# Opening Stem Cell Research and Development: A Policy Proposal for the Management of Data, Intellectual Property, and Ethics

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## INTRODUCTION

Intellectual property scholars and the biomedical community have noted a decline in the tradition of openness and sharing in the biomedical sciences over the past thirty years.[1] This decline appears to be a function of multiple factors. First, and best known, are changes in intellectual property (IP) law, specifically the Federal Circuit's re-interpretation of patent law to expand the scope of patentable claims;[2] the passage of the Bayh-Dole Act of 1980, allowing universities to patent inventions made in the course of federally-funded research;[3] and the creation of new legal rights and mechanisms for the privatization and commercialization of scientific data.[4] Second, and perhaps as a direct consequence, universities and their life science researchers have significantly increased interaction with the private sector, whether through accepting sponsored research, licensing IP, or spinning off companies.[5] These activities have dramatically increased the exchange of discoveries, capital, and labor across the industrial-academic interface, and they have added more private money to the

1. *See*, *e.g.*, NAT'L RESEARCH COUNCIL, SHARING PUBLICATION-RELATED DATA AND MATERIALS: RESPONSIBILITIES OF AUTHORSHIP IN THE LIFE SCIENCES 1 (2003) [hereinafter SHARING DATA & MATERIALS], *available at* http://newton.nap.edu/catalog/10613.html.

2. *See* Rebecca S. Eisenberg, *Biotech Patents: Looking Backward While Moving Forward*, 24 NATURE BIOTECH. 317, 318 (2006) (noting how "[o]ver the past quarter century, following the Supreme Court's broad directive in *Diamond v. Chakrabarty*, the Federal Circuit has gradually eviscerated what once appeared to be time-honored categorical exclusions from the patent system for such subject matter as 'business methods' and 'mathematical algorithms' in favor of a 'big tent' approach to patent eligibility").

3. Bayh-Dole Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. §§ 200-212 (2000) (specifically empowering federal research grantees and contractors to seek patent protection on subject inventions made using government funds and to license those inventions with the goal of promoting their utilization, commercialization, and public availability); *see generally* Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 68 LAW & CONTEMP. PROBS. 289 (2003).

4. *See, e.g.*, 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, 319-21 (2003) (arguing at 320 that these "new laws pose the danger of disrupting the normative customs at the foundation of public science, especially the traditional and cooperative sharing ethos, by producing both the pressures and the means to enclose the scientific commons and to greatly reduce the scope of data in the public domain").

5. *See, e.g.*, DAVID C. MOWERY ET AL., IVORY TOWER AND INDUSTRIAL INNOVATION: UNIVERSITY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOLE ACT IN THE UNITED STATES 85-98 (2004); P. Mirowski & E. Sent, *The Commercialization of Science and the Response of STS*, *in* THE HANDBOOK OF SCIENCE AND TECHNOLOGY STUDIES 635-89 (Michael Lynch, Olga Amsterdamska & Ed Hackett eds., 2008).

mix of research support for university life sciences.[6] But the increase in university participation in economic life has also introduced tensions between the emerging commodification of knowledge[7] and longstanding scientific norms regarding open access and dissemination of research results, data, research tools, and other scientific advances.[8]

In traditional sociological accounts, the advance of science is predicated upon mechanisms of open information, peer review, and materials exchange, which are socially reinforced by norms that undergird open access.[9] Knowledge that is withheld from community scrutiny cannot be validated or agreed upon by the community. On this basis, it is presumed that greater degrees of openness promote not only efficiency in the advance of science, but also trust in the scientific endeavor by society.[10] Moreover, in standard economic accounts, the mechanisms of open exchange also have important efficiency, equity, and ethical implications in terms of the direct contributions that science makes to social welfare, particularly in the development of new technologies, products, and services. In theory, actors across industrial and state sectors can put scientific knowledge to efficient and equitable use when it is freely accessible as a public good, assuming full information and virtually costless transactions.[11] When the

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6. *See* Henry Etzkowitz, *Bridging the Gap: The Evolution of Industry–University Links in the United States*, *in* INDUSTRIALIZING KNOWLEDGE: UNIVERSITY–INDUSTRY LINKAGES IN JAPAN AND THE UNITED STATES 203-233 (Lewis Branscomb & Fumio Kodama eds., 1999).

7. *See* Reichman & Uhlir, *supra* note 4, at 319 (noting the "progressive privatization and commercialization of scientific data" and "the attendant pressures to hoard and trade them like other private commodities").

8. *See generally* PAUL A. DAVID, THE DIGITAL TECHNOLOGY BOOMERANG: NEW INTELLECTUAL PROPERTY RIGHTS THREATEN GLOBAL 'OPEN SCIENCE,' *available at* http://129.3.20.41/eps/dev/papers/0502/0502012.pdf; *see also* Sara Boettiger & Alan B. Bennett, *Bayh-Dole: If We Knew Then What We Know Now*, 24 NATURE BIOTECH. 320-23 (2006); Rebecca S. Eisenberg, *Bargaining Over the Transfer of Proprietary Research Tools: Is this Market Failing or Emerging?*, *in* EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY 223 (Rochelle Dreyfuss et al. eds., 2001).

9. *See* ROBERT K. MERTON, *The Normative Structure of Science*, *in* THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS 267 (1973); Paul A. David, *Common Agency Contracting and the Emergence of 'Open Science' Institutions*, 88 AM. ECON. REV. 15 (1998); Michael Polanyi, *The Republic of Science: Its Political and Economic Theory*, 1 MINERVA 54 (1962).

10. *See* NAT'L RESEARCH COUNCIL, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 50 (2006) [hereinafter REAPING THE BENEFITS] ("The tradition of sharing materials and results with colleagues speeds scientific progress and symbolizes to the nonscientific world that the goals of science are to expand knowledge and to improve the human condition. One reason for the remarkable success of science is the communal nature of scientific activity.").

11. *See, e.g.*, Ian M. Cockburn & Rebecca M. Henderson, *Publicly Funded Science and the*

results of scientific investigation are withheld in secrecy or maintained as private property, practical applications may be delayed, directed only towards lucrative markets, or priced in ways that are socially inefficient or unjust.[12]

However, it is not clear that efficiency and equity in the applications of science are always better served by greater openness. In terms of efficiency, openness can introduce a "free rider" problem, undermining incentives to invest in developing scientific discoveries that can contribute to social welfare. Indeed, this is arguably why our IP laws grant private exclusive rights for inventors to develop inventions into useful applications.[13] Furthermore, in terms of equity, as Chander and Sunder argue in *The Romance of the Public Domain*, freely accessible materials and information are not necessarily accessed equally by all: Those with greater ability to exploit an open access information resource, such as those with greater knowledge, social stature, or control over complementary assets, will tend to benefit disproportionately.[14] They suggest, however, that "[t]here are strategies available . . . to help . . . restructure the distribution of benefits . . . especially the possibility of creating 'limited commons property' regimes for . . . information."[15] The solution for greater efficiency as well as equity in the exploitation of science, it seems, lies in finding a proper balance or hybridization between openness and enclosure, public good and private asset. Striking the most efficient and equitable balance between public and proprietary science is quite difficult in practice, in no small measure because the very categories of basic and applied science are breaking down in practice.[16] Nevertheless, many legal commentators warn that with Bayh-Dole, the pendulum may have swung too far towards a private competitive model of university science.[17]

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*Productivity of the Pharmaceutical Industry*, *in* 1 INNOVATION POLICY AND THE ECONOMY 1 (Adam B. Jaffe, Josh Lerner & Scott Stern eds., MIT Press 2001); Richard R. Nelson, *The Role of Knowledge in R&D Efficiency*, 97 Q. J. ECON. 453 (1982).

12. *See* Patrick L. Taylor, *Research Sharing, Ethics, and Public Benefit*, 25 NATURE BIOTECH. 398 (2007).

13. Economist Richard Nelson observes more generally that "[t]echnology itself is a hybrid term with two roots—one 'technique,' referring to a way of doing something, and the other 'logy' referring to theory. . . . [e]ven in rivalrous industries, institutional mechanisms have developed that tend to keep the 'logy' public, even though the technique is kept private. . . . This practice . . . makes considerable sense from a social point of view." *See* Nelson, *supra* note 11, at 467-68.

14. Anupam Chander & Madhavi Sunder, *The Romance of the Public Domain*, 92 CAL. L. REV. 1331 (2004).

15. *Id.* at 1337.

16. Rebecca S. Eisenberg & Richard R. Nelson, *Public vs. Proprietary Science: A Fruitful Tension?*, 131 DAEDALUS 89, 90-91 (2002).

17. See, for example, the various papers in the special issue of *Law and Contemporary Problems* devoted to the public domain, 66 LAW & CONTEMP. PROBS. (SPECIAL ISSUE) (2003),

In response to dominant patterns of propertization, competition, and decentralization in the modern life sciences, new forms of "open and collaborative" research have, as if by necessity, recently emerged. These have centered in fields like open source bioinformatics software, genomic and other databases, and to a lesser extent, wet-lab biology.[18] These novel forms of collaboration, pooling, and sharing have arisen from both private and public sectors, or at the interface between the two. Some of these collaborative initiatives, such as the SNP Consortium developed by the pharmaceutical industry,[19] have emerged from the efforts of private entities worried about the cumulative inefficiencies of too much upstream patenting.[20] Government funders and international pressures promoting greater data sharing among scientists have driven others, such as the Human Genome Project and International Haplotype Map Project.[21] Concerned scientific innovators themselves have developed other projects adopting more open behaviors, such as the BioBricks Foundation at MIT, which seeks to coordinate a synthetic biology "commons"—a resource owned and used by a community for common benefit.[22] These important efforts emanating from the public and private sectors, however, remain the exception rather than the rule, and broad areas of biomedical research have yet to experiment with such novel collaborative architectures seeking the blend of openness and exclusion with the greatest scientific and public utility.

Presently, the exploding field of stem cell research is characterized by a lack of any deeply collaborative architecture, yet it is a field that arguably requires

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*available at* http://www.law.duke.edu/journals/journaltoc?journal=lcp&toc=lcptoc66winterspring2003.htm.

18. For a good overview of some of these efforts, see Arti K. Rai, *"Open and Collaborative" Research: A New Model for Biomedicine*, *in* INTELLECTUAL PROPERTY RIGHTS IN FRONTIER INDUSTRIES: SOFTWARE AND BIOTECHNOLOGY 131, 140-45 (Robert W. Hahn ed., 2005).

19. *See, e.g.*, Robert Langreth, Michael Waldholz & Stephen D. Moore, *DNA Dreams: Big Drug Firms Discuss Linking Up To Pursue Disease-Causing Genes*, WALL ST. J., Mar. 4, 1999, at A1. The SNP Consortium systematically identifies localized variations in the genetic code, known as single nucleotide polymorphisms or SNPs ("snips"). This consortium of twelve pharmaceutical and technology companies, the Wellcome Trust, and leading academic centers of the Human Genome Project made data for over one million SNPs available.

20. *See* Robert P. Merges, *A New Dynamism in the Public Domain*, 71 U. CHI. L. REV. 183 (2004) (documenting a trend whereby private biotechnology firms are increasingly engaging in "property-preempting investment," injecting scientific data and discoveries into the public databases to forestall blocking property claims further downstream the innovation process).

21. *See* Rai, *supra* note 18, at 141-43. See *infra* Section II.C a discussion of these kinds of initiatives.

22. Arti Rai & James Boyle, *Synthetic Biology: Caught Between Property Rights, the Public Domain, and the Commons*, 5 PLOS BIOLOGY 0389 (2007), http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pbio.0050058.

more coordination than others due to the particular trajectory of its development. There is broad agreement, although not consensus, among life scientists that stem cells, and in particular human embryonic stem cells (hESCs), hold unique promise for advancing biomedicine, especially in the areas of toxicology, pharmacology, functional regeneration, and developmental biology.[23] These cells maintain a state that is almost identical to early embryonic cells and therefore may be directed to mature into any cell type found in humans. For developmental biology, hESCs represent an integral tool for studying human development and differentiation in the Petri dish, as limited sources of human embryonic tissue are available for research. For regenerative medicine, hESCs provide a rich source for cell therapeutic efforts at the site of disease or injury—in essence a flexible building block to make replacement tissues. In addition, hESCs, or the mature cells derived from them, may be cultured with various chemical compounds to discover new drugs or assay the toxicity of chemicals in a human cell system.

However, as in other areas of biomedical research, serious technical and proprietary barriers have arisen.[24] Beyond problems in patents and data sharing, ethical and regulatory complications cloud the prospects for stem cell research and development (R&D) to a greater extent than other fields in the life sciences.[25] Indeed, the proprietary, regulatory, and technical characteristics of the stem cell field present a set of limiting conditions or "bottlenecks" that stand to constrain and divert R&D efforts and investments.[26] Furthermore, IP scholars and policymakers promoting open forms of life science research and collaboration have tended to ignore the ways in which these areas of complexity and constraint can be mutually compounding.[27]

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23. For a detailed overview of the potential of stem cell research, see DEP'T OF HEALTH & HUMAN SERVS., REGENERATIVE MEDICINE (2006) [hereinafter REGENERATIVE MEDICINE], http://stemcells.nih.gov/info/scireport/2006report.htm; see also George Q. Daley & David T. Scadden, *Prospects for Stem Cell-Based Therapy*, 132 CELL 544 (2008).

24. *See infra* Section I.A-B.

25. In the United States, federal 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. OFFICE FOR HUMAN RESEARCH PROTS., DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES 3 (2002) [hereinafter GUIDANCE FOR INVESTIGATORS], *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf (stating that "[r]esearch on existing [hESC] 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").

26. This thesis is developed *infra* Part I.

27. The paucity of literature dealing with the interaction of the technical, proprietary, and ethical domains is a key premise of this article, although there are a few notable exceptions. *See, e.g.*, Kenneth S. Taymor, Christopher Thomas Scott & Henry T. Greely, *The Paths Around Stem*

Drawing on an interdisciplinary analysis spanning law and bioethics, economics, and stem cell biology,[28] we argue that opening stem cell R&D and maximizing public benefits from public investment will require striking a better balance between the public and private domains and developing the integrative management of data sharing, IP rights, and ethics-driven regulation. In particular, a coordinated effort addressing these bottlenecks could help facilitate an efficient, equitable, and ethically accountable advance of stem cell research. In Part I of this Article, we discuss in more detail the problems and complexities constraining the advance of stem cell research within three traditional policy domains: the technical, the proprietary, and the ethical. We also review the efforts that have been organized to address those problems, and we argue why those efforts must go further and deeper. In Part II, we propose a series of design principles for collective action in stem cells based on the previous discussion and policy models observed in other fields. These design principles address the conceptual and pragmatic aspects of institution-building in a complex environment. In Part III, we outline a proposed mechanism to coordinate the conduct and governance of human stem cell R&D: a collaboration among funders, researchers, science journals, and academic institutions to 1) build a data architecture for stem cell work that spans a rich array of technical, proprietary, and ethical information, and 2) develop and execute common solutions in technology licensing to free up R&D. In Part IV, we discuss incentives from the perspectives of major institutional actors to participate in the proposed collaboration, as well as the unique aspect of our proposal to integrate solutions spanning the technical, proprietary, and ethical domains.

## I. BOTTLENECKS IN THE TECHNICAL, PROPRIETARY, AND ETHICAL DOMAINS

The expansion of public funding for stem cell research at both the federal and state levels has been grounded in its potential for advancing public health

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*Cell Intellectual Property*, 24 NATURE BIOTECH. 411, 411-13 (2006).

28. Each of the authors has previously raised critiques and advanced suggestions for the conduct of stem cell R&D—including issues of ethical governance, IP and technology licensing, and technical data sharing. KARL BERGMAN & GREGORY GRAFF, CTR. FOR INTELLECTUAL PROP. STUDIES & PUB. INTELLECTUAL PROP. RESEARCH FOR AGRIC., COLLABORATIVE IP MANAGEMENT FOR STEM CELL RESEARCH AND DEVELOPMENT (2007); Karl Bergman & Gregory D. Graff, *The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development*, 25 NATURE BIOTECH. 419 (2007); David E. Winickoff, *Bioethics and Stem Cell Banking in California*, 21 BERKELEY TECH. L.J. 1067 (2006); David E. Winickoff, *Governing Stem Cell Research in California and the USA: Towards a Social Infrastructure*, 24 TRENDS IN BIOTECH. 390 (2006); Krishanu Saha, Navigating to the Right Stem Cell Line (2006) (unpublished manuscript, on file with author).

and human welfare.[29] However, the technical, proprietary, and regulatory environment (consisting of closed information, congested IP entitlements, and regulatory uncertainty) presents formidable challenges for the conduct of research and the development of applications based on that research. Many are claiming the essential technical building blocks of stem cell research—including the cell lines themselves—as private assets, following trends of extensive patenting seen elsewhere in the life sciences.[30] Further, the lack of disclosure and standardization of technical data involved in stem cell research acts as a limiting factor on the advance of this novel line of research.[31] Problems of congested IP and data-withholding are certainly not unique to stem cell research, but we contend that these issues are aggravated in the stem cell research context.[32]

Further compounding these special challenges, there remains broad political and ethical disagreement over the conditions under which this line of research should advance, if at all. Stem cell research challenges common notions of the natural and the sacred, introducing new ways to use and manipulate nascent human life, gametes, and trans-species hybrids.[33] These aspects of stem cell science have produced a deeply contested ethical terrain and a lack of regulatory harmonization. As we explore in this Section, conditions within each of these three domains—the technical, proprietary, and ethical—present serious problems for the pace of innovation, the distribution of resulting health benefits, and the public accountability of research. Furthermore, these problems may be mutually reinforcing.

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29. Individual states have collectively allocated $3.33 billion for stem cell research, with three billion dollars of that from California alone. JAMES W. FOSSETT, ROCKEFELLER INST., FEDERALISM BY NECESSITY: STATE AND PRIVATE SUPPORT FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2007), *available at* http://www.rockinst.org/pdf/health_care/2007-08-09federalism_by_necessity_state_and_private_support_for_human_embryonic_stem_cell_research.pdf.

30. *See* Jeanne F. Loring & Cathryn Campbell, *Intellectual Property and Human Embryonic Stem Cell Research*, 311 SCIENCE 1716, 1716-17 (2006); Sander Rabin, *The Gatekeepers of hES Cell Products*, 23 NATURE BIOTECH. 817, 817-19 (2005); *see also* Bergman & Graff, *The Global Stem Cell Patent Landscape*, *supra* note 28.

31. Stem cell scientists as a whole have articulated the need to determine the characteristics that define hES cells by sharing data across many cell lines. *See* Emma L. Stephenson, Peter R. Braude & Chris Mason, *International Community Consensus Standard for Reporting Derivation of Human Embryonic Stem Cell Lines*, 2 REGENERATIVE MED. 349 (2007); Editorial, *Registries and Banks*, 10 NATURE CELL BIOLOGY 111 (2008).

32. *See infra* Section I.A-B.

33. David E. Winickoff, *Bioethics and Stem Cell Banking in California*, *supra* note 28, at 1070.

### *A. Technical Domain: Scientific Data and Materials Sharing*

Potential problems of data and materials sharing within stem cell research occur in the context of larger concerns about the erosion of the public domain in scientific data and materials. The deposition and sharing of materials—including reagents, tissue, and cell lines—and data associated with published research findings play an important role in the life-sciences community.[34] The sharing of data and materials has long been necessary for scientific experimentation and confirmation of results. Computational analysis of data now drives many fields of science, such as bioinformatics and the empirical environmental sciences.[35] However, new laws and practices threaten to produce both "the pressures and the means to enclose the scientific commons and to greatly reduce the scope of data in the public domain."[36] Furthermore, traditional norms around sharing research materials are running headlong into the desire of institutions to protect IP in materials and research tools, giving rise to the proliferation of material transfer agreements even among nonprofit research institutions.[37]

The larger science policy community has made restrictions on data, information, and materials derived from scientific research a central theme for over twenty years.[38] Recently, the National Research Council has taken up the topic in a series of influential reports.[39] Under traditional assumptions, scientific findings and data enter the public domain through publication and become part of the commonly accessible scientific knowledge base. According to the National Research Council, practices around data release at the time of publication are far from adequate from the perspective of the public good.[40] Recently enacted and announced policy changes at some scientific journals, such as *Science* and *Nature*, have attempted to promote better practices.[41] However, these journal

34. SHARING DATA & MATERIALS, *supra* note 1, at 17.

35. NAT'L. RESEARCH COUNCIL, BITS OF POWER: ISSUES IN GLOBAL ACCESS TO SCIENTIFIC DATA 1-17 (1997) [hereinafter BITS OF POWER]; *see also* Reichman & Uhlir, *supra* note 4, at 318.

36. Reichman & Uhlir, *supra* note 4, at 320.

37. REAPING THE BENEFITS, *supra* note 10, at 128-31; Katherine Ku & James Henderson, *The MTA—Rip It Up and Start Again?*, 25 NATURE BIOTECH. 721 (2007).

38. REAPING THE BENEFITS, *supra* note 10, at 50.

39. *See, e.g.*, NAT'L. RESEARCH COUNCIL, A QUESTION OF BALANCE: PRIVATE RIGHTS AND THE PUBLIC INTEREST IN SCIENTIFIC AND TECHNICAL DATABASES 15 (1999) [hereinafter A QUESTION OF BALANCE]; BITS OF POWER, *supra* note 35; SHARING DATA & MATERIALS, *supra* note 1.

40. *See, e.g.*, A QUESTION OF BALANCE, *supra* note 39, at 15; SHARING DATA & MATERIALS, *supra* note 1, at 1.

41. *See* Nature, Guide to Publication Policies of the Nature Journals (July 14, 2008), http://www.nature.com/authors/gta.pdf (editorial policy for *Nature* requiring authors "to make materials, data and associated protocols available in a publicly accessible database . . . or, where one does not exist, to readers promptly on request."); Science, General Information for Authors,

policies are far from uniform across scientific publishing,[42] and it is unclear how well such policies are actually enforced.[43]

In the case of data, there may be two sources of tension regarding traditional norms and practices around sharing. The best-known source consists in what members of the legal and scientific community see as new practices of delay and secrecy resulting from the penetration of private investment into university life sciences.[44] Reichman and Uhlir document problems with the current system of publication, blaming cultural changes within science as well as new legal protections over data in copyright law for threatening the science commons.[45]

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http://www.sciencemag.org/about/authors/prep/gen_info.dtl (last visited Nov. 13, 2008) (editorial policy for *Science* requiring that "after publication, all data necessary to understand, assess, and extend the conclusions of the manuscript must be available to any reader of *Science*" subject to "discipline-specific conventions or special circumstances." And "[a]fter publication, all reasonable requests for materials must be fulfilled. A charge for time and materials involved in the transfer may be made. *Science* must be informed of any restrictions on sharing of materials [Materials Transfer Agreements or patents, for example] applying to materials used in the reported research. Any such restrictions should be indicated in the cover letter at the time of submission, and each individual author will be asked to reaffirm this on the Conditions of Acceptance forms that he or she executes at the time the final version of the manuscript is submitted. The nature of the restrictions should be noted in the paper. Unreasonable restrictions may preclude publication."); *see also 2008 Information for Authors*, 319 SCIENCE 634 (2008), *available at* http://www.sciencemag.org/cgi/issue_pdf/admin_pdf/319/5863.pdf (published, abbreviated version of publication policies for *Science*).

