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Enabling Stem Cell Research and Development

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ENABLING STEM CELL RESEARCH AND DEVELOPMENT

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Abstract

The expansion of public funding for stem cell research at both the U.S. federal and state levels promises real opportunities for advancing public health and human welfare. However, the technical, proprietary, and regulatory conditions currently giving shape to stem cell R&D are far from ideal: closed information, congested entitlements, and regulatory uncertainty present formidable challenges for the conduct of research and its translation into practical applications. Such an environment is likely to slow the pace of innovation, skew the distribution of health benefits towards the wealthy, and force ethical decision-making that lacks public accountability.

Here we propose an institutional mechanism to coordinate the conduct and governance of human stem cell R&D: a collaboration among academic institutions to collect and make available information detailing the technical, proprietary, and ethical characteristics of cell lines and research tools developed at participating institutions. Centralization would help promote more efficient transfer and use of available and ethically preferential technologies. The coalition could also leverage the collected information to assemble and disseminate complex enabling research tools under common material transfer agreements or patent pools in those cases where multiple patents are necessary but are fractionated across multiple owners. The goal of such collective action would be to support more efficient exchange of technologies within the stem cell research community and for product development in industry, to orient stem cell research to the more pressing public health needs, and to promote the least ethically-controversial forms of stem cell research.

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Acronyms: freedom to operate (FTO), human embryonic stem cell (hESC), institutional review board (IRB), intellectual property (IP), International Society for Stem Cell Research (ISSCR), material transfer agreement (MTA), U.S. National Academies of Science (NAS), U.S. National Institutes of Health (NIH), research and development (R&D), somatic cell nuclear transfer (SCNT), stem cell research oversight committee (SCRO), technology transfer office (TTO).

I. INTRODUCTION

There is broad agreement, though not consensus, among life scientists that stem cells, and in particular human embryonic stem cells (hESCs), hold unique promise for advancing toxicology, pharmacology, functional regeneration, and developmental biology. At the same time there is broad political and ethical disagreement over the conditions under which this line of research should advance, if at all. Stem cell research challenges popular notions of the natural – it introduces new ways in manipulating of nascent human life, novel uses of gametes, and proliferates the use of trans-species hybrids. In sum, these conditions have produced a deeply contested ethical terrain and a lack of regulatory harmonization. In addition to the uncertainty surrounding the ethics and regulation of stem cell research, both proprietary and technical constraints have arisen. Many essential technical building blocks, including hESC lines themselves, are being claimed as private assets, following trends of extensive patenting seen elsewhere in the life sciences. 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.

These structural conditions within the field of stem cell research today have created limiting conditions, or "bottlenecks", that stand to constrain and divert research and development (R&D) efforts and investments. The following analysis and proposal takes an integrated approach, as it flows from a dialogue among a bioethicist, an economist, and a scientist, each of whom has previously raised critiques and advanced suggestions for the conduct of stem cell R&D—including issues of ethical governance[4], intellectual property (IP) and technology licensing[5], and technical data sharing.[6] Out of these discussions, it has become clear that a coordinated effort addressing these bottlenecks together could significantly facilitate a more efficient, fair, and ethically-accountable advance of stem cell research. Here we propose an institutional mechanism to coordinate the conduct and governance of human stem cell R&D: a collaboration among academic institutions to collect and make available information detailing the technical, proprietary, and ethical characteristics of cell lines and research tools developed at the participating institutions.

II. BOTTLENECKS IN THE TECHNICAL, PROPRIETARY, AND ETHICAL DOMAINS

The expansion of public funding for stem cell research at both the federal and state levels promises real opportunities for advancing public health and human welfare. However, the technical, proprietary, and regulatory conditions currently giving shape to stem cell R&D are far from ideal: closed information, congested IP entitlements, and regulatory uncertainty present formidable challenges for the conduct of research. Such an environment is likely to slow the pace of innovation, skew the distribution of resulting health benefits towards the wealthy, and force ethical decision-making along the way that lacks public accountability.

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[4] DE Winickoff, "Bioethics and Stem Cell Banking in California", *Berkeley Technology Law Journal*, 1067-1105 (2006); DE Winickoff, "Governing Stem Cell Research in California and the USA: Towards a Social Infrastructure", *Trends in Biotechnology*, 24,9: 390-394 (2006).

[5] K Bergman & GD Graff (2007) "The global stem cell patent landscape: implications for efficient technology transfer and commercial development" *Nature Biotechnology* 25(4): 419-424; K Bergman & GD Graff, *Collaborative IP management for stem cell research and development*, CIP: Göteborg, Sweden, and PIPRA: Davis, CA, USA (2007).

[6] K Saha, "Navigating to the Right Stem Cell Line." *Science, Technology, and Engineering White Paper Competition*, University of California Berkeley (2006).

Technical complexity and bottlenecks

In terms of technical complexity, scientists wanting to use stem cells in their research are confronted with two major problems: the navigation of stem cell behavior through a vast number of potential cell fates and the integration of many disparate technical tools. Stem cells, whether adult or embryonic, have the remarkable ability to differentiate into a large number of cell types (Figure 1). For any research with stem cells, scientists must know how mature their stem cell population is (or in the context of Figure 1 exactly where along the cellular tree of differentiation a 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 history of signals that the cell has experienced- on the particular growth factors that have been added to the media, on the substrate of the culture, and the duration of such events.[7] Therefore, appropriately using these cells connects to its derivation and propagation stages (Figure 2). In each of the many technical stages during routine use of stem cells for medical research (Figure 2), many technologies—including cell lines, growth factors, culture substrates, implantable materials, and genetic engineering vectors—are utilized, each of which can affect stem cell behavior. Whenever a new technology is used in conjunction with stem cells, a wide array of possibilities exist for integrating different technologies. This wide array is difficult to experimentally explore in one lab for all important cell lineages (e.g., undifferentiated embryonic stem cells, neurons, cardiac progenitors, pancreatic endocrine cells).

Although many details concerning stem cell technologies are published in journal articles, scientists in practice depend upon personal communication with other scientists to acquire other essential information about particular stem cell technologies. Publications are not necessarily enabling. 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. Furthermore, important information is frequently obtained through negative results, which are less likely to be published. 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). Lacking formal mechanisms to widely disperse these details, a network of emails and phone calls between stem labs transfer information about key details when using stem cell technologies.

Recent work in the stem cell scientific community[8] suggests that the need for descriptive details associated with cell lines will only increase, which in turn will further accentuate these challenges. While current research has thus far focused largely on details of the culturing history, genetic and epigenetic effects are beginning to be explored as scientists gain access to more stem cell lines. Nascent tools to connect genetic data with gene expression data on an integrated website are actively being developed.[9] Even the diet of the oocyte donor can influence the phenotype of an embryonic stem cell line, by producing different epigenetic effects on particular chromosomal loci.[10] It is not surprising that scientists

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[7] Genetic and epigenetic intrinsic factors as well as soluble and matrix extrinsic factors are cell fate determinants of stem cells. Boyer LA, Mathur D, Jaenisch R. "Molecular control of pluripotency." *Curr Opin Genet Dev* (2006). ; Boiani M, Scholer HR. "Regulatory networks in embryo-derived pluripotent stem cells." *Nat Rev Mol Cell Biol*, **6**:872-884 (2005).

[8] International human embryonic stem cell characterization projects have listed more stringent technical criteria to ensure that a population of cells retain stem cell characteristics. Personal communication with Jonathan Auerbach, GlobalStem, Inc. Also see Baker, DE *et. al.*, "Adaptation to culture of human embryonic stem cells and oncogenesis in vivo," *Nature Biotechnology* **25**:2 (2007).

[9] Personal communication with GlobalStem, Inc. and Dr. Mahendra Rao of www.stemcellcommunity.org.

[10] Acetylation patterns on the oocyte are connected to maternal diet. See DI Martin, R Ward and CM Suter, "Germline epimutation: A basis for epigenetic disease in humans," *Ann N Y Acad Sci* 1054 (2005).

have already tried to document all known information about hESC lines, such as sex and ethnicity.[11] However, obtaining further information about the donor is rarely possible, since the identity of the donor is encrypted to protect his/her privacy.

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 a significant volume of legwork for every scientist, which in many cases are simply bypassed. Facing grant and publication deadlines, scientists quickly peruse 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. Work typically must, and does go ahead, but does so at the risk of depending upon poorly chosen tools or materials that could compromise the success of the work. Nascent databases[12] are attempting to address this challenge, but the scale and scope of these efforts, and their lack of widespread use, has thus far kept the information-gathering and experimental design processes time-consuming and inefficient.

Complexity of property rights

Several analysis show a significant rate of accumulation of new patents over stem cells and related technologies[13], with some concerns in the literature that the proliferation of stem cell patent claims and proprietary data is becoming problematic.[14] Indeed, given the particular characteristics of stem cells as an enabling technology—that is, enabling a broad range of new research possibilities as well as the development of commercial applications—the field may be particularly susceptible to the emergence of a patent thicket. Also known in property rights theory as an "anti-commons", a patent thicket could become a significant drag on, or impose a significant skewing of the development of stem cell based therapies.[15] In a patent thicket, the existence of many overlapping patent claims begins to block the pathways to market and choke commercialization—both by causing uncertainty about freedom to operate (FTO) and by imposing multiple transaction costs—such that even owners of dominant patents cannot themselves be certain of reaching market unhindered.

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[11] Donor characteristics are beginning to be provided on the U.K. stem cell bank catalogue and other websites (e.g., www.stemcellcommunity.org).

