judicial decisions in the face of creative claiming strategies for new technologies, particularly information technology. *See, e.g.*, State Street Bank & Trust Co. v. Signature Fin. Group, 149 F.3d 1368 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1093 (1999); AT&T Corp. v. Excel Commc'ns, Inc., 172 F.3d 1352 (Fed. Cir. 1999). Last term, the Supreme Court granted certiorari in the case of *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 370 F.3d 1354 (Fed. Cir. 2004), *cert. granted*, 126 S. Ct. 543 (2005), *vacated, reconsidered, and cert. granted*, 126 S. Ct. 601 (2005), limiting the scope of its review to the question of patentable subject matter. Ultimately the Court dismissed the writ of certiorari as improvidently granted, with three justices dissenting. *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 126 S. Ct. 2976, 2921 (Breyer, J. with whom Stevens, J. and Souter, J. join, dissenting). Although the case ultimately failed to generate an authoritative opinion from a majority of the Supreme Court, the numerous amicus briefs filed in support of the defendant suggest a surprising level of discomfort in the business community with the trend toward more expansive patent eligibility. *See* Rebecca S. Eisenberg, *Biotech Patents: Looking Backward While Moving Forward*, 24 NATURE BIOTECH. 317 (2006).

30. 499 U.S. 340 (1991). The *sine qua non* of copyright is originality. To qualify for copyright protection, a work must be original to the author. Original, as the term is used in copyright, means only that the work was independently created by the author (as opposed to copied from other works), and that it possesses at least some minimal degree of creativity. To be sure, the requisite level of creativity is extremely low; even a slight amount will suffice. The vast majority of works make the grade quite easily, as they pos-

jected a claim of copyright in an alphabetized list of names and phone numbers. In this story, copyright law treats information as a mere byproduct of efforts that deserve protection only insofar as they yield some other, more creative output. Contemporary critics charge that copyright law has failed to appreciate the importance of information as an artifact of human ingenuity with value in its own right. In this view, as this value grows and becomes more vulnerable to misappropriation with the expanding capabilities of IT, this limitation on legal rights becomes more anomalous.[31]

From another perspective, the failure to protect data may reflect a reverence for information. Information is so valuable that society will not permit it to be monopolized. This is the sense that emerges from reading cases about disclosure in the patent system, in which courts treat the informational content of patent applications as the public's quid pro quo that justifies the issuance of patents.[32] In this story, disclosure of unprotected information is not an incidental byproduct of a process that aims to motivate something more worthwhile, but is the whole purpose of the system. We promote disclosure of precious information by rewarding disclosure with exclusionary rights in something else.

By requiring public disclosure of information about an invention while limiting the exclusive rights to the inventions defined in claims, patent law

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sess some creative spark, "'no matter how crude, humble or obvious' it might be . . . [F]acts do not owe their origin to an act of authorship. The distinction is one between creation and discovery: the first person to find and report a particular fact has not created the fact; he or she has merely discovered its existence . . . [O]ne who discovers a fact is not its 'maker' or 'originator.' 'The discoverer merely finds and records.'" *Id.* at 345-47 (citations omitted).

31. *See, e.g.*, Jane C. Ginsburg, *U.S. Initiatives to Protect Works of Low Authorship*, *in* EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY (R. Dreyfuss et al. eds., 2001).

32. *See, e.g.*, Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 481 (1974) ("When a patent is granted and the information contained in it is circulated to the general public and those especially skilled in the trade, such additions to the general store of knowledge are of such importance to the public weal that the Federal Government is willing to pay the high price of 17 years of exclusive use for its disclosure, which disclosure, it is assumed, will stimulate ideas and the eventual development of further significant advances in the art."); Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 151 (1989) ("[T]he ultimate goal of the patent system is to bring new ideas and technologies into the public domain through disclosure. State law protection for ideas and designs whose disclosure has already been induced by market rewards may conflict with the very purpose of the patent laws by decreasing the range of ideas available as the building blocks of further innovation."); United States v. Dubilier Condenser Corp., 289 U.S. 178, 186 (1933) ("[The inventor] may keep his invention secret and reap its fruits indefinitely. In consideration of its disclosure and the consequent benefit to the community, the patent is granted.").

not only fails to protect information but actually pushes it into the public domain as a spillover.[33] Yet, while the information disclosed in a patent application is publicly available, the exclusionary rights from the patent might still protect the patent owner from its unauthorized use if the use involves infringing the patent claims. If an inventor discloses in a patent application how to make and use a new mousetrap and a patent issues with claims drawn to the mousetrap, anyone who follows the directions in the disclosure to make and use the claimed mousetrap would be liable for infringement. A reader, on the other hand, who uses the disclosed information to problem-solve and devise a new spring-loaded device falling outside the scope of the mousetrap patent claims would not be liable, though the patent disclosure may have been invaluable to the reader in solving his problem. While patent claims legally constrain the use of information disclosed in patent specifications, the public disclosure of the information may also facilitate other non-infringing uses of that information.

Patent law concerning the scope of "prior art" that is used to evaluate the patentability of inventions has complex effects on incentives for information disclosure. The rules of patentability count all publicly available information, including the inventor's own disclosures, as prior art.[34] Consequently, those who hope to file patent applications may be inclined to defer disclosure of data until after filing related patent applications. On the other hand, those who wish to defeat the potential patent applications of their scientific or commercial rivals may disclose information early in the hope of creating more prior art.[35] The creation of patent-defeating prior art

33. *See* 35 U.S.C. § 112 ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."). An inventor who fails to file a patent application within a year of putting an invention to use loses the right to obtain a U.S. patent, *id.* § 102(b), forcing inventors to choose promptly between entering into the bargain of disclosure in exchange for a patent or secrecy and loss of right to patent.