42. Heather A. Piwowar, Roger S. Day & Douglas B. Fridsma, *Sharing Detailed Research Data Is Associated with Increased Citation Rate*, PLOS ONE, Mar. 2007, at 1, http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0000308; Heather A. Piwowar & Wendy W. Chapman, *A Review of Journal Policies for Sharing Research Data*, NATURE PRECEDINGS, Mar. 20, 2008, http://precedings.nature.com/documents/1700/version/1/files/npre20081700-1.pdf.

43. Differences between the journal data sharing policy and actual practice have been commented on in the scientific editorial literature. *See, e.g.*, Editorial, *Got Data?*, 10 NATURE NEUROSCIENCE 931 (2007).

44. *See* REAPING THE BENEFITS, *supra* note 10, at 50-51 (noting how the increase in patenting and relevance of science to the commercial world have put pressures on norms of openness and access in science); *see also* Robert P. Merges, *Property Rights Theory and the Commons: The Case of Scientific Research*, *in* SCIENTIFIC INNOVATION, PHILOSOPHY, AND PUBLIC POLICY 145, 145 (Ellen Frankel Paul, Fred D. Miller, Jr. & Jeffrey Paul eds., 1996).

45. Reichman & Uhlir, *supra* note 4, at 321 ("First, as a growing commercial or cultural phenomenon, the data may have been conditionally deposited or imperfectly revealed at the time of publication. Second, recent changes to copyright law make it possible to control online access to the supporting data, even though the data as such are technically ineligible for copyright protection. Third, European states have adopted a new *sui generis* database right, which allows scientists to directly control access to and reuse of aggregations of facts, whether these have been disclosed as part of their research publications or made available as a separate database . . . . Finally, . . . a

The second source stems from the enhanced capacity to produce, manage, and disseminate data through new information technologies.[46] Advances in database technology and networking power create opportunities both for accelerating knowledge creation and for engaging in new forms of rent-seeking.[47] As technological constraints on sharing are removed and new sharing opportunities enabled, the prevailing norms must be renegotiated.[48]

Both sets of conditions have given rise to renewed debates about the manner and timing of data release in the sciences,[49] and evidence of a problem is mounting. Recent studies of the genetics research community suggest that "data withholding" is common.[50] Patrick Taylor, a legal scholar and member of the General Counsel's Office at Harvard, recently concluded in a literature review that data sharing needs to be enhanced across the life sciences.[51] Whether framed as a problem or opportunity, one thing is clear: the potential power to move science forward through deeper data sharing is vast.

Like data, the exchange of biological research materials is also subject to competing norms of propertization and openness, within both the scientific and university licensing communities. Although patenting by nonprofit research institutions has been embraced and promoted through public policies such as the Bayh-Dole Act, concerns are mounting that proprietary claims in research materials and "tools" are impeding research, even in non-commercial settings.

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combination of digital rights management technologies and standard-form contracts may enable publishers to impose limits on the redissemination and use of supporting data even after formal publication of a scientific article.") (footnotes omitted).

46. *See, e.g.*, Rebecca S. Eisenberg, *Patents and Data Sharing in Public Science*, 15 INDUS. & CORP. CHANGE 1013 (2006).

47. *See generally* YOCHAI BENKLER, THE WEALTH OF NETWORKS (2006).

48. This process through which new technologies and new normative and social structures co-emerge illustrates what science and technologies studies scholars have termed "co-production." *See* STATES OF KNOWLEDGE: THE CO-PRODUCTION OF SCIENCE AND SOCIAL ORDER (Sheila Jasanoff ed., 2004).

49. *See, e.g.*, Rebecca S. Eisenberg & Arti K. Rai, *Harnessing and Sharing the Benefits of State-Sponsored Research: Intellectual Property Rights and Data Sharing in California's Stem Cell Initiative*, 21 BERKELEY TECH. L.J. 1187, 1189-91 (2006) ("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.").

50. David Blumenthal et al., *Data Withholding in Genetics and the Other Life Sciences: Prevalences and Predictors*, 81 ACAD. MED. 137, 137-45 (2006); Taylor, *supra* note 12, at 398-401; C. Vogeli et al., *Data Withholding and the Next Generation of Scientists: Results of a National Survey*, 81 ACAD. MED. 128, 128-36 (2006).

51. Taylor, *supra* note 12, at 400.

Despite a 1999 NIH Guidance promoting the sharing of research tools and materials,[52] an in-depth survey conducted under the auspices of the National Research Council on IP rights in genomics concluded that access to materials and the proliferation of Material Transfer Agreements (MTAs) are serious problems.[53] Indeed, MTAs are nearly omnipresent in the practice of the biological sciences.[54]

An MTA sets contractual rights and obligations when one party transfers cell lines or other materials to another, usually focusing on terms for the physical handling, use, and further distribution of the material. In some cases, MTAs are essential for communicating important ethical terms concerning use of the transferred materials. However, obtaining materials across laboratories can often be delayed or encumbered by these contracts as well as by purposeful withholding prompted or enabled by the need for signing them.[55] MTAs can even be written to include onerous provisions concerning downstream patent rights that might be derived from work on these materials; if these terms are not accepted, the transfer of biological materials may not take place.[56]

Within the field of stem cell research, the sharing of materials has been a much more obvious problem than the sharing of data. This has largely been due to a combination of the Bush Administration's restrictive funding policies[57] and the commanding patent position of the Wisconsin Alumni Research Foundation

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52. Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources, 64 Fed. Reg. 72,090 (Dec. 23, 1999) [hereinafter NIH Principles and Guidelines].

53. The largest survey to date on materials transfer practices among researchers was commissioned by the National Academies of Sciences. *See* JOHN P. WALSH, CHARLENE CHO & WESLEY M. COHEN, NAT'L ACAD. OF SCI., COMM. ON INTELLECTUAL PROP. RIGHTS IN GENOMIC AND PROTEIN-RELATED INVENTIONS, PATENTS, MATERIAL TRANSFERS AND ACCESS TO RESEARCH INPUTS IN BIOMEDICAL RESEARCH 2-3 (2005) (reporting "substantial evidence" that "difficulties in accessing proprietary research materials, whether patented or unpatented" are more important than patents in hindering research); REAPING THE BENEFITS, *supra* note 10, at 3.

54. Ku & Henderson, *supra* note 37, at 721.

55. Zhen Lei, Rakhia Juneja & Brian Wright, Implications of Intellectual Property Protection for Academic Agricultural Biologists (Jan. 2008) (unpublished manuscript, on file with authors).

56. *See* Sean O'Connor, *The Use of MTAs To Control Commercialization of Stem Cell Diagnostics and Therapeutics*, 21 BERKELEY TECH. L.J. 1017, 1017-18 (2006). It is difficult to dispute that requirements for signing MTAs constitute, in the very least, a transaction cost not encountered when freely exchanging research materials. It is more difficult to establish whether MTAs result in a global net decrease in the overall exchange of biological materials within the contemporary life sciences research community. For, without some of the assurances provided under these contracts, some materials might not be able to be shared at all, particularly given how the life sciences—and particularly the field of stem cells—is constantly expanding in terms of the volume, sophistication, and ethical sensitivity of the research materials necessarily employed.

57. The number of viable federally-approved hESC lines has dropped to twenty-one.

(WARF),[58] the technology transfer arm of the University of Wisconsin. Based on work in the laboratory of James Thompson that was funded by a combination of NIH and a biotechnology company, Geron, WARF received several broad foundational patents that cover both derivation techniques for hESCs as well as many of the cell lines approved for federal funding under President Bush's policy.[59] The case of using stem cell line materials has become a notorious example of the dilemmas posed by strong IP in the life sciences: While strong rights can create incentives for private funding of research, in this case by Geron and its investors, they can also lead to serious delays in follow-on innovation due to restricted access to existing materials and research tools. Long considered the standard for evaluating the behavior of any other human pluripotent lines, the WARF cell lines are among the most widely used lines in the field. WARF has used its patents and its physical control of these stem cell lines to exert a dominant position in the stem cell research community.[60] For many stem cell scientists in both the private and public sectors, WARF's restrictive licensing policies with respect to both derivation methods and the stem cell lines themselves have impeded access to research materials and the advance of research.[61]

A combination of legal and policy interventions has helped free up the use of Wisconsin's proprietary cell lines.[62] First, in October 2001, the Public Health Service completed a Memorandum of Understanding with WARF and its affiliated nonprofit stem cell provider, WiCell, which enabled any NIH-funded investigator in the country to receive WARF stem cells and a license to practice WARF's patented inventions for an access fee of no more than $5000.[63] Previously, university researchers had faced the specter of having to negotiate individual licenses from WARF for any conduct of stem cell research, whether using the WARF cell lines or not. Second, in January 2007, under the shadow of a patent reexamination that threatened to limit the scope of the patents' claims

58. The Wisconsin Alumni Research Foundation is the nonprofit technology transfer office of the University of Wisconsin-Madison. It is a significant source of research support, independent of federal grants. It currently contributes about $45 million per year, giving the university's research programs a "margin of excellence." *See* Wisconsin Alumni Research Foundation, http://www.warf.ws (last visited Nov. 13, 2008).

59. Rabin, *supra* note 30, at 817.

60. For a detailed and extremely useful history of WARF stem cell licensing practices, see O'Connor, *supra* note 56, at 1027-48.

61. Loring & Campbell, *supra* note 30; Meredith Wadman, *Licensing Fees Slow Advance of Stem Cells*, 435 NATURE 272, 272-73 (2005), *available at* http://www.nature.com/nature/journal/v435/n7040/pdf/435272a.pdf.

62. *See generally* R.S. Eisenberg & A.K. Rai, *Proprietary Considerations*, *in* 1 HANDBOOK OF STEM CELLS 793-98 (Robert Lanza et al. eds., 2004).

63. Wadman, *supra* note 61, at 272.

and increasing political pressure from the stem cell community to further improve access to stem cell lines,[64] WARF announced changes to its licensing policies that would provide greater access to its foundational cell lines.[65] The patent challenge ultimately failed. Although the United States Patent and Trademark Office (USPTO) issued a preliminary ruling rejecting some aspects of these patents that had been challenged by public interest groups,[66] the key claims were later definitively upheld.[67] Nevertheless, before the final USPTO ruling came down, WARF instituted a policy change that eliminated the previous requirement that industry sponsors of academic research receiving any rights back from the university—such as an option to negotiate a license or patent rights to subsequent inventions—needed a commercial license from WARF or risked patent litigation. The new policy also formalized permission for the transfer of non-WARF stem cell lines from lab to lab without need for a special license from WARF.[68]

Even if the licensing policies on WARF's lines are further opened, the sharing of other hESC lines is encumbered by a series of general challenges with the production, legal status, and transfer agreements associated with hESC lines. Some of this is due to new technological developments. New derivation techniques, especially the widely touted induced pluripotent stem (iPS) cell lines

64. *See, e.g.*, Constance Holden, *Prominent Researchers Join the Attack on Stem Cell Patents*, 317 SCIENCE 187 (2007). Patent challenges come in two forms. An infringing business can sue for a declaration of patent invalidity. This method can be risky and also very expensive: the challenger's continuing use of the patent may lead to damages if the challenge is unsuccessful, and the lawsuits themselves are often very costly. Alternatively, challengers can petition the USPTO directly to "reexamine" the patent. This is what occurred in the WARF case. This is usually a far less costly procedure. However, whereas an invalidation lawsuit features multiple opportunities for discovery, cross-examination of experts, and judges and juries independent of the USPTO, a reexamination features only limited opportunity to present evidence and cross-examine. For a reexamination, the USPTO is the decision-maker. *See* Aurora Plomer et al., *Challenges to Human Embryonic Stem Cell Patents*, 2 CELL STEM CELL 13, 14 (2008).

65. Wisconsin Alumni Research Found., *Wisconsin Alumni Research Foundation Changes Stem Cell Policies To Encourage Greater Academic, Industry Collaboration*, WARF NEWS, Jan. 23, 2007, http://www.warf.ws/news/news.jsp?news_id=209.

66. The groups were the Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation in New York. The core of the patent challenge is that the achievement of James Thomson, the patent holder, was obvious to many of the scientists working in the field. *See, e.g.*, Constance Holden, *U.S. Patent Office Casts Doubt on Wisconsin Stem Cell Patents*, 316 SCIENCE 182 (2007).

67. Constance Holden, *Wisconsin Stem Cell Patents Upheld*, 319 SCIENCE 1602 (2008).

68. Carl Gulbrandsen, Letter, *WARF's Licensing Policy for ES Cell Lines*, 25 NATURE BIOTECH. 387, 387 (2007). This policy also certifies that the California Institute of Regenerative Medicine can proceed with its grant-making powers without first requiring a WARF license for stem cell work.

may rapidly increase the number of pluripotent cell lines with properties similar to embryonic-stem cells.[69] The USPTO has ruled that iPS derivation techniques are outside the scope of the WARF patents.[70] This may help alleviate blockage with respect to the WARF lines, but new proprietary struggles will soon ensue over access to this new technique.[71]

Other special challenges of sharing hESC lines exist. These materials require significant expertise via current methods to maintain an undifferentiated state for distribution. They also require extensive characterization to ensure that they contain no genetic abnormalities or adventitious agents.[72] Cell banking has helped reduce this burden on individual labs for distribution, but this infrastructure has yet to relieve much of the routine work necessarily associated with cell line sharing.[73] Finally, hESCs must go through an institutional review by the recipient's institution, likely having to satisfy a complex patchwork of regulations, discussed in Section C below. Together, these challenges of maintaining the quality of hESCs, satisfying institutional review, and negotiating MTAs constitute complex barriers to sharing hESC within the stem cell research community.

In comparison, data sharing issues are less debated, but equally significant. Indeed, stem cell research may be particularly hindered by problems of data access because conducting follow-up work requires rich data sets detailing the characteristics of cell lines. Scientific researchers and institutions that want to use stem cells in their research are confronted with two major challenges: the

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69. *See* W.E. Lowry et al., *Generation of Human Induced Pluripotent Stem Cells from Dermal Fibroblasts*, 105:8 PNAS 2883, 2883-88 (2008); In-Hyun Park et al., *Reprogramming of Human Somatic Cells to Pluripotency with Defined Factors*, 451 NATURE 141 (2008); Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861 (2007); Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

70. Holden, *supra* note 67, at 1603.

71. *Id.*

72. Duncan E. Baker et al., *Adaptation to Culture of Human Embryonic Stem Cells and Oncogenesis* In Vivo, 25 NATURE BIOTECH. 207 (2007); International Stem Cell Initiative, *Characterization of Human Embryonic Stem Cell Lines by the International Stem Cell Initiative*, 25 NATURE BIOTECH. 803 (2007).

73. Lyn E. Healy, Tenneille E. Ludwig & Andre Choo, *International Banking: Checks, Deposits, and Withdrawals*, 2 CELL STEM CELL 305 (2008); P. Pearl O'Rourke, Melinda Abelman & Kate Gallin Heffernan, *Centralized Banks for Human Embryonic Stem Cells: A Worthwhile Challenge*, 2 CELL STEM CELL 307 (2008).

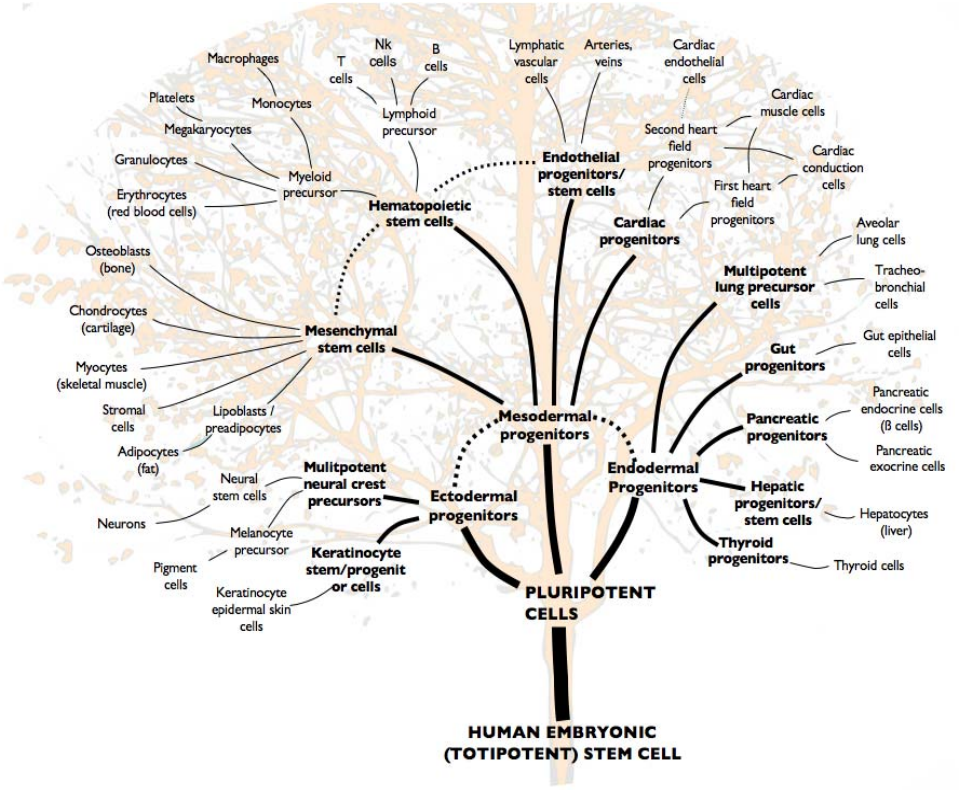


**FIGURE 1. The Tree of Cellular Differentiation**
Major thoroughfares in obtaining differentiated cell types from human embryonic stem cells are denoted by thicker lines. Note that not all lineages are shown.

navigation of stem cell behavior through a vast number of potential cell fates (Figure 1) and the integration of many disparate technical tools.[74] Stem cells, whether adult or embryonic, have the remarkable ability to differentiate into a large number of cell types (see Figure 1),[75] but to conduct research, a scientist

74. Material from this Section is based on conversations with stem cell scientists by the authors, as well as talks presented at the conference, "Institutional Landscape in Stem Cell Research & Development: Problems & Solutions." For an overview of this conference in the published literature, see Monya Baker, *Thickets and Gaps Blocking Stem Cell Science*, NATURE REPORTS STEM CELLS (Mar. 6, 2008), http://www.nature.com/stemcells/2008/0803/080306/full/stemcells.2008.42.html (last visited Nov. 13, 2008) (describing conference hosted by U.C. Berkeley Stem Cell Center that featured stem cell scientists, industry leaders, and policy actors from across the United States on Feb. 6, 2008); and U.C. BERKELEY STEM CELL CENTER, RAPPORTEUR'S REPORT: INSTITUTIONAL LANDSCAPE IN STEM CELL RESEARCH & DEVELOPMENT (2008), http://stsc.berkeley.edu/Events/StemCellFeb6-Rapporteur%27s%20Report.pdf [hereinafter RAPPORTEUR'S REPORT] (providing rapporteur's report and conference agenda).

75. REGENERATIVE MEDICINE, *supra* note 23.

must know how mature their stem cell population is (or, in terms of Figure 1, exactly where along the cellular tree of differentiation the cell population resides). Obtaining full knowledge about differentiation is not simple: The differentiation of a stem cell is heavily dependent not only on its genome, but also on the cell's culture history. For example, the particular growth factors that have been added to the media, the substrate of the cell culture, and the duration of such events all affect a cell's differentiation.[76] The appropriate use of these cells depends on understanding the condition of their derivation and propagation stages (Figure 2).[77] In each of the many technical stages during routine use of stem cells for medical research (Figure 2), many technologies are needed—including cell lines, growth factors, culture substrates, implantable materials, and genetic engineering vectors—each of which can affect stem cell behavior.[78] A wide array of possibilities exists for integrating different technologies. This wide array is rarely explored experimentally in one lab for all important cell lineages (e.g., undifferentiated embryonic stem cells, neurons, cardiac progenitors, pancreatic endocrine cells). Labs and even whole institutions can have specialized expertise with only a few cell types or lineages.

Recent work in the stem cell scientific community suggests that the need for descriptive details associated with cell lines will only increase, which in turn will further accentuate these challenges.[79] Research has thus far focused largely on details of the culturing history, but as scientists gain access to more stem cell

76. Genetic and epigenetic intrinsic factors as well as soluble and matrix extrinsic factors are cell fate determinants of stem cells. Michele Boiani & Hans R. Scholer, *Regulatory Networks in Embryo-derived Pluripotent Stem Cells*, 6 NATURE REVS. MOLECULAR CELL BIOLOGY 872 (2005); Laune A. Boyer, Divya Mathur & Rudolf Jaenisch, *Molecular Control of Pluripotency*, 16 CURRENT OPINION GENETICS & DEV. 455 (2006); Rudolf Jaenisch & Adrian Bird, *Epigenetic Regulation of Gene Expression: How the Genome Integrates Intrinsic and Environmental Signals*, 33 NATURE GENETICS 245 (2003).

77. For example, culture methods using low oxygen can prevent subsequent cardiac differentiation. Toshihiko Ezashi, Padmalya Das & R. Michael Roberts, *Low $O_2$ Tensions and the Prevention of Differentiation of hES Cells*, 102 PROC. NAT'L ACAD. SCI. 4783 (2005).

78. Even regular *in vitro* culture of stem cells requires media and substrates to work faithfully with growth and differentiation factors. David Schaffer, *Exploring and Engineering Stem Cells and Their Niches*, 11 CURRENT OPINION CHEMICAL BIOLOGY 355 (2007). Genetic manipulation of such cells would likely use genetic engineering reagents, and if such cells are used to produce implantable cell therapies—a celebrated goal of stem cell R&D—one can expect cell carriers and scaffolds to be involved. Freshly harvested stem cells themselves rarely grow by themselves outside the body. A series of carefully engineered tools assay and manipulate the behavior of these cells to produce R&D.

79. International hESC characterization projects have listed more stringent technical criteria to ensure that a population of cells retains stem cell characteristics. Personal Communication with Jonathan Auerbach, President, GlobalStem, Inc. (June 2006—July 2008); *see also* Baker et al., *supra* note 72.

