Democracy Derived? New Trajectories in Pluripotent Stem Cell Research

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How has the development of human induced pluripotent stem cells (hiPSCs) modified the trajectory of stem cell research? Here, coauthorship networks of stem cell research articles and analysis of cell lines used in stem cell research indicate that hiPSCs are not replacing human embryonic stem cells, but instead, the two cell types are complementary, interdependent research tools. Thus, we conclude that a ban on funding for embryonic stem cell research could have unexpected negative ramifications on the nascent field of hiPSCs.

Just 5 years ago, the term pluripotence referred to a characteristic feature of only one type of human cell: human embryonic stem cells (hESCs). But when human induced pluripotent stem cells (hiPSCs) burst upon the scene in 2007, this all changed. hiPSCs are derived by reprogramming somatic cells into an embryo-like state through the expression of specific transcription factors. Like hESCs, hiPSCs are capable of differentiating into any tissue type in the body (Takahashi et al., 2007; Yu et al., 2007). Thus, hiPSCs have been hailed as groundbreaking because they offer a much clearer path to disease-based modeling and individualized therapies compared to older, more genetically homogeneous hESC lines (Mosher et al., 2010). Given that generating hiPSCs involves a relatively straightforward reprogramming technique, will hiPSCs "democratize" the stem cell field by bringing pluripotent cells within the reach of many labs that have shied away from the use of more controversial and restricted hESCs?

In general, United States policy prohibits research on human embryos and restricts federal funding to hESC lines previously approved and listed on a national registry. This changed dramatically in August 2010 when a federal circuit judge issued an injunction blocking funding for new hESC research. By contrast, hiPSCs are made with somatic cells, not embryos, and therefore are not as controversial as hESCs and not subject to federal restrictions. But what is still not clear is how the emergence of these new pluripotent technologies, combined with these policies, impacts the adoption of new lines, the dissemination of existing lines, and the extent to which hiPSCs are supplanting or augmenting established hESC research. Complicating matters, some investigators now suspect that hiPSCs and hESCs differ significantly, issuing calls for research that uses both types of cells, most especially comparative studies. New findings have underscored these distinctions, provoking debate about the possible use of hiPSCs for disease models and therapies (Pera, 2011; Lister et al., 2011; Hu et al., 2010; Zhao et al., 2011).

Are reprogramming technologies broadening access to pluripotent cell lines and expanding the reach of stem cell research? If so, we hypothesize that we would expect the following: (1) the uptake of hiPSCs in the published literature to be significantly faster than that observed for more restricted hESC lines; (2) the amount of research that uses hiPSCs without also relying on hESC lines to grow, indicating that the new technology obviates the need for scientists to choose embryonic cell lines; (3) scientists working with hiPSCs to report less apprehension about or difficulty with access to research materials and funding than investigators whose research depends wholly on more restricted hESCs; and (4) the use of hiPSCs to increase in labs with little or no experience using hESCs.

This Commentary examines these four assertions by mapping the trajectories of hESC and hiPSC technologies. We analyze data collected from 2086 hESC and hiPSC publications and brief face-to-face surveys with 118 active researchers (30.9% of 381 poster presenters at the 2010 ISSCR meeting in San Francisco) to examine how hiPSCs have been used in the years immediately following their discovery. These data allow us to evaluate the impacts that hiPSCs might exert on the more mature field of hESC research.

hiPSCs are a young technology, and the field may yet grow in unexpected directions as it matures. Nevertheless, our data offer important insights for contemporary legal and policy debates about the legality and scope of federal funding for hESC research. Our findings strongly suggest that judicial or legislative decisions that bear upon support for human embryonic stem cell research are likely to strongly impact the character and direction of human induced pluripotent stem cell research. In particular, removing or curtailing federal funding for the former will also have disastrous consequences for the latter because research using the two different types of