34. *Id.* §§ 102-103. An inventor's own disclosures will not defeat the novelty of an invention under U.S. law because they do not show prior invention, knowledge, or use by another prior to the invention date, *id.* § 102(a), (g), but they may nonetheless give rise to a "statutory bar" against a patent if the disclosure occurred more than a year before the inventor's filing date. *Id.* § 102(b).

35. *See* Gideon Parchomovsky, *Publish or Perish*, 98 MICH. L. REV. 926 (2000); Douglas Lichtman, Kate Kraus & Scott Baker, *Strategic Disclosure in the Patent System*, 53 VAND. L. REV. 2175 (2000); Rebecca S. Eisenberg, *The Promise and Perils of Strategic Publication to Create Prior Art: A Response to Professor Parchomovsky*, 98 MICH. L. REV. 2358 (2000).

appears to have played a role in the development of disclosure rules for some large-scale biological resource projects.[36]

III. STRATEGIC CONSIDERATIONS OF SPONSORS IN DATA SHARING

A. Private Sponsors

Absent statutory protection, such as a patent or copyright, that survives beyond disclosure, a standard commercial strategy for preserving the value of data and databases has been secrecy, or more accurately, restricted access. Some owners of valuable databases permit only internal access to the data. Others make data available only to paying subscribers under the terms of database access agreements. Such owners may protect their databases as trade secrets, or at a minimum, under the law of contracts. Even without having to enforce legal rights in court, database owners may exercise considerable practical control over data sharing by restricting online access to databases to only particular internet addresses.

These strategies allow database owners to exclude free riders, and perhaps thereby capture enough value to justify creating the database. All the same, they are wasteful from a social perspective. These strategies restrict the dissemination of information that would have greater social value if more widely used and that could be made freely available at minimal cost. Restricting access leads to socially wasteful duplication as competitors create similar databases for their own use. It encumbers data consolidation, making it more difficult to aggregate data from multiple sources to create more comprehensive databases. Nonetheless, trade secrecy, contracts, and digital technology have an important role to play in encouraging firms to invest in the creation of databases.

B. Public Sponsors

The case for trade secrecy and other measures is weaker for information generated at public expense. Public funding mitigates concerns about the adequacy of incentives to generate information and makes the social waste inherent in secrecy more troubling. While some value may be created by interactions between creators and users of data when creators control access to data, broad dissemination often better serves the mission of public sponsors to advance science.[37] Further, data disclosure can provide

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36 *See infra* Part IV.A. and note 79.

37. *Compare* Ashish Arora & Robert Merges, *Specialized Supply Firms, Property Rights, and Firm Boundaries*, 13 INDUS. & CORP. CHANGE 451 (2004) (discussing value

a valuable check on fraudulent research claims. This risk has, regrettably, become salient in the recent experience of stem cell research.[38] Data disclosure also provides a check against over-claiming in the political arena, another concern for stem cell research.[39]

Public sponsors have an interest not only in advancing science but also in ensuring that research discoveries made in the course of funded research are effectively disseminated and practically utilized. The Bayh-Dole Act emphasizes this interest and aims to promote it by encouraging grantees to patent their inventions and then to license these patents to firms that will undertake further development and commercialization.[40] The theory is that licenses, especially exclusive licenses, will provide necessary protection against competition during the risky and costly commercialization process. Although one might expect the interests of state sponsors to be similar to those of the federal government, CIRM in fact faces more significant (and more parochial) constraints under the terms of Proposition 71.

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of customization of research inputs for particular users), *with* NIH STATEMENT, *supra* note 23.

38. *See* Sei Chong & Dennis Normile, *How Young Korean Researchers Helped Unearth a Scandal. . . And How the Problems Eluded Peer Reviewers and Editors*, 311 SCI. 22-25 (2006).

39. *See* David A. Shaywitz, *Stem Cell Hype and Hope*, WASH. POST, Jan. 12, 2006, at A21.

40. 35 U.S.C. § 200. Other interests noted in the Bayh-Dole statute include encouraging participation of small business firms in federally supported research and development (R&D), promoting collaboration between commercial concerns and nonprofit organizations, promoting competition and enterprise without unduly encumbering future R&D, promoting "the commercialization and public availability of inventions made in the United States by United States industry and labor," ensuring that the government obtains sufficient rights in federally supported inventions to meet its needs, and minimizing administrative costs. *Id.* Federal research sponsors are not charged by statute with recovering revenues from technologies patented by grantees except in the case of inventions made in a government-owned, contractor-operated facility (i.e. a national laboratory). Under 35 U.S.C. § 202(c)(7), sponsors are directed to include in funding agreements requirements for sharing royalties with inventors and for using remaining income, after payment of costs, to support scientific research or education. A different rule applies to funding agreements for the operation of a government-owned, contractor-operated facility; these agreements are to require payment to the U.S. Treasury of 75% of the excess revenues after payment of expenses if the balance exceeds 5% of the annual budget of the facility. *Id.* § 202(c)(7)(E). Although the Bayh-Dole Act directs grantees to give a preference in the award of exclusive licenses to firms that agree to manufacture the invention in the United States, if that constraint proves to be problematic, then the sponsor may waive it. *Id.* § 204.