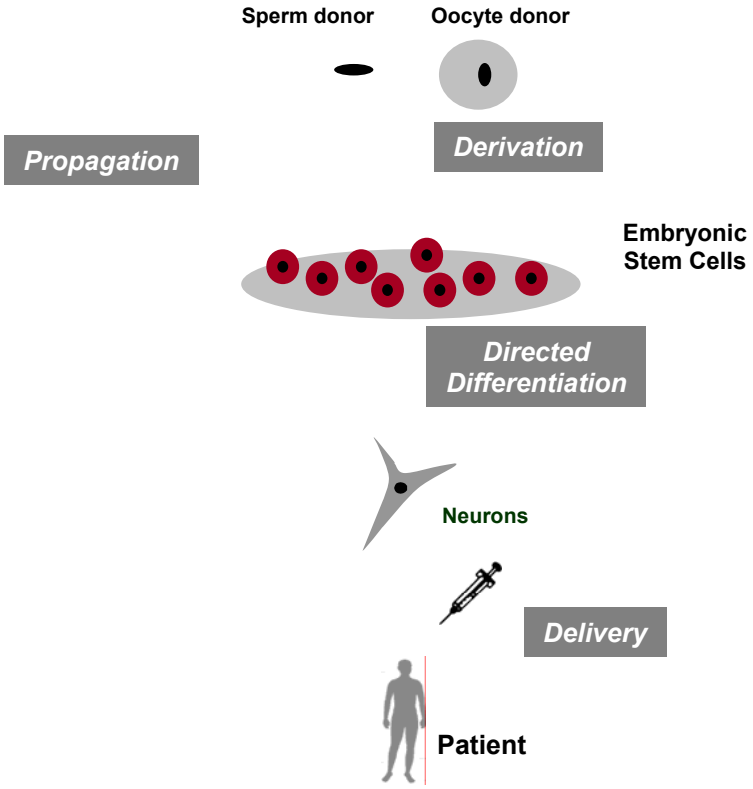


**FIGURE 2. The Many Technical Stages of Embryonic Stem Cell Research**
Four key methodological stages are delineated in gray for one particular application. In the application schematically shown, mature neurons are created from stem cells, which are then implanted into a patient to induce regeneration. This schematic only illustrates one application of stem cells in regenerative medicine. Other uses of stem cells (e.g., toxicology, pharmacology, and developmental biology) typically will need to generate cell lines of specific phenotypes, all of which will move through controlled derivation, propagation, and differentiation stages.

lines they are beginning to explore genetic and epigenetic effects[80] and are actively developing nascent tools to connect genetic data with gene expression data on an integrated website.[81] Even the diet of egg donors can influence the

80. Baker et al., *supra* note 72; International Stem Cell Initiative, *supra* note 72.

81. Personal Communication with Auerbach, *supra* note 79; Personal Communication with Dr. Mahendra Rao, Vice President, Research, Stem Cells and Regenerative Medicine, Invitrogen

phenotype of an embryonic stem cell line by producing different epigenetic effects on particular chromosomal loci.[82] It is not surprising that scientists have already tried to document all known information about hESC lines, such as sex and ethnicity.[83] However, obtaining further information about the donor is rarely possible, since identity is concealed to protect privacy.

Journal articles have limited capacity to communicate much of this data, as methodological details of stem cell culturing history, genome, and derivation are rarely published fully in the main text of journal articles: many times they are edited out or moved to supplemental information that is not as readily accessible. This is in part because standards on reporting around derivation and characterization are still developing along with the fast-moving frontier of the field itself.[84] Furthermore, important information is frequently obtained through negative results, which are less likely to be published.[85]

The general difficulty of obtaining essential technical details about the numerous technologies regularly employed in experiments or applications creates a bottleneck for stem cell R&D. This process of gathering information involves significant and redundant legwork for every scientist.[86] Facing grant and publication deadlines, scientists read the scientific literature and call close colleagues in order to choose a technology to work with. In cases where scientists devote considerable time to do this legwork, even after extensive communication with their network of colleagues, scientists are uncertain whether they have the most up-to-date information available, knowing that there are many experts with relevant data outside of their personal network.[87] Work typically must proceed at the risk of depending upon poorly chosen tools or materials that could

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Corporation (April—June 2006).

82. Acetylation patterns on the oocyte are connected to maternal diet. *See* David I.K. Martin, Robyn Ward & Catherine M. Suter, *Germline Epimutation: A Basis for Epigenetic Disease in Humans*, 1054 ANNALS N.Y. ACAD. SCI. 68 (2005).

83. Donor characteristics are beginning to be provided on the U.K. stem cell bank catalogue and other websites. *See, e.g.*, The Stem Cell Community, www.stemcellcommunity.org (last visited Nov. 13, 2008).

84. *See, e.g.*, Stephenson, Braude & Mason, *supra* note 31.

85. For example, if a scientist seeks particular properties in stem cell derivatives (e.g., test neurons from hESC line "A"), then prior details of difficulties in differentiating a hESC line into the desired lineage are exceedingly important (e.g., hESC line "A" is difficult to differentiate into neurons). Only recently has this phenomenon been studied and published systematically for particular lineages. Kenji Osafune et al., *Marked Differences in Differentiation Propensity Among Human Embryonic Stem Cell Lines*, 26 NATURE BIOTECH. 313 (2008).

86. *See* RAPPORTEUR'S REPORT, *supra* note 74; Personal Communication with Auerbach *supra* note 79.

87. *See* RAPPORTEUR'S REPORT, *supra* note 74; Personal Communication with Auerbach, *supra* note 79.

compromise the success of the work.[88] In addition, inquiries relying on comparison across multiple cell lines, such as across disease-specific hESC lines, remain closed due to incomplete and sparse data.

### *B. Proprietary Domain: Patent Rights and Innovation*

IP scholars in the biological sciences have long warned that private patent rights in biomedical technologies may foster an "anti-commons" or "patent thicket" whereby a proliferation of property claims and their frequent litigation can discourage commercial development.[89] The emergence of many densely packed patent claims—whether actually overlapping in technical subject matter or simply interdependent or complementary in the marketplace—raises uncertainty about freedom to operate and imposes transaction costs. Even the owners of dominant patents may not themselves be assured of reaching market unhindered. As a result, companies may under-invest in the development of technology applications.[90] Although the anti-commons effect in biomedicine is difficult to measure and remains controversial,[91] the National Research Council recently concluded that the patent landscape in biomedicine, already complicated in certain areas of research such as gene expression and protein-protein interactions, could become considerably more burdensome over time.[92]

In a best-case scenario under the conditions of an anti-commons or patent

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88. *See* RAPPORTEUR'S REPORT, *supra* note 74; Personal Communication with Auerbach, *supra* note 79.

89. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE. 698 (1998); Peter Lee, *Patents, Paradigm Shifts, and Progress in Biomedical Science*, 114 YALE L.J. 659 (2004); Carl Shapiro, *Navigating the Patent Thicket: Cross-Licenses, Patent Pools, and Standard Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY 119-50 (Adam B. Jaffe, Josh Lerner & Scott Stern eds., 2001).

90. *See* Gregory D. Graff, Gordon C. Rausser & Arthur A. Small, *Agricultural Biotechnology's Complementary Intellectual Assets*, 85 REV. ECON. & STAT. 349 (2003); Robert P. Merges, *Contracting into Liability Rules: Intellectual Property Rights and Collective Rights Organization*s, 84 CAL. L. REV. 1293 (1996); Norbert Schultz, Francesco Parisi & Ben Depoorter, *Fragmentation in Property: Towards a General Model*, 158 J. INSTITUTIONAL & THEORETICAL ECON. 594 (2002); Carl Shapiro, *supra* note 89; Rosemarie Ham Ziedonis, *Don't Fence Me In: Fragmented Markets for Technology and the Patent Acquisition Strategies of Firms*, 50 MGMT. SCI. 804 (June 2004); Soma Dey, Are Patents Discouraging Innovation? (June 2006) (unpublished manuscript, on file with the Department of Business Policy, National University of Singapore).

91. *See, e.g.*, Richard A. Epstein & Bruce N. Kuhlik, *Is There a Biomedical Anticommons?*, REGULATION, Summer 2004, at 54, 54-58 (arguing that Heller and Eisenberg overstate the case against patent protection at both the theoretical and empirical levels); John P. Walsh, Charlene Cho & Wesley M. Cohen, *View from the Bench: Patents and Material Transfers*, 309 SCIENCE 2002 (2005).

92. REAPING THE BENEFITS, *supra* note 10, at 2.

thicket, a company that commercializes a complex biomedical product would need to spend significant resources negotiating and paying multiple royalty "tolls" to the owners of rights to "thoroughfare" enabling technologies infringed by that product. In a worst-case scenario, even after concluding legal analysis and deals assumed to establish reasonable freedom to operate, a company may find its product infringing yet other (previously unidentified) patents, inciting costly litigation or settlements. Most commonly, however, a patent thicket can be expected to result in innovation malaise born of unwillingness on the part of investors to put money behind projects because of the uncertainty over whether a cost-viable path to market will be found for the new, unproven technology. Of course, the most valuable of treatments—in terms of expected revenues—will invariably find willing investors and thus find their way to market through licensing deals, settlements, or even mergers or acquisitions. When enough money is on the table, the sheer size of potential winnings can drive deals to completion. Projects in the "long tail" with negligible valuations are terminated for reasons other than IP. We would expect the remaining projects in the middle range of potential payoffs, between the two extremes, to be at the greatest risk of getting sidelined because of IP concerns.

Could an anti-commons or patent thicket become a significant drag on the development of stem cell based therapies? As a preliminary matter, it is important to point out that patent and innovation issues are intertwined with the discussion of materials sharing and MTAs developed in the previous Section. As mentioned above, WARF's restricted licensing strategy depended both on the physical control of stem cell lines and their ownership of the underlying IP.[93] WARF's foundational patents have clearly shaped the field: Such ownership of a "thoroughfare" technology has arguably slowed movement in the field and by some accounts dampened stem cell innovation in the start-up sector.[94] Furthermore, WARF's newly announced policy does nothing to change the fact that any entity seeking to commercialize hESC technology will have to negotiate a commercial license from WARF. There has been ample policy attention paid to this problem, and it remains to be seen how liberally WARF will make such licenses available.

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93. *See* O'Connor, *The Use of MTAs*, *supra* note 56, at 1044-48.

94. *See* Loring & Campbell, *supra* note 30. Of course, such assessment must be made relative to the likely pace of progress in the absence of incentives for Geron to fund stem cell research at the University of Wisconsin. Perhaps the same inventions would have emerged from the Thompson lab solely from NIH-funded research, or perhaps the inventions would never have occurred at all. However, given that the grounds of the patent reexamination filed with the USPTO in 2006 were that the inventions by Thompson were obvious to those versed in the art, it is hard to defend a counterfactual scenario in which hESCs would not have been created somewhere, by someone in the field, and even within a roughly comparable time frame. *See supra* text accompanying note 64.

But single-minded attention to the WARF patent as the extent of proprietary hold-ups in the field would be a mistake. First, as mentioned earlier, stem cell scientists have developed cell reprogramming techniques to produce pluripotent stem cells (iPS) without using WARF's patented embryonic stem cell methods. In the wake of litigation on the WARF patents, it was determined that this iPS technique and associated cell lines would not infringe WARF's patents.[95] There is still scientific disagreement about whether iPS cell lines could ever fully replace the need for hESCs in either research or therapeutics,[96] but these techniques have been deemed a major discovery with the potential to avoid the need for human embryos in the production of useful stem cell research tools and therapies. Meanwhile, patent applications on these new techniques and cell lines are reportedly flooding the patent office, creating the potential for serious constraints on these materials down the road.[97]

Second, patents covering derivation techniques and stem cell lines seem to be the tip of the iceberg of existing stem cell patents, and conditions in the field could set the stage for a classic patent thicket problem that will hinder innovation. Several analyses show a significant rate of accumulation of new patents over stem cells and related technologies,[98] with problematic implications for downstream innovation.[99] Indeed, given the particular characteristics of stem cells as an enabling technology—i.e., a necessary technology for undertaking a broad range of new research endeavors and commercial applications—the field may be particularly susceptible to the emergence of a patent thicket.

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95. *See* Holden, *supra* note 67.

96. *See id.* at 1603 ("ES cells are still needed to validate iPS cells, and even if iPS cells prove viable substitutes for ES cells in research, some scientists believe they will never be suitable for cell therapy."); Insoo Hyun et al., *New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells*, 1 CELL STEM CELL 367 (2007).

97. *See* Holden, *supra* note 67, at 1603.

98. *See* DAVID CAMPBELL, MICHEL NOISEUX & GRÉGOIRE CÔTÉ, POTENTIAL FOR STEM CELLS SCIENCE AND TECHNOLOGY IN CANADA: GREAT PROMISES AND CHALLENGES (2004), http://www.science-metrix.com/pdf/SM_2003_015_IC_Stem_Cells_Potential_Canada.pdf; WOLFGANG GLÄNZEL ET AL., STEM CELLS: ANALYSIS OF AN EMERGING DOMAIN OF SCIENTIFIC AND TECHNOLOGICAL ENDEAVOUR (2004), http://www.steunpuntoos.be/rapportstamcellen_June2005.pdf; Robert W. Esmond, Robert A. Schwartzman & Ted J. Ebersole, *Stem Cells: The Patent Landscape*, 18 INTELL. PROP. & TECH. L.J. 1 (2006); Robert C. Scheinfeld & Parker H. Bagley, *The Current State of Embryonic Stem Cell Patents*, N.Y.L.J., Sept. 26, 2001, at 3, *available at* http://www.law.com/jsp/article.jsp?id=900005523511#.

99. *See* Sean M. O'Connor, *Intellectual Property Rights and Stem Cell Research: Who Owns the Medical Breakthroughs?*, 39 NEW ENG. L. REV. 665 (2004-2005); Todd N. Spalding & Michele M. Simkin, *How Will Patents Impact the Commercialization of Stem Cell Therapeutics?*, 2 J. PHARMACEUTICAL INNOVATION 23 (2007), *available at* http://springerlink.com/content/rtx5013k15882g00/fulltext.html.

A substantial number of patents have been granted in the relatively young field of stem cells,[100] yet the road to actual stem cell products remains long. Such products will have to navigate a significant number of additional property claims if future patenting rates follow current trends: Annual rates of patent filings have grown rapidly in recent years, along with more modest but significant gains in actual patent grants.[101] Ownership of stem cell patents is fragmented across multiple organizations, with no single organization dominating the field. The largest patent holding accounts for just three percent of the patents in the field.[102] This landscape implies that the task of coordinating access to complex enabling technologies could involve an intensive process of searching and negotiating. Furthermore, in contrast to most fields of technology, government and academic institutions own a very large share of the patents in stem cells: fully forty-four percent of the stem cell patents in the United States (compared to an average of less than three percent in most fields of technology).[103] Given that academic and public research organizations file for patent protection primarily in order to license the technologies and not to build integrated patent portfolios, there may be an even greater dispersion of technology ownership than would be observed in fields more dominated by companies with strategic product development and IP management goals.

Moreover, the technical content of the stem cell patent landscape is highly complex, with stem cell lines, stem cell preparations, and growth factors subject to intense patenting activity.[104] The sheer complexity of the "tree" of mammalian cellular differentiation has important efficiency implications, with numerous lineages emanating from pluripotent stem cells and branching off to arrive at fully differentiated functional tissue cells (Figure 1). It is likely that the complex set of technologies—the growth factors, hormones, other proteins, small molecules, and culture conditions—necessary to control the early stages of differentiation (represented by the heavier lines in Figure 1) will not have many alternatives, while they are likely to be owned separately. Nevertheless, they represent the major (patented) "thoroughfares" that will need to be traversed by many seeking different cellular destinations.

### *C. Ethical Domain: Ethical and Regulatory Complexity*

As if technical and proprietary complexities were not enough, few issues in the life sciences have been as ethically and politically contested as the production

100. *See* Bergman & Graff, *Global Stem Cell Patent Landscape*, *supra* note 28, at 422.
101. *See id.* at 420.
102. *See id.* at 421.
103. *See id.*
104. *See id.*

and use of stem cells.[105] Both in the United States and abroad, sharp divisions on the moral status of the embryo have engendered conflict in the domain of political morality[106]—the terrain on which ethics connects with politics, where human values meet formal and informal forms of collective governance such as laws, regulations, and standards.[107] Beyond the threshold issue of whether embryo rights ought to prevent state funding of the work, the large-scale implementation of stem cell research entails many other problematic issues around the procurement of human tissue, different techniques of deriving stem cell lines, and particular applications of the technology.

The ethical and political landscape for stem cell research has given rise to two major problems for the efficient and accountable governance of the work. First, in the United States, the moratorium on the creation of new hESC lines has resulted in a vacuum not only of research funding, but also of federal regulation. As mentioned above, current federal policy limits national public funding to research conducted on hESC lines created before August 2001.[108] As a result, even as private and state-funded hESC research moves ahead, a national approach to regulation is lacking. This means that rules within and across many jurisdictions are either absent or unclear. Observing this regulatory gap at the federal level, the National Academies of Sciences has published recommended guidelines for the conduct of hESC research, but these remain voluntary.[109] The core of the system they recommend is the establishment of an additional layer of oversight at institutions conducting the research, a Stem Cell Research Oversight Committee (SCRO) that functions in parallel to the Institutional Review Board featured in Federal Human Research Subject Protections.[110]

The response of various states to the federal situation has produced a second problem for stem cell governance: within the United States, state funding

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105. *See* PRESIDENT'S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH (2004), *available at* http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

106. For more on "political morality," see MICHAEL L. GROSS, ETHICS AND ACTIVISM: THE THEORY AND PRACTICE OF POLITICAL MORALITY 1-2 (1997) (defining political morality as "the moral principles governing public policy and the cognitive and behavioral mechanism citizens use to preserve the ethical foundation of civil society").

107. For an ethical analysis of the stem cell field that deals explicitly with the institutional quandaries of moral disagreement in civil society, see Rebecca Dresser, *Stem Cell Research: The Bigger Picture*, 48 PERSP. BIOLOGY & MED. 181 (2005).

108. *See* GUIDANCE FOR INVESTIGATORS, *supra* note 25.

109. NAT'L RESEARCH COUNCIL & INST. OF MED., GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2005) [hereinafter NRC-IOM GUIDELINES].

110. *Id.* at 44-48. Federal funding agencies require that all institutions receiving federal money bring their research into compliance with this so-called "common rule," and its IRB requirement. 45 C.F.R. § 46.109 (2005).

programs have given rise to a proliferation of state regulatory regimes, creating a patchwork that is increasingly difficult to navigate.[111] In the United States, the November 2004 election marked a sea change in the public funding environment for hESC research when the voters of California approved the so-called California Stem Cell Research and Cures Initiative.[112] This program earmarked $3 billion in direct state spending, excluding interest payments, for stem cell research and related work over the next ten years.[113] Following California's lead, many other states saw economic and political opportunity in the national stalemate and initiated their own programs of funding for stem cell research.[114] These include Connecticut,[115] Wisconsin,[116] Illinois,[117] Massachusetts,[118] New

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

112. *See* Connie Bruck, *Hollywood Science: Should a Ballot Initiative Determine the Fate of Stem-Cell Research?*, NEW YORKER, Oct. 18, 2004, at 62 (detailing the campaign in California for Proposition 71).

113. California Stem Cell Research and Cures Act of 2004, CAL. HEALTH & SAFETY CODE § 125291.30 (West 2008).

114. *See* Fossett, *supra* note 29; *see also* Sarah Webb, *A Patchwork Quilt of Funding*, NATURE REPORTS STEM CELLS, Nov. 1, 2007, http://www.nature.com/stemcells/2007/0711/071101/full/stemcells.2007.110.html.

115. *See* CONN. GEN. STAT. ANN. §§ 19a-32d–19a-32g (West Supp. 2008) (providing public funding in support of embryonic and human adult stem cell research); CONN. GEN. STAT. ANN. § 4-28e(c)(3) (West 2007) (providing that, for the fiscal years 2008 through 2015, the sum of $10 million shall be disbursed from the Tobacco Settlement Fund to the Stem Cell Research Fund).

116. In April 2006, the Governor authorized $5 million to recruit private stem cell companies to move to Wisconsin, and negotiated key licensing incentives from WARF to help recruit new companies. He has also announced a much larger funding program, but it had not been initiated as of 2006. *See* Stayn, *supra* note 111, at 8.

117. The Illinois Governor's Executive Order created the Illinois Regenerative Medicine Institute (IRMI) providing for grants to medical research facilities for adult and embryonic stem cell research. Office of the Governor of Illinois, Exec. Order No. 6 (2005), amended by Exec. Order No. 3 (2006), *available at* http://www.illinois.gov/gov/execorder.cfm?eorder=46. Ten million dollars went to this new program, with grants awarded in April 2006. Press Release, Gov. Blagojevich, Comptroller Hynes Announce $10 Million in State Stem Cell Research Grants, Office of the Governor of Illinois (Apr. 24, 2006), *available at* http://www.idph.state.il.us/public/press06/4.24.06StemCellGrants.htm. In 2006, $5 million were appropriated and allocated to the stem cell program for 2007. Press Release, Gov. Blagojevich Announces Recipients of $5 Million in New State Stem Cell Research Funding, Illinois Regenerative Medicine Institute (Aug. 17, 2006), *available at* http://www.idph.state.il.us/irmi/news_081706.html. In 2007, the Illinois General Assembly enacted the Stem Cell Research and Human Cloning Prohibition Act, which permitted IRMI to conduct research on stem cells from any source. 410 ILL. COMP. STAT. 110/1-50 (2007).

118. Overriding the Governor's veto, Massachusetts legislators created an institute for stem cell research and regenerative medicine at the University of Massachusetts with an appropriation of $1

Jersey,[119] and New York.[120] These programs have brought explicit policy attention to the ethical and political aspects of implementing large-scale stem cell research programs.[121]

These states differ, sometimes only slightly, on three sets of regulatory issues facing the governance of hESC.[122] First, states differ in the regulation of the procurement of the gametes, embryos, and other cells from human donors for the generation of new hESC lines. Putting aside for a moment the potential of the announced discovery of so-called cell reprogramming technologies to change the derivation landscape,[123] new hESC lines need to be derived from human embryos at an early stage of its development called the blastocyst, for which there are three major pathways of donation. The first is the *in vitro* fertilization (IVF) process and the supernumerary embryos created thereby. *In vitro* fertilization 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. The second source of embryos is 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 (SCNT), also known as cloning. Through this method, scientists insert genetic material from an adult cell and inject it into an egg cell, stimulating it to reproduce. An advantage of SCNT is that it may avoid the problem of rejection

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million to be spent on stem cell biology. They also established a center and a "Life Sciences Investment Fund" with $10 million to promote research in stem cell, regenerative medicine, biotechnology, and nanotechnology. Nat'l Conference of State Legislatures, *supra* note 117; 2005 Mass. Acts, Chapter 111L, *available at* http://www.mass.gov/legis/laws/seslaw05/sl050027.htm.

119. In 2005 and 2006, the New Jersey Stem Cell Institute was allocated a total of $23 million in general revenues. Since 2005, grants have been awarded to at least seventeen institutions for research on stem cells from embryos and other sources. In 2007, voters rejected a ballot measure to allow the sale of bonds to fund stem cell research. Nat'l Conference of State Legislatures, *supra* note 117; *see also* State of New Jersey, Comm'n on Sci. & Tech., Stem Cell Research in New Jersey, http://www.state.nj.us/scitech/stemcell (last visited Nov. 13, 2008).

120. New York legislators created a Special Revenue Fund called the "The Empire State Stem Cell Trust" in 2007 "to collect and distribute grants in support of stem cell research" on lines from any source. One hundred million was earmarked for FY 2007-2008 and $500 million was earmarked at $50 million per year for ten years beginning in FY 2008-2009. Applications for the first grant awards were due in January 2008. *See* N.Y. State, A New Stem Cell Research Fund, http://www.ny.gov/governor/ press/lt_stemcell.html (last visited Nov. 13, 2008); N.Y. PUB. HEALTH LAW §§ 265, 265-a-e, 235-f (McKinney 2008), *available at* http://stemcell.ny.gov/about_ nystem_esc_board_statute. html.

121. *See* NRC-IOM GUIDELINES, *supra* note 109; Winickoff, *Bioethics and Stem Cell Banking in California*, *supra* note 28.

122. *See generally* Nat'l Conference of State Legislatures, *supra* note 117; *see also* Stayn, *supra* note 111.