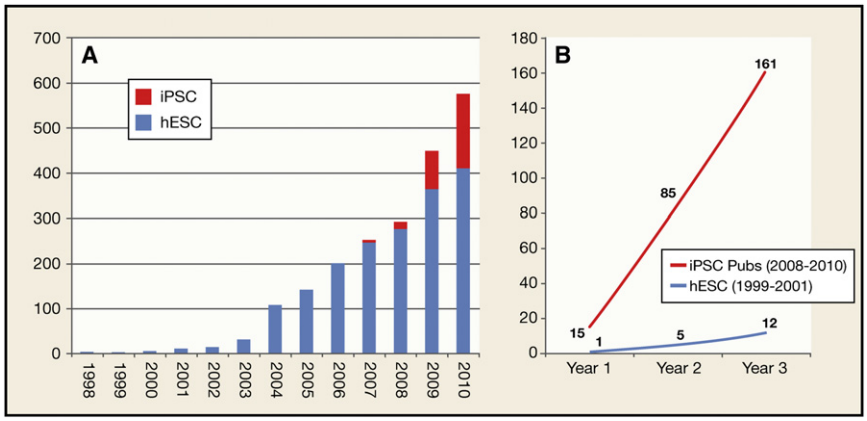

Figure 1. Publication Analyses
(A) hESC and hiPSC publication trends from 1998 to 2010.
(B) Uptake of hESC and hiPSC in publications immediately following initial discovery.

cell lines is deeply, perhaps inextricably, intertwined.

The Rise of Reprogramming Technologies

If hiPSCs are increasing access to pluripotent cell types, we expect to see relatively quick uptake of the new method. Indeed, tracking the number of publications yearly since 1998 that use human pluripotent stem cells (Figures 1A and 1B) suggests that this is the case. Since the publication of the first two papers on hiPSCs in 2007 through 2010, we see a rapid rise of both hESC and hiPSC publications.

Several factors may contribute to the fast emergence of publications on iPSCs, including their ease of use and access, their therapeutic potential, the entrance of new labs and investigators into the field, and the application of previously optimized hESC culture conditions. This increase could also be due to the reaction of established hESC scientists to 8 years of funding restrictions under the Bush administration and the funding uncertainties for hESC lines. On the other hand, the Obama administration has made some new lines eligible for funding since 2009, and thus the rise in hESC use may result from the adoption of these new lines, anticipation of increased federal funding under the new administration, or access to increased sources of state support for hESC research across this time period (Karmali et al., 2010).

Nevertheless, the uptake of induced pluripotent cell methods is dramatically faster than the rate observed for hESC lines in the 3 years immediately following their discovery in 1999 (Figure 1B). Although labs working with hESCs in the 1990s were claying the scientific groundwork and publishing their results in a growing number of journals, we believe these differences may be due in part to the profound difference in the policy environments surrounding these technologies. Embryonic stem cell researchers in the late 1990s and early 2000s faced not only a restrictive political and regulatory environment but also public controversy surrounding the use of frozen embryos to derive new lines and a complicated and expensive process for accessing existing cell lines protected by patent rights. The chilling effect of George W. Bush-era policies is also clear from Figure 1A, which suggests that it took hESC publications a full 6 years (until 2003) to surpass the number of hiPSC articles published just 2 years after their discovery. In broad strokes, it appears that hiPSC technologies are being adopted much more rapidly than hESCs were.

hiPSCs and hESCs Together or Separately?

But are hiPSCs complements or substitutes for hESCs? Using information from the body of papers and supplemental material, we characterized the types of pluripotent stem cell lines used in publications from 2008–2010 (Figure 2). We coded the papers as using hiPSCs alone, hESCs alone, or both cell types. We also coded the cell lines used in 381 research posters presented at the June 2010 International Society of Stem Cell Research (ISSCR) meeting held in San Francisco, CA.