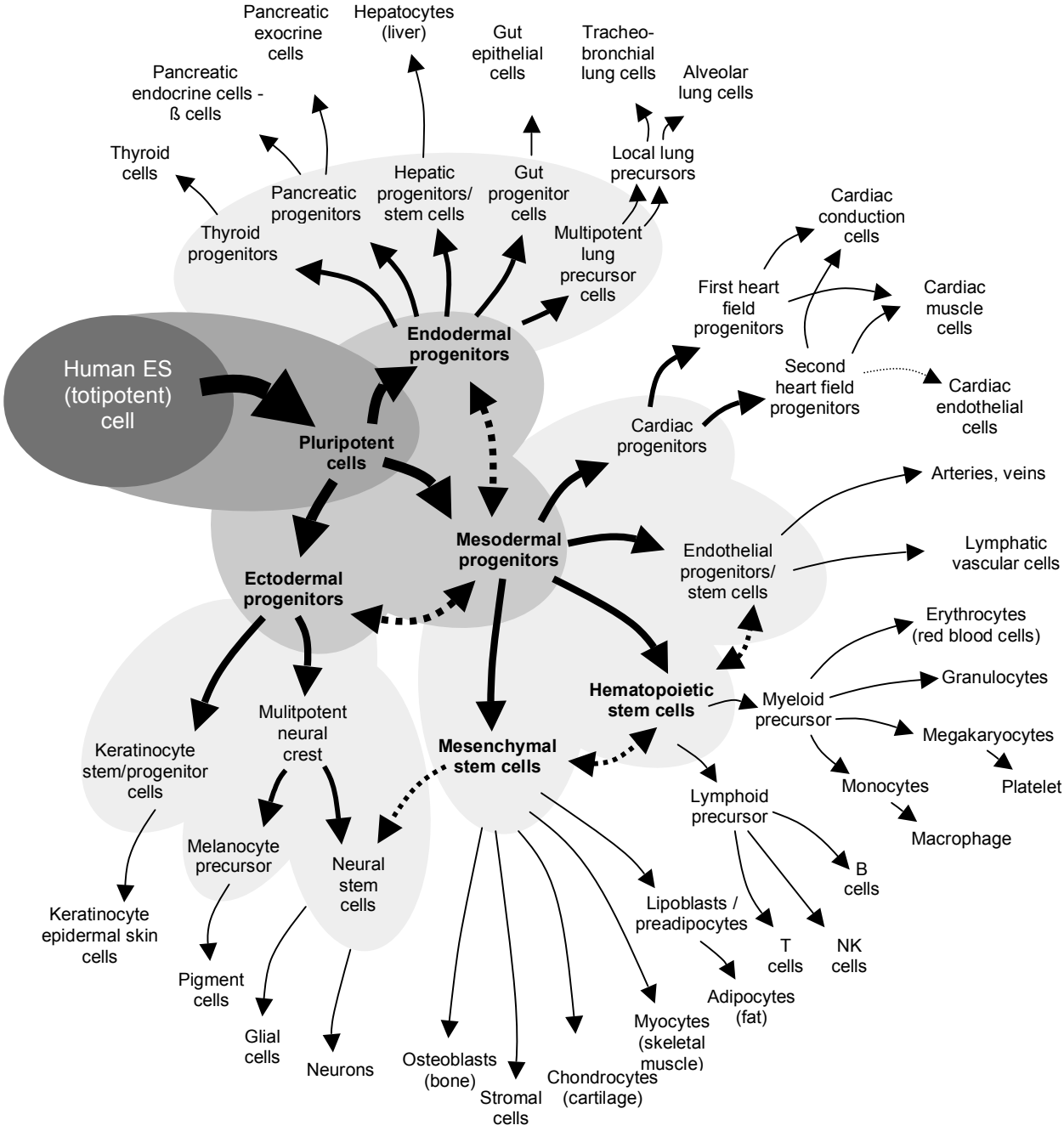
[12] Popular registries as of March 2007 include the U.K. stem cell bank catalogue, NIH national stem cell registry, and www.stemcellcommunity.org.

[13] Glänzel, W., "Stem Cells - Analysis of an emerging domain of scientific and technological endeavour." Steunpunt O&O Statistieken, K.U. Leuven (2004); Campbell, N., Coté, "Potential for stem cells science and technology in Canada: Great promises and challenges." *Science-Metrix and MNBC*: Montréal (2004); Esmond, S., Ebersole, "Stem Cells: The Patent Landscape." *Intellectual Property & Technology Law Journal*, 18 (2006), p. 1-4.

[14] Scheinfeld, R.C., and P.H. Bagley, "The current state of embryonic stem cell patents." *New York Law Journal*, 226 (2001); Simkin, M. "How will intellectual property factors affect the commercialization of stem cell therapeutics." Presented at *BioEurope* (2005); Rai, A.K, and R.S. Eisenberg, "Harnessing and sharing the benefits of state-sponsored research: Intellectual property rights and data sharing in California's stem cell initiative," *Duke Law School Working Paper* 69 (2006).

[15] Eisenberg, R.S. and A.K. Rai. "Proprietary Considerations," in *Handbook of Stem Cells*, R. Lanza, et al., Eds. Elsevier Academic: Burlington, MA. (2004). ; Heller, M.A. and R.S. Eisenberg. "Can patents deter innovation? The anticommons in biomedical research." *Science*, 280, p. 698-701 (1998).

Figure 1. The Complex "Tree" of Cellular Differentiation. Embryonic stem cells can differentiate into all three embryonic germ layers—ectoderm, mesoderm, and endoderm—resembling or recapitulating stages of early embryogenesis and adopting discrete lineages. By manipulating culture conditions these can be directed into specific cell lineages. Protocols are currently available to generate a few specific cell types—including neural, cardiac, pancreatic β-cells, and hepatocytes. However, in theory all cellular lineages could be created beginning from these general pathways. Furthermore, several studies have suggested that lineage- or tissue-specific adult stem cells (such as mesenchymal or hematopoietic stem cells) may be able to transdifferentiate into cell types in other lineages or be able to regain pluripotency and plasticity by dedifferentiating through nuclear reprogramming.



Source: K. Bergman & G.D. Graff, *Collaborative IP management for stem cell research and development*, CIP: Göteborg, Sweden and PIPRA: Davis, CA, USA. (2007), p. 14.

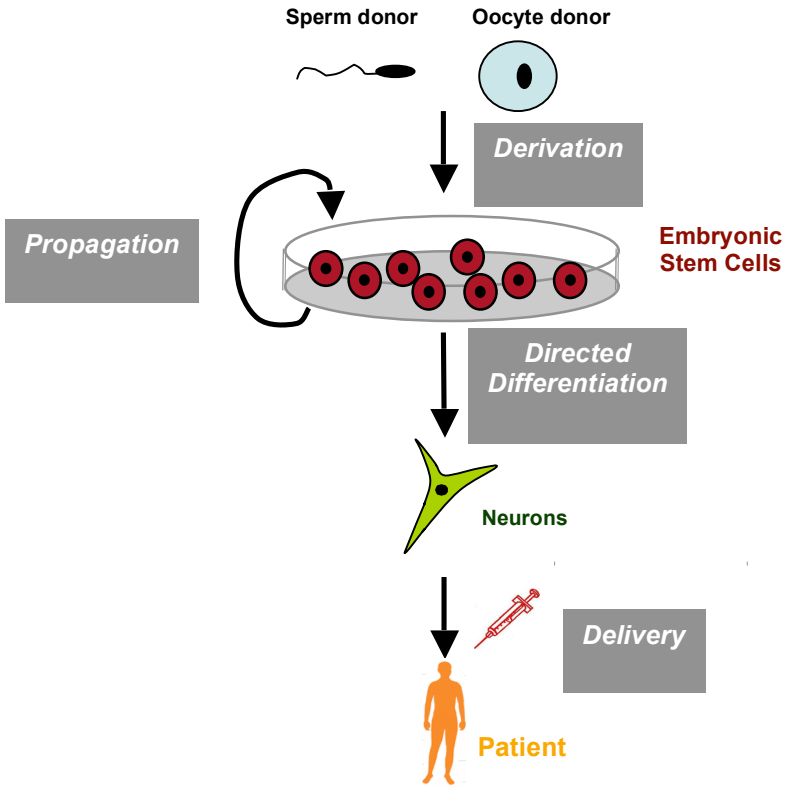
According to recent analysis[16] it is clear that already a substantial number of patents have been granted in this relatively young field. There is still a long way to go in R&D before stem cell products are likely to start entering the market. If future patenting rates follow current trends, any such products will have to navigate a significant number of additional legal obstacles. Annual rates of patent filings and grants show very rapid growth in applications in recent years with more modest but significant gains in actual patent grants. Ownership of stem cell patents is quite fragmented across multiple organizations, with no single organization dominating and the largest holding just 3 percent of the patents in the field. This implies, however, that the task of coordinating access to complex enabling technologies could involve an intensive process of searching and negotiating. And, in contrast to most fields of technology, government and academic institutions own a very large share of the patents in stem cells: fully 45 percent of the stem cell patents in the U.S. (compared to an average of 3 percent in most biomedical fields). Given that academic and public research organizations file for patent protection primarily in order to out license the technology, this suggests that there may be an even greater fractionation of the necessary technology components for complex enabling technologies or complex stem-cell based products. Finally, analysis shows that the technical content of the stem cell patent landscape is highly complex, but stem cell lines, stem cell preparations, and growth factors are the areas where the most intense patenting activity has been recently.

The sheer complexity of the "tree" of cellular differentiation—with numerous lineages emanating from pluripotent stem cells and branching off to arrive at fully differentiated functional tissue cells (Figure 1) holds important IP implications. While much is still uncertain about the differentiation processes for many specific cell lineages, 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 arrows in Figure 1) together with cell types of greater potency (the shaded regions in Figure 1) will not have many alternatives, will each be owned separately, often by separate owners, and yet will be needed together in many diverse research and product development efforts aimed at the broad array of different potential end results. They are the major "thoroughfares" that will need to be traversed by many.

In a best case scenario under the conditions of a patent thicket, a company that commercializes a stem cell based product would need to negotiate and pay multiple royalties to the owners of the IP rights held over those "thoroughfare" technologies that it must traverse. In a worst case scenario, even after conducting legal analysis and concluding a round of deals assumed to be sufficient to establish FTO, a company finds their product accused of infringing yet other patents, inciting litigation or costly settlements. Most commonly, however, a patent thicket merely causes innovation malaise, borne of unwillingness on the part of investors to put money behind projects because of the uncertainty over whether a cost-viable path to market can be found. Of course, the most valuable treatments always find their way to market through licensing deals and/or settlements, and even through mergers or acquisitions: when enough money is on the table, it drives deals to completion. Projects with little or no foreseeable value are, of course, terminated for reasons other than IP. It is projects in the middle range of potential payoffs, between these two extremes, that are most at risk of being sidelined because of IP concerns.

[16] K. Bergman & G.D. Graff, *Collaborative IP management for stem cell research and development*, CIP: Göteborg, Sweden, and PIPRA: Davis, CA, USA (2007).

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 below, 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 – in toxicology, pharmacology, and developmental biology - typically will need to generate cell lines of specific phenotype, all of which will move through controlled derivation, propagation, and differentiation stages.



Ethical and regulatory complexity

As if technical and proprietary complexities were not enough, few technologies have been as ethically and politically contested as the production and use of stem cells. Both in the U.S. and abroad, sharp divisions on the moral status of the embryo have engendered serious conflict in the domain political morality- the terrain on which ethics meets politics, where contesting human values meet formal and informal forms of collective governance–i.e., law, regulations, standards.[17] This contested ethical domain has impeded ethical governance of the research in two main ways. First, in certain polities, such as the federal United States, there persists a troubling political stalemate owing to the tortured politics of the embryo. This stalemate has resulted in a vacuum not only of research funding, but also of research governance. As a result, even as private and locally-funded hESC research moves ahead, a national approach to regulating the research is lacking. Second, California and other states that have seen economic and political opportunity in the national stalemate, seek to act well by implementing their own governance regimes, but

[17] See, e.g., R.H. Hare, *Essays on Political Morality*. (1998).

collectively threaten to produce a new regulatory thicket. In the interest of ethical coordination, esteemed scientific communities have advanced recommendations at the national and global level, though such principles and rules remain largely voluntary and aspirational.[18] Nevertheless, the current patchwork of laws, regulations, and ethics rules emerging across nations, individual U.S. states, and individual institutions is sowing confusion and stymieing potential scientific collaborations.