In addition to promoting the development of stem cell therapies, Proposition 71 identifies a number of goals that are more narrowly focused on the interests of California constituencies, including: to "[p]rotect and benefit the California budget . . . by providing an opportunity for the state to benefit from royalties, patents, and licensing fees that result from the research"; to "[b]enefit the California economy by creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues in our state"; and to "[a]dvance the biotech industry in California to world leadership, as an economic engine for California's future."[41] Proposition 71 enhances the likelihood that the California focus of these goals will be taken to heart by requiring California institutional affiliations for each member of the ICOC, the committee charged with governing CIRM.[42]

Of course, it is not at all surprising that a California voter initiative that appropriates $3 billion in research funding would promote the interests of California constituencies. Indeed, in the Bayh-Dole Act, the federal government made a similar move to promote the interests of U.S. firms by directing recipients of U.S. research funding to give preferences for exclusive licenses to firms that would manufacture in the U.S.[43] These strategies allow taxpayers to capture more of the benefits of tax-funded programs. To the extent that spillovers to non-local interests limit incentives for governments to invest in research and development ("R&D"), such strategies may be necessary to encourage government-funded R&D.

Nonetheless, state-focused preferences in the management of intellectual property are more limiting than national preferences, and thus are more troubling. If state-sponsored R&D initiatives become more prevalent, a proliferation of local preferences could threaten to balkanize valuable IP among the states, making it difficult for firms to collect the rights needed to move forward with product development. Even a single state-sponsored research initiative such as CIRM could significantly restrict dissemination through local preferences if it controls access to broad, cross-cutting technologies, like stem cells, that may have implications for a range of problems.[44]

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41. *Proposition 71*, *supra* note 4, at 147.

42. *Id.* at 147-48; California Stem Cell Research and Cures Act, CAL. HEALTH & SAFETY CODE § 125290.20(a) (2006).

43. Note, though, that if that constraint proves to be problematic, the sponsor may waive it. 35 U.S.C. § 204.

44. It is interesting to compare the interests of state research sponsors in furthering the interests of local constituents with the interests of private research sponsors in furthering the interests of shareholders. Private sponsors are unlikely to care whether the money

Moreover, in contrast to the Bayh-Dole Act, Proposition 71 directs CIRM to recoup revenues for the California state treasury.[45] This revenue goal is in tension not only with the goal of ensuring widespread dissemination of research results, but also, to a lesser degree, with the goal of commercialization. To the extent that product developers are expected to return money to the state treasury, such a requirement acts as a tax on commercialization.

Although the Bayh-Dole Act and Proposition 71 focus on patent rights in technologies emerging from sponsored research, data sharing in the context of sponsored research poses similar tradeoffs between capturing value for political constituencies and promoting scientific progress.

IV. SPECIFIC CHALLENGES FOR CIRM

The challenge for CIRM is to capture an adequate return for its constituents on its investment in stem cell research without unduly limiting its overall social value. In examining this challenge, we address four highly interdependent issues that any effort to promote data sharing must consider:[46] (1) incentives to contribute data; (2) who gets access and under what conditions; (3) what gets deposited and when; and (4) database architecture, maintenance, and curation. Throughout our discussion, we draw upon the experiences of prior database initiatives, particularly those at the federal level, which have attempted to promote widespread dissemination and sharing. In the absence of information on the specific research CIRM is likely to fund, we make these observations at a relatively high level of generality.

A. Incentives to Contribute Data

In order to be effective, data release policies must give scientists clear incentives to contribute their data. This Section focuses on incentives in

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they are making emanates from activity in California or in Massachusetts, and are therefore less likely to restrict dissemination on the basis of geography. On the other hand, private sponsors may be less likely than state counterparts to disseminate information in ways that benefit the public but do not benefit their own bottom lines. CIRM might be content to spend money in ways that mean more medical treatments and more jobs for California voters even if no money flows back to the state coffers, but commercial firms that are obligated to return value to shareholders cannot afford to be so public-spirited.

45. *Proposition 71*, *supra* note 4, at 147.

46. For purposes of this article, we put to one side thorny problems regarding privacy that might be raised by data associated with personally identifiable information. We will assume that data involved in stem cell research would not trigger concerns about personally identifiable information or that the data could be effectively de-identified to address such concerns.

two somewhat distinct contexts: centralized data production projects and more decentralized, investigator-driven science.

As a general matter, incentives are necessary because most rewards in research science, including academic appointments, promotion, and grant funding, depend on a record of frequent publication. Scientists may perceive sharing data, even after an initial publication, as providing advantages to competitors in the race to generate further publications. Scientists may also be reluctant to share data because of involvement in commercial activities. Sharing may imperil patent applications or destroy trade secrecy. Emerging evidence reveals that some research communities in the life sciences are reluctant to share data even after publication. For example, a survey conducted by Eric Campbell and his colleagues found that 47% of academic geneticists who had made a request to another academic had been denied access to data or materials associated with a published article at least once in the preceding three years.[47] Scientific competition and commercial involvement were both important predictors of refusal to share.[48]

Although NIH now requires grant applicants to include a data sharing plan in grant applications exceeding $500,000 per year,[49] so far it has done little to enforce compliance. If CIRM wants its grantees to share data, it should consider mechanisms for ensuring compliance from the outset in order to offset the powerful incentives that scientists face to withhold access to data. Mechanisms might include rewards for compliance or sanctions for noncompliance, such as loss of continued funding. A possible reward might involve privileged access to data analysis tools for those who contribute data to an archive. CIRM could also track downloads of

47. Eric Campbell et al., *Data Withholding in Academic Genetics: Evidence from a National Survey*, 287 JAMA 473, 477 (2002). The Campbell study did not distinguish between data and tangible materials. Because one important impediment to sharing identified by the study—the effort and financial cost associated with replication and transfer, *id.* at 478, —is much lower for data than for tangible materials, the study may overestimate impediments to data disclosure. *Cf.* John Walsh et al., *View from the Bench: Patents and Materials Transfers*, 309 SCI. 2002 (2005) (indicating that problems in transfer of tangible materials appear to have risen since Campbell's study, but not addressing the question of data). Nonetheless, as discussed earlier, a series of workshops and reports emanating from the biomedical research community confirms a growing perception of departures from the principle of data sharing upon publication.