The proportion of papers using hiPSCs and hESCs together is growing faster than those using hiPSCs alone. In 2008, only 5.1% (15) of all papers analyzed used any induced pluripotent cell lines and only 20% (3) of those combined hESCs and hiPSCs in the same research manuscript. By 2010, 28.0% (161 of 574) of all pluripotent cell papers used hiPSC technologies, but 62.1% (100 of 161) of those paired induced and embryonic cell lines. Thus, although induced pluripotent stem cells are quickly becoming an important part of the field, they do not appear to be replacing work using embryonic cell lines. Instead the two types of cells are increasingly used together. Figure 2 suggests that hiPSCs may provide a limited avenue for new investigators to enter the field if established hESC researchers come to dominate in publications using the new technique. On the other hand, we could be witnessing a vetting period for hiPSCs as experienced researchers contrast the true utility of a possible eclipsing technology.

Access and Utility in Cell Lines

In prior work, we have shown that the patterns of research materials used by scientists can be gleaned from analyzing the research literature, but the underlying reasons why researchers chose particular cell lines over others are not always obvious from publications (Scott et al., 2009, 2010). To probe this question, we surveyed 118 researchers who presented posters about pluripotent stem cells at the 2010 ISSCR meeting. We scored and categorized the surveys based on two major themes that characterize the field: the "utility of materials" category scored comments about why the lines were used, and the "access to specific materials" category scored comments on how the lines were obtained (for details, see Supplemental Information and Table S1).

Access

Investigators using only hESCs manifested the most complicated thinking about access to research materials. Perhaps because embryonic lines are the core of their research programs they evinced greater concerns about access

to federal funding and the eventual disposition of particular lines under the Obama policy. They also expressed greater reliance on state funding as an alternative to federal funding and described more diverse routes to access specific lines.

Many scientists explained how regulatory uncertainty and funding dilemmas could impede their research. For example, a California researcher who relies on a specific hESC line said, "Bottom line is the ability to work with them. CIRM [California Institute for Regenerative Medicine] gives me confidence because I know I'm funded. I'm glad I'm in California." The vagaries of federal regulation caused one New Jersey researcher to derive a new line for NIH approval when state funding was dropped for a project using H9. After a 9 month delay, H9 was eventually approved under new NIH guidelines. Another scientist remarked that federal policy has "a huge impact on the study, as our investigation had to give up NIH funding to work on the cell lines."

Geography also played a role. One US investigator moved to Belgium in order to derive new lines. "I work on methods for improved derivation of hESC lines. We created 15 new lines in the process of [our] investigation." Researchers working in other countries remarked that their ability to derive and use new lines either was not encumbered by restrictions (Sweden) or was handicapped in some fashion (Germany).

Researchers accessed hESC lines in numerous ways. Some purchased them from companies whereas others obtained them from collaborators. Others continued to use specific lines because they were repeating previous work or because they were assigned to an ongoing project. Banking, core facilities, and other repositories also played a role. One researcher remarked, "I needed a line and I learned I could get them across the street at the New York Stem Cell Foundation. They gave a vial to me the same day."

In contrast, the remarks by scientists using only iPSCs suggested that access was unproblematic because deriving new cell lines was easy. Most concerns involved whether to derive lines specific to the needs of the lab or to obtain them from collaborators. When investigators volunteered information about the source of somatic cells used for reprogramming, they generally reported easily accessible tissue banks as their sources. There were very few mentions of funding worries and none of policy restrictions. Investigators were split about evenly between those who derived their own lines and those who requested materials from other labs.

Researchers who used both iPSC and hESC lines declared less concern with federal funding and access than those using only hESCs but more worries than those who focused only on iPSCs. There was little concern among these scientists about the uncertainty introduced by changes in federal funding rules under the Obama administration and state alternatives to NIH research support. We attribute this to the fact that many of the combinatorial experiments featured federally approved hESC lines, most notably H1, H7, and H9. In some cases, laboratories in this category were experienced hESC users, and thus studies comparing iPSCs and hESCs were the logical next step: "H1, H7, and H9 were already in the [lab]," one researcher said. "…so we used the three lines as controls."