Interactions between technical functionality, property rights, and ethics

So far, discussions in the scholarly literature on stem cells have tended to focus on the technical, the proprietary, and the ethical as isolated domains[19], but enabling the efficient progress of ethically-steered research will require considering them together. Interaction among these three types of bottlenecks can complicate and confound the selection of appropriate materials and technology options. New patent claims, novel technologies, and ethical requirements are being produced every year. In addition, full information about all of these bottlenecks is not available. As a result, selecting appropriate technologies for R&D applications must be taken in a case-by-case basis. Overall, the complex interplay of technical functionality, property rights, and ethics can be very costly to navigate and creates situations of uncertainty and risk in pursuing stem cell R&D.

In order to illustrate how these complexities can operate, consider three examples of stem cell technologies for which the degree of interaction across different domains of complexity varies: a single growth factor, a single stem cell line, and a multi-component technology like a neural differentiation kit.

For a single protein like the fibroblast growth factor, one that is frequently used to propagate undifferentiated stem cells, technical use can be easily controlled via media conditions and production via recombinant methods has already been approved for many biomedical research procedures. Technically, it is not clear whether its use as a propagation technology restricts subsequent cell lineages during the use of different differentiation technologies. However, the primary bottleneck in using this molecule in stem cell R&D exists in the proprietary domain: it is not clear what the FTO situation is with fibroblast growth factor. It is therefore an example where bottlenecks in the proprietary domain interact minimally with bottlenecks in the technical and ethical domains. As we show in the subsequent section, analysis even just in the IP domain to clarify questions about FTO is challenging enough.

At the next degree of complexity, the selection of a stem cell line for an experimental—let alone a therapeutic—application requires an assessment of the relevant property rights, but also its genetic and other technical characteristics. Furthermore, depending on the jurisdiction within which the scientist is working, or in which the product development company wants to market the therapeutic application, the ethical characteristics of the cell line may have to be established. For instance, assurances that the line was developed with the donor's informed consent. 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. Analysis must occur across all three domains—technical, IP, and ethical—and may prove cumbersome.

The requisite analysis becomes even more cumbersome for a multi-component technology like the neural differentiation kit. Figures 1 and 2 together illustrate the process of obtaining differentiated neural cells

[18] National Research Council & Institute of Medicine, *Guidelines For Human Embryonic Stem Cell Research* (2005). Also, the Hinxton Group, International Consortium on Stem Cells, Ethics, and Law, Consensus Statement (February 24, 2006), at http://hinxtongroup.org/Consensus.Statement.doc.

[19] Important exceptions include, e.g., Taymor, K.S., C.T. Scott, and H.T. Greely, "The paths around stem cell intellectual property." *Nature Biotechnology*, **24**:4, (2006).

from hESCs. In this case, a number of different component technologies are needed 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 research institution or company. And each may have different ethical requirements on the provenance of cell lines used or the testing of cells in animals, a procedure which raises concerns over creation of chimeras. Again, analysis must span all three domains—technical, IP, and ethical—and tradeoffs among the three are likely: that which is technically optimal may not have FTO, and it may be more ethically problematic than other options. Deliberation that goes beyond the scope of expertise of the individual lab or even the individual organization could be necessary to resolve which neural differentiation method to use.

The uncertainties and the transaction costs involved in resolving those uncertainties are not insignificant in the current stem cell R&D climate, and this has troubling implications. First, these conditions act as a disincentive to even conduct stem cell R&D in the first place, reducing the overall volume and pace of stem cell R&D. Second, these conditions act to skew the mix of stem cell R&D being conducted, discouraging work in areas with lower expected payoffs, without regard for their potential contributions to human welfare. Third, they narrow the set of ethical options available as well as limit the opportunities for collective decision making about the ethical acceptability of all possible technology options.

III. A ROADMAP TO ENABLE STEM CELL RESEARCH AND DEVELOPMENT

Policy initiatives have been attempted in each of these three domains: technical, proprietary, and ethical. Stem cell database initiatives have been started at the international level and seek to coordinate information within scientific literature and among members of academia. The U.S. National Institutes of Health (NIH) licensing guidelines have been brought to bear on some broad embryonic stem cell patents necessary for virtually all research in stem cells, which patent pools have been proposed to consolidate IP in order to simplify obtaining FTO with widely used research tools and methods. Voluntary ethical guidelines have sought to harmonize oversight over stem cell research. However, since these various initiatives do not take an active role in understanding the interaction between the three constraining domains, at best they solve only part of the problem, and at worst do nothing. The current dominant institutions within each domain are not addressing adequately the needs of a fast-moving, complex field of research. Simply publishing research results in the scientific literature is not enough to inform and enable other researchers technically. Leaving individual universities and research institutions to balance open science objectives against the maximization of their own IP positions may not lead to an optimal global solution for stem cell R&D. Relying on traditional research oversight is unlikely to adequately address the complex ethical issues specific to stem cells.

Concerted, collective action, however, may be able to realize this vision of an integrated approach across all three domains and support more efficient exchange of technologies within the stem cell research community, orient stem cell research toward the most pressing public health needs, and promote the least ethically-controversial forms of hESC research.

To undertake such a collective action, we propose an institutional initiative, that can be progressively developed or matured through a multi-stage process (see Figures 3 through 9), with each stage building upon the previous ones.[20] Activities and involvement in each stage are voluntary and self-determined by

[20] These stages are loosely based on a similar initiative that has been advanced by the Rockefeller Foundation in the agricultural biotechnology community called the Public Intellectual Property Resource for Agriculture or PIPRA (www.pipra.org), which maintains a comprehensive database of agricultural biotechnologies available from a

the participating institutions. Each stage, by itself, can generate significant benefits for the participating institutions and for stem cell R&D in general. In addition, each stage prepares the way for the next, in a logical progression. The incentives for participating institutions to initiate the progression to each next stage are nothing more than institutional self interest, the desire for freedom to pursue and fulfill institutional, professional, scientific, and economic goals. However, the progression to subsequent stages is not essential: undertaking even just the first one or two would still improve the general environment for stem cell R&D. Attaining all five stages of this proposed initiative would have the greatest impact, but would also require the greatest degrees of commitment, coordination, and leadership. Here we outline a template for how collective action to enable stem cell R&D can be undertaken in five progressive steps.

First, academic institutions could form a coalition pledging to work together "*to promote the efficient access, transfer, and use of effective, available, and ethically preferential stem cell technologies*." Second, the coalition of institutions could collect, standardize, and organize into a single database information they each hold detailing the technical characteristics, the IP status, and the ethical provenance of the stem cell lines and research tools developed at their institutions. Third, the coalition of institutions could organize systematic analyses of key stem cell research tools (such as our earlier examples of fibroblast growth factor or a neural differentiation kit) where technical, proprietary, or ethical bottlenecks, in some combination, have stymied work at a number of the participating institutions or their commercial partners. The results of such analyses would dissect the bottlenecks and explore what various options might be to relieve those bottlenecks, such as: Who owns the patents that claim different uses of fibroblast growth factor with stem cells? What are the technical issues and ethical status of the feasible component technologies for effective neural differentiation kits, and whose patents claim them? Fourth, the coalition could deliberate, design, and assemble or bundle technologies—recommending the technically most feasible, accessible, and ethically acceptable option or options for overcoming the constraining bottlenecks. Fifth, the coalition of institutions could physically distribute those bundled technologies, facilitating the necessary ethical and regulatory approvals, and providing FTO for research use through common material transfer agreements (MTAs) or for commercial use through patent pools.

Stage 1: Initiating a coalition of stakeholders

While government authorities could impose a variety of coordinating policies from above, a more efficient form of action for those directly engaged in stem cell R&D would be one self-organized from within that research community. The leadership of a few large institutions engaged in stem cell R&D, particularly universities, foundations and non-profit research institutions, could elicit the formation of a coalition, rallying a critical mass of technology interests and sources, with a mission to solve the complex coordination problems (Figure 3). Surveys of stem cell research activities and patenting suggest that academic research universities are among those with the biggest stakes in the rate and direction of R&D, in terms of the size of their patent portfolios.[21]

Research universities would be attracted to participating in efforts to foster greater coordination in the stem cell area as a matter of enlightened self-interest. Centralizing certain ethical, regulatory and technical functions (Figure 4) could save universities time and money, promote the use of their stem cell inventions, and reduce the risk to which the institution is exposed when taking controversial decisions or actions alone. For instance, coordinating ethical oversight across all of the institutions within the coalition

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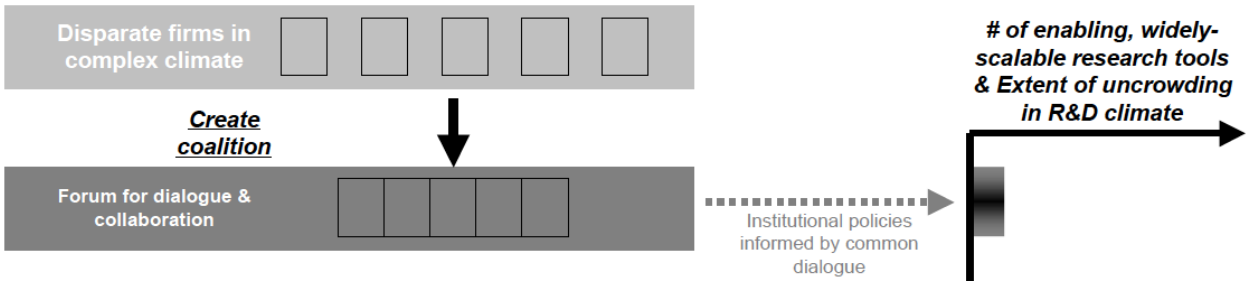
coalition of research institutions, and actively seeks to pool patents from its members around essential research tools or enabling technologies.

[21] K. Bergman & G.D. Graff, *Collaborative IP management for stem cell research and development*, CIP: Göteborg, Sweden and PIPRA: Davis, CA, USA. (2007).

could prevent each institution's research ethics committee from grappling with overarching questions, such as the moral status of the embryo, and allow them to spend more time addressing local ethical issues.

Figure 3. **A gathering of leading institutions in stem cell R&D, making a commitment to efficient, effective, & accountable collective action.** The first stage for coordinating access to enabling stem cell research tools in a complex technical, IP, ethical and regulatory environment. Passive reliance upon either markets or the public domain has failed to solve complex coordination problems. There is a need to rally a critical mass of technology interests & sources of inputs.



Furthermore, universities are increasingly faced with difficult ethical and policy dilemmas regarding the distribution of and access to materials and information—including data, research materials, and IP. They are increasingly looking to the power of exclusive control to induce private sector investment to develop their technologies (and not incidentally to thereby generate revenue), but institutional missions and traditional scientific norms support an ethic of sharing and collaboration. Coordination across the university sector of institutional IP policies or "best practices" for stem cells could offer a way through such policy dilemmas, by advancing common practices that balance the dual goals of information sharing and inducing technology development. The coalition's technical expertise can be coordinated through any existing university-wide stem cell initiatives or centers and would leverage existing national and global professional stem cell organizations [e.g., National Academies of Sciences (NAS) and International Society for Stem Cell Research (ISSCR)].

