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## STEM CELL RESEARCH IN THE COURTS: *SHERLEY V. SEBELIUS*

Human embryonic stem cell (hESC) research has a long history of controversy, both politically and ethically. Because hESCs have the ability to grow into different types of cells, research in this area provides hope of new treatments to millions suffering from an array of devastating conditions such as diabetes, spinal cord injuries, Alzheimer disease, and heart disease. However, the creation of hESC lines for research involves the destruction of embryos, and as a result, there are many ethical and religious concerns. While the United States has afforded human embryos a special status and some protection under the law, there is no set of clearly defined policies addressing hESC research.

In this policy void, the debate on federal funding for hESC research shifted into the courtroom. In August 2009, adult stem cell researchers James Sherley, M.D., Ph.D., and Theresa Deisher, Ph.D., challenged the federal funding of hESC research in the court case *Sherley v. Sebelius*, Civ. No. 1:09-cv-01575. They argued that federal monies for hESC research were prohibited by the Dickey-Wicker Amendment, an appropriations rider added to each Department of Health and Human Services (DHHS) appropriations bill since 1996. This amendment prohibits the use of federal funding for research that destroys a human embryo (Livingston 1996), and has historically been interpreted to allow federal funding of research using hESCs while prohibiting funding for the derivation of the lines. In August 2010, Judge Royce Lamberth ruled that federal funding of hESC research contradicted federal law and struck down the National Institutes of Health (NIH) July 2009 guidelines for hESC research.

Ultimately, the decision was overturned on appeal, but the case highlights the problems associated with the funding of and the lack of a permanent federal policy addressing hESC research.

This report examines the controversies surrounding development of a coherent U.S. policy for hESC research. We review stem cell biology and ethics, discuss the current U.S. stem cell research regulatory framework, and provide a summary of legal issues, including the *Sherley v. Sebelius* case. We also make recommendations for the formation of a well-defined U.S. stem cell policy.

### STEM CELL BIOLOGY

Cells are the basic building blocks of the human body. They comprise every tissue and organ and serve a specific role in the tissue's or organ's function. Stem cells are a special type of cell that can divide and renew for long periods of time (a process termed "self-renewal") and have the ability to differentiate down multiple pathways. There are several types of stem cells that differ in their source, in the types of cells that they are able to become, and their uses in therapies. The three types discussed in this article include adult stem cells (ASCs), embryonic stem cells, and induced pluripotent stem (iPS) cells.

ASCs are found in many major organs or tissues in the body. They are usually present in small numbers in tissues and are often hard to isolate and grow in large quantities in a laboratory. ASCs are also limited in the cells that they can become, often differentiating only into the types of cells found in the organ in which they reside. The most

characterized type of ASC is the hematopoietic stem cell or blood stem cell, which is used in bone marrow transplants to treat blood diseases such as lymphoma and sickle cell anemia.

By contrast, hESCs are isolated from early stage, pre-implantation embryos (usually five to six days post-fertilization). The cells are removed at this primitive stage prior to the beginning of specialization. hESCs are termed pluripotent because they have the ability to differentiate into any cell type in the body. Large populations of hESCs are relatively easy to isolate compared to most adult stem cells and can be readily grown in the laboratory (NIH 2012; Matthews and Rowland 2011). hESCs were first created in 1998 by James Thomson's group at the University of Wisconsin and have stirred up a considerable amount of controversy due to their source (Thomson et al. 1998).

Because of their ability to become any cell, many scientists postulate that hESCs can be useful in treating and possibly curing various diseases by replacing damaged or diseased cells or tissues; this is often referred to as regenerative medicine. The U.S. Food and Drug Administration (FDA) has approved three human therapies employing hESCs for clinical trials to determine the safety and efficacy of utilizing hESCs for tissue replacement. One protocol generates new nerve cells from hESCs for victims of spinal cord injuries. The other two FDA-approved therapies use eye cells differentiated from hESCs to treat patients with macular degeneration, a genetic disorder that causes vision loss. In addition, researchers are currently investigating the use of hESCs for numerous other diseases, such as Parkinson disease, multiple sclerosis, Alzheimer disease, and diabetes.

iPS cells are the newest type of stem cells, first created in 2007 in the laboratories of two scientists: Shinya Yamanaka, M.D., Ph.D., at Kyoto University and James Thomson, Ph.D., at the University of Wisconsin, the same scientist who pioneered hESC creation (Takahashi et al. 2007; Yu et al. 2007). These cells are generated by turning on genes in adult cells, like skin or

muscle cells. This causes the cells to revert back to a pluripotent state, one in which they can differentiate into all cell types in the body, similar to hESCs. This is advantageous because a patient's own cells can theoretically be used in therapies to replace diseased or missing tissues. By using an individual's own cells, doctors could prevent an immune response, which would result in the rejection of the new cells. In addition, iPS cells avoid some of the ethical issues that surround hESCs because a human embryo is not required.