123. *See supra* note 69.

that is common in stem cell transplantation procedures.[124] Individual states differ with regard to the sources of acceptable materials and the methods of procurement, specifically in the terms and provisions for informed consent, payment of donors, and levels of oversight.[125]

Second, many new state regulatory regimes address the derivation of new hESC lines in different ways, due to the open-ended controversies about different derivation techniques.[126] There is agreement that human embryos enjoy some sort of special status, even among those who favor proceeding with hESC research, leading to various kinds of restrictions and oversight. Furthermore, the use of SCNT to derive new hESC lines is especially controversial, raising issues of embryonic manipulation and reproductive cloning, since the embryos produced could in theory become cloned human beings.[127] As a result, individual states differ as to what types of materials can be used, in what ways, and with what kind of oversight.[128]

Third, oversight regimes address different research uses of hESC lines, an area that is currently only minimally regulated under federal research rules in the United States.[129] A number of highly controversial types of research are possible using hESCs. Because of their potential to develop into human nerve and brain cells, hESCs could be used to create animals with a significant number of human cells. These chimeras may be useful for conducting biomedical experiments, but blur the boundary between humans and animals, introducing ethical complexity

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124. *See, e.g.*, NRC-IOM GUIDELINES, *supra* note 109, at 13. Rules around procurement will help establish the processes and contexts through which donation of gametes, embryos, and adult cells may occur, as well as the rights and duties between researcher and donor that the process gives rise to.

125. Susan Stayn, Senior Univ. Counsel, Stanford Univ., Presentation to the Planning Meeting to Establish an Interstate Alliance for Stem Cell Research: Overview of State HESC Research Laws (May 23-24, 2007), *available at* http://www.iascr.org/docs/StateSummaryTable.pdf.

126. This is true across the United States and other nations. For review of current laws, see The Hinxton Group, World Stem Cell Policies, http://www.hinxtongroup.org/wp.html (last visited Nov. 13, 2008).

127. *See* NRC-IOM GUIDELINES, *supra* note 109, at 1-2. Many bioethicists and scientists agree that if the use of this technique is to proceed, it should be regulated.

128. *See* Stayn, *supra* note 111; Stephen Smith, *Officials from Across the Nation Meet To Foster Stem-Cell Research*, BOSTON GLOBE, Oct. 24, 2007, *available at* http://www.boston.com/yourlife/health/blog/2007/10/officials_from.html ("States differ in their interpretation of what constitutes a legal line of stem cells. In some states, such as New York, scientists hunting for treatments for a disease can produce embryos using sperm and eggs donated by families stricken with the ailment. The resulting stem cells can then be used to understand a disease and to look for treatments. But in Massachusetts, state law does not allow the production of embryos for the express purpose of scientific exploration").

129. NRC-IOM GUIDELINES, *supra* note 109, at 52-61.

into questions of human research subject protection and animal experimentation.[130] Furthermore, if the rights of human donors to limit certain research uses are recognized and documented, it will be necessary to enforce these limitations either contractually or through regulatory oversight. States disagree, and may continue to disagree, for instance, on how to handle these issues of chimeras and donor limitation on use.[131]

So far, we have examined only regulatory complexity within the United States. A similar range of differences occurs across nations that have regulatory regimes for stem cell research in place.[132] International variation in regulation across countries exacerbates the complications posed by the patchwork nature of the U.S. regime.

Technological fixes may ease, but not solve, some of this ethical and regulatory complexity. The emergence of a new array of derivation techniques may present different sets of ethical quandaries and disagreements.[133] For instance, recent advances in cell reprogramming[134] may resolve some of the ethical complexities of this research because they may reduce the need to use "spare" embryos or create new ones through SCNT.[135] However, many stem cell researchers still see the need for developing hESC lines.[136] Cell reprogramming

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130. *See* Jamie Shreeve, *The Other Stem-Cell Debate*, N.Y. TIMES MAGAZINE, Apr. 10, 2005, *available at* http://www.nytimes.com/2005/04/10/magazine/10chimera.html. 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, 487-90 (2006).

131. *See generally* Stayn, *supra* note 111.

132. For a useful synopsis of regulatory differences across nations, see StemGen, http://www.stemgen.org (last visited Nov. 13, 2008) ("StemGen . . . is a research database of international, regional and national normative instruments concerning the socio-ethical and legal aspects of stem cell research and related therapies. It was created as a free tool for the dissemination of information relevant to policy-making, the goal being to make the information accessible to as many people as possible without geographic or cost barriers.").

133. Take for instance the announcement by the biotechnology company, Advanced Cell Technology, that it had "dramatically improved a technique for producing human embryonic stem cells without destroying embryos." Colin Nickerson, *Firm Says It Can Get Stem Cells No Harm to Embryos*, BOSTON GLOBE, Jan. 11, 2008, at A10. This advance assuages some ethical qualms, e.g., the concern with sacrificing the lives of embryos to extract usable hES cells, while reintroducing others, e.g., the ways this technique might pave the way for human reproductive cloning.

134. *See supra* note 69.

135. Gina Kolata, *Scientists Bypass Need for Embryo To Get Stem Cells*, N.Y. TIMES, Nov. 21, 2007, *available at* http://www.nytimes.com/2007/11/21/science/21stem.html.

136. *See* Monya Baker, *From Skin Cell to Stem Cell*, NATURE REPORTS STEM CELLS, June 7, 2007, http://www.nature.com/stemcells/2007/0706/070607/full/stemcells.2007.6.html (stating that "despite the promise, most researchers believe the potential of iPS cells for drug screens or therapies is no reason to abandon work on ES cells"); *see also* Holden, *supra* note 67, at 1603; Hyun et al., *supra* note 96.

to produce pluripotent stem cell lines also raises its own set of ethically vexing questions. For example, can normal cells from any person be used to create viable human germ cells in a Petri dish?[137] As the number of techniques for derivation of lines proliferates, it only increases the needs for further harmonization of regulatory documentation.

The current patchwork of laws, regulations, and ethical rules emerging across nations, individual states, and individual institutions causes repetitive work across institutional SCROs and could stymie scientific collaborations across regulatory jurisdictions.[138]

### *D. Current Efforts to Address These Problems*

Stem cell scientists and policymakers have recognized many of these problems, and there have been some important initiatives attempted within each of these three domains. These efforts should be applauded and then extended in a number of ways. First, none of them goes far enough to solve the problems within its specific domain. Second, since they are largely domain-specific, these existing efforts neglect the important interconnection of problems across domains and thus miss taking an integrative approach that promises to be more effective.[139]

#### *1. Ethics and Regulation*

Some of the deepest efforts to date have occurred in the domain of ethics, where regulatory gaps threatened public acceptance of the entire research field. Within the United States, as discussed above, the National Academies published an influential set of guidelines in 2005, with updates in 2007, in order to fill holes in existing regulation and to foster a harmonized federal approach to regulating stem cells.[140] As mentioned above, these guidelines remain voluntary, though they have exerted a significant effect on many institutions conducting stem cell research. This did not, however, prevent the proliferation of differences across

137. *See* Charis Thompson, *Can Opposition to Research Spur Innovation?*, NATURE REPORTS STEM CELLS, Dec. 13, 2007, http://www.nature.com/stemcells/2007/0712/071213/full/stemcells.2007.128.html; *see also* Robert Lanza, Letter, *Stem Cell Breakthrough: Don't Forget Ethics*, 318 SCIENCE 1865, 1865 (2007).

138. The Hinxton Group, Consensus Statement (Feb. 24, 2006) [hereinafter Hinxton Consensus Statement] *available at* http://www.hinxtongroup.org/docs/Hinxton%202006%20consensus%20document.pdf (stating that "inconsistent and conflicting laws prevent some scientists from engaging in this research and hinder global collaboration"). The Hinxton Group Consensus Statement is described in more detail *infra*.

139. The point will be developed *infra* Section II.A.

140. *See* NRC-IOM GUIDELINES, *supra* note 109.

state jurisdictions. In 2007, in order to begin addressing this problem, a group of state regulators and interested stakeholders came together around the problems caused by the federal approach to stem cell funding and regulation, founding the so-called Interstate Alliance on Stem Cell Research.[141]

At the international level, a number of initiatives seek to facilitate international collaboration and encourage research institutions to cohere around base-level ethical norms and practices. First, in February 2006, the so-called Hinxton Group—an international and interdisciplinary team of "scientists, philosophers, bioethicists, lawyers, clinicians, journal editors and regulators" convening in Hinxton, United Kingdom—issued a consensus statement setting out principles and strategies for promoting the ethical conduct of stem cell research across countries.[142] In an effort to foster international scientific collaboration and ethical scientific conduct in the face of value pluralism, the Hinxton Group outlined general principles for how research in this area ought to proceed given national variations in policy.[143] The statement, however, sets out few specifics.[144]

Second, in December 2006, the International Society for Stem Cell Research (ISSCR) issued more specific recommendations aimed at the international community of stem cell scientists. The ISSCR is the leading international society for stem cell scientists, who engage in yearly scientific meetings that also address matters of policy and regulation.[145] As such, it has become one of the most important international venues for discussing means to promote better international and cross-institutional collaboration on scientific and policy issues. Encompassing the National Academy of Sciences guidelines, as well as regulations promulgated by the California Institute of Regenerative Medicine (CIRM) and the Human Fertilisation and Embryology Authority (HFEA) in the United Kingdom,[146] the ISSCR guidelines were developed over the course of a

141. This group has made important strides in documenting the problem of regulatory discord across the states, seeking to make state rules more transparent, and initiating cross-state conversations. "The goals of IASCR are to (a) identify and increase opportunities for interstate collaboration; (b) identify and decrease obstacles to collaborative research across state lines; and (c) assist states that wish to develop or improve public funding programs in this area." Interstate Alliance on Stem Cell Research, About IASCR, http://www.iascr.org/about.shtml (last visited Nov. 13, 2008).

142. Hinxton Consensus Statement, *supra* note 138, at 1.

143. *Id.*

144. It does assert, *inter alia*, general principles of respect for donors, the duties of beneficence, the need to be "circumspect when regulating science" and "citizens' conduct extraterritorially," and the need for broad consultation in developing regulations. *Id.*

145. *See* International Society for Stem Cell Research, http://www.isscr.org (last visited Nov. 13, 2008).

146. George Q. Daley et al., *The ISSCR Guidelines for Human Embryonic Stem Cell Research*,

year by an international panel of scientists, lawyers, ethicists, and policymakers. Like the National Academy of Sciences, the ISSCR recommends making institutions responsible for ensuring that hESC research under its auspices have been subject to "impartial" and "rigorous" review by Stem Cell Research Oversight Committees.[147] SCRO review, which could occur at local, national, or international levels, ensures compliance with particular guidelines and constraints on types of research, procurement of cell lines, informed consent, cell banking, and provenance.[148]

These efforts at the national and international levels mark the beginning of a long-term project of promoting greater harmonization in regulations, coordinating the ethical review of stem cell lines and materials, and promoting transparency and enforcement of existing regulations. Developing common sets of norms and practices, they help ease some of the problems in the ethical domain, as discussed above. But they hardly go deeply enough. First, all of the efforts mentioned above are voluntary statements. Some jurisdictions, including many U.S. states, continue to lack legally binding rules. At the same time, significant regulatory differences have emerged among jurisdictions that have adopted rules. At present, it is costly and inefficient to assess and analyze whether and how particular cell lines and materials satisfy requirements of different jurisdictions. The individual SCROs that have grown up at major institutions involved in stem cell research currently conduct this sort of analysis. Opportunities for coordination and consolidation in these review functions have not been developed, which allows for redundancy.

In one of the more promising efforts in this area, the ISSCR plans to "curate and maintain a website listing of human stem cell lines that testifies to independent validation of the provenance of the cell lines."[149] The Hinxton Group encourages the creation of such a database.[150] This sort of activity, if it could be expanded to be an international ethical and regulatory clearinghouse, could

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315 SCIENCE 603, 603 (2007). Note, however, that "the ISSCR guidelines diverge subtly from the U.S. NAS guidelines" in a number of ways, being more permissive towards "breeding of animals that might carry human gametes" and recommending exemption from SCRO review of certain in vitro experiments that use established cell lines, such as the teratoma assay." *Id*. at 604.

147. Int'l Soc'y for Stem Cell Research, ISSCR GUIDELINES FOR THE CONDUCT OF HUMAN EMBRYONIC STEM CELL RESEARCH § 8.2 (2006) [hereinafter ISSCR GUIDELINES], *available at* http://www.isscr.org/ guidelines/ISSCRhESCguidelines2006.pdf.

148. *Id.* §§ 10, 11, 11.3, and 12 respectively.

149. The ISSCR Standards Committee is charged with the responsibility of verifying this provenance. *Id.* § 12.4.

150. Hinxton Consensus Statement, *supra* note 138 (stating at 3, "We encourage the creation of a public database for the deposition of statements of ethical conduct and guidance, research protocols, consent forms, information provided to potential human subjects and tissue donors and other related documents that bear on the ethics of stem cell research.").

provide a crucial service for more effective and efficient tracking of stem cell materials across the regulatory patchwork that has emerged. Unfortunately, the ISSCR's ethical database remains underdeveloped, due to a lack of funding and a general lack of interest within the scientific community.

*2. Sharing Data and Materials Access*

Among stem cell researchers and policymakers, there is broad recognition of the importance of access to scientific data and materials. A number of data and materials sharing guidelines, stem cell banks, and data registries—including the efforts described above to promote the transfer of the WARF cell lines—have begun to address the constraints imposed by these issues.

Scientific conferences are, of course, important channels through which ideas and knowledge flow, and the stem cell community has many such meetings, both national and international in scope. Beyond meetings, however, the research community—through deliberative bodies such as the National Academy of Sciences, ISSCR, and the Hinxton Group—has articulated loftier goals and has developed certain policies around data and materials access. The ISSCR has been the most active of these groups, stressing the importance of "the open exchange of scientific ideas and materials to maximize exploration, to promote innovation and to increase the probability of public benefit through affordable advances."[151] Consistent with this goal, the ISSCR has established clear policies on data sharing for its affiliated academic journal, *Cell Stem Cell*: "One of the terms and conditions of publishing in *Cell Stem Cell* is that authors be willing to distribute any materials and protocols used in the published experiments to qualified researchers for their own use," including "cells, DNA, antibodies, reagents, organisms, and mouse strains or if necessary the relevant ES cells."[152] These must be provided "with minimal restrictions and in a timely manner."[153] Furthermore, authors are also "encouraged to deposit materials used in their studies to the appropriate repositories for distribution to researchers." The ISSCR Guidelines also recommend that institutions grant "unhindered access" to materials and promote nonexclusivity and broad accessibility in their licensing practices, especially for non-commercial research.[154]

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151. ISSCR GUIDELINES, *supra* note 147, §§ 1.4, 7.

152. Cell Stem Cell, Author Guidelines, http://www.cellstemcell.com/misc/page?page =authors (last visited Nov. 13, 2008).

153. *Id.* (also stating that "it is acceptable to request reasonable payment to cover the cost of maintenance and transport of materials" and that "if there are restrictions to the availability of any materials, data, or information, these must be disclosed in the cover letter and the experimental procedures section of the manuscript at the time of submission").

154. ISSCR GUIDELINES, *supra* note 147, § 7.2 ("[I]nstitutions engaged in human stem cell research, whether public or private, academic or otherwise, develop procedures whereby research

Centralized stem cell banks and registries are a tangible way to provide exchange of materials and data across labs, institutions, and political jurisdictions,[155] and these efforts have sprung up both in the United States and elsewhere. In collaboration with WiCell Research, the NIH developed "the National Stem Cell Bank (NSCB)," a repository that distributes the recently liberalized WARF cell lines and other lines approved for federal research funding.[156] In addition to covering only a few cell lines, the bank and its associated NIH Registry have disappointing limitations regarding the provision of useful data: They simply list the federally-approved lines and provide contact information on how to acquire them.[157] The registry does not include information needed to perform follow-up work, nor does it contain provenance or ethical information.[158] Furthermore, the $3 billion California stem cell initiative has not developed banking and materials distribution capacity, despite calls within California for centralizing governance through stem cell banking and even explicit plans to do so.[159]

The lack of good ethics data and provenance data in the NIH Registry turned out to be a critical omission, illustrating the need for more robust cell line databases. A 2008 study of the provenance and consent conditions for all twenty-one government-approved hESC lines found that none of these consent forms meet the standards set out recently by the National Academy of Sciences, and some depart significantly.[160] While it is being debated whether the cell lines are

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scientists are granted, without undue financial constraints or bureaucratic impediment, unhindered access to these research materials for scientifically sound and ethical purposes, as determined under these Guidelines and applicable laws. The ISSCR urges such institutions, when arranging for disposition of IP to commercial entities, to take all possible care to preserve nonexclusive access for the research community, and to promote public benefit as their primary objective. The ISSCR endorses the principle that as a prerequisite for being granted the privilege of engaging in human stem cell research, researchers must agree to make the materials readily accessible to the biomedical research community for non-commercial research.").

155. Indeed, the National Academy of Sciences, Hinxton Group and ISSCR have made strong recommendations to enhance efforts in these areas. *See* ISSCR GUIDELINES, *supra* note 147, § 12.2; NRC-IOM GUIDELINES, *supra* note 109, § 5; Hinxton Consensus Statement, *supra* note 138, § 8.

156. Editorial, *Registries and Banks*, *supra* note 31.

157. *Id*.; *see also* NIH Human Pluripotent Stem Cell Registry, http://stemcells.nih.gov/research/registry (last visited Nov. 13, 2008).

158. Editorial, *Registries and Banks*, *supra* note 31.

159. Winickoff, *Bioethics and Stem Cell Banking in California*, *supra* note 28, at 1094-1105; David Winickoff, The California Public Biorepository and Trust (CPBT): A Governance Model for Ethics and IP of Stem Cell Research (Sept. 27, 2005) (unpublished white paper and written testimony to public hearing of the Ethics and Standards Working Group of the California Institute of Regenerative Medicine in San Francisco) (on file with author).

160. Robert Streiffer, *Informed Consent and Federal Funding for Stem Cell Research*, HASTINGS CENTER REP., May—June 2008, at 42-44.

in violation of ethical guidelines in place at the time of President Bush's 2001 announcement,[161] it is clear—if the report is accurate—that new regulations in certain jurisdictions bar the use of some of these lines. For example, researchers using some of these cell lines in California may actually be in violation of recently enacted ethical regulations, prompting Stanford and other universities to announce that they are re-examining the approval of work using those lines.[162] If these alleged violations are born out, research may be seriously set back because of failure to perform appropriate due diligence and tracking of cell provenance and ethical requirements.

At the international level, both stem cell banks and data registries have emerged that seek to improve materials and data sharing across research communities. The best known and most developed to date is the UK Stem Cell Bank (UKSCB), funded by the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC).[163] Launched in 2002, the UKSCB was recently renewed with a grant of nearly £10 million[164] to establish a permanent repository for all types of human stem cell lines (adult, fetal, and embryonic) with clinical applicability.[165] UKSCB deposited its first line in 2005 and hopes to scale up as a bank and distributor of both U.K. and international cell lines for the global stem cell research community.[166] A basic online database has also emerged along with the UK Stem Cell Bank, although its capacity is only to catalogue the lines in the bank, not to provide substantial technical data.[167]

Small international data registry projects for stem cell lines have emerged, such as the International Stem Cell Forum (ISCF) housed within the International Stem Cell Initiative.[168] However, the most advanced and ambitious registry to

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161. In 2001, President Bush "declared that only lines already in existence could receive federal support." Monya Baker, *Consent Issues Restrict Stem-Cell Use*, NATURE NEWS, July 28, 2008, http://www.nature.com/news/2008/080728/full/454556a.html (last visited Nov. 13, 2008).

162. *Id.*

163. *See* UK Stem Cell Bank, http://www.ukstemcellbank.org.uk (last visited Nov. 13, 2008). For a discussion of UK Stem Cell Bank's governance structure, and potential adaptation to the U.S. situation, see David E. Winickoff, *Bioethics and Stem Cell Banking*, *supra* note 28, at 1095-105.

164. Editorial, *Registries and Banks*, *supra* note 31.

165. UK STEM CELL BANK, DEVELOPMENT OF THE UK STEM CELL BANK PHASE II: PROPOSED PLAN FOR 2006-2010, http://www.ukstemcellbank.org.uk/documents/UKSCB%20Development%20Plan%202006-2010.pdf (last visited Nov. 13, 2008).

166. *Id.* at 5 ("The Bank aims to consolidate its position as the foremost repository of both UK and international stem cell lines in order to provide ethically sourced and well characterized stocks of human stem cells banked with a stringent quality framework.").

167. *See* UK Stem Cell Bank, Catalogue Overview, http://www.ukstemcellbank.org.uk/catalogue.html (last visited Nov. 13, 2008).

168. ISCF was set up in January 2003 with the aim "to bring together nine international funding

date is the European hESC Registry (hESCreg) launched in Berlin in January 2008.[169] Funded by the European Union, hESCreg has explicitly international ambitions and scope, growing out of a European "demand for a collaborative and interdisciplinary platform where researchers, regulators, as well as the general public can access comprehensive information about all human embryonic stem (ES) cell lines available."[170] The registry's mission is "to provide comprehensive information on existing hESC lines, their derivation, molecular characteristics, use and quality, and to act as a platform for coordination and cooperation." The registry makes this information freely accessible to the public "in order to further open-up the field and promote the validation of research findings and the efficient use of existing hESC lines."[171] The project aims to better characterize human ES cells, and to standardize research in the field by linking to other repositories, cell banks, regulatory bodies, and specific research projects.[172]

With these emerging efforts, some data and materials have been moving faster, but there is significant room for improvement. One gap involves deficiencies in the amount and type of data included in database efforts. Although hESCreg and the ISCF registries contain significant technical data, much of the methodological details of stem cell culturing history, genome, and derivation residing in supplemental information websites of journals (and even in the e-mail exchanges between researchers) could still be captured in the emerging efforts to centralize key information.

Furthermore, despite their promise, the current registries and banks remain too thinly funded, uncoordinated, and fragmented.[173] Outside of the United

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agencies that were already united in the belief that bilateral collaboration and information-sharing would accelerate progress and improve global practice in stem cell research." Int'l Stem Cell Forum, Background and Aims, http://www.stemcellforum.org/about_the_iscf/background_&_aims.cfm (last visited Nov. 13, 2008). Although this initiative remains nascent and under-funded, its parent organization, the ISCF, is made up of twenty one prominent funders from around the world. *See* Int'l Stem Cell Forum, Members, http://www.stemcellforum.org/about_the_iscf/members.cfm (last visited Nov. 13, 2008).

169. European Human Embryonic Stem Cell Registry, About hESCreg, http://www.hescreg.eu/typo3/index.php?id=14 (last visited Nov. 13, 2008) ("The European Human Embryonic Stem Cell Registry (hESCreg) is funded as a Specific Support Action under the 'Life Sciences, Genomics, and Biotechnology for Human Health' Priority within the 6th Framework Programme for Research and Technological Development of the European Commission. The Project commenced operations in April 2007 and has an envisaged duration of 3 years.").

170. Editorial, *Registries and Banks*, *supra* note 31 (quoting Joeri Borstlap, joint coordinator of the program).

171. European Human Embryonic Stem Cell Registry, Mission & Objectives, http://www.hescreg.eu/typo3/index.php?id=23 (last visited Nov. 13, 2008).