The threshold to enter such a coalition would be low—at least initially—and easily offset by the potential benefits of joining, including even just the access to enhanced technical, ethical, and IP information. Most importantly, joining the coalition signals an institutional commitment to collaborate in designing and implementing feasible solutions to the complex coordination problems. Details of such solutions need not be decided and would not be dictated at the initial stage.[22] Indeed, one of the privileges of taking an early role as a founding member of the coalition is the ability to take a leadership role in shaping the agenda and the proposing the solutions to be enacted by the group. Any commitments made, at any step in the process, are merely to take the next step, which can be considered in turn at each step.[23]

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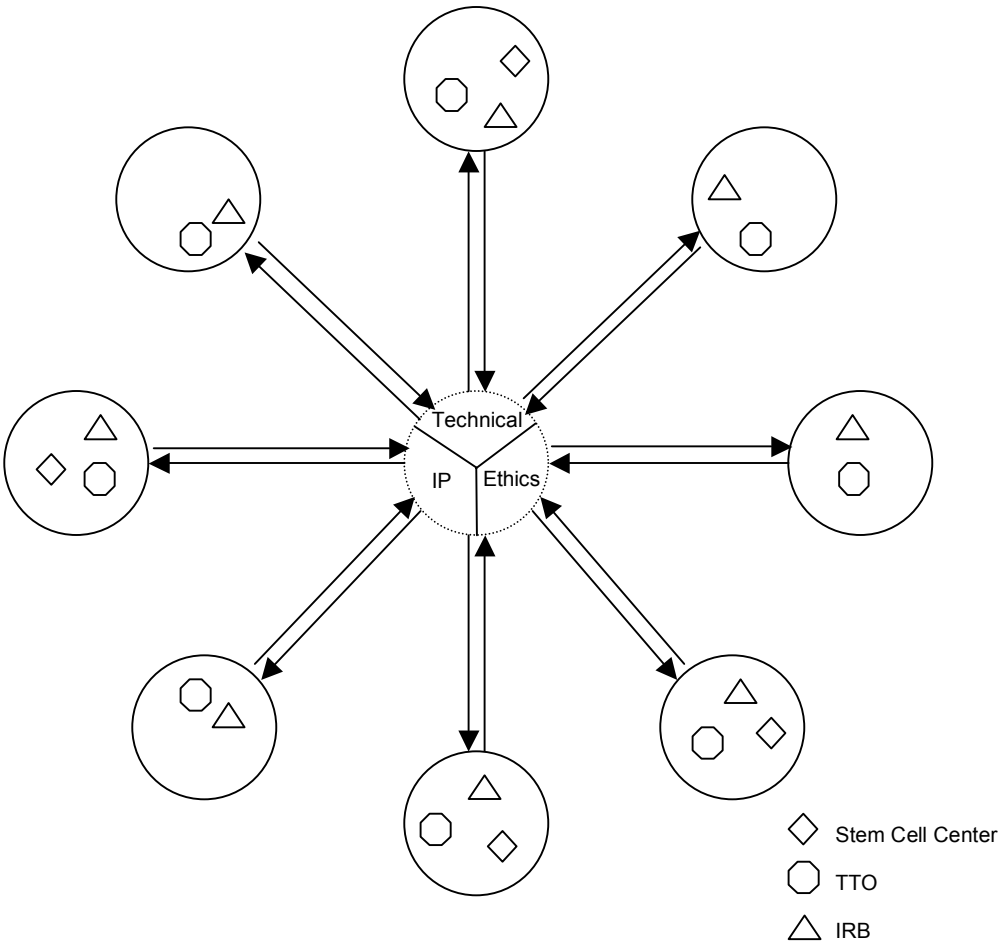
[22] Three details that will need to be immediately addressed are as follows: terms of membership, the legal status of the coalition, and which personnel would be involved from each institution. Although these will be self-defined by the coalition, here are some possible solutions. Membership may be defined simply as institutions that are "engaged in stem cell R&D and have a physical lab." If headquartered in the U.S., the legal status of the coalition could be a 501(c)(3) nonprofit corporation. Finally, responsible university officers from TTOs, IRBs, and various scientific departments could devote time to activities at the coalition.

[23] Scientists have already begun listing some commitments to formalize norms in the community, such as sharing of materials via ISSCR guidelines [PL Taylor. "Research sharing, ethics and public benefit." *Nature Biotechnology*, **25**:398-401 (2007)]. The coalition could adopt such commitments potentially in collaboration with ISSCR and formalize them in the coalition.

Figure 4. **The stem cell coalition as a coordinating hub for member institutions' decision makers.** Each member of the coalition has an internal institutional review board (IRB) providing internal policies and guidance on the ethics of stem cell research and a technology transfer office (TTO) managing IP owned by the institution. In addition, each member institution's stem cell initiatives or centers 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 takes decisions based upon their own limited information. The coalition provides a central forum for the responsible university officers to consult with one another and exchange information, benefit from commonly supported analyses, and provide input on the design of common technology platforms and standards.

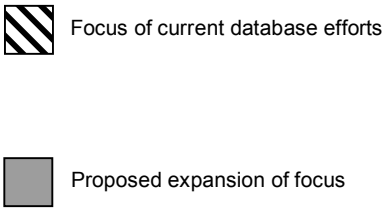


Stage 2: Construction of database and information sharing

Search costs and information asymmetries are fundamental sources of the technical, IP, and ethical issues described in Section II. Establishing a central information resource, or database, could help alleviate information problems and thus help to coordinate stem cell R&D. Scientific and technical information published in the public domain is symmetrically available to all parties at low cost, but key meta-information about technologies is often not readily available. While databases associated with stem cell research have heretofore focused on technical information on stem cell lines, an increase and centralization of the technical data and an expansion of the data to include IP, ethical, and regulatory information could produce synergies (Figure 5).[24]

Figure 5. **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 information about stem cell lines. We propose expanding such data centralizing efforts to include more stem cell technologies and more types of information.

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



For both the current and anticipated uses of stem cells in biology and medicine, the scientific literature and professional scientific organizations have characterized a variety of stem cell technologies central to stem cell R&D.[25] At the core of the field are, of course, specific *stem cell lines* (see Appendix A). Anonomyzed genetic and other cell biology characterization would be provided by the suppliers of the stem cell lines, while scientists at member institutions would provide details about other technical characteristics, such as clinical grade, karyotype, immunohistochemical markers, gender, pluripotency, availability of a single nucleotide polymorphism (SNP) profile, or infectious agent tests.[26]

Since scientists tend to choose stem cell lines not just based on the line's technical characteristics but also with respect to the line's ability to interface with other stem cell technologies, it will be helpful to list compatibility with other associated technologies (see Figure 2). Other associated characteristics of stem cell materials and technologies can be divided into five primary categories, including *derivation*, *growth*,

[24] Because of the potentially proprietary nature of such information, deposits of data may require some degree of internal commitment by institutions, terms of which can be jointly decided by the coalition.
[25] Notable examples include the ISSCR Standards Committee and the International Stem Cell Forum characterization project. For details, see Loring, J.F. and M.S. Rao, "Establishing Standards for the Characterization of Human Embryonic Stem Cell Lines." *Stem Cells*, **24**:1 (2006). & "The International Stem Cell Initiative: toward benchmarks for human embryonic stem cell research." *Nature Biotechnology*, **23**:7 (2005).
[26] The details within each will necessarily evolve and expand over time as stem cell biology and characterization increases in sophistication.

characterization, *differentiation*, and *delivery*.[27] 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.[28] Details of each derivation method[29] are expected 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.[30] The last two categories of *differentiation* and *delivery* address more downstream uses of stem cells (see Figure 2). Differentiation, or maturation, of a stem cell line into a particular cell lineage is an inherent property of stem cell that is typically exploited by researchers. Differentiation technologies include factors and culture materials that in many times recapitulate natural development in a cell culture or exploit novel pharmacological compounds. Finally, the celebrated application of stem cells to use the 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/injury, researchers use an array of delivery technologies to maximize cell survival and integration with the host.[31]

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. 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 MicroPatent, Delphion, or Derwent. The patent data can be further customized by analysts/programmers employed by the coalition to make the listings more useful to stem cell researchers, such as by indicating whether a patent is no longer in force, assembling related patents claiming parts of the same technology into "patent families", and associating the technologies claimed in patents with publications in the research literature.

In addition, non-confidential information about the licensing status of each patent could be provided by the participating institutions, indicating the availability for licensing of each of their stem cell patents—even simply identifying each as "available for all fields of use", "available for all fields of use, non-exclusively", "available for some fields of use", or "unavailable". Such information provides a service that is analogous to a "universal listing" of real estate on the market in a given metropolitan area. By participating in such a universal listing of their IP estates, coalition members could achieve an enhanced degree of efficiency in the technology transfer market in stem cells.

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[27] For an individual technology within one of these categories, information is needed concerning which specific technologies within the other categories work effectively in concert with it to accomplish particular tasks. In the example of technologies needed to obtain differentiated neural cells, information characterizing the different possible component technologies is needed —the stem cell lines, vectors, and culture media—as well as information on which specific options among these components work together most effectively.

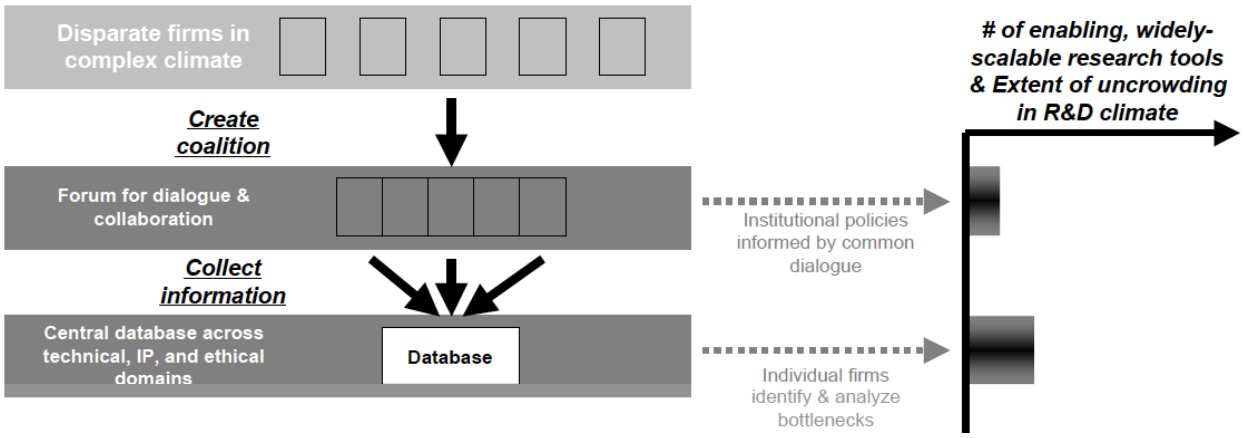
[28] For instance, a stem cell researcher may want to use a specific epigenetic characterization technology that only works with hESCs grown on a synthetic culture substrate without feeder cells. It would be helpful to list which hESC lines have been used successfully with each epigenetic characterization technology. In general, every stem cell researcher will need data from characterization assays, including expression patterns of selected surface antigens and genes marking undifferentiated stem cells, assessments of the 'epigenetic' status, determination of a DNA fingerprint of each line, microbiological status, particularly with respect to endogenous retroviruses, and a karyotype assay.