Research utilizing iPS cells for treating many different diseases is being conducted throughout the United States. Before these cells can be used therapeutically, however, their safety must be thoroughly evaluated. Manipulating genes, some of which are associated with cancer, may have long-term consequences that are yet unknown. Also, recent research has called into question iPS cells' ability to avoid immune rejection.

Stem cells have the potential to change medicine and the treatment of disease, though there is no consensus on which type of stem cell is best. At the 2009 Baker Institute event "Stem Cell Policy in the Obama Age," keynote speaker Lord Naren Patel, chairman of the U.K. National Stem Cell Network Steering Committee, remarked that, "At this stage we cannot be sure which [type of stem cells] will deliver the treatments, and it is likely that all of them will deliver treatments but of a different nature and of different diseases."

Indeed, discoveries in one field will often lead to breakthroughs in another. For example, iPS cells were created using knowledge gleaned from the study of hESCs (Lee et al. 2009). Research into all forms of stem cells may allow scientists to develop cures for diseases that currently have none.

## **ETHICAL IMPLICATIONS OF STEM CELL RESEARCH**

There has been a great deal of controversy surrounding stem cell research globally. Although the most publicized debate has focused on the moral status of the human embryo, there are other areas of concern, particularly as novel

stem cell therapies are developed. These issues include informed consent procedures, intellectual property rights, and compensation for cell donation. In addition, there are other safety concerns regarding the creation of alternative stem cell sources such as iPS cells.

The debate in the United States regarding stem cell research primarily revolves around the moral standing of the embryo. Advisory panels examining the issue have agreed that a human embryo deserves special status and some protection under the law (Doerflinger 2010; Warnock 1984), but there is no consensus on what that special status should be.

Those who oppose hESC research believe that a human embryo is the moral equivalent of a living person: Embryos have the potential to become a human, and it is wrong to impede this potential in any way. Moreover, it is never acceptable to sacrifice an embryo by removing cells from it, no matter how noble the cause (Hyun 2010). Especially vocal in their opposition to hESC research are Catholic and Fundamental Christian churches.

Supporters of hESC research have varying viewpoints. Some supporters do not equate an embryo's moral status with that of a living human because "unimplanted embryos, which are a collection of undifferentiated cells, lack the physical characteristic to have the attributes which they view as essential for moral status" (Robertson 2010). Others believe that moral standing is gained later, after birth. Several religions, including Judaism, Islam, Hinduism, Buddhism, and some Protestant Christian denominations, do not give embryos full moral status until after implantation or up to eight weeks after conception (Hyun 2010; Monroe, Miller, and Tobis 2008). Others agree that the embryo has moral standing but believe that the potential benefit of hESC therapies to numerous patients outweighs the cost of an embryo's life at this very early developmental stage.

The U.S. federal government rationalized hESC research by only supporting research on hESC lines obtained from surplus *in vitro* fertilization (IVF) embryos, which were primarily created for

reproductive purposes but were ultimately not used or required. Proponents of this method argue that because surplus IVF embryos are eventually destroyed, they should be donated to research so some good can come from them.

However, these arguments can be considered ethically fallacious by some because an embryo is destroyed in the creation of any hESC line, regardless of embryo source or why it was sacrificed. And, if the destruction of any embryo is morally wrong, it is always morally wrong. "If the embryos are at the same stage of development in each case, then how can one set of embryos deserve protection and the other set not?" (Robertson 2010). In fact, President Bill Clinton's National Bioethics Advisory Committee (NBAC) saw no moral distinction between creating embryos for the sole purpose of generating hESCs and using leftover IVF embryos as an hESC source. In contrast, both President George W. Bush and President Barack Obama recognize a distinction between the derivation of hESC lines and research on existing hESC lines. The current NIH guidelines for hESC research do not justify ethically why it is permissible to fund one and not the other (Condic and Rao 2010).

As a result of this controversy, a great deal of research into alternative pluripotent stem cell sources, such as iPS cells, has been conducted to avoid these ethical issues. However, as iPS cell and hESC research continues and more cell therapies are developed, many new ethical issues arise and shift the debate. With the new federal policies in place that allow the use of IVF embryos as an hESC source, as well as the use of ASCs in research and therapies, adequate informed consent guidelines for both donors and patients have become a necessity. As a result, the International Society for Stem Cell Research (ISSCR) has developed guidelines for basic hESC research, as well as for clinical trials and treatments utilizing hESCs, to protect people and ensure their safety (ISSCR 2006; Hyun 2010; ISSCR 2008).

There is also a discussion surrounding the donation of cells and tissues, especially after the publication of *The Immortal Life of Henrietta*

Lacks, which describes the use of tissues from a patient for research without permission from the donor or her family (Skloot 2010). Currently, the NIH requires that a donation of surplus IVF embryos be done freely without compensation, financial or otherwise. This way, there is no incentive to create embryos for purposes other than for fertility treatments or other reproductive therapies. The belief is that the donation should be for the sake of science and not for the financial benefit of the donor. However, there has only been limited discussion regarding the consequences of possibly commercializing stem cell lines or technologies established through donated cells and tissues.