48. *See* Campbell, *supra* note 47, at 478.

49. *See* NIH DATA SHARING POLICY, *supra* note 24.

data from a centralized archive and give special acknowledgements or other rewards to scientists whose data was downloaded frequently.[50]

It may be easier to achieve compliance with a data sharing plan within a tightly knit community of scientists. For example, at the height of the Human Genome Project (HGP), the five major production labs that contributed large amounts of sequence to the public GenBank database teleconferenced on a weekly basis.[51] In this environment the normative pressure to comply with data disclosure—even pre-publication disclosure—was unusually strong. Some data users from the HGP and other community resource projects have also argued that widespread data availability was the quid pro quo for the major centers receiving large sums of money to complete these projects without undergoing peer review of each individual portion.[52] CIRM may be able to create similar normative pressure to comply with data disclosure obligations if it funds large-scale, centralized data production.[53]

It bears emphasis, though, that researchers in the HGP were motivated not only by a public-spirited desire to make data quickly available (without any background patents on associated material)[54] but also by a competitive desire to outdo rival private sector efforts. Measures of the volume of data accumulating in GenBank served as a conspicuous marker of accelerating productivity for the HGP. Public availability served as a salient point of distinction from the proprietary databases of commercial rivals.

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50. Although rewards of this sort might not be as attractive as preserving exclusive access so as to mine the data for additional publications (particularly if university tenure and promotion committees continue their current practice of considering publication to be the primary benchmark of success), they might provide some incentive.

51. JOHN SULSTON & GEORGINA FERRY, THE COMMON THREAD: A STORY OF SCIENCE, POLITICS, ETHICS AND THE HUMAN GENOME 193 (2002) (discussing the Friday conference calls that took place among the "G5" to coordinate activities).

52. Steven Salzberg et al., *Unrestricted Free Access Works and Must Continue*, 422 NATURE 801 (2003) (correspondence from bioinformaticians arguing that obligations of scientists in large-scale data production centers differ from those of traditional scientists).

53. For example, CIRM might fund a group of centers to produce data on gene expression at different stages of stem cell differentiation.

54. In February 1996, scientists from the major sequencing centers in the HGP explicitly disavowed patenting. Eliot Marsh, *Data Sharing: Genome Researchers Take the Pledge*, 272 SCI. 477, 477 (1996). NIH followed up with an April 1996 policy statement strongly discouraging patenting by HGP grantees. National Human Genome Research Institute, NHGRI Policy Regarding Intellectual Property of Human Genomic Sequence—Apr. 9, 1996, http://www.genome.gov/10000926. Though it may be in some tension with Bayh-Dole, this "no patenting norm" has also been part of subsequent NIH-sponsored "community resource" projects. *See* Arti K. Rai & Rebecca S. Eisenberg, *The Public Domain: Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 289 (2003).

Public access helped to justify continued public support for a project that appeared to duplicate work being done in the private sector. Moreover, rapid data availability might have been expected to frustrate commercial rivals by creating prior art to defeat future gene sequence patents.[55] Rapid public disclosure also undermined the viability of private sector business models that entailed charging license fees for database access. Although they were able to raise investment capital to create their databases, private sector rivals were ultimately not able to survive in the database business.[56]

Given its mandate to "[a]dvance the biotech industry in California to world leadership, as an economic engine for California's future,"[57] it seems unlikely that CIRM would want to drive out private sector data producers in any large-scale data production efforts that it might fund. CIRM might, therefore, count impediments to private R&D as a cost to weigh against the benefits of a public domain approach to research inputs like data. A public domain approach eliminates the significant costs that are likely to be associated with negotiating access, but it also imposes some costs of its own. In addition to making public funding necessary in many cases, aggressive versions of a public domain approach may undermine the types of small firms that tend to provide specialized research inputs in the marketplace. To the extent that these foregone market incentives for innovation by specialized firms are superior to the incentives that operate

55. Although raw genomic data would not undermine claims to specific genes of identified function, annotated data might do so. A major goal of annotation is to identify coding regions in the genome and add information about the function of the protein for which the region codes. A recent empirical study suggests that at least 20% of human genes are in fact covered by patents; some genes are covered by multiple patents. *See* Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239 (2005). The extent to which these patents are valid over the prior art is unclear.

56. The major private sector rival to the public database, Celera Genomics led by Craig Venter, was ultimately unsuccessful in its efforts to charge for its database and released its data into the public domain. Emma Marris, *Free Genome Databases Finally Defeat Celera*, 435 NATURE 6 (2005). Although public availability of the human genome avoids the potentially crippling costs that might have been associated with negotiating access, and is thus a welcome development, the presence of a private sector rival had some benefit. The private sector effort arguably provided the competition necessary for the public sector to work efficiently. In particular, private sector competition may have been the catalyst necessary to overcome the public sector's resistance to the whole genome shotgun sequencing approach, a methodology that has proved to be successful. *See* Rebecca S. Eisenberg & Richard Nelson, *Public vs. Proprietary Science: A Fruitful Tension?*, 131 DAEDALUS 89 (2002).

57. *Proposition 71*, *supra* note 4, at 147.

in large, vertically integrated firms or in the public sector,[58] that cost may be significant.