[29] Stem cell derivation technologies address the question of how to make stem cells. Such technologies include adult cell harvests taken from tissue samples, *in vitro* fertilization, SCNT, cell fusion, and genetic engineering of somatic cells.

[30] A few critical factors and materials are currently popularly used in stem cell research, including fibroblast growth factor, commercial media formulation (e.g., Cambrex XVIVO), and culture substrates (e.g., BD Sciences Matrigel).

[31] These technologies include co-injected or co-implanted solutions or materials, such as cell scaffolds, immune suppressing drugs, or carrier solutions.

Figure 6. Build a database of stem cell technologies that includes technical, legal/IP, & ethical/regulatory characterizations. A two-stage schematic for coordinating access to enabling stem cell research tools in a complex technical, IP, ethical and regulatory environment. Full information about stem cell technologies is highly dispersed, or outright unavailable. Yet, it is needed by many to inform their decision making.



Basic terms of availability for research exchange under a MTA could be indicated, and contact information for obtaining materials and necessary documentation could be provided. Furthermore, scientists may post information about additional terms of exchange, such as co-authorship requirements, which they may choose to place on the distribution of a particular cell line or 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 specific combinations of technologies. Considering the example introduced earlier, researchers seeking technologies for obtaining differentiated neural cells could utilize this information to identify a set of component technologies—including an appropriate cell line, a vector, and culture media—where all of the pieces are in fact available for the intended use. Indeed, information about the complex of IP covering specific combinations of technologies commonly employed together could also be developed by scientists and legal analysts at the behest of the coalition (see Stage 3) and listed or referenced amongst the IP information made available.

Lastly, the information resource or database would bring together information detailing the provenance and oversight associated with particular stem cell lines and related research material. Different regulations on stem cell research have emerged across countries and US states, creating a complicated patchwork of laws.[32] National or regional regulations 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 derived, regulation of gamete/embryo procurement, derivation details, and whether the line has "ethical approval" by oversight committees and other stem cell repositories. (For details, see Appendix A.)

[32] Isasi, Rosario M.; Knoppers, Bartha M.; Singer, Peter A.; Daar, Abdallah S. Legal and ethical approaches to stem cell and cloning research: a comparative analysis of policies in Latin America, Asia, and Africa, *Journal of Law, Medicine and Ethics* 2004 Winter; 32(4): 626- 640

Furthermore, users would want to know whether particular cell lines satisfy the law in these different jurisdictions, and/or the different voluntary guidelines recently adopted by the NAS[33] and by the ISSCR.[34] 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 constraints imposed by embryo and gamete donors. Data would be assembled from regulatory bodies, advisory boards, stem cell repositories, and from the member institutional oversight committees [e.g., stem cell research oversight committees (SCROs) or institutional review boards (IRBs)]. Finally, such a resource might also include data from social scientific studies of public attitudes towards different forms and uses of stem cell technologies.

Stage 3: Conducting analysis of key constrained technologies

For widely-used cell lines, technologies, or methods, it can be expected that many researchers will approach the database with similar concerns and questions, with many of them separately engaging in very similar analyses. Efficiency gains can be made by doing the most important analyses once for all (Figure 7). The coalition could identify and prioritize the most common "bottlenecks" in stem cell R&D: areas where access is complicated by failure to arrive at agreed technical, IP, or ethical terms of use. Subsequently, the coalition could conduct or commission analyses that characterize the salient technical, IP, & ethical dimensions of those particular bottlenecks in detail. While participating member institutions will largely shape this effort, through consultation and review processes, some of the bottlenecks likely to be proposed by member institutions are anticipated below.

Stem cell researchers rarely choose a stem cell technology in isolation: they carefully consider combinations of the technology with other technologies. For example, a cell line will be analyzed with respect to the availability and effectiveness of the line when used in combination with a variety of propagation methods, differentiation methods, and delivery methods. Or consider again the question of obtaining differentiated neural cells. Many of these technologies are not modular: they cannot be interchanged without reconsidering the rest of the technologies being used. Thus, researchers encounter a complex calculation of mapping technical characteristics of a single technology, not just pair wise to another technology, but in a multiple combinations with other interacting technologies.[35] In the many steps involved in the development of a stem cell product, researchers must repeat this process many times, considering just the technical domain. Introducing the additional layers of complexity involved in IP and ethical considerations, it is easy to see why individual labs struggle to find coherent bundles of stem cell technologies with which to work. The coalition would be uniquely positioned with its comprehensive database and ties to technical expertise across a wide array of member institutions to analyze these complex interdependent technologies.

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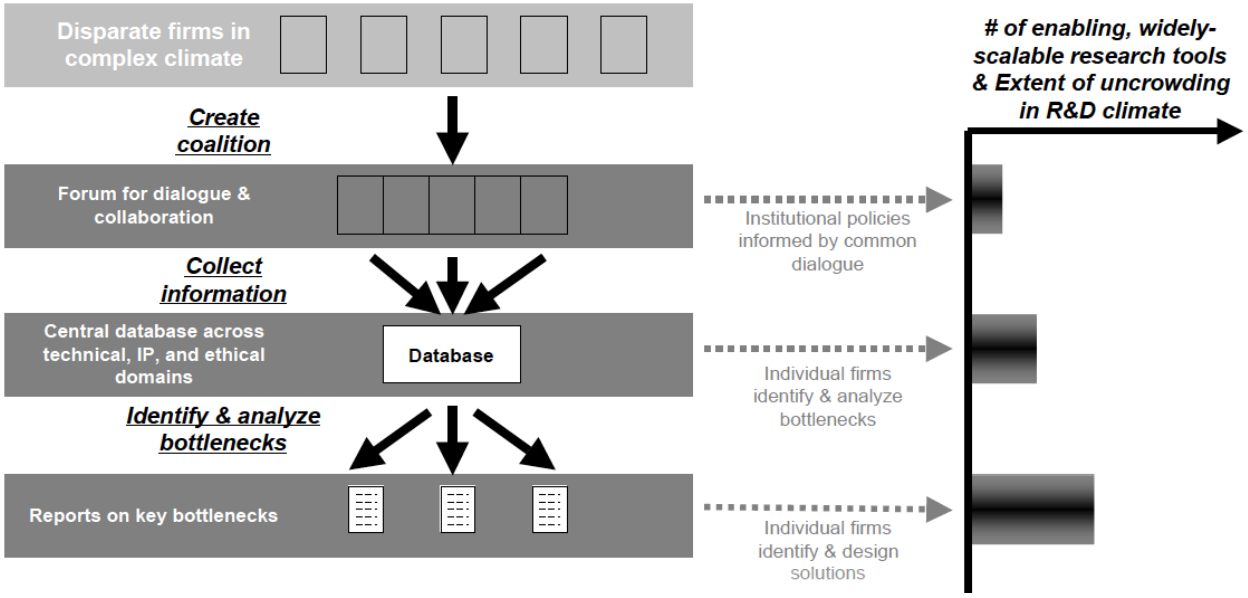
[33] National Research Council & Institute of Medicine, *Guidelines For Human Embryonic Stem Cell Research* (2005).

[34] George Q. Daley, Lars Ahrlund-Richter, et al., The ISSCR Guidelines for Human Embryonic Stem Cell Research, *Science* 315: (603-4).

[35] Consider the example of the neural differentiation kit. Details of each derivation method are expected to be important for the subsequent properties of the stem cell line in the kit. Choices of derivation technology may impact the choice of propagation materials, as certain genetic engineering strategies in the kit necessitate the presence of particular selectable factors in the culture media. Differentiation protocols necessarily couple with characterization assays of stem cells, as proper differentiation implies an absence of stem cell markers. And finally, drugs or material properties to enable injected or implanted cells to function properly will depend on the stem cell properties that derive from use of differentiation and propagation technologies.

Figure 7. Identify and prioritize common "bottlenecks," i.e. where access is complicated by failure to arrive at agreed technical, IP, or ethical terms. The first three stages for coordinating access to enabling stem cell research tools in a complex technical, IP, ethical and regulatory environment. For certain widely used technologies or methods, many researchers will be approaching the database with similar concerns, each engaging in the same analysis separately. Efficiency gains can be made by doing it once for all. Characterize the technical, IP, & ethical dimensions in detail.



Understanding which IP claims apply to a given technology for use under a given set of circumstances is not always a simple matter. 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 FTO 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. Such general assessments of how IP conditions are likely to affect FTO within typical commercial scenarios could be conducted by analysts employed by the coalition and/or legal experts that agree to provide such services to the coalition. These analyses could then be promulgated among the member institutions to inform researchers' decisions about likely options for avoiding common IP bottlenecks.

For any given research tool, cell line, or technology, it will be useful to develop an analysis of the real, potential and imaginable ethical issues raised. These issues might include the provenance of embryos and gametes–such as consent and payment, the issue of transgressing species barriers in new ways through chimeric materials, the issue of limiting subsequent uses of stem cells, the management of jurisdictional differences, and the problem of disagreement regarding the very procedure through which ethical decision-making was made. Detailed analysis on these parameters needs to be made for the most important stem cell materials in existence, in order to identify where new solutions are needed. We anticipate that the centralized ethics discussions would feedback to 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 both major and minor in order to lay the groundwork for the design of research tools and materials that would be least controversial.

Although these analyses may be initially done by scientists alone for the technical complexity, IP lawyers for the proprietary complexity, and ethicists alone for regulatory issues, it will be imperative for the coalition to bring these three units together. Reports synthesizing these three analyses will be the most valuable in describing the interaction of bottlenecks (see Section I) that troubles today's stem cell R&D climate.