Notably, when asked about access, researchers who used both hESCs and iPSCs almost unanimously replied by describing how they obtained their hESC lines. Although survey respondents reported multiple means to access hESC lines, they focused on informal routes and the legacies of past research.

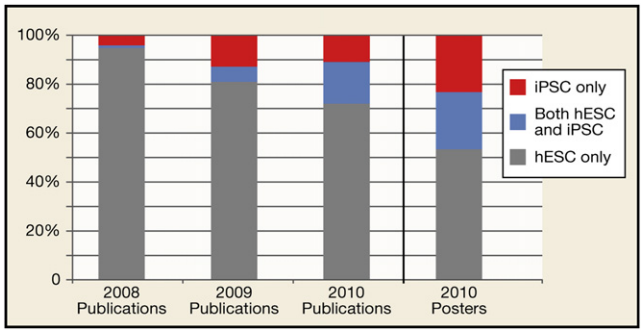

Figure 2. Proportion of Research by Cell Line Type Used

Utility

In the 38 interviews with hESC researchers for whom utility was an important theme, 25 (65.8%) mentioned the H1, H7, or H9 lines explicitly. Discussions about the utility of particular research materials thus hinged on determining which line among a small set of available possibilities was the most satisfactory. Investigators using only hESCs evinced different conceptions of utility. Particular lines were considered valuable because they were known quantities (in scientific and regulatory terms) and thus were valuable as references in experiments that used or derived new lines. "We wanted to use H1 because they're less likely to spontaneously differentiate," a researcher noted.

Overwhelmingly, investigators using only iPSCs picked the cells because of the scientific excitement surrounding the technology, for their ease of derivation, and for their therapeutic usefulness. This researcher summed it up: "[We use iPSC] because it is an exciting new technique and it's fascinating to figure out potential therapeutic implications. And, it's a powerful comparison to what we know about hESCs." Descriptions were framed in reference to particular diseases or markers for specific patient populations or because the disease-based tissue banks were readily available. Somatic cells were sourced in the US, Africa, Italy, Australia, Finland, and Germany, and diseases and disorders included autism, cardiac disease, HIV, TB, and liver failure, suggesting a broad genetic diversity of lines.

For researchers using both types of lines, utility was framed in terms of comparing iPSCs to the best-known qualities of hESCs. Only one researcher noted disease as a study aim and then only in the context of obtaining patient-specific lines. Because many of these labs had already studied hESCs, it was only natural that comparative work would follow. "It's always good to use at least H9 as confirmation," noted one researcher. Another said, "H9 is the standard. It's needed for a positive control." One scientist noted the conspicuous presence of hESC