Unlike the HGP, most community resource projects in genomics have not sought to drive out private sector competitors. These projects may therefore provide a more appropriate model for CIRM. Non-HGP community resource projects have, of course, lacked the incentives for disclosure provided by a race with a high-profile private sector competitor. They have made up for the absence of such incentives, however, by explicitly seeking to preserve some of the rewards of publication for scientists who contribute to public databases prior to publication. A report from the Wellcome Trust on *Sharing Data from Large-Scale Biological Research Projects: A System of Tripartite Responsibility* proposes that producers of database resources publish a project description at the beginning of the project describing their plans.[59] These project descriptions should provide for production, analysis, and release of the data and give a citation for referencing the sources of the data.[60] The Wellcome Trust report not only admonishes data users to cite the proper reference source but it also urges them to "recognize that the resource producers have a legitimate interest in publishing prominent peer-reviewed reports describing and analyzing the resource that they have produced . . . ." Indeed, the report indicates that data users might best "promote the highest standards of respect for the scientific contribution of others," by discussing or coordinating their publication plans with resource producers.[61] In comparable community resource projects, CIRM could use its leverage with both data producers and the data users it funds to encourage compliance with these suggested principles.

There is an obvious tension between preserving opportunities for those who disclose data to publish their own future analyses and allowing outside users full access to the data. Unlike the Wellcome Trust report, which does not endorse explicit delays on publication by outside data users, some community resource projects have tried to restrict publication. One example is the Genetic Association Information Network (GAIN),[62] a public-private partnership of the NIH and several private firms, currently Pfizer,

58. *See* Arora & Merges, *supra* note 37; Ashish Arora et al., *Markets for Technology and Their Implications for Corporate Strategy*, 10 INDUS. & CORP. CHANGE 419 (2001).

59. *See* TRIPARTITE RESPONSIBILITY, *supra* note 21.

60. *Id.* at 3-4.

61. *Id.* at 4.

62. Foundation for the NIH, GAIN Program Home Page, http://www.fnih.org/GAIN/GAIN_home.shtml (last visited Aug. 3, 2006).

Affymetrix, and Abbott Laboratories.[63] GAIN aims to understand the complex set of genetic factors influencing risk for common diseases by conducting a series of whole genome association studies that employ samples from patients with such diseases.[64] The GAIN publication policy gives contributing investigators a period of nine months during which they have the exclusive right to submit publications based on their data.[65] At the same time, the policy gives approved users, who sign a restrictive agreement, access to the data during this period.[66] CIRM may need to consider whether the type of formal restriction on publication adopted by GAIN unduly favors initial producers of data relative to subsequent users.

In any event, the model adopted for community resource projects in genomics is likely to be inappropriate for decentralized, investigator-initiated work. Detailed information about the characteristics of all available stem cell lines, for example, is likely to emerge not from a top-down data production effort, but rather from decentralized contributions of individual labs. Stem cell scientists would presumably generate such information as they worked with, and published on, particular lines. A database that accumulated such information, which some stem cell scientists have proposed,[67] might include details of derivation, genetic details, and results indicating pluripotence and antibody markers.

For such work, the federally funded Protein Data Bank (PDB) may be a better model. In 1971, a group of crystallographers established the PDB as a centralized repository for three-dimensional protein structure data. Deposit of structures, though, did not begin in earnest until the 1980s, as the community began to see collective advantages of deposition. In 1989, the International Union of Crystallography (IUCr) reinforced community views by calling on researchers to deposit data once they submitted for publication a research article based on the data.[68] Actual data release,

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63. *See* Foundation for the NIH, GAIN Program Partnerships, http://www.fnih.org/GAIN/Partnerships.shtml (last visited Aug. 3, 2006).

64. *See* Foundation for the NIH, GAIN Program Overview, http://www.fnih.org/GAIN/Background.shtml#Program (last visited Aug. 3, 2006).

65. Foundation for the NIH, Policies and Procedures: GAIN Publication Policy, http://www.fnih.org/GAIN/policies.shtml#Publication (last visited Aug. 3, 2006) [hereinafter GAIN Publication Policy]; Foundation for the NIH, GAIN Data Use Certification Terms of Access, http://www.fnih.org/GAIN/documents/Data_Use_Certification.pdf, ¶ 6 (last visited Aug. 3, 2006) [hereinafter GAIN Terms of Access].

66. GAIN Publication Policy, *supra* note 65.

67. Krishanu Saha, Navigating to the Right Stem Cell Line (working paper, on file with authors). A preliminary version of such a database is currently available at The Stem Cell Community, http://www.stemcellcommunity.org (last visited Aug. 3, 2006).

68. SHARING DATA & MATERIALS, *supra* note 6, at 74-75.

however, did not have to be immediate: the IUCr allowed researchers to request a one-year hold before public release of the data by the database.[69] IUCr justified this one-year hold as a reward for the difficulties in determining protein structure. As these difficulties decreased, leaders within the community began to call for immediate release of data upon publication. In 1999, the NIH announced a policy of data release upon publication for its grantees.[70] Major scientific journals such as *Science* and *Nature* now require data deposition in PDB as a condition of publication.[71]

In contrast with recent community resource projects in genomics, the PDB effort does not have a prohibition on patenting. Although the PDB does not keep track of background patents,[72] protein structure data could be associated with background patents on the gene, protein crystal, or perhaps even on a computer model of a protein binding pocket that purports to allow the investigator to test drug candidates.[73] In a decentralized project such as PDB, a prohibition on patents might have served as a significant disincentive to scientific participation.

The PDB story exemplifies cooperation between scientific leaders in the protein crystallographic community and research sponsors over several decades to make data deposition an essential aspect of publication.[74] A similar combination of sustained sponsor pressure and leadership from key leaders in the stem cell community may also be critical in order for data sharing in routine CIRM-funded work to succeed.

B. Access: By Whom and Under What Conditions

Incentives to contribute are also likely to be affected by scientists' perceptions regarding who may access their contributions, and under what conditions. The issue of access is an important one, both for ensuring maximum benefit from CIRM-sponsored research and for determining how CIRM, and the state of California more generally, reap returns on their investment.

A pure public domain approach to scientific resources would place no restrictions on who could seek access or on what they could seek. In the

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69. *Id.* at 75.