Stage 4: Designing and assembling enabling research tools

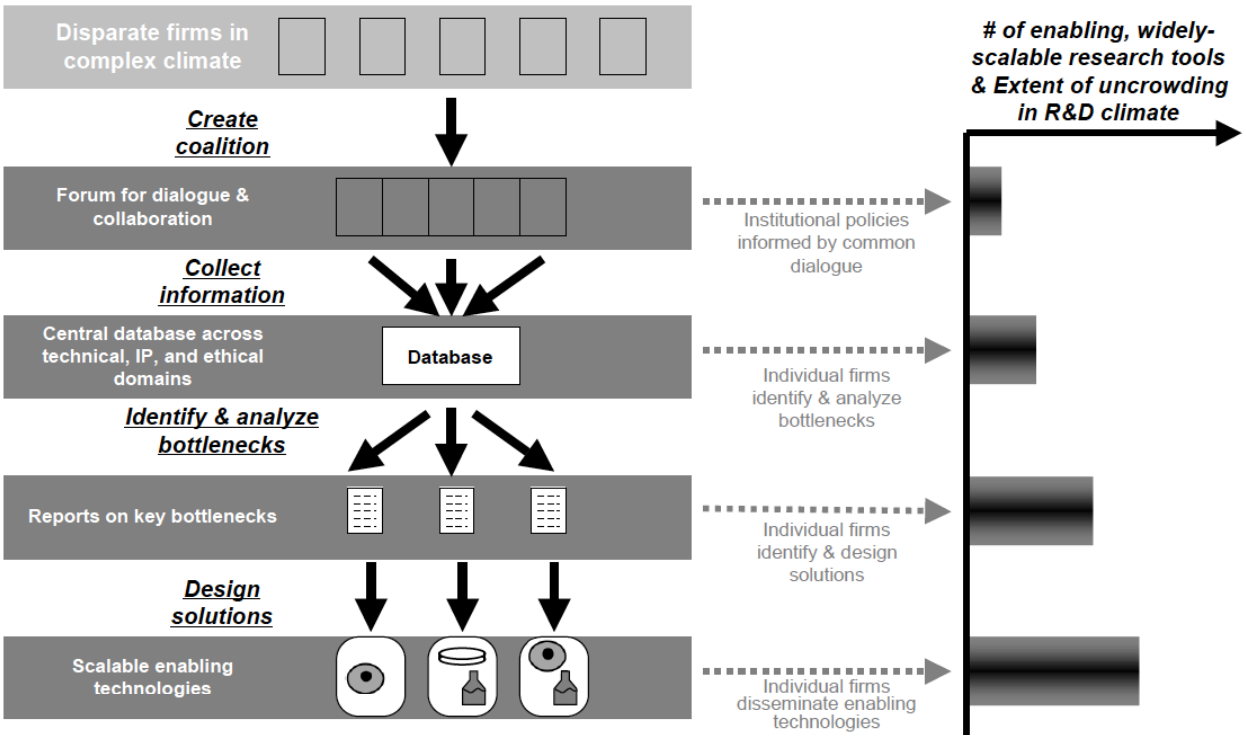
After analyzing the common bottlenecks arising from technical, IP, and ethical/regulatory considerations and the interactions among these three, the coalition can proceed to use the results of those analyses to inform the design of technology platforms or research tools that work around the most important bottlenecks freeing up research. The coalition designs and builds an enabling research tool by aggregating together technology components into a bundle that best meet technical, IP, and ethical parameters for a wide range of common applications (Figure 8). For example, a bundle could be assembled that consists of an appropriate cell line or lines, a vector, and culture media and thus enables researchers to obtain neural cells from the embryonic stem cells. The components are chosen because they work well together and are technically well characterized, they are all determined to be available for license from the institutions that own them, and the methods thus employed have been cleared by a preponderance of leading ethical review boards and are found to fall within reasonable bounds of regulatory approvals, at least within the necessary major jurisdictions.

The centralized effort of developing an enabling research tool platform once for many users increases efficiency in stem cell R&D. Furthermore, the coalition creates a natural venue for deliberating the content of the research tools, including technical input on preferred standards, legal input on whose owns the IP and whether it is available for broad licensing, and multiple expert decisions on ethics. Priority is necessarily placed on *widely scalable* enabling technologies to address the most important technology bottlenecks, where solutions would have the widest impact in terms of freeing up or "uncrowding" the R&D environment. By drawing upon the results of information compiled and analyses conducted in the previous steps, a fairly clear picture begins to emerge of the patterns of demand or need amongst researchers for particular technology bundles.

A cohesive assembly or "bundle" of stem cell technologies combines a complex platform of mutually complementary components, with each component enhancing the other's value or utility. Professional societies could likely shape this process by advancing consensus concerning which technologies are or could be most widely needed within research efforts. Often times, steps spanning across the range of derivation, propagation, characterization, differentiation, and delivery technologies described above are dependent on each other and together 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 just a single category, say a suite of factors for inducing cellular differentiation along a major developmental pathway, might be needed in concert in many research applications. In these cases, the design of that particular enabling research tool bundle would include that set of interdependent components.

The choice of technological components for inclusion in an enabling research tool "bundle" hinges upon the disposition of those components as IP. The component technologies that make up the enabling research tool platform could be either public domain or proprietary. Those that are owned would need to be included under pre-negotiated terms within a patent pool and licensed collectively to users of that research tool.

Figure 8. Design & build enabling research tools by aggregating technology components that best meet that technical, IP, & ethical parameters necessary for enabling broad access & use. The first four stages for coordinating access to enabling stem cell research tools in a complex technical, IP, ethical and regulatory environment. Greater efficiency of developing enabling research tools once for many users.



Component technologies that reside in the public domain are most favored for inclusion, as they carry the fewest property restrictions. However, 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 transaction of and access to knowledge. Still, for those technologies that can be clearly shown to reside in the public domain, inclusion in an enabling research tool bundle reduces the number of proprietary considerations that must be made in order to disseminate that bundle.

Component technologies owned by coalition members have advantages in being considered for inclusion, both because the terms of availability are already known, based on the information gathered for the database (see Stage 2), and because the members of the coalition are already informed and engaged in the overall process (see Stage 1). It is not uncommon to find university-owned technologies uncommitted, in whole or in part. Those technologies for which all fields of use are already exclusively licensed are generally not available for inclusion, although even this situation does not preclude seeking a sublicense from the licensee.

Occasionally, component technologies owned by outside parties may be deemed essential for either technical or ethical reasons. The owner or exclusive licensee can be approached with an offer to license the use of the technology as part of the enabling research tool platform. Incentives for their participation would include the prospect of licensing revenue via participation in the patent pool and any good will or reputation effects of participation. These latter may not be insignificant motives for smaller biotech firms.

The proposition for a technology owner to include their technology in a patent pool being designed by the coalition is, of course, a separate and much later consideration than the initial invitation to join the coalition. It is to be expected that 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 great benefits were to be gained from having ones technology included in an industry standard patent pool, such as MPEG or DVD, participation in a coalition designed research tool may be a good route toward achieving the licensing and utilization of a patented technology.[36]

Overall, the process for creating each research tool bundle will require substantial bi-lateral and multi-lateral 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 FTO with each of the individual components and combinations of the components (see Stage 3). This FTO 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 and/or a royalty- or fee-bearing license for commercial uses under pre-negotiated non-exclusive terms. Finally, the process may require formal evaluation of any anti-trust issues arising from the development of a patent pools in the respective areas of stem cell technology. In sum, the basic IP criteria to be applied in designing enabling research tools is the maximization of FTO (or conversely the minimization of IP constraints) with the assembled technologies.

Decades of work in the social studies of technology has demonstrated the ways in which technological artifacts embed human choices, which in turn have been shaped both by material conditions but also by ethical, social, legal, and economic considerations.[37] One implication of this work is that ethics and values can and do provide important design principles. Certain stem cell research tools would be inherently less controversial given the large questions of public morality. Bundles of technologies that are built using best practices that satisfy most or all extant guidelines could be developed, such that the resulting research materials and tools actually embody ethical choices and considerations. For instance, perhaps the stem cell lines designed and promoted by the coalition could be derived from "spare" embryos rather than somatic cell nuclear transfer (SCNT), the more controversial technology. Perhaps materials could be donated, rather than paid for, as a way to satisfy regulations in the largest number of jurisdictions.

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[36] In other new technology areas, such as in vitro fertilization treatment and music software, as companies become established, they seek stable markets and regulation: Spar, D. L. *The Baby Business: How Money, Science, and Politics Drive the Commerce of Conception.* Boston: Harvard Business School Press, 2006. and Spar, D. L. *Ruling the Waves: Cycles of Invention, Chaos and Wealth*. Harcourt Brace Inc., 2001.

[37] Wiebe E. Bijker and John Law, eds., *Shaping Technology/Building Society: Studies in Sociotechnical Change.* Cambridge: MIT Press, (1992).

One of the big issues here is who would decide which ethical standards to build into the chosen research tools. Here the coalition could foster some sort of deliberative process. If university partners could be drawn from states across the U.S., and countries across the globe, this process might have a better chance at achieving a sort of global normative legitimacy lacking in global regulatory guidelines generated to this point (NAS & ISSCR). Member institutions could deliberate upon what standards would be implemented. Clearly controversial technologies could be avoided if at all possible, such as chimeric entities, in order to promote the design of materials that minimize the sources of political controversy.

We see such a forum for deliberation and design having 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 existing lines, so that fewer embryos are destroyed for this purpose. In addition to promoting ethical transparency, using ethical principles to guide stem cell line design would literally build ethics into the material architectures of the science.

Stage 5: Providing & distributing enabling research tools

The coalition can provide a powerful mechanism to streamline negotiations, approvals, and procurement procedures for enabling research tools (Figure 9). Suppliers of stem cell technologies can work with the coalition to provide standardized forms and methods of distribution of cell lines, biological materials, etc. For particular technologies that could benefit from such distribution, coordinated dissemination of enabling research tools would reduce transaction costs and puts the "right" tools in researchers' hands. Below we outline the efficiencies the technical, IP, and ethical domains.