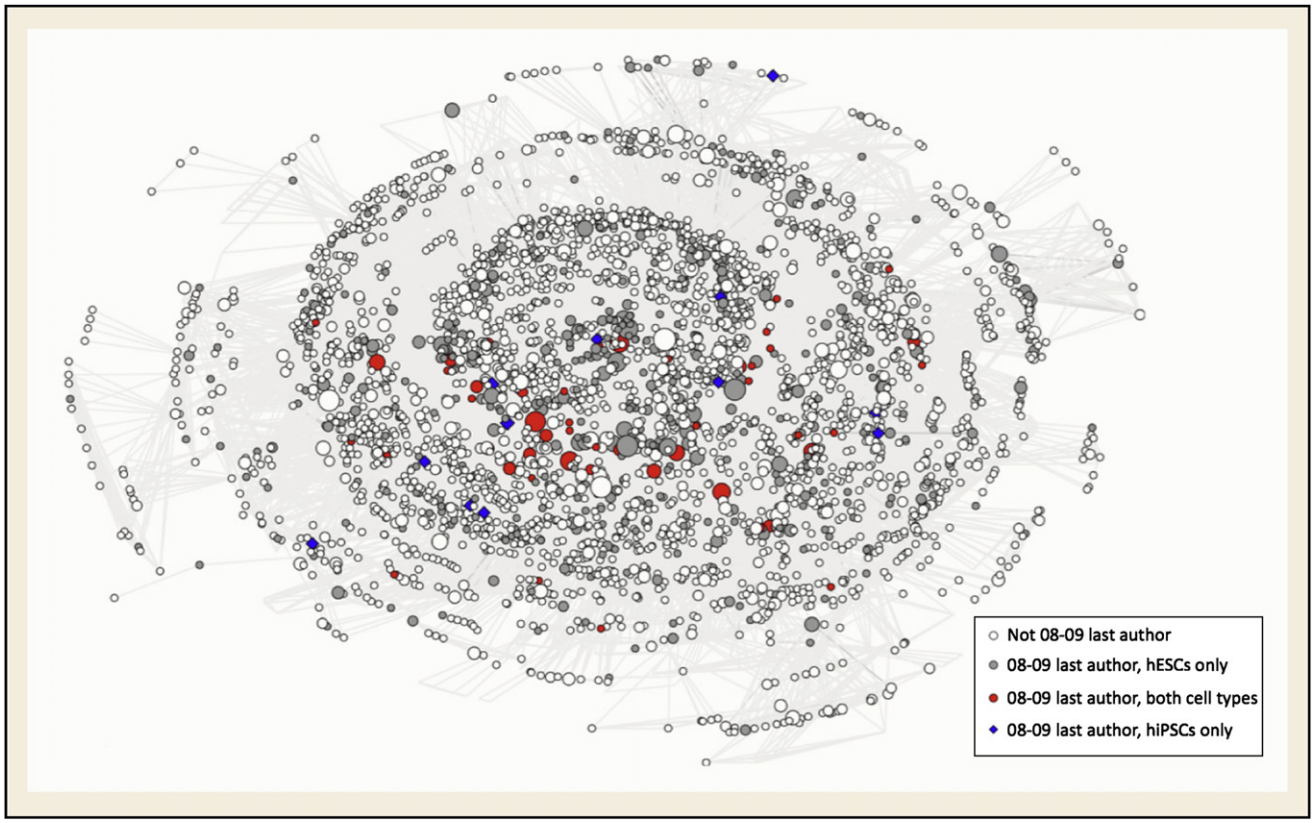

Figure 3. Coauthorship Network of Human Pluripotent Research Articles
The network represents coauthorship connections among 5004 researchers publishing articles on hESCs and hiPSCs from 1998 to 2009. 509 (9.23%, n = 5513) authors are not connected to the primary network component and are not represented. Node size is proportional to articles on hESC or hiPSC articles in 2008–2009.

controls in the literature: "…we haven't seen papers on iPSCs without comparison to ES lines."

Coauthorship and Collaboration

In this final section, we analyze networks of coauthorship to determine whether senior researchers who use hiPSC technologies are also deeply embedded in the established field of hESC research. Coauthorship of publications is a key relationship defining scientific disciplines and fields (Moody, 2004; Newman, 2010), and it often encompasses sharing of materials, expertise, goals, and sometimes students and fellows. We treat the last authors on publications as senior representatives of labs, and we do not account in our images for the possibility that joint senior authorship driven by multilab collaborations may be represented by shared corresponding authorship.

We present two network figures that portray the penetration of hiPSC research into the hESC field, focusing on the work performed by more senior scientists (Figure 3 and Figure 4). First, we assembled the entire coauthorship network for stem cell articles published between 1998 and 2010 (Figure 3). In this image, nodes represent authors, and ties represent coauthorship on one or more papers. Repeated patterns of coauthorship create a network structure that includes the majority (90.8%) of scientists who have published using hESC and hiPSC lines.