70. *Id.* at 76.

71. *See* Science, Database Deposition Policy, http://www.sciencemag.org/about/authors/prep/gen_info.dtl#datadep (last visited Aug. 3, 2006).

72. Telephone Interview with Helen Berman, Professor, Department of Chemistry and Chemical Biology, Rutgers University, in Piscataway, N.J. (Mar. 2, 2005). Professor Berman is a leader of the PDB community.

73. Although the last category of patent appears quite close to a patent on data, the U.S. Patent & Trademark Office has issued such patents.

74. Interview with Helen Berman, *supra* note 72.

area of publication-related biomedical materials, CIRM has already departed from a pure public domain approach in favor of a policy that favors California researchers. The CIRM IPPNPO requires grantees to share biomedical materials described in published scientific articles within 60 days of receiving a request for such materials. But the IPPNPO appears to limit grantee obligations to those who are seeking the materials for "research purposes in California."[75]

CIRM might similarly choose a tiered approach to data access in order to benefit various constituents. It might, for example, permit access by: (1) CIRM-funded nonprofit researchers only; (2) all CIRM-funded researchers; (3) all California researchers; (4) all stem cell researchers who had contributed their own data (and/or agreed to contribute their own annotations/improvements to the database); or (5) all stem cell researchers. Certain categories of researchers could be excluded altogether or could be given access under restrictive conditions. CIRM could require for-profit institutions, or non-California institutions, to pay for access. Non-price methods of tiering, such as early access by certain favored categories of researchers, could favor preferred groups while still permitting broad access.

Providing preferential access to CIRM-funded researchers, or to researchers based in California, could promote Proposition 71's goal of stimulating the California economy. Charging for-profit institutions for access may promote its goal of direct returns to the California budget. Furthermore, giving preference to those who themselves contribute data, whether through initial contributions or through improvements or annotations to the initial contribution, could provide an additional incentive to contribute.

These benefits come at some cost though: the more conditions CIRM places on access, the more potential investigators are excluded. Moreover, because data are not protected by intellectual property rights, contract-based access must specifically include restrictions against the possibility of dissemination to third parties. Thus, in order for any contractual restrictions to be effective, they must include a restriction on further dissemination.

Again, recent experience with publicly funded genomics databases provides a useful background for examining the costs and benefits of restricting access. In the case of the HGP, data were released into the public

75. IPPNPO, *supra* note 1, at 16. Similarly, the IPPNPO restricts its requirement that CIRM-funded patents materials be made available for research purposes to "California research institutions." *Id.*

domain without restriction. The public domain approach was chosen over the objection of some public sector scientists who did not view creating prior art as the best weapon for defeating proprietary claims. Because the data were freely available, those who accessed the data could blend it with their own privately-held information and make the combination proprietary.[76] These scientists suspected that Craig Venter, the major private sector challenger to the HGP, had adopted this approach.[77]

The frustration of these public sector scientists appears to have influenced the approach toward data sharing in subsequent community resource projects. For example, the International Haplotype Map (HapMap) project, which receives funding from both the NIH and the Wellcome Trust, initially took a very different approach to data release. In that case, the raw data on single base DNA variations, also known as single nucleotide polymorphisms (SNPs), were not released into the public domain. Rather, they were made available via a clickwrap license explicitly modeled on the General Public License (GPL) used by open source software developers.[78] Until December 2004, when the license restrictions were lifted, the license prohibited licensees from combining the data with their own so as to seek product patents on combinations of SNPs known as haplotypes.[79]

The HapMap experience illustrates some of the difficulties involved in adapting the GPL to the release of biomedical research data.[80] First, the

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76. SULSTON & FERRY, *supra* note 51, at 211-13.

77. There is some controversy over the extent to which the Venter project actually relied on the public data. *Compare* Robert H. Waterston et al., *More on the Sequencing of the Human Genome*, 100 PROC. NAT'L ACAD. SCI. 3022, 3024 (2003) (claiming that Celera's assembly is "appropriately viewed as a refinement built on the HGP assemblies") *with* Mark D. Adams et al., *The Independence of Our Genome Assemblies*, 100 PROC. NAT'L ACAD. SCI. 3025, 3026 (2003) (claiming that Celera produced an "independent assembly" and that HGP contribution to the structure and content was minimal).

78. International HapMap Project, Public Access License–Version 1.1, Aug. 2003, http://www.hapmap.org/cgi-perl/registration [hereinafter HapMap License]. The HapMap License includes an acknowledgement to the GNU General Public License of the Free Software Foundation. *Id.*

79. *See id.* ¶ 2(b)(i) ("[Y]ou shall not file any patent applications that contain claims to any composition of matter of any single nucleotide polymorphism ('SNP'), genotype or haplotype data obtained from the Genotype Database or any SNP, haplotype or haplotype block based on data obtained from the Genotype Database.") Haplotypes are SNP clusters that are inherited together. Haplotypes associated with particular phenotypes can be used as markers for diagnostic tests and drug targets. *See generally* International HapMap Project, What is the HapMap?, http://www.hapmap.org/whatishapmap.html.en (last visited Aug. 7, 2006).