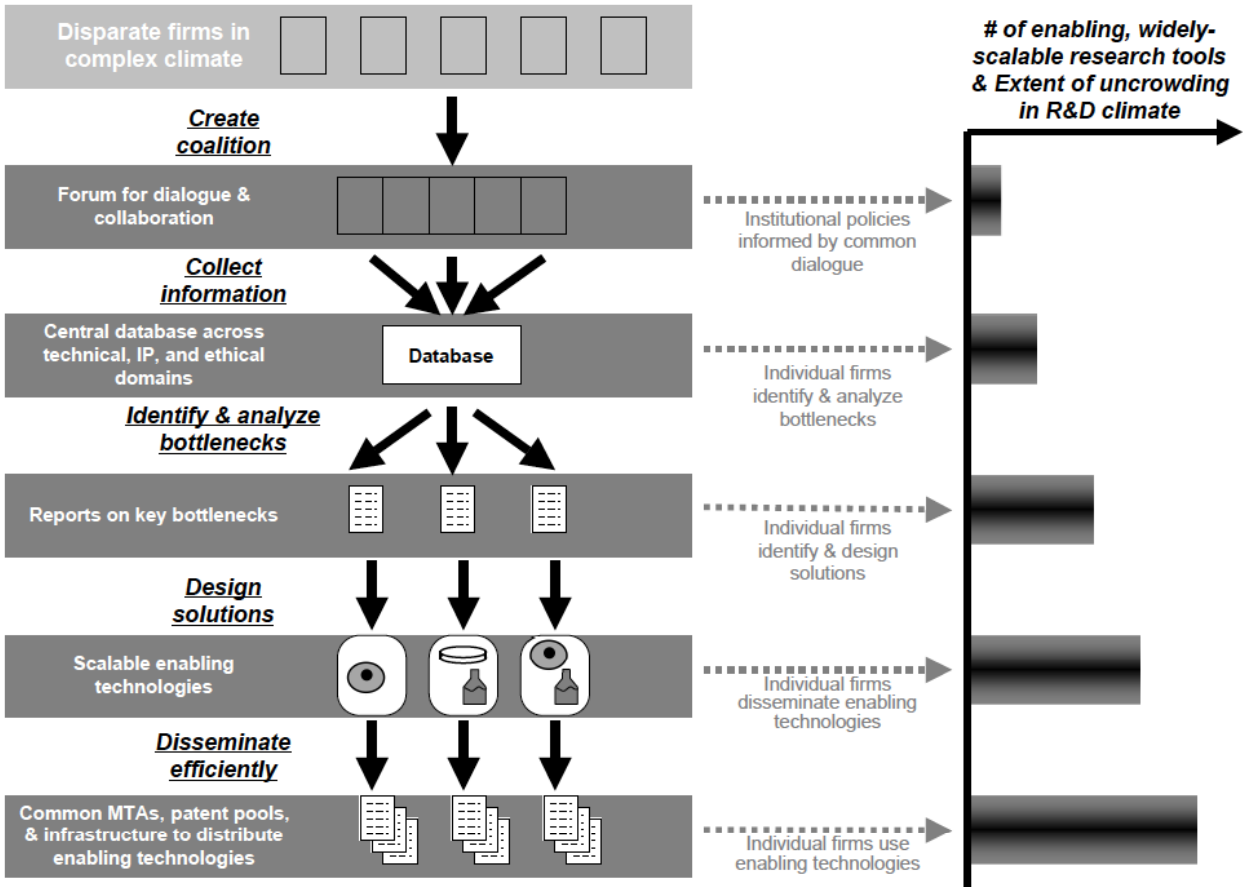
Stem cell kits are increasingly being offered by suppliers of characterization technologies (e.g., Invitrogen & Chemicon), however these kits seldom include the cell line themselves or the other propagation, differentiation, and delivery technologies. If the coalition indicates a clear demand for stem cell kits that encompass all technologies, i.e., enabling research tools, then the supply side will likely work together to provide such integrated kits.

Physically building facilities to disseminate enabling technology tools is not required; however, there may be some technical efficiency that accompanies centralized biological material handling. A centralized repository of stem cell lines has already been pursued in the U.K., and researchers note satisfaction with lower lot-to-lot variability and a strong validation of banked cells. While it is not currently clear whether such benefits exceed the high capital costs of building central facilities, in time building such facilities may be warranted. In the meanwhile, participating institutions such as WiCell may have facilities that could be contracted or utilized to provide any necessary centralized handling/distribution of biological materials.

The coalition may choose to develop a reporting infrastructure within member institutions for researchers to share protocols and to document efficacy of the transformation vectors/methods and other technologies. This may even entail building an interactive workspace by constructing or contracting lab space at member institutions. Such proactive investigation of technical bottlenecks would help feed information into the coalition database and create a reinforcing positive feedback for the coalition's actions.

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 as necessary, participating in enforcement actions against those using the research tools without the proper permissions.

Figure 9. Streamline negotiations, approvals, & procurement procedures. Five stages for coordinating access to enabling stem cell research tools in a complex technical, IP, ethical and regulatory environment. For certain technologies, this stage would reduce transaction costs & puts the "right" tools in researchers' hands.



In addition, the enabling research tool projects will have the potential to generate new IP in the area of stem cells, arising from improvements to the technologies in-licensed as part of a patent pool or representing entirely new strategies. Issues that would need to be addressed include the rules to manage inventorship issues resulting from multi-institutional collaboration and strategies to protect and manage collectively developed IP. Neither of these, however, should be insurmountable, as precedents exist from the management of complex research consortia in closely related fields, such as genomics.

Lastly, the coalition could provide novel means of including and enforcing ethical standards for stem cell technologies. Technologies that are distributed via the coalition's actions would gain salience in that they have been put through a rigorous ethical review. The popular use of such technologies could provide a standard in the R&D field to which other technologies are compared against.

Figure 10. **Activities of the coalition with respect to three technology examples.** The five stages will have different ramifications depending on the type of technology being managed through the coalition's effort. For example, for a seemingly simple technology like fibroblast growth factor, both technical and IP information are collected and shared. Subsequently analysis may be needed to clarify the FTO or technical functionality.

Stages of Coalition Involvement			
1: Create Coalition			
	Technology Example Fibroblast growth factor	HSF6 embryonic stem cell line	Neural differentiation kit
2: Collect information	• Cell lineages obtained after using it as a propagation technology • IP	• Genetic, epigenetic data • Regulatory approval • Chimera uses	• Growth factor, cell line, and vector technical characteristics • Provenance data • Chimera uses
3: Identify & analyze bottlenecks	• Report on its use as a propagation technology in making cardiac cells • Report on FTO	• Report on FTO • Report on provenance characteristics • Report on technical characteristics	• Report on FTO on each component • Report on provenance characteristics of cell line • Report on technical characteristics on each component
4: Design solutions			• Bundle scalable technologies into a kit • Provide supporting technical data about the kit components and their interoperability
5: Disseminate efficiently			• Common MTA or patent pool for kit • Distribution agreement with vendor to sell kit

IV. DISCUSSION

In the preceding pages, we have outlined an approach to overcoming difficulties caused by technical, IP, and ethical complexities in stem cell research. The multi-stage model goes beyond traditional approaches of simply collecting and disseminating technical data commonly used in stem cell research. Instead, this proposal defines a new, robust forum and process for managing the development and utilization of foundational stem cell technologies. In doing so, the proposal responds to some of the more systemic debates concerning the propertization of scientific research, collective action among research institutions, and management of the interface between science and society.

Collective action to define a knowledge commons

Neither markets nor the public domain—nor the complex interplay of the two that characterizes the world of R&D today—has been able to solve the complex coordination problems that researchers in the field of stem cells confront. Nor is it clear that either option of shifting the boundaries of IP towards weaker or towards stronger rights would categorically improve the situation. Instead, definitive progress requires more nuanced mechanisms that are able to recalibrate the various degrees of exclusivity that an owner may choose to exercise versus degrees of openness with which that technology is available to be recombined and deployed with other technologies.

This proposal outlines the means and advantages of constructing a common knowledge resource intended to regain some of the efficiencies of broader access, characteristic of the public domain, prudently balanced against the efficiencies of maintaining property rights. This protected "knowledge commons" is constructed at the interface between the public domain and private property, as a hybrid form, designed to facilitate productive interaction between the public and private domains.[38]

While free markets are in most cases the best mechanism available for solving complex coordination and resource allocation tasks such as those involved in R&D, markets in knowledge and technology—the typical inputs and outputs of R&D—often do not exhibit all of the conditions necessary to operate efficiently, including clearly defined property rights, the availability of full information, and competition in both supply and demand. The complex coordination problems in the case of classic public goods, such as knowledge, are solved by their public provision within the public domain, where free and open access helps to minimize the coordination costs and attendant uncertainties. Yet, while putting knowledge into the public domain solves some market failures, it introduces others, most notably an erosion of incentives for private investments in R&D. The notion of a protected knowledge commons seeks to minimize, at least, most of the attendant market failures associated with the provision and exchange of knowledge or technologies.

Indeed, collective action among disparate communities can help to preserve common resources for mutually beneficial activity. Examples of traditional protected "commons" are forests or fisheries, while our proposal is a more abstract protected "knowledge commons." In the context of natural resources or land use, the institution of a protected commons is intended to mitigate unsustainable levels of harvest and alleviate other problems of mismanagement.[39]

The role of the academic sector

We view international academia as the crucial sector for the creation of this multi-step collaboration to promote the transparent and ethical conduct of this controversial biotechnology. International legal agreement concerning the conduct of stem cell research will not be soon forthcoming, and this would be a clear advance over the status quo in terms of governance. The university's inherent mission of advancing and disseminating knowledge, along with its status as the navel of societal knowledge, sets the university apart from the corporate sector. No other sector in society has such a mandate for knowledge dissemination and global collaboration.

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[38] See A. Chander & M. Sunder "The Romance of the Public Domain" *California Law Review*, 92(5) (2004), pp. 1331-1374; Rai, Arti K. (2005) *Proprietary Rights and Collective Action: The Case of Biotechnology Research With Low Commercial Value*, in Maskus, Keith E. and Reichman, Jerome H., Eds. *International Public Goods and Technology Transfer in a Globalized Intellectual Property Regime*, pp. 288-306.

[39] Elinor Ostrom, *Governing the Commons*. (1990).

Although recent efforts of national and international scientific communities to establish voluntary governance over stem cell science should be applauded, "international academia" does not mean, in our view, the international community of stem cell researchers. Such a construction of institutional leadership is likely will fail to garner the sort of public acceptance and legitimacy that such an institution will require. Especially in the ethical sphere, design principles must be developed within an inclusive deliberative process that embraces delegates from the humanities and social sciences, which can help clarify, deepen, and advance such discussions in important ways.

Expanding efficiency, utility, and distributive equity

Efficiency gains can be framed as "enabling more entrepreneurship in stem cell research." This characterization is apt in today's public-private research climate. As we have argued in Section II, the real hurdles and rip tides that bedevil stem cell research can dissuade firms from entering the field in the first place. The communities knowledgeable in stem cell science, IP, and ethics can navigate these barriers better as an integrated whole. The resulting course would not be set blindly, but in a direction that most broadly provides access to enabling tools for the good of society. In the U.S., primary purpose of the Bayh-Dole Act was the translation of academic research into real applications, and society benefits from such private sector engagements as entrepreneurship, development, and manufacturing. Consumers benefit when new technologies become embodied in products and therapies that they can use. A deeper theoretical understanding of cell biology residing in the public domain is not the only result that taxpayers envision when they vote to fund stem cell research. They want products that will help to advance healthcare.

Lowering marginal costs of initiating work and increasing FTO are likely to have beneficial distributional effects. By bringing down the expected costs of doing adaptive research and product development, it is easier for all companies, including large and small alike, to investigate a wider range of products benefiting a wider range of markets. Making entrepreneurship easier on smaller scales expands the universe of potential applications, allowing more companies to fill more market niches, including those serving underrepresented populations and 'neglected' diseases. Overall, the process of reducing costs and increasing ethical acceptability expands stem cell research away from exploring only potential blockbuster therapies and towards a much larger constellation of stem cell therapies. When more options are available, everyone is better off. Again, we believe this is what the taxpayers envision when choosing to fund stem cell research. Furthermore, the coalition's efforts to transparently enable a broader array of health care applications may help appease larger worries over the purpose of stem cell research in today's complex public debate over cost and equity in the health care system.