172. Editorial, *Registries and Banks*, *supra* note 31.

173. *Id.*

Kingdom, funders for banking and databases have not delivered on commitments. For instance, California's CIRM has been in a position, as the leading funder of research in the United States, to actively promote banking and data sharing,[174] but it has yet to make this a priority. As more hESC and iPS cell lines are derived, and requests to access such lines come from across the global research community, it is clear that neither individual labs nor the regional or national stem cell banks can easily distribute the lines. Furthermore, there has been no sustained international effort to coordinate among the ISCF, ISSCR, and hESCreg databases.[175]

Lastly, journal policies are uneven, ranging from *Cell Stem Cell*'s strong policy on sharing to no stipulations on sharing at all,[176] and more harmonization among these policies in the science publishing industry could help the community collectively move towards greater sharing of materials and data. Because the scale and scope of these efforts remain limited, gathering information remains a burdensome activity for many scientists. Given the current capacities for sharing, policy lags far behind the need and opportunities for mutually advantageous collective action.

*3. Patents and Innovation*

Whereas important initiatives have begun in the areas of ethics and data sharing, few have addressed constraints imposed by patents on innovation. The developments with the WARF patents and cell lines have been important, but these changes affect neither the landscape of patents beyond WARF's holdings, such as the emergent iPS area, nor the bottlenecks anecdotally occurring in the start-up biotechnology sector. As discussed above, these issues are closely linked to the ultimate accessibility of stem cell lines and research tools. Indeed, stem cell banks will only be useful for making materials available insofar as the patenting and licensing issues are addressed. For instance, the UKSCB will not release any lines to researchers until the depositor certifies that the depositor, researchers, and third-party users of the cell lines have agreed to terms regarding IP.[177]

Existing funders of stem cell research have constructed some policy solutions to this problem. For instance, CIRM has stipulated that any CIRM-funded inventions must be licensed to other CIRM grantees for non-commercial

174. *See* Eisenberg & Rai, *supra* note 49, at 1191.

175. *See* Healy et al., *supra* note 73; O'Rourke et al., *supra* note 73. A consensus statement and a common portal to search across these databases are being discussed but have not yet materialized.

176. *See, e.g.*, Piwowar & Chapman, *supra* note 42, at 2.

177. *See* UK Stem Cell Bank, Materials Access Agreement, http://www.ukstemcellbank.org/documents/UKSCB%20Materials%20Access%20Agreement%20-%20(v6%2019-08-08).pdf (last visited Nov. 13, 2008).

research use at reasonable cost.[178] This policy, however, fails to provide for sharing to non-CIRM grantees, making it a rather insular solution to a larger problem and yet another detrimental consequence of the patchwork nature of regulation in the United States. Similar guidance by NIH would have leverage over a much larger number of scientists and institutions. Furthermore, while international bodies like the ISSCR have urged that patent holders use non-exclusive licenses whenever possible in order to promote the greatest public benefit,[179] the group has advanced no specific policies regarding the collaborative management of IP, even within the academic sector. Clearly, further thought in this area is needed.

## II. DESIGN ELEMENTS FOR OPENING UP STEM CELL R&D

The discussion will now shift from a descriptive to a prescriptive mode, turning to the question of what might be done to advance solutions to the coordination problems in stem cell research outlined above. Any response to these problems must build upon existing initiatives in each domain, while also looking to creative solutions from other fields. Broadly speaking, we argue that collective action can be a basis for opening up stem cell R&D in the face of multiple compounding constraints. In particular, such opening up would result in a more efficient exchange of data, materials, and tools within the stem cell research community. Such collective action could also advance new applications of regenerative medicine, orient stem cell research toward the most pressing social needs, and promote more accountable ethical oversight of stem cell research. To achieve these goals under the current situation of stem cell R&D, we advance six interrelated design principles for institutional collaboration in stem cell R&D.

### *A. Integration Across Technical, Proprietary, and Ethical Domains*

Discussions in academic and policy circles have focused on the technical, proprietary, and ethical arenas as isolated domains.[180] This ignores their key

178. *See* 17 CAL. CODE REGS. tit. 17, § 100306 (2008) ("Grantee Organization agrees to make its CIRM-funded patented inventions readily accessible on reasonable terms, directly or through a licensee or licensees, to other Grantee Organizations for non-commercial purposes, upon request from a Grantee Organization.").

179. *See* ISSCR GUIDELINES, *supra* note 147, § 7.2 ("The ISSCR urges such institutions [involved in stem cell research], when arranging for disposition of IP to commercial entities, to take all possible care to preserve nonexclusive access for the research community, and to promote public benefit as their primary objective.").

180. Important exceptions include, for example, Vickie Brower, *Human ES Cells: Can You Build a Business Around Them?*, 17 NATURE BIOTECH. 139 (1999); and Kenneth S. Taymor,

interactions. Any decision by a researcher to use an existing technology, tool, or method in the laboratory inevitably begins with consideration of its technical efficacy, but the decision must also factor in whether that technology is owned as IP and whether the contemplated use complies with ethical requirements. Investigators will likely make tradeoffs among the three types of bottlenecks. For example, the selection of a more ethically acceptable method or tool may render the experiment less capable of achieving desired technical results; similarly, the selection of a technology with more freedom to operate may be more constrained by regulation. In fact, all such decisions carry implications in all three domains—technical, IP, and ethical—whether or not the researcher knows it. Furthermore, these decisions will embed technical, ethical, and proprietary characteristics of the tools chosen within the research results, and therefore within subsequent or derivative lines of work. Early choices, then, will impose conditions or limitations on future directions, such as the commercialization of therapies based on that work. In practice, technical expediency often dictates researcher choice, IP considerations are left to legal counsel, and ethics are delegated to a review board. Given such specialization in the R&D decision-making processes, interactions are often overlooked.

Overlooking interaction among the three domains involves both a conceptual and a practical error. The conceptual error is to ignore the profound ways in which these domains are mutually constitutive categories: norms and practices of sharing data and materials, even "scientific practices" enabling technical laboratory work, are simultaneously issues of property (e.g., in what ways are data and materials individual property or joint property?) and ethics (e.g., what constitutes best practice and ethical conduct with respect to the sharing of data sets and materials?). Likewise, too often, issues of property rights in works, data, and inventions are compartmentalized within science policy discussions, and therefore divorced from larger concerns of ethics in science or bioethics. As a result, IP policy is sometimes managed as if it were only a technocratic system that did not implicate important ethical and political questions, such as the distribution of resources, social justice, and the ethos of science. Conversely, IP issues are rarely raised within international bioethics documents, and this is a major shortcoming.[181] Data sharing questions are, at their root, property questions, which are, in turn, ethics questions. To separate these questions is to perform a conceptual purification that prevents optimal solutions.

Yet the overlap is not merely conceptual; it is also practical, as the preceding discussions of each domain in Part I suggested. As the recently encountered

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Christopher Thomas Scott & Henry T. Greely, *The Paths Around Stem Cell Intellectual Property*, 24 NATURE BIOTECH. 411 (2006).

181. For example, the Hinxton Consensus Statement, *supra* note 138, discusses cell banking but barely addresses issues of property in data, materials, and patents.

problems with some of the NIH hESC lines illustrate, ethical accountability can be promoted only to the extent that provenance characteristics and data about cell lines are shared.[182] Consider also the ISSCR's recommendation promoting both cell line banking and clear and accessible MTAs. This is an important aspiration, but MTAs depend entirely on the specific material and IP terms controlled by the depositor. Materials and data access issues are strongly connected to material and IP issues: Together they dictate how smoothly a cell bank will be able to facilitate access. As a consequence, efficient progress of ethically accountable stem cell research will require the consideration of complexities and bottlenecks emanating from all three domains.

In order to illustrate more deeply how these three dimensions of complexity operate together, consider three different stem cell technologies for which degrees of interaction across these domains would vary significantly: 1) a single protein growth factor; 2) a single hESC line; and 3) a multi-component or "platform" technology like a neural differentiation kit.

For a single protein like the fibroblast growth factor,[183] frequently used to propagate undifferentiated stem cells, there are minimal technical constraints in using it in stem cell culture, since its function is simply controlled by its concentration in media and its production utilizes standard recombinant methods. Production of recombinant proteins based on human proteins typically faces minimal regulatory hurdles as it uses standard biotechnology processes to make therapeutics.[184] However, the primary bottleneck in using this molecule in stem cell R&D is the uncertainty over IP claims: It is not necessarily clear whether freedom to operate extends to the use of the fibroblast growth factor to propagate stem cells. This would turn on a detailed analysis of the claims in any patent(s) granted over the fibroblast growth factor. In this example, bottlenecks in the proprietary domain interact minimally with bottlenecks in the technical and ethical domains.

At a higher degree of complexity, the selection of a hESC line for an experimental application requires an assessment not only of the relevant property rights, but also of the cell line's genetic and other technical characteristics. Furthermore, for research materials that are derived from human tissues,

182. *See supra* notes 160-162 and accompanying text.

183. Growth of hESCs has been shown to depend on this protein. *See, e.g.*, Sean C. Bendall et al., *IGF and FGF Cooperatively Establish the Regulatory Stem Cell Niche of Pluripotent Human Cells* In Vitro, 448 NATURE 1015 (2007).

184. Regulatory approval will depend on the exact administration and application of basic fibroblast growth factor, but it is being tested in clinical trials under the name Trafermin for patients with periodontitis. *See* ClinicalTrials.gov, A Phase 2 Clinical Trial of Trafermin in Patients with Marginal Periodontitis in Japan, http://clinicaltrials.gov/ct2/show/NCT00199290 (last visited Nov. 13, 2008).

researchers must take into account significant ethical or regulatory considerations. Obviously, in the United States this begins with the decision of whether to select one of the twenty-one federally-approved hESC lines. But ethical and regulatory analysis must go well beyond this. The consent forms for the donation of embryos or other human tissue used to create cell lines may restrict the scope of the resulting research, creating contractual and ethical constraints on the uses of resulting cell lines. This is precisely what has happened with the WARF cell lines. Carl Gulbrandsen, WARF's Managing Director, has repeatedly defended the strict requirement that WARF cell lines cannot be shared with third parties without an MTA from WARF on *ethical* grounds, namely that restrictions on types of research promised to embryo donors needed to be contractually protected and enforced.[185] As a result, scientists who wish to access these cell lines have to worry not only about infringing IP, but also about recognizing constraints on certain experiments, like implanting the cells into embryos, generating new embryos, or implanting cells into a uterus.[186]

As individual jurisdictions have created enforceable standards on informed consent, payment to donors, and limitations on certain types of experiments, researchers will have to establish the ethical provenance of cell lines they seek to use. For instance, are there assurances on record that the line was developed with the donor's informed consent in ways that are permitted in the scientist's home jurisdiction? The stem cell line with the best technical characteristics (e.g., low passage and clinical grade for implantation studies) may be available only for research use and may have been procured in a manner contrary to a state's provenance guidelines. For instance, the line may have been derived with materials that were paid for in contravention to California's state laws.[187] This situation is far from hypothetical: The recently discovered ethical problems with the provenance of the federally-approved hESC lines illustrate the setbacks researchers face if these conditions are not tracked carefully.[188]

The interwoven complexities facing researchers trying to find a suitable stem cell line do not end there. It is becoming apparent that the personal, medical, and biological characteristics of donors are also relevant to follow-up work with the cells derived from their donations. Donor diversity is relevant not only for basic

185. Wadman, *supra* note 61. Gulbrandsen has also stated in a *Nature Biotechnology* editorial that "WARF has always had to balance the private interests of industry, which first funded hES cell research, with promises made to donors of embryos regarding what research could be performed with them, with ethical, religious and political issues, and both state and federal policies." C. Gulbrandsen, Editorial, *WARF's Licensing Policy for ES Cell Lines*, 25 NATURE BIOTECH. 387, 387 (2007).

186. Wadman, *supra* note 61, at 273.

187. *See* CAL. HEALTH & SAFETY CODE § 125340 (West Supp. 2008).

188. *See generally* Streiffer, *supra* note 160.

scientific work, but also for uses downstream.[189] Sharing the personal genotypic and phenotypic details of material donors across laboratories may give rise to new privacy concerns and thus new responsibilities to obtain consent from donors. It is apparent that the evolving need for richer datasets implicates new ethical questions, a clear example of domain overlap.

The requisite analysis becomes even more cumbersome for a multi-component or "platform" technology like a neural differentiation kit. Figure 2 illustrates the process for obtaining differentiated neural cells from hESCs. In this case, several different component technologies need to work in concert, including an appropriate stem cell line, a vector, and culture media. Each of these components may be owned as IP by a different institution. Use of each may involve compliance with different ethical requirements.[190] Again, in this case, analysis must span all three domains—technical, IP, and ethical—and tradeoffs among the three are likely. The technology platform that is preferred for technical reasons may be encumbered by IP claims over most desired uses; while an alternative technology platform for which there is greater freedom to operate may be ethically proscribed. Thus, in order to find (or design) an enabling platform technology, all three types of bottlenecks must be considered together. Conversely, once platform technologies become packaged and standardized, they tend to lock in the technical, ethical, and proprietary characteristics of their component parts, likely narrowing the range of subsequently available alternatives for researchers.

Overall, the interplay of technical functionality, property rights, and ethics can be costly to navigate and can create situations of uncertainty and risk in pursuing stem cell R&D.[191] First, these costs act as a disincentive to conduct stem cell R&D. This disincentive reduces the overall volume and pace of stem cell R&D. Second, these costs act to skew the mix of stem cell R&D being

189. Jeanne F. Loring, Ctr. for Regenerative Med., Scripps Research Inst., Presentation at Institutional Landscapes in Stem Cell Research and Development Conference: Technical Problems Facing Stem Cell R&D (Feb. 6, 2008) (presenting work on "ethnic" SNP profiles of different hESC lines); *see also* Jeanne F. Loring, Problems and Solutions: Technical Problems Facing Stem Cell R&D, http://stsc.berkeley.edu/Events/2008%20Stem%20Cell%20Speaker%20PDFs/J_LORING.pdf (last visited Nov. 13, 2008) (slides from presentation). Nascent work has investigated whether donor characteristics—such as genomic imprinting—are maintained during culture of hESC lines. *See* Int'l Stem Cell Initiative, *supra* note 72.

190. Some culture components, like animal serum, might be isolated using procedures deemed unethical by proponents of animal rights. For example, fetal bovine serum is harvested from bovine fetuses and is commonly obtained by means of cardiac puncture without anesthesia. Animal welfare committees may argue to minimize animal suffering during such procedures. *See* Megha S. Even, Chad B. Sandusky & Neal D. Barnard, *Serum-Free Hybridoma Culture: Ethical, Scientific and Safety Considerations*, TRENDS BIOTECH., Mar. 2006, at 105.

191. *See* sources cited, *supra* note 74.

conducted, discouraging work in areas with lower expected payoffs (regardless of their potential contributions to human welfare). Third, as suggested above, they can actually narrow the set of ethically viable options available. Having fewer technical options reduces the number of ethical options, which in turn limits opportunities for collective decision-making about the ethical acceptability of technology options.

An *integrated* approach to solving problems across the three domains would increase both the efficiency and efficacy of public policy. Despite potential synergies of working across the three domains, they remained balkanized. Although a scientific data sharing architecture would certainly create efficiencies in the field, by itself it would do nothing to simplify onerous regulatory review at the institutional level, and it could even trigger new forms of regulation—e.g., if personally identifiable information on material donors were included along with cell line information. The communities knowledgeable in stem cell science, IP, and ethics would be better positioned to navigate these obstacles if they could approach them in a more integrated fashion.

### *B. Balancing Access and Property Through a Protected Commons*

While free markets are, in many cases, the best available mechanism for solving complex coordination and resource allocation problems, it has long been recognized that markets do not efficiently provide informational or knowledge-based resources such as new technologies—the very inputs and outputs of R&D.[192] The fundamental conditions necessary for markets to operate efficiently include the clear definition of property rights, access to all relevant information, and perfect competition in both supply and demand. These conditions are not met, almost by definition, for scientific knowledge and early-stage technologies, which, in their raw form as pure information, are classic public goods. In the case of classic public goods, complex coordination problems are typically solved by their public provision within the public domain, where free and open access helps to minimize transaction costs and attendant uncertainties. Yet, while open access provision within the public domain solves some market failures, it introduces others, most notably an erosion of incentives for private investment and the resultant "free rider" problem.[193]

It is also well-known that focused collective action strategies such as cooperatives or land-use associations can provide solutions for the use of open-

192. *See* Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Innovation*, *in* NAT'L BUREAU OF ECON. RESEARCH, THE RATE AND DIRECTION OF INVENTIVE ACTIVITY 609 (1962).

193. *See, e.g.*, Richard C. Levin, *A New Look at the Patent System*, 76 AM. ECON. REV. 199 (1986).

access natural resources and agricultural lands.[194] Legal scholars have argued that collective strategies to manage IP resources through a "protected commons" may be preferable to putting them in the public domain.[195] Others have suggested that targeted, industry-led, technology-specific "collaborative rights organizations" can be more efficient than government interventions, such as compulsory licenses, in ameliorating holdups or transaction costs endemic to heavily patented technology fields, such as the life sciences.[196] Reichman and Uhlir have argued that properly aligning incentives within a community of researchers through a "contractually reconstructed research commons" could overcome the prisoners' dilemmas so often confronted when sharing technical data and research materials.[197] A well-calibrated protected knowledge commons can, in theory, provide some relief from market failures associated with the provision and exchange of information, research materials, and IP rights.

Just how a protected commons might achieve this goal is best understood by decomposing the protected commons into its two aspects: the commons and its protection. The "commons" aspect of a protected commons regime seeks to regain some of the efficiencies of open access. This operates on what we might consider the upstream end of R&D, bringing together resources that many will need to share and draw upon for their downstream R&D. Likely pieces of such a commons include information about the resource or how to make its component parts interoperable; property rights or permissions to use the resource (or any of its respective components); and, if the resource is not purely informational or intangible, the actual physical components. Gathering these pieces together should minimize the marginal costs of disseminating the information or even the physical components that embody the resource, as well as the costs of engaging in negotiations or transactions to obtain it.

The "protection" aspect of a protected commons involves controlling who can use that common resource in its downstream applications. In particular, to the extent that uses of the resource are separable, its collective owners can regulate those uses separately, such as segmenting the market and charging differentiated prices or writing different contracts over those different uses. Such control can allow for a broader range of objectives to be achieved. While abuse of market

194. Elinor Ostrom, GOVERNING THE COMMONS: THE EVOLUTION OF INSTITUTIONS FOR COLLECTIVE ACTION (1990) (demonstrating that common pool resources in the environmental goods context evince a broad array of formal and informal governance structures that can and do prevent overuse, thus casting doubt on the conclusion that joint ownership necessarily leads to a "tragedy of the commons").

195. *See* Chander & Sunder, *supra* note 14, at 1337.

196. *See* Robert Merges, *supra* note 20, at 183; *see also* Gregory D. Graff & David Zilberman, *An Intellectual Property Clearinghouse for Agricultural Biotechnology*, 19 NATURE BIOTECH. 1179 (2001).

197. *See* Reichman & Uhlir, *supra* note 4, at 416-52.

power cannot be ruled out as an objective, a protected commons can enhance welfare by seeking to preserve investment incentives in those fields of use that are commercially viable, while simultaneously making the resource broadly available for most other uses at essentially zero cost, approximating the efficiencies of the public domain. Indeed, it has been suggested that constructing a protected commons at the interface between the public domain and private commerce, as a hybrid form, can better facilitate interaction between the public and private domains than relying upon either the complete exclusivity of control afforded by property rights or the complete freedom of the public domain alone.[198] A number of such collective action initiatives have emerged in the life sciences among researchers and their institutions within both the public and private sectors in order to coordinate access to data and IP.[199]

*1. PIPRA as a Model of a Protected Commons*

Models do exist for such a protected commons. One initiative, the Public Intellectual Property Resource for Agriculture (PIPRA), demonstrates well the principles and operation of a protected commons. With headquarters at University of California (U.C.) Davis, PIPRA was established in 2003 by a coalition of a dozen universities and research institutes with funding from the Rockefeller Foundation.[200] Today, the organization is growing rapidly and employs a professional staff of legal analysts and scientists.[201] The goal of PIPRA is to make agricultural biotechnologies more easily available for the development and distribution of "orphan crops"—meaning both subsistence crops developed for humanitarian purposes in the developing world and specialty crops developed for smaller-scale and often regional commercial markets. These goals are supported by analyzing and providing freedom to operate with the key research tools and enabling technologies of agricultural biotechnology.[202]

198. *See* Chander & Sunder, *supra* note 14, at 1331-74; Rai, *supra* note 18.

199. *See supra* text accompanying notes 18-22.

200. Richard C. Atkinson et al., *Public Sector Collaboration for Agricultural IP Management*, 301 SCIENCE 174 (2003); *see also* The Public Intellectual Property Resource for Agriculture, http://www.pipra.org (last visited Nov. 13, 2008).

201. Graff has been affiliated with PIPRA over its entire history and still works with the organization. Much of the material that follows is based on his personal experience with the organization. Some of this information is available on the PIPRA website, *supra* note 200; *see also* Alan B. Bennett et al., *Intellectual Property in Agricultural Biotechnology: Strategies for Open Access*, *in* PLANT BIOTECHNOLOGY AND GENETICS: PRINCIPLES, TECHNIQUES, AND APPLICATIONS 325 (C. Neal Stewart, Jr. ed., 2008).

202. For a short description of PIPRA's mission and core activities, see The Pub. Intellectual Prop. Res. for Agric., About Us, http://www.pipra.org/en/about.en.html (last visited Nov. 13, 2008).

PIPRA has grown into a collaboration of roughly fifty public and private nonprofit research institutions and universities that conduct agricultural research.[203] Most member institutions are U.S.-based, but there are members in Canada, Italy, Tanzania, the Philippines, Peru, Chile, Mexico, Vietnam, and Taiwan, with most of the recent growth in membership coming from institutions outside the United States. When joining PIPRA, an institution signs a Memorandum of Understanding (MOU) whereby it agrees to cooperate with other members of the collective on a number of issues.[204] First, the institutions agree to work together to develop guidelines for licensing standards that will encourage product development for the broader public benefit, such as retaining rights for research use and for humanitarian use of licensed technologies.[205] The institutions also agree to contribute non-confidential information to a common database detailing which agricultural technologies in their portfolios are still available for licensing and which have become fully encumbered. Finally the institutions agree simply to explore possibilities for bundling or pooling technologies.

One of the key functions of PIPRA is to reduce uncertainty around the IP status of commonly used technologies, identifying the extent to which there may be freedom to operate or how it might be negotiated. PIPRA has launched its public database in collaboration with PatentLens, a nonprofit patent data initiative that provides web-based patent data search and patent landscape analysis.[206] The PIPRA patent database contains the agricultural portion of the patent portfolio held by PIPRA members and gives a clear picture of the availability of agricultural technologies developed across the full set of PIPRA institutions. The database contains, in addition to patent text, patent status information (such as whether it is in application, in force, or expired), and licensing status (such as whether it is available for license or sublicense, licensed exclusively, licensed non-exclusively, or licensed in all or some fields).

Beyond providing a patent database, PIPRA conducts analysis to advance common goals of researchers within its member institutions. First, PIPRA

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203. According to its website, "PIPRA membership is open to any university, public agency, or nonprofit research institution actively engaged in agricultural research." *Id.*

204. *See* The Public Intellectual Property Resource for Agriculture, *supra* note 200.