We color-coded nodes to highlight the activities of last (or senior) authors on papers published in 2008 and 2009. The size of the node reflects the number of papers that an author published in 2008–2009. Large white nodes represent first and middle authors from 2008–2009 publications. Small white nodes overwhelmingly represent authors on pre-2008 stem cell publications who did not publish new articles between 2008 and 2009. The dark gray, blue, and red nodes represent senior authors on papers that used hESC lines only, hiPSC lines only, or both types of lines, respectively. In Figure 3, consider Harvard University's George Daley, who published 12 papers on human pluripotent stem cells during this time with 6 articles listing him as last author. Daley is a rare senior author in our database in that, during 2008–2009, he published papers using hESCs alone, hiPSCs alone, and both cell types. We thus code him as a last author who has used both hESCs and hiPSCs. Daley appears in our network images as a large red circle.

Finally, the relative position of nodes in these images is meaningful. The network drawings are optimized using a pair of "spring embedder" algorithms that use the connectivity of a network system to establish the Euclidean distance among nodes (Fruchterman and Reingold, 1991; Kamada and Kawai, 1989). A position in the outer ring of the image represents

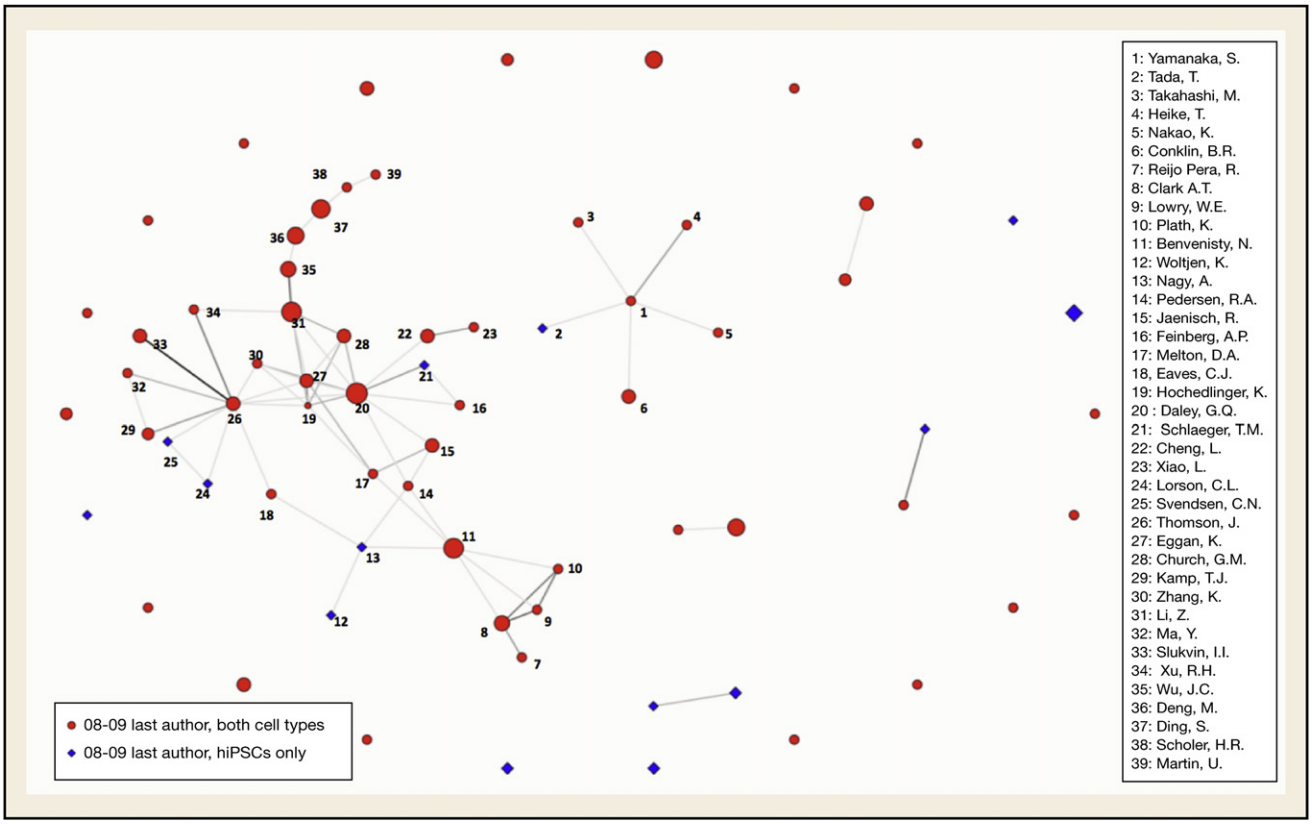

Figure 4. Network of Last Authors Using hiPSCs

This network image represents coauthorship connections among the 69 last authors working with hiPSCS in 2008–2009. The large network on the left side of the figure includes 33 (47.83%) authors, dominated by researchers at Harvard University and the University of Wisconsin. The "star" in the center contains five last authors connected to Shinya Yamanaka.

a collaboration profile that has few ties into the most connected portions of the field. Likewise, scientists who are positioned close together are proximate because they are direct collaborators or they share coauthors in common, creating relatively short indirect network paths between them.

Figure 3 represents 90.8% of pluripotent stem cell scientists. If hiPSCs are a widely disseminated technology that allow newcomers to enter the field without recourse to prior working relationships with established hESC investigators, we would expect to see (1) more blue nodes than red nodes, indicating that a large portion of senior authors are using hiPSCs instead of hESCs; (2) red and blue nodes smaller than gray nodes, indicating that those researchers using hiPSCs alone or in concert with hESCs are newer, less prolific investigators; and (3) red and blue nodes nearer the periphery of the image than its center, indicating that senior investigators using hiPSCs are relatively less well connected to the researchers at the established core of the hESC network.