Deliberative institutions to manage the interface between science and society

The proposed coalition is an institution that coordinates, with society, the production of new knowledge and more useful technologies. The membership of the coalition is self-defined and self-selected. At first one may find it duplicative to have yet another institution to address concerns of the scientific enterprise. But this proposal sets out a new sort of international forum to think through scientific, property, and ethical problems simultaneously and in collective conversations to promote collective problem solving. Because some of the problems are inherently political, and deal with the lack of public acceptance of current approaches, involving publics as stakeholders will be crucial. New groups, such as oocyte donors, patient groups, and taxpayer councils, can interact and play constructive roles within the proposed coalition. Once again, the non-profit university sector possesses the cognitive authority across scientific, social scientific, and humanistic fields in inquiry to help orchestrate and deepen the range of

considerations, as well as to garner public approval. Where high politics has failed—for instance at the federal level in the U.S.—to provide leadership and guidance for the conduct of this new technology, such an institution might succeed, and do so in a more globally collaborative mode.

The deliberative forum introduces a new mechanism to design research technologies. Social studies of technology provide rich examples of cases of when technological artifacts themselves powerfully pattern relationships between people.[40] Just as buildings without elevators or wheelchair ramps preclude participation of disabled groups from activities in the building, design aspects of research technological artifacts may restrict access to particular segments of society. For example, the first propagation technologies to grow hESCs entailed irradiating mouse embryonic fibroblasts to create a culture substrate for hESCs. Only institutions that had the safety infrastructure to handle radiation equipment and the resources to house and buy expensive radiation equipment could easily research hESCs. This forum would attempt to predict the distribution of uses of particular stem cell technologies and accordingly deliberate whether additional capabilities need to be designed into the technology to ensure access to particular polities. For the case of using hESCs, the coalition may make a primary goal to disseminate propagation technologies that do not entail radiation, simply in order to expand the access of hESCs to more labs. If public universities members want to emphasize the particular public health research goals, the forum can incorporate design elements that allow the use of stem cell technologies in anticipated public health research. By including more voices in the analysis of stem cell technologies, a wider array of designs can be promulgated in the stem cell R&D environment.

Precedents for collective action

The research community is ripe with examples of sub-communities that have self-organized to coordinate research action. Technical self-organizing efforts have largely facilitated sharing of data and materials only. Databases have historically enabled scientists to build upon previous work, and numerous examples of data sharing organizations have arisen to collect and centralize data, Stage 2 in our proposal.[41] More wide examples of research organizations that encompass building a coalition and coordinating technical research activities (i.e., stages 1, 2, and 5 in our proposal) include, in the U.S., Collaborative Research Grants ("Glue Grants") created by the National Institute of General Medical Science, the Developmental Studies Hybridoma Bank created by NIH, and BayGenomics created by the National Heart, Lung, and Blood Institute. Precedents of self-organizing initiatives with an IP dimension include the Human Genome Project, the HapMap project, and PIPRA. Prior self-organizing precedents by the ethics community typically entail workshops conducted by agencies or scientific organizations where social scientists and institutional oversight committee members discuss common ethical dilemmas.[42] Indeed, the California Institute for Regenerative Medicine has attempted to broaden participation in its governance by holding public meetings.

Such prior self-organizing efforts in research have had variable success in coordinating action among its members, and none has attempted to organize activity across all of the technical, IP and ethical domains.

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[40] Wiebe E. Bijker and John Law, eds., *Shaping Technology/Building Society: Studies in Sociotechnical Change* (Cambridge: MIT Press, 1992). and S. Jasanoff, "In a Constitutional Moment: Science and Social Order at the Millennium," in *Social Studies of Science and Technology: Looking Back, Ahead (Sociology of the Sciences Yearbook)* B. Joerges and H. Nowotny eds., (Kluwer, 2003) pp. 155-182.

[41] Several examples include GenBank, HIV Resistance Database, Evaluated Nuclear Structure Fundamental Data File, and Chemical Abstracts.

[42] Examples include, at the national level, the NAS Stem Cell Research Oversight Regional Meetings of 2007 (Irvine, CA; Chicago, IL; Cambridge, MA) and at the international level, "Session-XIII: Guidelines & Regulations" at the Stem Cell Research Forum of India, January 31-February 1, 2007.

We at the onset recognize that many of these precedents blend into one another and accordingly propose to create a forum such that these domains can talk to one another. The prior precedents highlight that resources - not only data, but also materials and coordinating research reagents - may reside outside academia. Non-profit, corporate, and federal agents have helped to coordinate the definition of many prior precedents themselves and moreover have helped to fund them. However, even the simple collection of technical information in scientific research has arguably been under funded.[43] Notably in stem cell research in the U.S., ethical considerations have blocked such broad organization activities by federal agents. We anticipate our proposed hybrid institution to require hybrid funding arriving from a variety of federal, international and non-profit agencies.

V. CONCLUSIONS

Stem cell researchers today commonly encounter risks of using poorly characterized technologies, infringing multiple patent rights, and violating proscribed ethical standards. The norms of open science press on researchers to make their tools widely available, but simultaneously they are pushed by society to specify property rights in order to translate their work into useful products. As a result, a patchwork of technical information is transferred on only selectively disseminated technologies. Deciding on the use of technologies under such circumstances is suboptimal for the field as a whole. In addition, technology licensing further confounds and constrains such choices offering stem cell tools under inexact terms that may become clear only after extensive investment of time and energy or resources, and may not provide the requisite FTO. The larger public in approving certain research uses of ethically sensitive stem cell materials worries that the benefits incorporated in their moral calculus are not unduly influenced by these confounding factors. Such worries, coupled with a limited set of blunt political tools to influence research, have resulted in inflexible policies that are stalling or diverting stem cell R&D. Continuing to operate under such conditions threatens the sustainability of stem cell R&D.

The institutional mechanism proposed here to coordinate the conduct and governance of human stem cell R&D carries significant promise for overcoming bottlenecks and challenges in the three domains, in part by seeing the problem from multiple angles. Technically, stem cell research can move forward by having more tools that can be more easily implemented in the current research environment. This process would coordinate and vet standards for such tools, and furthermore would enable many technological components to interface more easily. Second, the coalition removes transaction costs for translating research into stem cell products. The coalition's primary criterion for negotiating IP access concerns how broadly a tool is needed. Therefore the coalition's coordination of IP helps the community as a whole. The coalition creates a "protected commons" for stem cell R&D: simultaneously preserving and protecting private property rights while facilitating ready access to broad enabling technologies and making them accessible on reasonable market terms. In the ethical domain, the efforts help to ensure that the research tools that are broadly used are put through a commonly recognized process of ethical deliberation. It reduces duplicative work and harmonizes ethical standards setting across many institutions. In combination, these benefits are likely to have significant network effects that would serve to expand the efficiency and utility of stem cell research globally, supporting a broad range of applications.

[43] S. M. Maurer, R. B. Firestone and C. R. Scriver, "Science's Neglected Legacy," *Nature* 405.6783 (2000), S. M. Maurer and S. Scotchmer, "Database Protection: Is It Broken and Should We Fix It?," *Science* 284.5417 (1999).

APPENDIX A: ANTICIPATED DATA FIELDS FOR DATABASE OUTLINED IN SECTION III.

Informed by content of the NIH registry and other online registries.
Format of the list: *Data field name* [data entry]

General Line Information
Label [HSF6/H1/H9]
Provider [WiCell/UCSF/UKSCB]
Available [Yes, passage 43 / No (The cells failed to expand into undifferentiated cell cultures.)]
Academic Use Price [$5,000/$500]

Stem Cell Line Characterization
Passage # [> 70 / < 5]
Clinical Grade [Yes/No]
Karyotype [Normal/46XX/TBD]
Stem Cell Immuno Markers [SSEA-1- / SSEA-3+ SSEA-4+ TRA1-60+ TRA1-81+ Oct-4+ AlkPhos+]
Gender [Male/Female/TBD]
Frozen/Thawed, Short-term [Yes/No]
Frozen/Thawed, Long-term [Yes/No]
Pluripotent [Yes/No]
SNP Profile Available [Yes/No]
Infectious Agent Tests [Yes/No]

Stem Cell Derivation method
Growth Factors Used in Derivation [None/FGF]
Oocyte Donor Hormone Treatment [Standard/Other]
Oocyte Extraction Surgical Technique [Standard/Other]

Stem Cell Propagation Method
Animal Products in Culture [Yes/No]
Mouse Feeder Cells Used at any time [Yes/No]

Stem Cell Differentiation Methods
Lineages [Neural/Cardiac]
Factors used
Scaffolds used

Stem Cell Delivery Methods used with line
Drugs
Scaffolds

Published References
e.g., field for H1 hESC line, the link uses “H1” & “human embryonic stem cell” search terms in Google Scholar [http://scholar.google.com/scholar?q=H1+%22human+embryonic+stem+cell%22&hl=en&lr=&btnG=Search]

Embryo Provenance
Source [IVF Clinic/Private Industry]
Category [Fresh/Frozen]
IVF Status [Discarded—unacceptable for further use]
Satisfies ISSCR Provenance Guidelines [Yes/No]
IRB Review [UCSF SCRO/UPenn IRB/None]
IRB Concerns [Oocyte donor compensation/Continued medical treatment not given to donor]
Growth Factors Used in Derivation [None/FGF]
Oocyte Donor Hormone Treatment [Standard/Other]
Oocyte Extraction Surgical Technique [Standard/Other]

Intellectual Property

For each patent, US and international
Patent ID [US6998515]
- *Title* [Use of a stem cells in skin grafts]
- *Assignee* [Cornell Research Foundation, Inc. Ithaca NY US]
- *Primary US Classification* [800/278]
- *Primary International Classification* [C12N 5/08]
- *Priority Date* [27-Jan-1997]
- *File Date* [20-Jun-2000]
- *Issue Date* [14-Feb-2006]
- *Etc…*

Supplementary information for each patent, US and international
Patent ID [US6998515]
- *In force* [yes/no]
- *Legal status*
- *Associated scientific publications*
- *Associated patent family members (US and international)*

Non-confidential licensing information for each patent, US and international
- *Licensed: All fields exclusive* [yes/no]
- *Licensed: Some fields exclusive* [yes/no]
- *Licensed: Non-exclusive* [yes/no]
- *Optioned: All fields exclusive* [yes/no]
- *Optioned: Some fields exclusive* [yes/no]
- *Optioned: Non-exclusive* [yes/no]
- *Unlicensed* [yes/no]
- *Other* [yes/no]
- *None* [yes/no]
- *ISSCR Academic Use MTA Available* [Yes/No]

Ethical Information

Legally / ethically derived within its own jurisdiction [Yes/No]
Derived via public funds [Yes/No]
Informed consent constraints on future use [Yes, see types of use, jurisdiction, & marketization stipulations of subsequent materials]
Payment of women egg donors [Yes/No]
Composition of IRB / SCRO review [Mix of expert and lay]
Derivation Techniques [SCNT or other]
"Ethical approval" of UK Stem Cell Bank [Yes/No]
"Ethical approval" of CIRM [Yes/No]
"Ethical approval" of NAS [Yes/No]