205. Once developed, these standard licensing terms are voluntarily adopted by PIPRA member institutions and, as with any boilerplate language, are modified and adapted to specific situations. The fact that the standard licensing terms have been thoroughly vetted and standardized, however, makes them more broadly accepted by those in industry negotiating technology licenses with PIPRA member institutions. *See* Ashley J. Stevens & April E. Effort, *Using Academic License Agreements To Promote Global Social Responsibility*, 43 LES NOUVELLES: J. LICENSING EXECUTIVES SOC'Y 85, 89 (2008).

206. *See* Patent Lens, http://www.patentlens.net (last visited Nov. 13, 2008); Pub. Intellectual Prop. Res. for Agric., PIPRA Patent Search, http://search.pipra.org (last visited Nov. 13, 2008).

conducts preliminary searches of patent and non-patent prior art to support freedom to operate analyses of important technologies, looking at the question of global ownership.[207] The analyst team at PIPRA identifies relevant patents and licensing information, and it makes preliminary validity assessments. The end result is a set of recommendations that public sector researchers can consider when deciding how to proceed with research or commercialization. These include suggestions on strategies to "invent around" or to acquire sublicenses to blocking technologies. A number of law firms support PIPRA in this public service by conducting freedom to operate analyses on a pro bono basis.[208] Second, PIPRA maps IP across broad sets of technology. These "patent landscapes" can vary in degree of detail but generally do not go into the same level of detail as a freedom to operate analysis. Rather, a patent landscape of a broad set of technologies can provide a starting point for freedom to operate research on a narrower subset of technologies or support research on industry trends and policy shifts that may affect or be affected by IP in agriculture.[209]

Based upon its database resources and IP analysis, PIPRA is developing enabling technologies for plant biotechnology. The first project undertaken involves a vector for the insertion of DNA into a range of plant cells, an important crop development tool in agricultural biotechnology. Currently, IP on this vector has effectively blocked its commercial use outside of the several major corporations that have integrated dominant patent portfolios in plant biotechnology, clamping down innovative activity in this space.[210] In order to avoid this bottleneck, PIPRA is attempting to develop a novel transformation vector in the lab[211] using technologies for which freedom to operate has been established, whether because they are in the public domain[212] or owned by

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207. Gillian M. Fenton, Cecilia Chi-Ham & Sara Boettiger, *Freedom to Operate: The Law Firm's Approach and Role*, *in* 2 INTELLECTUAL PROPERTY MANAGEMENT IN HEALTH AND AGRICULTURAL INNOVATION: A HANDBOOK OF BEST PRACTICES 879 (Anatole Krattiger et al. eds., 2007), *available at* http://www.iphandbook.org/handbook/chPDFs/ch14/ipHandbookCh%2014%2004%20Fenton-Chi-Ham-Boettiger%20FTO%20and%20Law%20Firm%20Roles.pdf.

208. Some of the legal affiliates are listed on the PIPRA website. *See* The Public Intellectual Property Resource for Agriculture, *supra* note 200. PIPRA also engages pro bono services through the Public Interest Intellectual Property Advisors (PIIPA) network. *See* Public Interest Intellectual Property Advisors, http://www.PIIPA.org (last visited Nov. 13, 2008).

209. *See, e.g.*, Bergman & Graff, *Global Stem Cell Patent Landscape*, *supra* note 28; Gregory D. Graff et al., *The Public-Private Structure of Intellectual Property Ownership in Agricultural Biotechnology*, 21 NATURE BIOTECH. 989 (2003).

210. Graff et al., *supra* note 209.

211. *See* Alan B. Bennett et al., *Enabling Technologies for Grape Transformation*, *in* PIERCE'S DISEASE RESEARCH SYMPOSIUM PROCEEDINGS 239, 240 (2007), *available at* http://pd.pipra.org/Proceedings/2007/2007_249-252.pdf.

212. *See* Sara Boettiger & Cecilia Chi-Ham, *Defensive Publishing and the Public Domain*, *in* 1

PIPRA member institutions and available for license. In the end, roughly six of the fifty PIPRA members will be contributing technologies to the vector system and will do so under a separate and more complex IP agreement than the MOU establishing PIPRA membership.[213] PIPRA is developing an out-licensing model for the vector whereby the bundle of technologies that comprise the vector can be made widely available under a single non-exclusive license—in effect a patent pool—but with separate terms for research, humanitarian, and commercial uses.[214] Much effort has gone into discussions and negotiations with the technology owners, all of which are PIPRA member institutions, to find a balance that preserves commercial interests while carving out space for public research and humanitarian uses.[215] If the project is successful, vectors will be distributed free of charge within the public sector for research and humanitarian use. Private companies will pay a royalty to use the vectors commercially. The royalties will help to cross-subsidize the administration of the patent pool for research and humanitarian uses. Any remaining royalties will be distributed among the owners that made their technologies available for use in the vector. The project requires close collaboration between researchers in the lab, PIPRA staff performing the IP searches, and supporting law firms doing the freedom to operate analysis. This degree of IP "self awareness" guiding the research design is uncommon, but is gaining momentum in the public sector.[216]

What may be our most nuanced observation of the PIPRA model is the multiple cascading or concentric protected commons that have emerged around

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INTELLECTUAL PROPERTY MANAGEMENT, *supra* note 207, at 879, 889, *available at* http://www.iphandbook.org/handbook/ch10/p01.

213. Henry Lowendorf, Presentation at the 2008 Annual Meeting of the Association of University Technology Managers: PIPRA Vector Licensing Strategy (Feb. 29, 2008).

214. *See* Gregory D. Graff et al., *Intellectual Property Clearinghouses as an Institutional Response to the Privatization of Innovation in Agriculture*, 3 AFRICAN TECH. DEV. F. J. 11, 14 (2006), *available at* http://www.atdforum.org/IMG/pdf/ATDF_Journal_October_2006_V3_I3.pdf; Amy Yancey & C. Neal Stewart, Jr., *Are University Researchers at Risk for Patent Infringement?*, 25 NATURE BIOTECH. 1225 (2007).

215. It is important to point out that PIPRA does not have ambitions to in-license technologies and offer sublicenses. Rather, as a collective of public sector institutions that routinely out-license their own agricultural technologies, PIPRA's role is to identify anti-commons issues and then set up and help manage the complex licensing arrangement between the technology owners. Specific arrangements are likely to differ markedly depending on the nature of the particular technology involved, the set of owners, and its commercial potential.

216. Anatole Krattiger, *Freedom to Operate, Public Sector Research, and Product-Development Partnerships: Strategies and Risk-Management Options*, *in* 2 INTELLECTUAL PROPERTY MANAGEMENT, *supra* note 207, at 1317, 1320-26, *available at* http://www.iphandbook.org/handbook/chPDFs/ch14/ipHandbook-Ch%2014%2001%20Krattiger%20FTO%20and%20Public%20Sector%20Strategy.pdf.

the initiative. First, PIPRA's MOU requirement creates a boundary that, however faint in legal terms, helps define a community with common interests. The act of signing the MOU triggers an internal dialogue at each institution, wherein the officers and researchers of that institution must at least consider and endorse the principles of collective action espoused by the PIPRA community. The next definitive collective act is that of contributing IP status data to the PIPRA database, which requires some commitment of time, resources, and information. This act creates a common resource. A third level of common resource emerges from the many freedom to operate and patent landscape analyses that PIPRA conducts: a rapidly accumulating body of knowledge and expertise about the IP landscape specific to the field of plant biotechnology. The raw freedom to operate data informing this body of knowledge is indeed a protected resource: Freedom to operate opinions are not published, in part to protect the contributing pro bono attorneys' opinions from public disclosure and associated liabilities, but also to maintain some degree of strategic benefit on behalf of the public institutions that make up PIPRA. This common knowledge resource is made available to PIPRA members in three main forms: first, through technical advice and freedom to operate recommendations made directly to scientists and technology transfer officers; second, through published studies and IP landscapes; third and perhaps most importantly, through the technical choices designed into the enabling technology platform licensed under a patent pool. That specific technology platform, which requires IP permissions granted under a single license with different terms and royalties for different fields of use, is the fourth and highest level of protected commons achieved by PIPRA.

*2. Lessons from PIPRA for Stem Cell Research*

The model for bundling or pooling IP observed in PIPRA's transformation vector project—to be licensed for a wide range of commercial and non-commercial uses—may well be useful in stem cell research and other areas of the life sciences. Indeed, patent pooling has been proposed for the field of stem cells to consolidate IP and simplify the process for obtaining freedom to operate with the most widely used research tools and methods.[217] However, drawing lessons from PIPRA for the opening of stem cell R&D requires attention to those issues and constraints confronting stem cell R&D that are distinct from those in plant biotechnology.

For a cascading set of protected commons to be useful, it will need to unfold differently. For instance, the set of member institutions involved in a stem cell

217. Bergman & Graff, *Global Stem Cell Patent Landscape*, *supra* note 28; Ted J. Ebersole, Robert W. Esmond & Robert A. Schwartzman, Stem Cells–Patent Pools to the Rescue? (June 2005) (unpublished manuscript, *available at* http://64.237.99.107/media/pnc/8/media.668.pdf).

initiative may need to encompass biotech companies as well as publicly funded research institutions, given the central role that companies have played in the development of this technology. Furthermore, for stem cell R&D, the design of a common data resource may need to encompass more than just IP data, as the PIPRA data resource does. Given the intersections of the domains discussed above, such a resource ought to integrate technical characterization, ethical provenance, and regulatory compliance data. To the extent that multiple types of data are included, the protections maintained around that data commons may need to be stronger and may even need to include differentiated levels of access for different kinds of users and uses.

Finally, while potential commercial payoffs from stem cell therapies are difficult to establish at this early stage, high expectation held by researchers or institutions may make them reluctant to take any actions that they might perceive as relinquishing control over a valuable technology. Yet, on the other hand, the expectation of high payoffs may itself invoke the very value of creating common resources. High expectations of commercial payoffs may also, conversely, increase the need for reliable strategies that would enable non-commercial, small market, or generic applications of the technology.[218]

### *C. Push from Funders*

In the classic collective action problem, a diverse set of actors may share common interests that can only be achieved through collective action, yet no one individual actor's incentives are sufficient to overcome the inertia of inaction. Mobilization requires leadership in the form of coordination and making fixed initial investments. This certainly seems to be the case for addressing the problems facing stem cell R&D. Sufficient conditions for collaboration have not yet developed in any one of the three domains discussed, nor have they developed across domains. Under such circumstances, it will be necessary to motivate potential actors through the use of various carrots and sticks.

Here we can draw on the experience of successful collaborations in the life sciences for ideas. The examples of PIPRA and the Human Genome Project, discussed below, suggest that a push from funders may be critical. Forward-looking project funders can help motivate diverse institutions and can help establish the architectures that enable collaboration. For PIPRA, the initial push came from the willingness of the Rockefeller Foundation to convene meetings of key players in 2000 and 2001 and make grants that funded the initial personnel for the activities described above. The Rockefeller Foundation, with its long

218. *See* Stevens & Effort, *supra* note 205 (suggesting a licensing approach with differentiated prices or terms in order to simultaneously serve both the commercial and the social or humanitarian goals of university technology commercialization).

history of funding research in crop genetic improvement for agriculture in low-income countries, provided not only financial leadership, but also clear moral leadership around commonly-held humanitarian goals. These actions proved sufficient to mobilize the original coalition of universities and research institutes to engage in collective action that generated benefits well beyond the scope of the Rockefeller Foundation's initial goals.

The Human Genome Project and its follow-on projects exemplify how large funders of public science can drive international collaborative research efforts to create common data resources for widespread use.[219] From the mid-1990s, both the Wellcome Trust in the United Kingdom and the NIH in the United States supported data sharing of the human genome sequence as it was generated. The Wellcome Trust provided the critical leadership in this regard, sponsoring a meeting of international scientists and funders in 1996 that gave rise to the "Bermuda Principles."[220] These principles state that funded centers generating the human genome sequence should make that information freely available in order to encourage its broad use in research and maximize benefits to society.[221] The Bermuda Principles also state that primary genomic sequence information should be released "as soon as possible" and that assemblies greater than one kilobase should be released on a daily basis.[222]

Public funders have acted decisively to implement the Bermuda Principles and other data sharing initiatives within genomics. For instance, the NIH made its commitments to the Bermuda Principles clear in its request for proposals for large-scale sequencing centers, using its funding power to receive assurances from grantees that they would act in accordance with the Bermuda Principles.[223]

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219. For detailed accounts of how this was accomplished, see Eisenberg & Nelson, *supra* note 16, at 94-99; see also Robert Cook-Deegan, *The Science Commons in Health Research: Structure, Function, and Value?*, 32 J. TECH. TRANSFER 133, 136-45, 149-52 (2007).

220. WELLCOME TRUST, SHARING DATA FROM LARGE-SCALE BIOLOGICAL RESEARCH PROJECTS: A SYSTEM OF TRIPARTITE RESPONSIBILITY (2003), *available at* http://www.genome.gov/ Pages/Research/ WellcomeReport0303.pdf; Human Genome Project Information, Policies on Release of Human Genomic Sequence Data, 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 (last visited Nov. 13, 2008) [hereinafter Bermuda Principles].

221. Bermuda Principles, *supra* note 220.

222. *Id.*

223. *The Human Genome Project: How Private Sector Developments Affect the Government Program: Hearing Before the Subcomm. on Energy and Environment of the H. Comm. on Science*, 105th Cong. 21 (1998) (testimony of Francis S. Collins, Dir., Nat'l Human Genome Research Inst.), *available at* http://www.hhs.gov/asl/testify/ t980617a.html; *see also* Eisenberg & Nelson, *supra* note 16, at 97-98 (stating that "[t]he public sponsors of the Human Genome Project stressed the importance of prompt and unrestricted access to the sequence, which they ensured by requiring

Free access to the genome became a touchstone across the public genomics community, thereby prompting pre-publication disclosure policies and the acceleration of public funding to complete the sequence before private competitors appropriated it as a private resource.[224] Furthermore, the Wellcome Trust and NIH used their funding power to promote a public consortium on Single Nucleotide Polymorphisms (SNPs), though it was ultimately the private sector that determined it was in their common interests to form a public database of SNPs called the "SNP Consortium."[225] The NIH houses an important SNP database,[226] and sharing within the International Haplotype Map project has also been driven by funder involvement.[227]

Complementing this important role of funders, journal publication policies have also played a key role in promoting open access to genome data, especially with regard to the private sector competitors of the public genome projects. Craig Venter and his company Celera acknowledged the importance of free access in the form of quarterly data release,[228] but he later repudiated this idea.[229] As Eisenberg and Nelson describe it, "[a]lthough Celera's promised quarterly data releases never occurred, Celera agreed to provide limited access to its data free of charge on its own web site as a condition of publication in *Science*, subject to restrictions that preserved the market for its proprietary products."[230]

The experience with genomics carries important design lessons for opening up stem cell R&D. Because of the competitive nature of laboratory work at the cutting edge of a potentially lucrative field, it is likely that only public funders will have sufficient clout to mobilize players to overcome the reluctance or inertia of the classic collective action problem. Funders are well positioned not only to construct data sharing architectures, but also to enforce them through the power of the purse and moral suasion.[231] As a collaborative architecture comes

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grantees to deposit new sequence data in the publicly accessible Genbank database within twenty-four hours").

224. Eisenberg & Nelson, *supra* note 16, at 96-98.

225. Cook-Deegan, *supra* note 219, at 151-52.

226. *See* NCBI, Entrez Single Nucleotide Polymorphism, http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp (last visited Nov. 13, 2008).

227. *See* International HapMap Project, http://www.hapmap.org/index.html (last visited Nov. 13, 2008); *see also* Eisenberg & Rai, *supra* note 49, at 1191 (noting that "[w]ithin genomics, public research sponsors like NIH and the U.K.'s Wellcome Trust have applied normative pressure to achieve widespread data dissemination").

228. J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304, 1306 (2001).

229. Cook-Deegan, *supra* note 219, at 141.

230. Eisenberg & Nelson, *supra* note 16, at 98.

231. *See* Reichman & Uhlir, *supra* note 4, at 332 (arguing that government funding agencies "are in a position to reinforce the underlying norms of science by suitable contractual provisions

into being, funding agencies could make data contribution and participation a contractual obligation of grantees, in order to enhance or at least maintain the public value generated by their research grants.

The lack of U.S. federal funding and leadership on hESC research has meant that the field, at least in the United States, has lacked a clear leader with a coordinating mandate. Even the simple collection of technical information in scientific research has arguably been under-funded.[232] Yet, within the United States, it is precisely the major funding agencies, such as CIRM or the NIH,[233] that have important roles to play in supporting and enhancing a protected knowledge commons in stem cell research.

### *D. Use of a Contractual Legal Regime*

Although we imagine the role of public funders such as government agencies and legislatures to be quite important in providing the impetus for promoting sharing and in coordinating the domains of ethics and patents, we do not believe that such solutions should as a general matter be driven by statutory change, whether in data protection law, patent law, or reform of the Bayh-Dole Act. Rather, a regime of liability rules developed through contracts ought to drive the solutions in stem cell research. Such a regime would entail both funding agreements between public funders and research institutions, and commitments among major research institutions as manifested in the PIPRA initiative.[234]

A first rationale underlying this preference for a contractual regime is our observation that effecting meaningful change in existing laws and regulations can be costly and time-consuming, particularly given the degree to which the current system represents a stalemate between competing interests that have chosen to use stem cells as a symbolic issue in larger cultural battles. Also, statutory changes are country-specific, and while positive changes in any individual jurisdiction are welcome, they are unlikely to be emulated in all other jurisdictions important to the global stem cell research community. Instead, a

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that regulate access to data before and after publication of the research results").

232. *See* Stephen M. Maurer & Suzanne Scotchmer, *Database Protection: Is It Broken and Should We Fix It?*, 284 SCIENCE 1129 (1999); Stephen M. Maurer, Richard B. Firestone & Charles R. Scriver, *Science's Neglected Legacy*, 405 NATURE 117 (2000).

233. It should be noted that NIH earmarked an estimated $42 million for work on hES lines for 2008 and $203 million for human non-embryonic, including adult, stem cell work. *See* Nat'l Insts. of Health, Estimates of Funding for Various Diseases, Conditions, Research Areas, http://www.nih.gov/news/fundingresearchareas.htm (last visited Nov. 13, 2008). It is likely, however, that federal support for hESC research will dramatically increase with the new administration in January 2009, although this is not reflected in the current official NIH estimates.

234. The classic description of such contractually-constructed organizations of property rights is Merges, *supra* note 90.

contractual regime has the flexibility and adaptability to coordinate action among researchers across multiple national jurisdictions. Developing a contractual regime depends on persuading only those institutions with a stake in stem cell R&D to agree and act, not legislatures, courts, or by extension all of the interest groups within society prevailing on those deliberative bodies.

Second, it is not necessarily clear which general legislative changes are warranted to achieve the goals of greater efficiency and equity in R&D. Even if an ideal statutory regime were to be achieved, it would certainly not eliminate all complexity or coordination problems, particularly given the rapid pace of technological change in the field. While legislative solutions might improve conditions around new discoveries going forward, it is not clear how or whether they would be able to alter the established legacy with respect to existing IP or the provenance of stem cell lines already harvested. Yet, at the same time, we can also imagine that certain statutory changes could be entirely consistent with and complementary to the contractual approach. In fact, a contractually constructed consortium that provides even some of the functions we have proposed could supply policymakers with both the integrative perspective and the analytical data needed to design and implement welfare improving reforms.

Third, we recognize that policies specific to stem cells perhaps should not (or could not) drive science policy in general. While it may very well be that changes in background property rules would be important for advancing national science and technology policy more broadly,[235] such a conclusion would require analysis that is beyond the purview of this article.

Fourth and finally, a contractual regime may be more flexible and adaptive to the ever-changing technical, IP, and regulatory environments. And even if, in the end, the policy community achieves an ideal statutory reform eliminating market failures in the stem cell R&D environment, it could be relatively simple and costless to dissolve a contractual regime and move on to new problems.

### *E. An International Scope*

Because the problems outlined above are international in character, the international level is the proper level for political action. As the Hinxton group says, both "intra- and international scientific collaboration are vital to the success and advancement of science."[236] Because research groups are distributed across the globe, there is a need to promote data and materials sharing globally. Patents

235. For commentary on the larger need to rethink the Bayh-Dole Act, see, for example, Boetinger & Bennett, *supra* note 8; David Mowery et al., *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh–Dole Act of 1980*, 30 RES. POL'Y 99 (2001); and Stevens & Effort, *supra* note 218.

236. Hinxton Consensus Statement, *supra* note 138, at 1.

are filed in jurisdictions all over the world, and the complexities of ethical regulation are compounded on the global scale. Markets for patents and cell lines are global, and the proper tracking of ethical compliance will require broad cooperation in the provision of provenance information and documentation of ethical compliance.

For all of these reasons, we imagine that solutions for the problems discussed above would be best addressed at the international level. While efforts to harmonize regulations across the United States are very useful, they do not go far enough. Efforts to establish a database to document the regulatory patchwork and the ethical validation of materials should be global in scope in order to address the international nature of science and the market in research materials.[237]

### *F. Self-Reflexivity and Multivalent Evaluation*

Stem cell R&D promises to be a complex, pervasive technology in many areas of health care.[238] Because modern biotechnologies deeply implicate many dimensions of human life and values, societies across the world have pushed for more transparent, accountable, and diverse evaluations of costs and benefits.[239] We imagine that any viable solution to alleviate R&D constraints on stem cell R&D, such as a contractually constructed commons described in Section D above, will require built-in systematic mechanisms to periodically evaluate its course. Mechanisms for "multivalent" evaluation should include participation from interest groups and individuals with different values and goals. Such methods can help to systematically reevaluate the distributive consequences of stem cell R&D as it unfolds across global markets and societies, to enhance civic deliberation, to incorporate ordinary citizens as active subjects in an expert discourse, and even to reframe regulatory and social policies.[240]

A contractually-constructed commons will have to distribute decision-making power among its various participants who contribute inventions or resources to be utilized within the protected commons. The power held by each participant will likely fluctuate as new inventions and resources arise or change in value. Further, new entrants into stem cell R&D may embrace goals different from those of the incumbents. All of these factors present challenges for just

237. *See* David Magnus & Mildred K. Cho, *Issues in Oocyte Donation for Stem Cell Research*, 308 SCIENCE 1747 (2005) (arguing the need to address the ethical and regulatory complexities involved in the international transmission of stem cell materials).

238. *See* REGENERATIVE MEDICINE, *supra* note 23.

239. *See* SHEILA JASANOFF, DESIGNS ON NATURE (2006).

240. *See generally* Sheila Jasanoff, *Technologies of Humility: Citizen Participation in Governing Science*, 41 MINERVA 223, 223 (2003) (arguing that policymakers need to utilize democratic, participatory strategies for critically evaluating and assessing "the unknown and the uncertain" risks posed by modern technologies).

governance of the contractual arrangements as conditions change.

Consider what kinds of periodic, multivalent evaluation mechanisms and methods can be developed. Social institutions often incorporate self-reflective elements to critically examine and guide the course of their development. For example, the scientific review board in corporate settings examines scientific progress of the company's projects. Further, if the law as a whole is viewed as a social institution, the appeal process could be considered a reflexive mechanism. Each step in the step-wise unfolding of the contractual regime could be used as a reflexive moment.[241]

Renewed calls for greater transparency and public participation in the governance of science have been particularly strident in the life sciences.[242] Structures to examine the relationship between stem cell R&D and human health are needed to respond to these calls for the democratization of R&D. Correspondingly, patient advocates, taxpayer groups, and foundations should be formally integrated into R&D decision-making through reflexive measures. While the effectiveness of particular measures like citizen juries and consensus conferences are the subject of current research,[243] forming an intellectual environment in which outsiders are encouraged to share their knowledge would likely increase the assurance of quality and reliability in commons-building projects undertaken and the types of R&D they enable.