Examining Figure 3 suggests that none of these expectations are born out. Red nodes outnumber blue nodes, with 55 senior investigators publishing papers using both hESCs and hiPSCs in 2008–2009 compared to only 14 senior investigators publishing papers using hiPSCs alone. Many red nodes are large, representing prolific authors that use both cell types. Blue nodes tend to be small, suggesting that the last authors on papers with only hiPSCs either are junior in the larger pluripotent field or are senior investigators in allied stem cell disciplines and are experimenting with reprogramming. Finally, although red and blue nodes appear spread across the entire network image in Figure 3, the majority of senior authors using hiPSCs are clustered in a band of large red nodes that crosses the lower left quadrant of the figure. In other words, many of the investigators using hiPSCs are established, prolific hESC scientists who are connected to each other directly or through short indirect paths defined by shared coauthors. Such close indirect connections occur in many fields as senior investigators hire postdoctoral fellows trained in the labs of other established investigators, or as departing scientists carry past collaborations with them to new faculty positions.

Figure 4 delves deeper into the relationships between senior authors using hiPSC lines. To create Figure 4, we first extracted all 69 red and blue nodes from Figure 3 and then reoptimized the connections so that the constellations of coauthorship among senior authors become clear. Figure 4 suggests that the clustering of red nodes in Figure 3 results largely from the large set of 33 (47.83%) senior stem cell investigators connected by past and current collaborations. This

cluster centers on researchers at Harvard University and the University of Wisconsin, and it contains some of the most prominent scientists working with both hiPSCs and hESCs. It also includes 5 of the 14 (35.7%) senior investigators who have published as last authors using hiPSCs alone. In other words, the most significant cluster of established hESC researchers using hiPSCs is also the source of more than 1/3 of the senior authors who are deploying hiPSC lines alone. Indeed, in Figure 4, the senior authors using only hiPSCs (blue diamonds) appear evenly split between those connected to and those unconnected to senior authors who have used hESCs and hiPSCs together (red circles).