80. For a general discussion of "open source" approaches in biomedical research, see Arti K. Rai, *Open and Collaborative Research: A New Model for Biomedicine, in*

GPL is structured as a license to intellectual property rights. In the context of open source software, the licensed rights consist of copyright in software, a right that has been recognized both by Congress and by the courts. Under U.S. law, there is no comparable intellectual property right in data to anchor the HapMap license. The HapMap license denies this difficulty, requiring those who would access the data to acknowledge, contrary to legal authority, that the data are protected by U.S. copyright law.[81]

Second, because there is no property right that survives disclosure to those not bound by the license, in order to ensure that third parties do not gain access to the data without agreeing to the terms of the license, the HapMap license imposes tight restrictions on dissemination. Researchers who accessed the data prior to December 2004 could not release the data to anyone who was not bound by the same license terms. Most notably, they could not include the data in publications based on the data.[82]

Third, the GPL is designed to preclude all downstream restrictions on dissemination, an approach that is possible in the area of software, where intellectual property has never been a particularly strong driver of R&D. In contrast, in the biopharmaceutical area, patents—particularly downstream patents on therapeutics—are clearly important. The HapMap license seeks to avoid imperiling downstream patents that might matter for future product development through the use of complex and ambiguous license provisions. These provisions appear to prohibit product patents on

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INTELLECTUAL PROPERTY RIGHTS IN FRONTIER INDUSTRIES: SOFTWARE AND BIOTECH (Robert Hahn ed., 2005).

81. The license states in relevant part: "You acknowledge that the Genotype Database and the data contained in it, to which access is provided under the terms of this License, are protected by law including, but not limited to, copyright laws of the United States . . . ", HapMap License, *supra* note 78, ¶ 5.

82. International HapMap Project, Data Access Policy, http://www.hapmap.org/cgi-perl/registration, ¶ G [hereinafter HapMap Data Policy] ("[While] you are free to publish the results of those analyses [of genotypic information], you may not include in such publications the details of the individual genotypes that the Project has not yet released.").

SNPs or haplotypes[83] but may allow for claims to certain uses of SNPs and haplotypes.[84]

Finally, the enforceability of open source licenses remains a somewhat open question. Clickwrap licenses are generally considered enforceable contracts, so long as the licensee has had the opportunity to view and assent to the terms.[85] However, if a public funding agency were to bring a breach of contract action against a license violator, the measure of damages would be unclear. Perhaps alleged infringers of patents that were obtained or enforced in violation of the agreement could assert that the patents were invalid or unenforceable for inequitable conduct, but there is no clear authority for such an argument. It may be that such agreements are better understood as efforts to define norms of forbearance from enforcement of intellectual property rights within a scientific community than as binding agreements that are themselves enforceable in a court of law.

More recent community resource projects have been less aggressive in their approach to restricting future intellectual property claims. Like the HapMap license, the GAIN Data Use Certification requires those who access the data to refrain from disclosing the data to anyone who is not bound by the same agreement.[86] It also urges registrants not to rely on GAIN-supported data to seek patents on markers that might be useful in diagnosis or identification of drug targets.[87] However, the language is entirely hortatory, calling upon approved users to "acknowledge the intent" of the GAIN IP policy, reminding them that "[i]n this spirit, it is expected" that data and conclusions will remain freely available, and stating that GAIN "encourages" compliance with various NIH policies that favor shar-

83. HapMap License, *supra* note 78, ¶ 2(b)(i). The policy explaining the license is more ambiguous on the question of product patents. It suggests that patents, presumably both product and process patents, on haplotypes with identified utility are acceptable so long as they do not block access to the underlying HapMap Data. *See* HapMap Data Policy, *supra* note 82, ¶ E ("This licensing approach is not intended to block the ability of users to file for intellectual property protection on specific haplotypes for which they have identified associated phenotypes, such as disease susceptibility, drug responsiveness, or other biological utility, as long as public access to, and use of, the data produced by the HapMap Project is preserved.").

84. HapMap License, *supra* note 78, ¶ 2(b)(ii) ("[Y]ou shall not file any patent applications that contain claims to particular uses of any SNP, genotype or haplotype data obtained from the Genotype Database or any SNP, haplotype or haplotype block based on data obtained from, the Genotype Database, unless such claims do not restrict, or are licensed on such terms that they do not restrict, the ability of others to use at no cost the Genotype Database or the data that it contains for other purposes.").

85. *See, e.g.*, Davidson & Assocs. v. Jung, 422 F.3d 630 (8th Cir. 2005).

86. GAIN Terms of Access, *supra* note 65, ¶ 4.

87. *Id.* ¶ 5.

ing.[88] Further, the document explicitly "recognizes the importance of the later development of IP on downstream discoveries, especially in therapeutics."[89]

The less rigid language used in the GAIN Data Use Certification makes good sense given the difficulty of determining ex ante just which patents will prove necessary to preserve economic incentives for product development in the biopharmaceutical area.[90] A small diminution in the incentives of public sector database contributors to contribute their data is a price worth paying for a safeguard against destruction of future incentives for product development.

In sum, experience with restrictions on access to genomics databases suggests that contract-based restrictions on access can provide incentives for data producers to contribute their data. Indeed, data producers may strongly prefer such restrictions. Contractual restrictions, however, are very difficult to enforce without sacrificing dissemination. Contractual restrictions on future intellectual property rights may be particularly ill-advised in an area as sensitive to patents as biomedical science.

C. What Gets Deposited and When

A third set of questions concerns what data get deposited and when. One benchmark is the standard set in the National Research Council report *Sharing Publication-Related Data and Materials*. This report calls for disclosure of "whatever is necessary to support the major claims of the paper and would enable one skilled in the art to verify or replicate the claims."[91] Tying disclosure obligations to publication has implications for both the scope and timing of disclosure obligations.

With respect to the scope of disclosure, the focus on verification and replication of publication claims allows for evolution in standards of disclosure over time within a given scientific community. In the case of the Protein Data Bank, for example, requirements for what gets deposited have evolved. Initially, crystallographers only deposited atomic coordinates. However, scientists subsequently determined that atomic coordinates did not necessarily provide all the information necessary for verification and improvement. Today there is general agreement that structural

88. *Id.*

89. *Id.*

90. Alternatively, it may reflect a recognition that simple release of GAIN-supported data is all that is necessary to invalidate marker patents.