## III. INSTITUTIONAL COLLABORATION FOR STEM CELL RESEARCH AND DEVELOPMENT: A MULTI-STAGE ROADMAP

The current scientific, social, economic, and legal institutions within each of the three domains are not adapted to the needs of this fast-moving, complex field of research. Norms around data and material sharing remain aspirational, with few enforcement mechanisms. The landscape of existing data registries and cell banks remains fragmented and underdeveloped. In their licensing transactions, individual universities and research institutions must balance collective goals of openness against individual objectives of maximizing revenue. Where innovation is complex and cumulative, the resulting system of bilaterally negotiated technology licenses is not likely to maximize public welfare. Furthermore, relying on decentralized research oversight is unlikely to address adequately the ethical issues specific to stem cells, including the need for transparent and

241. Of course, additional mechanisms at longer or short frequencies can evaluate the collaborative for different purposes of institutional reorientation and learning.

242. *See* Jasanoff, *supra* note 240, at 235-38.

243. In health care, see, for example, Julia Abelson et al., *Deliberations About Deliberative Methods: Issues in the Design and Evaluation of Public Participation Processes*, 57 SOC. SCI. & MED. 239 (2003).

efficient validation of stem cell materials as they move across jurisdictions. We argue that targeted collective action among those institutions actively engaged in stem cell research that takes an integrated approach across the technical, proprietary, and regulatory domains could advance a number of important policy goals.

Building on the design principles described in the preceding Section, we propose a template for undertaking collective action, outlined in a progression of three stages. In the first stage, an international coalition of research institutions and funders could establish a collaborative data architecture for the collection, standardization, and organization of non-confidential information. This information should include details of the technical characterizations, the IP status, and the ethical provenance of stem cell materials and research tools. Born out of existing efforts, this architecture would promote information sharing across research labs, institutions, and jurisdictions. Where previous efforts have foundered, large funding institutions could drive such an initiative by requiring grantees to upload data according to mutually determined norms. Such a commitment and implementation mechanism from funders would separate this proposal from past efforts that have fallen short.

In the second stage, the consortium members would identify high-priority technical, proprietary, or ethical bottlenecks. This stage would develop a centralized analysis of bottlenecks in the field and options for overcoming them, utilizing data collected in the first stage. In the third stage, collaborating institutions could deliberate, design, and deliver solutions that would break through or work around the selected bottlenecks. Specific products from stage three might include coordinated ethical reviews and pools of IP.

### *A. Building an International Collaborative Data Architecture*

The first step toward developing solutions to the problems discussed above would be the development of an international consortium of funding institutions and research institutions to lay the normative and political groundwork for a database architecture that goes beyond what has been accomplished to date. Disease groups and stem cell advocacy organizations could play a major role here, as the moral impetus should come, in part, from those groups whose constituencies depend critically upon global public goods.[244] But, it should also rely upon the professional self-interest of researchers to gain access to better data resources and thereby enhance their productivity and chances of scientific

244. It was just this sort of initiating action of a few leading institutions that enabled the PIPRA project to take root against collective action obstacles and disincentives. *See supra* note 200 and accompanying text.

success. [245] The lack of success to date in this arena suggests that generating and sustaining the support and interest for such an initiative will require new carrots and sticks from scientific funders. Furthermore, a successful architecture would necessarily include information reaching across the technical, proprietary, and ethical domains.

*1. Carrots and Sticks to Promote Research Sharing*

Such a consortium, which could grow out of a high-level meeting similar to the summit at which the Bermuda Principles were adopted for the genomics field, would articulate collective norms for the sharing of cell line characterization data, IP data, and ethical provenance data for major stem cell researchers around the world. The challenges for constructing and maintaining a useful international data architecture are significant. A simple articulation of norms would not go far enough: as discussed above, groups like the ISSCR and the Hinxton Group have already called for enhanced materials and data sharing, without robust results. Past experience here underscores the need for a stronger "push" for data sharing from institutional funders.

Accordingly, success will require common approaches to implementing such a data sharing policy across the major global funders of stem cell research. In short, governmental and non-governmental funding agencies alike—from the NIH, CIRM, and Wellcome Trust, to Howard Hughes and disease organizations—could create carrots for data and materials sharing using the mechanism developed in the Human Genome Project, namely through stipulations in Requests for Proposals (RFPs). These RFPs should articulate that the funding agencies have committed to the common principles articulated, and require specific data and materials sharing plans from applicants that would feed into the commonly developed data architecture and associated cell repositories. These plans should be a crucial aspect of proposals under review. Furthermore, continuation of funding should be contingent upon demonstrating that promised sharing activities have been carried out expeditiously.

Dialogue among the member institutions of the coalition and their primary research funders would be necessary to establish a workable data sharing architecture, with realistic incentives and constraints for contributing and accessing data. Good models exist for the development of funder-supported platforms for data sharing from distributed laboratories: NIH has already supported two significant examples in the Biomedical Informatics Research Network (BIRN)[246] and the cancer Biomedical Informatics Grid™ (caBIG™).[247]

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245. *See* Reichman & Uhlir, *supra* note 4, at 442 (discussing the need for commitment by universities to overcome impediments to the construction of an "e-commons" for scientific data).

246. *See* Biomedical Informatics Research Network, http://www.nbirn.net (last visited Nov. 14,

Past experiences should be leveraged. The work of the ISSCR and the Hinxton Group could be a launching point, as those groups have already articulated norms around data sharing, but these efforts lack mechanisms for further implementation. The productive activities of the European Stem Cell Registry and/or the International Stem Cell Forum could provide the physical and informational architecture of such a database, though having the norms and commitments in place would help these projects become better funded and more comprehensive. Other templates that could be incorporated into the architecture can be found in "data commons" approaches.[248] Key elements for such approaches include a commitment to broad dissemination of data for research use and an implementation of software tools to facilitate meta-analysis of the data.

*2. Contents of the Collaborative Data Architecture*

What would such a collaborative data architecture contain, and how would it go beyond existing efforts? Broadly, this effort would explicitly attempt to alleviate the search costs and information asymmetries described in Part I.

Ideally, researchers, technology transfer directors, and SCRO directors ought to determine the specific technical content of the collaborative data architecture in a dynamic and evolving process. However, certain features will obviously add great value. The scientific community has characterized a variety of stem cell technologies central to stem cell R&D and the data needs associated with them.[249] At the core of the field are, of course, specific *stem cell lines* established from human research subjects. The suppliers of the stem cell lines could provide

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2008).

247. *See* Nat'l Cancer Inst., Cancer Biomedical Informatics Grid™, https://cabig.nci.nih.gov (last visited Nov. 13, 2008).

248. For a detailed proposal for an inter-university project to protect the scientific data commons, and the logic of public good creation as well as university self interest underlying it, see Reichman & Uhlir, *supra* note 4, at 429 ("[U]niversities and nonprofit research institutions that depend on the sharing ethos, together with the government science funding agencies, should consider stipulating to suitable 'treaties' and other contractual arrangements to ensure unimpeded access to commonly needed raw materials in a public or quasi-public space. From this perspective, one can envision the accumulation of shared scientific data as a community asset held in a contractually reconstructed research commons to which all researchers have access for purposes of public scientific pursuits.") (internal citations omitted).

249. Notable examples include the ISSCR Standards Committee and the International Stem Cell Forum characterization project. *See* Peter W. Andrews et al., *The International Stem Cell Initiative: Toward Benchmarks for Human Embryonic Stem Cell Research*, 23 NATURE BIOTECH. 7 (2005); Jeanne F. Loring & Mahendra S. Rao, *Establishing Standards for the Characterization of Human Embryonic Stem Cell Lines*, 24 STEM CELLS 1 (2006) (outlining a plan to identify a set of standard methods for characterizing cell lines).

anonymized genetic and other cell biology characterizations, while scientists at member institutions could provide details about other technical characteristics, such as clinical grade, karyotype, immunohistochemical markers, sex of donor, pluripotency measures, availability of a single nucleotide polymorphism (SNP) profile, or infectious agent tests. Since scientists tend to choose a stem cell line based not only on the line's technical characteristics but also on its ability to interface with other stem cell technologies, it will be helpful to list compatibility with other associated technologies.[250] Figure 3 shows the proposed expansion of the informational content. The details within each category will necessarily evolve and expand over time as stem cell biology and characterization increases in sophistication.

The heart of the IP information gathered would consist of a detailed listing of all patents associated with stem cell lines and technologies that are owned by the members of the coalition. This would include non-confidential information about the licensing status of each patent, indicating the availability of that technology for research, non-commercial (i.e., public health), and commercial uses.[251]

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250. Other associated characteristics of stem cell materials and technologies can be divided into five primary categories, including *derivation*, *growth*, *characterization*, *differentiation*, and *delivery*. Characterization assays are highly useful for establishing the degree of heterogeneity that may arise because of different genotype, isolation and culture protocol, or long-term adaptation to culture. Stem cell scientists currently expect the details of each derivation method to be important for the subsequent properties of the stem cell line, and the effects of many derivation details have yet to be researched fully. Growth factors and culture materials are propagation technologies that address the question of how to grow and maintain stem cells effectively. The last two categories of *differentiation* and *delivery* address more downstream uses of stem cells. *See supra* fig.2. Differentiation, or maturation, of a stem cell line into a particular cell lineage is an inherent property of stem cells that is typically exploited by researchers. Differentiation technologies include factors and culture materials that in many respects recapitulate natural development in a cell culture or exploit novel pharmacological compounds. Finally, the celebrated use of stem cells themselves or their progeny at a site of disease or injury necessarily involves cell delivery technologies. For injected or implanted cells to function effectively at the site of disease or injury, researchers use an array of delivery technologies to maximize cell survival and integration with the host.

251. Basic data on published patents and patent applications can be obtained directly from the USPTO or any of a number of patent data providers such as Thomson Innovation. *See* Thomson Innovation, http://www.thomsoninnovation.com (last visited Nov. 13, 2008). The patent data can be further customized by analysts or programmers employed by the coalition to make the listings more useful to stem cell researchers, such as assembling related patents claiming parts of the same technology into "technology clusters" and associating the technologies claimed in patents with publications in the research literature. In addition, the non-confidential information about the licensing status of each patent provided by participating institutions can indicate the availability for licensing of each of their stem cell patents—even if merely identifying each patent as "exclusive

| ***Technology Category*** | ***Informational Domains*** | | |
|---|---|---|---|
| | Technical | IP | Ethical |
| Stem cell lines | | | |
| Derivation | | | |
| Growth | | | |
| Characterization | | | |
| Differentiation | | | |
| Delivery | | | |

Focus of current database efforts

Proposed expansion of focus

**FIGURE 3. Domains of Information Collection**
Stem cell technology data needs to cover multiple technologies and domains of information. This schematic indicates where current data-centralizing efforts in the stem cell research community are focused: on technical information about stem cell lines. We propose expanding such data centralizing efforts to include more stem cell technologies and more types of information.

Lastly, this information resource would bring together information detailing the provenance and oversight associated with particular stem cell lines and related research material. National or regional regulations[252] pertinent to particular technologies would be listed on a country-by-country or state-by-state jurisdictional basis. For any given cell line, potential users would want to know the jurisdiction in which stem cells were derived, regulation of gamete or embryo procurement, derivation details, and whether the line has various types of "ethical approval" by oversight committees and other stem cell repositories. Furthermore, users would want to know whether particular cell lines satisfy the law in these

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license available for all fields of use," "non-exclusive license available for all fields of use," "license available for limited fields of use," or "license unavailable." Basic terms of availability for research use under MTA could be indicated, and contact information for obtaining materials and necessary documentation could be provided. Scientists might even post additional terms of exchange, such as co-authorship requirements, which they may choose to place on the distribution of a particular cell line or a technology for research purposes. The compilation of information on coalition members' IP and its availability for research or for licensing can be quite useful for those analyzing the IP implications of combining specific technologies. Taken together, such information might be considered an IP analog to a "universal listing" of real estate within a given metropolitan area.

252. *See supra* Section I.C; *see also, e.g.*, Rosario M. Isasi et al., *Legal and Ethical Approaches to Stem Cell and Cloning Research: A Comparative Analysis of Policies in Latin America, Asia, and Africa*, 32 J.L. MED. & ETHICS 626-40 (2004).

different jurisdictions, and how the different voluntary guidelines recently adopted by the National Academy of Sciences[253] and by the ISSCR may apply to that line.[254]

*3. Promotion of Materials Sharing and Stem Cell Banks*

The collaborative data architecture could also help promote materials sharing within the research community. More technical characterization data on stem cell materials would enable their usage in more research projects that would increase the overall flow of materials in the community. Uncertainty about use of stem cell materials would be reduced, as key proprietary and ethical information would be made transparent. Stem cell banks are expected to be key participants in the development of the initial architecture, and better integration of data about their lines would likely increase usage of those lines. Overall, it will not be necessary to build more physical repositories of stem cell materials to increase the circulation of stem cell materials, but the data and the data architecture itself should function to leverage existing physical capacity for material production and distribution.

In the end, a collaborative data resource would couple well with current plans to network stem cell banks, such as the International Stem Cell Banking Initiative.[255] Bank participation would be a convenient way to gather high quality data on existing cell lines. Further, a collaborative data resource could also provide banks with a powerful and convenient way to manage their own information on their lines. In turn, banks would have a key role in producing and disseminating data on new cell lines, as funding mandates push labs to bank cells in public collections more quickly and reliably. Lastly, the banks could help coordinate international standards on issues relating to the cell line characterization and clinical applications of stem cells. Together, compatible architectures for data and cell line management have strong potential to open up stem cell research.

253. NRC-IOM GUIDELINES, *supra* note 109.

254. Daley et al., *supra* note 146. Salient aspects of the informed consent procedure for any material from human subjects would be listed, as well as whether there were any stipulations on the use of cell lines. These usage constraints might arise at the time the stem cell lines were derived as a result of member institutional review, or as a result of conditions imposed by embryo and gamete donors. Data would be assembled from regulatory bodies, advisory boards, stem cell repositories, and the member institutional oversight committees.

255. *See* Int'l Stem Cell Forum, ISCBI Scoping Plans, http://www.stemcellforum.org/forum_initiatives/international_stem_cell_banking_initiative/iscbi_scoping_plans.cfm (last visited Nov. 13, 2008).

*4. How Open?*

Post-publication technical data, patent data, and published regulatory data from academic institutions are public. As such, these large sections of data within the common architecture should be broadly available. As seen in the genomics experience, technical data have variable commercial potential with portions of potential interest to industry. Therefore, those sections of the database may be protected and reserved for use among members, according to agreed-upon protocols. Such sections could encourage the deposit of pre-publication technical data by researchers within particular subfields. Such protections are likely to change over time, but the overarching mission of disseminating technical data should prevail for data that lack strong rationale for protection. The consortium could also provide its members with software tools for data analysis.

### *B. Conducting Analysis of Key Constraints*

Developing a database architecture with the appropriate incentives to share data and materials would enable much greater data exchange and ethical transparency in the conduct of the research. Nevertheless, without further agreement among research institutions to improve the exchange and use of biological materials and other proprietary tools, the gains from a public data resource for stem cells will be limited. Here the PIPRA example is especially useful, illustrating how nonprofit institutions could pool resources to overcome some of the remaining bottlenecks in the field. Thus, as the data architecture is constructed, the consortium of institutions could initiate a series of other tasks that provide mutual advantages to the participants, moving the initiative from just an information clearinghouse to more of a user association.[256] This would initiate and enable the second stage of activities.

Following the needs of the stem cell research community, the second stage of key functions would be analytical, much as it was for PIPRA in the plant biotechnology research community. For widely-used cell lines, technologies, or methods, many researchers will approach the collaborative data architecture or its curators with similar concerns and questions, with many of them separately engaging in similar queries or analyses of their technical, IP, and ethical status. Conducting authoritative analyses of the most widely used cell lines and technologies and providing them to the coalition membership would create large efficiency gains for the research community.

256. Steven Wolf et al., *Institutional Relations in Agricultural Information Systems*, *in* KNOWLEDGE GENERATION AND TECHNICAL CHANGE: INSTITUTIONAL INNOVATION IN AGRICULTURE 233 (Steven A. Wolf & David Zilberman eds., 2001) (discussing various institutional arrangements for data provision across the academic and private sector in agriculture).

It is likely that in the discussion over what information to include or require in the database, coalition members will begin to identify and prioritize a set of key bottlenecks in stem cell R&D, areas where access to data and materials is particularly complicated by failure to arrive at technical, IP, or ethical terms of use. For those bottlenecks, the coalition could conduct or commission analyses that characterize the salient technical, IP, and ethical dimensions. Just as in the PIPRA example, law firms or even law school clinics could help perform such analysis on a pro bono basis. Understanding which IP claims apply to a given technology for use under a given set of circumstances is not always a simple matter.[257] These analysts could conduct such general assessments of how IP conditions are likely to affect freedom to operate within typical commercial scenarios.

For any given research tool, cell line, or technology, it will be useful to develop a more centralized analysis and validation of the real, potential and imaginable ethical issues. As discussed above, much of the burden of negotiating the patchwork of regulations has come to rest not on states or their governments, but on scientists and review committees at the level of individual research institutions.[258] At this tier, SCRO review itself would not necessarily be centralized. Rather, as illustrated in Figure 4, commonly used materials could be certified and validated centrally in ways that would save time for SCROs. Centralized ethics discussions would feed back into the individual research institutions themselves, such that expertise on local SCROs could be enhanced, enriched, and coordinated. This stage of work would entail ethical and regulatory analysis to identify bottlenecks and lay the groundwork for designing the least controversial research tools and materials.

Although these analyses initially may be conducted by scientists for technical complexity, IP lawyers for proprietary complexity, and ethicists for regulatory and ethical analysis, it will be imperative for the coalition to bring these three analyses together. Reports synthesizing these analyses will be valuable for describing the interaction of technical, IP, and ethical constraints that characterize the climate for stem cell R&D.[259]

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257. IP constraints on stem cell lines and associated technologies can include both patents and contractual obligations created by the signing of MTAs and other agreements. Determination of the IP environment typically requires detailed analysis by technically trained patent attorneys who then render an opinion on their client's freedom to operate with the given technology for that specified use. In general, however, it is still possible to survey the IP landscape around a technology and develop a reasonably well informed understanding of what IP rights are likely to circumscribe what kinds of uses.

258. This is one of the main reasons we pitch our policy solution at the level of the research institution, as explained *infra* Part II.

259. *See supra* Section II.A.

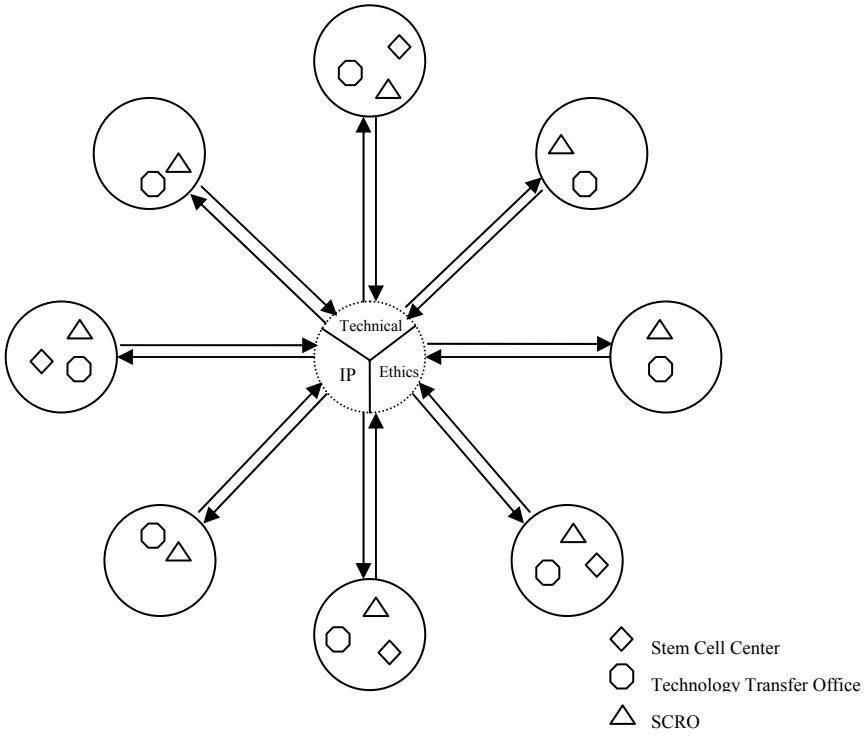


**FIGURE 4. The Stem Cell Coalition as a Coordinating Hub for Member Institutions' Decision-Makers**
Each member of the coalition has an internal SCRO providing internal policies and guidance on the ethics of stem cell research and a technology transfer office managing IP owned by the institution. In addition, each member institution's stem cell initiatives or center could directly communicate with the coalition. Alternatively, scientists may use existing national and global professional stem cell organizations to build relationships with the coalition. Without effective consultation and coordination across institutions, each of these campus-level offices makes decisions based upon its own limited information. The coalition provides a central forum for the responsible university officers to consult with one another, exchange information, benefit from commonly supported analyses, and provide input on the design of common technology platforms and standards.

### *C. Pooling, Cross-Licensing, and Other Solutions*

These analyses could illuminate important opportunities to develop solutions to common problems experienced by stem cell research institutions, labs, and start-up companies. Drawing explicitly upon the PIPRA model, the consortium could develop a protected common resource through cross-licensing and even patent pooling approaches to advance the dissemination and use of research tools to alleviate IP bottlenecks identified in the analyses of Section B above. Since these workarounds might become standard platform technologies incorporated

into a broad array of further R&D efforts, careful planning and discussion should guide the design of these tools. The tools should embody ethical choices that make the resulting technology as widely acceptable and broadly compliant as possible. Furthermore, the consortium members could pool resources and consolidate efforts in the ethical domain; this would allow SCROs to share reviews and files for commonly used technologies, improving efficiency and lowering barriers to entry.

After analyzing the common bottlenecks arising from technical, IP, and ethical/regulatory considerations and the interactions among the three, it would be feasible for the consortium to design new technology platforms or research tools that work around the most important bottlenecks. The coalition could design and build an enabling research tool by aggregating technology components into a bundle that best meets technical, IP, and ethical parameters for a wide range of the foreseeable applications of that tool—for example, a package consisting of an appropriate cell line, a vector, and a culture medium that enables researchers to obtain neural cells from embryonic stem cells. Furthermore, the coalition would serve as a natural venue—analogous in many ways to a standards-setting body—to deliberate about the content of the research tools, including technical input on preferred standards, legal input on who owns the IP and whether it is available for licensing, and expert analyses of ethical questions. A cohesive assembly of stem cell technologies would combine a complex platform of mutually complementary components, with each component enhancing the others' value or utility.[260]

Designing a technology bundle that succeeds in freeing up the R&D environment would be the top priority for the consortium at this phase. But a number of other principles would be important for the design of such a bundle. The components should work well together and be well characterized technically, making them ready for adoption in the laboratory. The choice of technological components for inclusion in a bundle should partially turn upon their public domain or proprietary status. Those components that are not in the public domain would need to be included under pre-negotiated terms within a patent pool and licensed collectively to users.[261] Component technologies that reside in the public

260. Often, steps spanning the range of derivation, propagation, characterization, differentiation, and delivery technologies are dependent on each other and encompass a full tool set for research into potential medical applications. For such an enabling research tool assembly, at least one interoperable technology component from each of the categories of derivation, propagation, differentiation, and delivery would be included. In other cases, a suite of technologies from within a single category (perhaps a suite of factors for inducing cellular differentiation along a major developmental pathway) might be needed in concert for many research applications. In these cases, the design of that particular enabling research tool bundle would include that set of interdependent components.