Conclusions and Policy Implications

Our analyses provide a mixed picture of whether reprogramming technologies have engaged new investigators to reorient the stem cell field. It is clear that iPSCs are not eclipsing hESCs but have instead emerged as a complimentary technology. Although the use of iPSCs is increasing at a rate greater than that observed for hESCs, we believe this is due largely to lower regulatory thresholds, less ethical worry, increased access, and scientific excitement. In terms of who uses specific cell lines, iPSCs may not be lowering barriers to pluripotent stem cell research. A large proportion of early hiPSC adopters are established users of hESCs, which suggests three main conclusions. First, the technology may be facile, but not so easy that a flood of new investigators is entering the pluripotent stem cell field. Experience with hESCs appears to transfer to research that employs induced pluripotent lines. Second, the incentives to use both types of cells in comparative studies are high. Finally, the furious activity we observe on the part of senior hESC researchers may be motivated by scientific curiosity and a dedication to pragmatic choices in uncertain funding environments. Scientists see themselves entering a new era defined by pluripotency, and it is only natural that experience in establishing primary cultures and derivations gives these labs an advantage no matter what cell enters the scene. That reprogrammed cells may unlock the mysteries of human disease is important for these researchers but comprise a different set of objectives.

On August 23, 2010, a Washington D.C. district judge, Royce Lamberth, issued a preliminary injunction to block Barak Obama's 2009 executive order expanding funding for hESC research. The plaintiffs, including two adult stem cell researchers, The Christian Medical Association, and the Nightlight Christian Adoptions (an embryo adoption agency), sued the NIH because they believed that the NIH's Guidelines for Research Using Human Pluripotent Stem Cells violated the restrictions on human embryo research under the Dickey-Wicker Amendment. This amendment, which has been added to the yearly Health and Human Services (HHS) appropriations bill since 1996, prohibits HHS from funding research that destroys human embryos. During that time, congress and three administrations agreed that funds could be used for research projects that did not destroy embryos but studied the lines themselves. In a stunning reversal of this longstanding agreement, Lamberth held that federal funding violates Dickey-Wicker. His injunction stopped new federal funding hESC research and threw more than a decade of work on human pluripotent stem cells into doubt.

A month later, a three-judge federal appeals panel paused the injunction while it considered an appeal by the Obama administration. On April 29th, 2011 the panel reversed Lamberth's ruling, concluding that "the plaintiffs are unlikely to prevail because the Dickey-Wicker Amendment is ambiguous and the NIH seems reasonably to have concluded that, although Dickey-Wicker bars funding for the destructive act of deriving an [h]ESC from an embryo, it does not prohibit funding a research project in which an [h]ESC will be used" (Sherley v. Sibelius, 2011). Lamberth now has two motions for judgment in front of him, one by the plaintiffs and one by the defendants, the US government. He granted the original injunction based on the likelihood that the plaintiffs would prevail. Three judges appointed by conservative Republican presidents decided, 2 to 1, to allow this research. However, Lamberth might maintain his original position, or he could rule on one of the judgments and either allow federal funding for hESC research or ban it outright.

The deeper implications of a federal ban or restrictions on hESC research are largely missing from the policy discussions surrounding the Lamberth decision. Restrictions, regulatory uncertainty, and spurious court decisions have undoubtedly retarded progress in the pluripotent stem cell field. We now have new data pointing to "collateral damage" that could be caused by ill conceived and politically motivated policy prescriptions. According to the data presented here, an entirely new technology, forged out of the crucible of political controversy, is at risk. A major finding from our study is that iPSCs and hESCs are deeply intertwined and interdependent technologies. We see a decade of research using human embryonic cell types carrying the new wave of reprogramming technologies. And, although hESC research has made great strides over this time, our lack of understanding of early human development cannot be overestimated. Unraveling the properties of the human embryo has broad consequences for both regenerative medicine and assisted reproductive technologies. The growing and significant number of comparative studies and experiments using hESCs, combined with the heavy use of iPSCs by senior hESC investigators, suggest that any federal policy that would deny funding for embryonic stem cell research would torpedo a nascent and exciting discovery that is propelling new directions in the biological sciences. Indeed, just as political debate draws artificial boundaries between adult and embryonic cell types, it is dangerous to assume the same divisions can be made for pluripotent cell types. The secrets of cells have no boundaries.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Extended Experimental Procedures and one table and can be found with this article online at doi:10.1016/j.cell.2011.05.032.

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