91. SHARING DATA & MATERIALS, *supra* note 6, at 5.

factors—the raw information from which researchers derive coordinates—should also be deposited.[92]

The issue of when data should be deposited is a critical one. As already noted, for community resource projects in genomics, the public sponsors have generally required immediate, *pre-publication* deposit.[93] CIRM should recognize, though, that pre-publication release of data is highly unusual in science. The data release policies for community resource projects in genomics offer a precedent for centralized data production projects that CIRM might fund. However, it is unlikely that scientists could be persuaded to agree to pre-publication release beyond that context. As discussed earlier, the current structure of investigator-driven academic science virtually requires some level of secrecy prior to publication. In this context, pre-publication data release might even be undesirable because it would interfere with the incentives provided by the reputation benefits attached to publication.

On the other hand, a significant drawback to the current system of tying data release to publication is that negative data often remain undisclosed. CIRM might be able to address this bias in a data release policy by requiring disclosure not only of the data that leads to the publication but also of any negative data that emerge along the way. Indeed, because negative data can prove highly useful for future researchers, CIRM would perform a valuable service by establishing data archives that require deposits of both positive and negative data.

If disclosure obligations are not tied to publication, it becomes necessary to establish another marker to signal when data are ripe for release. In the case of the HGP, the community originally determined that sequence assemblies of 1-2 kilobases or greater should be released. However, when the community switched in part to a different sequencing methodology that did not assemble completed sequences until much later in the project, it determined that tying data release to assembly was no longer appropriate. In 2000, NIH extended its release policy to include submission of raw sequence traces.[94]

Finally, it bears emphasis that the distinction between pre-publication data deposit and data deposit upon publication rests on a model that currently prevails in the life sciences in which peer review precedes print

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92. Interview with Helen Berman, *supra* note 72.

93. National Human Genome Research Institute, Reaffirmation and Extension of NHGRI Rapid Data Release Policies: Large-Scale Sequencing and Other Community Resource Projects—February 2003, http://www.genome.gov/10506537.

94. *See id.*

publication. This distinction may become less important in the future if the life sciences community adopts a model similar to that used in the physics community, as well as in other scholarly communities, where Web-based publication precedes peer review.

In the near term, publication is likely to provide a useful benchmark for both the timing and scope of data disclosure for most CIRM-funded research. This approach is less likely to disrupt traditional scientific rewards and incentives than a system of pre-publication disclosure, making it easier to persuade scientists to comply. It has the further advantage of allowing CIRM to rely on the judgments of journal editors and peer reviewers in determining when research results are ripe for disclosure.

D. Database Architecture, Curation, and Maintenance

A last set of issues relates to database architecture, curation, and maintenance. Such issues tend to be neglected, but they are critical to the long-term survival and usefulness of databases.

A centralized, Web-based data archive is the most obvious platform for data sharing. In biomedical research, some of the most prominent databases—GenBank for DNA sequence data and the PDB for 3-D structure data—are centralized repositories. A major advantage of a centralized database is that data are prominently available in a uniform, readily searchable format. Disadvantages include cost and the need for agreement on data standards. Even with these disadvantages, a centralized database is probably most appropriate for data that are most useful when aggregated, such as data on gene expression or on the characteristics of available stem cell lines.

Another format that might prove useful for certain projects is a federated approach, in which data are maintained and controlled at the level of the individual lab but can be integrated across databases. Federated systems might be useful even in situations where the core data reside on a central computer or server. For example, the distributed annotation system (DAS) that can be used on genomic data deposited at EMBL, the European counterpart to Genbank, allows those who want to annotate genomic data to do so on their own servers. Other DAS users can then designate which server annotations to layer over the core data.[95]

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95. Telephone Interview with Lincoln Stein, Researcher, Cold Spring Harbor Laboratory, in Cold Spring Harbor, N.Y. (May 13, 2005); *see also* Lincoln D. Stein, Sean Eddy & Robin Dowell, Distributed Sequence Annotation System, http://biodas.org/documents/rationale.html (last visited Aug. 26, 2006).

The format that is probably least useful, but may nonetheless be sufficient for certain investigator-initiated projects, is posting on a local lab server. This format maximizes investigator control over the data but is relatively inconvenient for access by other users.

For all three types of databases—centralized, federated, and local—funding for ongoing curation and maintenance is critical. Indeed, one of the central problems facing life sciences databases today is that funds for curation and maintenance are often not available. A recent survey of eighty-nine life science databases determined that fifty-one are struggling financially: they have either been shut down for lack of funding or are being updated sporadically.[96] As it considers what types of research to fund, CIRM should be aware of the importance of providing funding for the ongoing curation and maintenance of databases that serve as important resources for the stem cell community.

V. CONCLUSION

Proposition 71 calls upon CIRM to balance a number of competing interests, including not only scientific progress but also commercialization of research results and financial returns to the State of California. In the context of patenting, licensing, and tangible research materials, CIRM has enunciated a detailed plan for balancing these competing interests. With respect to the important issue of data sharing, however, the balance that CIRM aims to strike is less clear. Data sharing represents a significant opportunity for a show of leadership. The federal example binds CIRM less directly in the area of data sharing than it does in the area of patents and licensing. At the same time, because data sharing has been a prominent and recurrent source of tension in the global biomedical research community, CIRM has a rich history outside the state of California upon which to draw. Prior experience with data sharing in federally-funded research and multinational research efforts, such as the HGP and the HapMap Project, offers both instructive examples and cautionary tales. Achieving CIRM's multiple goals will require considerable creativity. However, if the CIRM data sharing experiment works successfully, aspects of its policy may serve as a model for other states or even for the federal government.

96. Zeeya Merali & Jim Giles, *Databases in Peril*, 435 NATURE 1010 (2005).