261. Where the patent landscape is fragmented across many actors, patent pools can create

domain would be favored for inclusion, as they carry the fewest property restrictions.[262] Component technologies owned by coalition members would have an advantage, both because the terms of availability would already be known based on the information gathered for the database, and because the members of the coalition would already be informed and engaged in the overall process.[263] Occasionally, component technologies owned by outside parties (non-coalition members) may be deemed essential for either technical or ethical reasons. The owner or exclusive licensee of those technologies could then be approached and invited to participate in the exercise by licensing the use of their technology as part of the enabling research tool platform.[264]

Overall, the process for creating each research tool bundle will require substantial bilateral and multilateral negotiations. Inclusion of certain crucial technologies will need to be gained through the use of carefully crafted licenses, allowing the owners to retain control in specified fields of use while still including the core technology in the bundle. Developing a patent pool will require, and build upon, intensive analysis of freedom to operate with each of the individual components and combinations of components.[265] Though the process

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substantial efficiencies because they coordinate and amalgamate multiple patents for the purpose of joint licensing. *See* Merges, *supra* note 90 (defining patent pools and describing their rationale as a general matter); Shapiro, *supra* note 89 (same).

262. *See* Boettiger & Chi-Ham, *supra* note 212, at 889. It must be noted, however, that determining a technology's residence in the public domain is not always straightforward. The public domain can be circumscribed by claims on specific improvements to a public domain technology, claims on the use of that technology in particular combination with proprietary technologies, and claim on use within particular processes. Further complications arise depending upon the choice of countries in which the patentee chose to file: the technology may in fact reside in the public domain within some countries while being patented in others. In other words, technical and legal complexities can interact to diminish the certainties of the public domain as an institution for the transaction of and access to knowledge.

263. University-owned technologies are often unlicensed in all or in some fields of use. Those technologies for which all fields of use are already exclusively licensed would naturally not be available for inclusion in a collective licensing arrangement, although even this situation does not preclude seeking a sublicense from the licensee.

264. Incentives for their participation would include the prospect of licensing revenues gained via participation in a patent pool as well as good will or reputation effects from participation. These latter motives may not be insignificant motives for smaller biotech firms.

265. This freedom to operate analysis would likely continue in parallel with negotiations, as there are likely to be numerous tradeoffs in the choices of technologies and the feasible terms of license and MTAs for various candidate technologies being considered for inclusion in the patent pool. The basic construction of the patent pool would involve non-exclusive licenses over each of the tool components that include rights to execute royalty-free transfers (e.g., MTAs) for research uses or a royalty- or fee-bearing license for commercial uses under pre-negotiated non-exclusive terms.

will require an evaluation of antitrust issues arising from the development of patent pools through such a consortium, these are likely to pass regulatory muster so long as they are intended to promote, not hinder, competition by enabling the broad distribution of research tools.[266]

Finally, the coalition could provide a powerful mechanism to streamline negotiations, approvals, and procurement procedures for enabling research tools. The primary IP concerns in distributing enabling research tools include managing the execution and monitoring of MTAs and license agreements with the users, collecting and disbursing royalty or fee shares back to the technology owners, and participating in enforcement actions against those using the research tools without the proper permissions. Suppliers of stem cell technologies can work with the coalition to provide standardized forms and methods of distribution of cell lines, biological materials, and other materials. For particular technologies that could benefit from such distribution, coordinated dissemination of enabling research tools would reduce transaction costs and put the "right" tools in researchers' hands. For example, suppliers of characterization technologies are increasingly offering stem cell kits.[267] However, these kits seldom include the cell lines themselves or the other propagation, differentiation, and delivery technologies. If the coalition indicates a clear demand for stem cell kits that encompass all technologies, i.e., enabling research tools, then the supply side could work together to provide such integrated kits.

Lastly, the coalition could provide a novel means of including and enforcing ethical standards for stem cell technologies. Technology bundles and platforms could embody ethical and normative goals.[268] Bundles of technologies that are

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266. Using pooling arrangements across nonprofit research institutions to promote dissemination of research tools is likely to be deemed "procompetitive," and thus is unlikely to attract regulatory scrutiny. *See* U.S. DEP'T OF JUSTICE & FED. TRADE COMM'N, ANTITRUST GUIDELINES FOR THE LICENSING OF INTELLECTUAL PROPERTY § 5.5 (1995) (stating that "[b]y promoting the dissemination of technology, cross-licensing and pooling arrangements are often procompetitive" but that "[c]ross-licensing and pooling arrangements can have anticompetitive effects . . . [and] may be deemed unlawful if they do not contribute to an efficiency-enhancing integration of economic activity among the participants").

267. For example, the ES Cell Marker Sample Kit (SCR002) is being offered by Millipore (Bedford, MA). Millpore, Kits for Pluripotent Stem Cell Research, http://www.millipore.com/cellbiology/cb3/pluripotentkits (last visited Nov. 13, 2008). The StemPro hESC SFM kit is offered by Invitrogen (Carlsbad, CA). Invitrogen, STEMPRO® hESC SFM - Human Embryonic Stem Cell Culture Medium, http://www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/Cell-Culture/Stem-Cell-Research/Stem-Cell-Research-Misc/stempro_hesc_sfm.htm (last visited Nov. 13, 2008).

268. Decades of research in the social studies of technology have demonstrated the ways in which technological artifacts embed human choices, which in turn are shaped both by material conditions and ethical, social, legal, and economic considerations. For classic works in the field,

built using best practices—or what we might call "best ethics"—that satisfy most or all extant guidelines could be developed, such that the resulting research materials and tools actually embody ethical choices and considerations. Ready availability of a technology could establish a practical or feasible ethical option, against which other technologies would thus have to measure up. For example, perhaps the stem cell lines designed and promoted by the coalition could be derived from "spare" embryos or reprogrammed somatic cells rather than SCNT, promoting technical options that are, broadly speaking, less ethically controversial across multiple cultures.[269]

Member institutions of the coalition, in consultation with other key players, could deliberate upon what standards should be implemented. If university partners could be drawn from states across the United States, as well as countries across the globe, this process might have a better chance of achieving a sort of global normative authority. Clearly, the coalition should avoid controversial technologies, such as chimerical entities, in order to minimize political controversy.

This would also be a natural stage in which to invite outside actors and stakeholders into the process in order to achieve a broader and "multivalent" evaluation process, to help guide the consortium towards outputs and activities with broad public benefit and acceptance. We anticipate that such a forum for deliberation and design would have broad political appeal. For instance, even those opposing the destruction of embryos for the creation of new hESC lines might embrace as a pragmatic option the project of distributing more widely the existing lines or lines created by the new technique of cell reprogramming[270] so that fewer embryos would be destroyed for research purposes. In addition to promoting ethical transparency, explicitly embracing the role of values to guide stem cell tool design would, literally, build ethics into the materials of research.

## IV. DISCUSSION: INCENTIVE ANALYSIS OF KEY ACTORS

Bringing together a diverse set of institutional actors at the international level across multiple domains requires a clear alignment of interests of the various parties. In stem cell R&D, different kinds of actors control the information, materials, and IP at issue. Data are often generated and controlled at the level of the individual laboratory. Materials may be controlled by a

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see Langdon Winner, *Do Artifacts Have Politics?*, 109 DAEDALUS 121 (1980). *See generally* THE SOCIAL CONSTRUCTION OF TECHNOLOGICAL SYSTEMS (Wiebe E. Bijker, Thomas P. Hughes & Trevor T. Pinch eds., 1987); SHAPING TECHNOLOGY/BUILDING SOCIETY: STUDIES IN SOCIOTECHNICAL CHANGE (Wiebe E. Bijker & John Law eds., 1992).

269. *See* Hinxton Group, *supra* note 126.

270. *See supra* note 69.

combination of the laboratory and university technology transfer personnel. Provenance and other ethical assurance data are usually controlled at the level of the individual SCRO, while patents are usually controlled by the research institution and managed by the technology transfer office. Here, we offer an analysis of how these interests converge around the development of common research resources.[271]

### *A. Perspective of Research Funders*

The development of a robust collective action mechanism to enable stem cell research would require that large funders of public science, particularly the NIH, the Wellcome Trust, and CIRM, view such an effort as important to their institutional goals and policies. Some public funders seem more concerned than others that sharing data and research resources might affect commercialization or even the pace of basic research. CIRM, for one, has not been as active as it might have been on issues of data and materials sharing, in part because the California initiative was conceived not only as a health research initiative, but also as an economic stimulus package.[272] Nevertheless, in communication with patient advocacy groups, companies, and university researchers, funders would likely find that making certain kinds of data and materials more accessible would help advance common goals.

Indeed, most of the large funding institutions already have general policies in place regarding the sharing of data, materials, and research tools produced through its funding. For instance, in 1999, in response to problems of access, the NIH issued an important set of guidelines on the dissemination of research tools.[273] Although these guidelines are not binding, they articulate strong norms of dissemination and minimally burdensome MTAs.[274] Furthermore, NIH began to use its funding power to require more active forms of data sharing in all of its program areas. Starting in October 2003, investigators seeking $500,000 or more in NIH grants in any single year were expected to include a plan for data sharing

271. We have made a conscious choice to limit the discussion that follows to key actors likely to control the information, materials, and IP at issue. We do not mean to suggest that patient advocacy groups, other citizen groups, and end-users are not key actors in this policy field, though we do not discuss them in this Section. To the contrary, these are precisely some of the groups that should be involved at various stages of the consortium. Hopefully we have already argued persuasively why such groups would benefit from the outlined mechanisms to open up stem cell research and development.

272. *See* Richard J. Gilbert, *Dollars for Genes: Revenue Generation by the California Institute for Regenerative Medicine*, 21 BERKELEY TECH. L.J. 1107, 1107-09 (2006).

273. NIH Principles and Guidelines, *supra* note 52.

274. *Id.* at 72,092-96.

or justify why data sharing was not possible.[275] This NIH Statement on Sharing Research Data states that "data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health," and endorses "the sharing of final research data to serve these and other important scientific goals."[276] As discussed above, the Wellcome Trust has been heavily involved in helping foster the research commons in genomics and other areas as a means of advancing its larger health mission. In its own policy on data sharing, the Wellcome Trust states that it attempts to ensure sharing in ways that maximize public benefit, and that "the benefits gained from research data will be maximized when they are made widely available to the research community as soon as feasible, so that they can be verified, built upon and used to advance knowledge."[277] These stated policies, along with important actions taken in other fields of biomedical research, suggest that funders are motivated to push policy in the ways we advocate.

### *B. Perspective of Individual Research Labs*

Strong incentives to engage in the collaborative activities described above already exist for individual labs and researchers, as evidenced by ample participation in scientific publishing, conferences, and nascent databases. However, to the extent that increased levels of data and materials sharing are required, as argued in Part I, there are strong reasons that the scientific community should support this goal and rally towards a greater degree of collaboration. First, data and materials sharing is a traditional practice within science that has been responsible for scientific advance. At a minimum, labs have a common interest in sharing materials and data to replicate experiments. Second, as part of the stem cell community that lobbies for funding, stem cell researchers around the globe also have a common interest in delivering on promises that the field will produce new therapies. Third, labs must use materials and procedures that satisfy their institutional review boards, and the proposed data architecture would allow labs to avoid ethically questionable materials. Lastly, the data resource could provide a trusted standard that would help labs avoid spending time and resources to characterize stem cell materials and instead focus on conducting their primary research.

Yet to overcome the collective action dilemma within the research community, funders and journals would need to break the inertia. Greater sharing of data and materials, especially pre-publication data, may be unrealistic in the

275. Nat'l Insts. of Health, Final NIH Statement on Sharing Research Data (Feb. 26, 2003), NOT-OD-03-032, http://grants.nih.gov/grants/guide/notice-files/not-od-03-032.html.

276. *Id.*

277. *See* Wellcome Trust, Policy on Data Management and Sharing, http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTX035043.htm (last visited Nov. 13, 2008).

absence of sufficient incentives for scientists. Since academic researchers who are primarily interested in advancing their careers seek, first and foremost, to publish, much could be accomplished by raising the standards for data sharing across the range of scientific journals in the field. Indeed, many journals have missions of promoting access to knowledge. In addition, journals may find that a collaborative data architecture could help them organize the increasing amounts of supplemental information that is submitted with publications. If more rigorous journal policies could be combined with stricter sharing requirements of funders, scientific labs would likely cooperate.

### *C. Perspective of Universities*

Research universities could be expected to participate at an institutional level in efforts to foster greater coordination in the stem cell area both as a matter of common interest (i.e., for the common good based on the public service mission of such institutions) and enlightened self-interest.[278] Even as universities increasingly look to the power of exclusive control to generate private investment and revenue, institutional missions and traditional scientific norms support an ethic of sharing and collaboration.[279] Indeed, universities share a common mandate to produce public benefits and to disseminate knowledge and information.[280] It is true that this mandate must be balanced with the goals of raising revenue through commercial research sponsorship and licensing, as well as stimulating local economic development, but universities have special duties that call for finding better ways to get biomedical information and inventions into wider use.[281]

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278. See *supra* note 248.

279. Rai & Eisenberg, *Bayh Dole Progress*, *supra* note 3, at 289-91; *see also* Reichman & Uhlir, *supra* note 4, at 370-71, 428, 440 (noting the increasing tension between the mandate to share data and databases based on the educational mission of universities and the traditional ethos of science, and the new push to commercialize scientific assets under the logic of Bayh-Dole).

280. *See, e.g.*, Amy Kapczynski et al., *Addressing Global Health Inequities: An Open Licensing Approach for University Innovations,* 20 BERKELEY TECH. L. J. 1031, 1084-85 (2005) (developing the argument for an open licensing approach to universities' biomedical innovations by emphasizing that "[u]niversities' core institutional principles include the production and dissemination of knowledge, as well as a related and more general dedication to improving human welfare"); Amy Kapczynski et al., *Global Health and University Patents*, 301 SCIENCE 1629, 1629 (2003).

281. *See, e.g.*, IN THE PUBLIC INTEREST: NINE POINTS TO CONSIDER IN LICENSING UNIVERSITY TECHNOLOGY (2007), http://news-service.stanford.edu/news/2007/march7/gifs/whitepaper.pdf (important consensus document developed by twelve leading research universities in the United States stating that "[u]niversities have a social compact with society. As educational and research institutions, it is our responsibility to generate and transmit knowledge, both to our students and the wider society. We have a specific and central role in helping to advance knowledge in many fields

Furthermore, this policy has the potential to advance the self-interests of individual universities, even narrowly construed: A collaborative environment promises direct savings and gains for universities and other nonprofit research institutions, both in the area of ethical review and in the area of IP. Figure 4 represents a hub-and-spokes model of institutional functions around technology transfer, ethical review, and the administration of stem cell centers. Centralizing certain ethical, regulatory, and technical functions could save universities time and money, promote the use of their stem cell inventions, and reduce the risks to which institutions are inevitably exposed when making controversial decisions alone.

In the domains of ethics and IP, the research institution itself bears primary legal responsibility. As discussed above, government and non-government actors at the state level have initiated productive discussions aimed at harmonizing state regulations,[282] but the burden of assuring compliance of research with the patchwork of rules remains squarely on the shoulders of individual research institutions and their SCROs. Coordinating or even just cross-referencing ethical oversight functions among the institutions within the coalition could prevent each institution's SCRO from unnecessarily repeating complex regulatory analyses. Further, as the PIPRA model shows, there are opportunities for mutual gain through inter-institutional coordination of licensing that reduces uncertainties and transaction costs, thereby increasing the general flow of licensing and new firm formation.[283] Surveys of stem cell research activities and patenting suggest that research universities hold some of the biggest patent portfolios in the field of regenerative medicine and thus have the most to gain in royalties from improvements in the overall rate of R&D.[284]

The proposition for a technology owner to include technology in a patent pool is, of course, a much later consideration than the initial invitation to join a coalition devoted to IP problem solving. Reasonable circumstances may preclude member institutions from allowing a particular technology to be considered in the design of an enabling research tool. Owners may also reasonably want to retain some degree of control over improvements to their technology. However, under the prevailing conditions of stem cell R&D, there may in fact be considerable enthusiasm on the part of owners to participate in a patent pool. Just as there are benefits to having one's technology included in an industry standard patent pool, such as MPEG or DVD, participation in a coalition-designed research tool may

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and to manage the deployment of resulting innovations for the public benefit. In no field is the importance of doing so clearer than it is in medicine").

282. *See supra* note 141 and accompanying text.

283. *See* Richard C. Atkinson et al., *Public Sector Collaboration for Agricultural IP Management*, 301 SCIENCE 174, 175 (2003); *see also supra* Subsection III.B.1 (discussing PIPRA).

284. *See* BERGMAN & GRAFF, *supra* note 28, at 5.

be a good route toward achieving the licensing and utilization of a patented technology.[285]

Finally, on the issue of using IP protected materials in conducting university research, the Federal Circuit's 2002 *Madey v. Duke University* decision denied academic researchers recourse to the common law experimental use exemption to patent law.[286] It seems that this decision has yet to disrupt the common practice among university researchers of disregarding the patent landscape, but this may change as infringement suits are brought against academic researchers.[287] Furthermore, stem cell scientists already need to license commercially provided research tools. Rendering research tools less expensive would lower the marginal costs of initiating R&D and in turn enable more research within the university sector.[288] The generation at the university level of forward-looking solutions to data sharing issues and patent thickets may be essential to the future health of university science.

### *D. Perspective of Companies*

Companies in the private sector are major players in stem cell R&D, but they are by no means homogeneous in purpose or size. Major classes of companies in

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285. *See* Robert P. Merges, *Institutions for Intellectual Property Transactions: The Case of Patent Pools*, *in* EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY 123 (Rochelle C. Dreyfuss, Diane L. Zimmerman & Harry First eds., 2001).

286. Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002) (refusing to excuse research work at Duke from patent infringement claims despite its non-commercial nature).

287. *See* WALSH, CHO & COHEN, *supra* note 53, at 27-28 (finding that "22% of our academic respondents were notified by their institutions to be careful with respect to patents on research inputs, up from 15% of our respondents who recalled receiving such a notice five years ago," but that "there was little difference in the behavior of those academics who had received such notification"); *see also* REAPING THE BENEFITS, *supra* note 10, at 122; Yancey & Stewart *supra* note 214, at 1225 ("Academic researchers have regularly ignored patents on key technologies as a strategy to maneuver around patent thickets and freedom-to-operate issues, but they may be at risk more than they realize.").

288. For some time, sociologists of technology have dispelled the notion that innovation occurs within a linear model in which there is a unidirectional flow from basic research to applied technologies and therapies. *See, e.g.*, UNIVERSITIES AND THE GLOBAL KNOWLEDGE ECONOMY: A TRIPLE HELIX OF UNIVERSITY–INDUSTRY–GOVERNMENT RELATIONS (Henry Etzkowitz & Loet Leydesdorff eds., 1997); Benoît Godin, *The Linear Model of Innovation: The Historical Construction of an Analytical Framework* (Project on the History and Sociology of S&T Statistics, Working Paper No. 30, 2005), *available at* http://www.csiic.ca/PDF/Godin_30.pdf. Research tools are innovations that feed back into the stream of basic knowledge production, introducing complexities when they are attached to onerous licensing provisions and material transfer agreements.

the stem cell R&D landscape include start-up biotech firms, large pharmaceutical firms, and specialty research tool or technology platform vendors. Even without active participation, we anticipate that private sector companies will benefit from some of these efforts, as common resources could help advance commercial research, potentially reducing in-house R&D costs. Companies, particularly in the start-up space, may benefit immensely from the availability of licensing pooled technologies. Specialty research tool companies may benefit if commonly available datasets or tools combine well with or increase the value of the technologies they provide.

It is quite likely that some companies will want to be more active partners in the data collaborative, as firms are increasingly interested in sharing pre-competitive data.[289] In stem cell R&D, the institutional boundaries that once demarcated basic research from technological development are increasingly porous, as academic research finds application in industry.[290] For example, the Stem Cell Community database encouraging academic research data deposit has been supported by three companies—Chemicon, Illumina, and Invitrogen.[291] A number of important examples of partnerships on data sharing across the public-private divide have developed in genomics, including the SNP Consortium and the Merck Gene Index project, where Merck and Washington University publicly released thousands of expressed human gene sequences.[292] More firms may want to join the collaboration if some sections of the database could be protected for industrial purposes for limited periods of time before public release.

## CONCLUSION

Striking the proper balance between openness and restraint in biomedical research and innovation is becoming a crucial policy issue in health policy, law, and bioethics. Innovative mechanisms of open and collaborative research have emerged in some life science fields, but not in the burgeoning area of stem cell research. The productive advance of R&D in the field of stem cells faces a number of challenges that neither markets nor the public domain—nor the complex interplay of the two that characterizes the world of R&D today—have been able to solve. In the previous two Parts, we outlined a cascading multi-stage model that goes beyond traditional approaches to solving complex coordination problems and defines a new forum and set of processes for the coordinated management of data and materials, licensing and technology transfer, and ethical

289. *See* Merges, *supra* note 20.

290. *See* Eisenberg & Nelson, *supra* note 16.

291. *See* Personal Communication with Jeanne Loring, Prof. of Chemical Physiology, The Scripps Research Inst. (Jan.—July 2008).

292. *See* Cook-Deegan, *supra* note 219, at 150-52.

oversight and regulation. In doing so, this proposal responds to some of the systemic debates over the role of research institutions in maintaining the "science commons."

A key point of departure of this proposal from existing efforts in stem cell research, and in other fields, is the explicit recognition of the need to work in an integrated way across the problem domains with data sharing, patents, and ethics. Conceptually and practically these problem domains, as well as best-solution sets, are interwoven. An integrated approach in the design phase would better advance platform technologies that may be less ethically controversial and more broadly enabling. (For example, the first propagation technologies to grow hESCs required irradiating mouse embryonic fibroblasts, but relatively few institutions had the physical infrastructure to do so.) As designers construct technology platforms to minimize proprietary constraints, they may advance other collective goals such as avoiding ethical conflicts and enabling more users.[293] We hope that a greater awareness of how values can inform the material architecture of stem cell research might attract a diverse and informed range of actors and stakeholders into the design process.

This integrative approach could promote greater entrepreneurship in stem cell research and also create positive distributional effects. Proprietary hurdles impeding stem cell research can dissuade firms from entering the field in the first place. By bringing down expected costs of doing adaptive or translational research and development, it is easier for all companies, large and small, to investigate a broader range of products benefiting a wider range of markets. The development of products intended for smaller scale markets expands the universe of potential applications, allowing more companies to fill more niches, including underserved patient populations and neglected diseases. Overall, the reduction of costs and integration of values entailed in this proposal could expand stem cell research beyond exploring only potential blockbusters and direct it towards a fuller constellation of potential stem cell therapies.

293. There is a consensus within the sociology of technology that design aspects of technologies can enable or restrict access to particular segments of society. *See* Winner, *supra* note 268.