### LEGAL ISSUES AND PATENTING OF hESCs

The first step to commercialization is patenting the technology. In the life sciences, this has been plagued with controversy. Many people believe that patenting biological components of humans infringes on human dignity. The issue first arose with the idea of patenting genes in the early 1980s. The human genome is a part of every person; so conceptually, it is difficult to understand how a gene itself can be patented. The distinction in what is patentable lies between what is merely discovered and what is actually invented or created by man. The arguments against patenting genes include: They are naturally occurring, have already been discovered, are not new or novel, and gene isolation and cloning have been used in research for the past three decades (Martin-Rendon and Blake 2007). These arguments can also be made for stem cells, which also were not “invented.” However, the techniques used to create stem cell lines might be novel and patentable (Martin-Rendon and Blake 2007), though it is unclear what a patent could encompass. Stem cells are able to differentiate into multiple cell types, so would both the pluripotent stem cell line, as well as cells that it produces, be protected under patent? If a pluripotent stem cell line is patented, then any therapy created from the hESC line or the cells originating from the line could conceivably be protected.

In 1980, the U.S. Supreme Court ruled in *Diamond v. Chakrabarty* that a living, genetically altered organism could be patented as a new composition of matter. The scope of patentable items was viewed to be “anything under the sun that is made by man” (Merrill and Mazza 2006). This meant that a strain of bacteria or a mouse that had been genetically altered and was distinctly different from the wild-type form of the species could be patented because it did not exist in nature and required human manipulation to exist. Dissenters of this ruling argued that living organisms were never meant to be patented. However, a July 2011 ruling on the case *Association for Molecular Pathology v. United States Patent and Trademark Office* (USPTO) by a federal appeals court deemed that genes were patentable because DNA isolated from the body was “markedly different” than DNA within the body (Lourie 2011). Due to the controversy surrounding the patenting of genes, the Supreme Court is expected to hear the case on appeal.

In 1998, the European Union (EU) dealt with this issue through the “EU Directive on Biotechnological Inventions,” which distinguishes between what is patentable in Europe and what is not. The directive states that certain things, such as the human body or one of its elements, are nonpatentable unless they are isolated from their natural states. Under the directive, some technologies, including ones that use human embryos for commercial or industrial purposes, are not patentable due to their intrinsic moral implications (“Directive 98/44/EC” 1998). However, the directive is somewhat vague, leaving much open to interpretation, specifically in the cases of DNA and genes. In practice, genes themselves have not been the subject of patents, but the application of the genes in novel technologies, such as a diagnostic test, has been considered patentable (Hawkins 2010). The issue of patentability is also unclear in cases concerning hESCs. Although embryos are required to create hESCs, hESCs are not technically embryos and therefore patentable (Bonetta 2009).

After creating the first hESC line, Thomson and the Wisconsin Alumni Research Foundation (WARF) filed patents in the United States on the work related to Thomson's discovery. The original patent regarding hESC lines was very broad and included the specific techniques that Thompson employed to create hESC cells, as well as any hESC lines that shared characteristics described in the patent. In practice, this would require anyone deriving hESC lines to license the technology regardless of the process used to create the lines (Plomer, Taymor, and Scott 2008).

The prospect of implementing these patents raised arguments that patents could stifle academic stem cell research and the accumulation of knowledge. Licensing procedures made hESC lines difficult to obtain, and organizations could obtain monopolies on hESC lines, which would limit access to the lines and any associated research. This argument was particularly relevant when scientists in the United States were restricted to 21 lines during the G.W. Bush administration (Caulfield 2003). Because no new lines could be used in research, the owners of these 21 lines stood to gain a huge profit. As a result, two watchdog groups challenged these patents, claiming that the research was not patentable because it did not fulfill the requirement of non-obviousness, meaning the science patented was obvious to other researchers in the field. The watchdog groups' lawsuit pointed out another research group, which published one year after Thomson (Reubinoff et al. 2000). In a preliminary hearing, the USPTO ruled the patents invalid. The patents were amended to narrow their scope and, after reexamination, were upheld (Shyntum and Kalkreuter 2009). In the end, it was argued that if Thomson's discovery was not groundbreaking, why did he receive so many awards for it (Reed 2008)?

As of 2009, WARF had licensed the hESC technology to 15 companies and 365 academic institutions, and in 2004 WARF sold \$1 billion worth of products under license (Shyntum and Kalkreuter 2009). Fiona Murray, Ph.D., an MIT associate professor of management of technological innovation and entrepreneurship, argues that

the patent itself is not prohibitive to research but rather the methods in which the patent contracts are imposed. She believes that a balance can be achieved to allow the transfer of materials and methods for academic research while maintaining the ownership rights to commercial products resulting from the research (Murray 2007).

In comparison with the United States, the debate on hESC patenting in Europe has mainly focused on morality issues as opposed to arguments concerning invention versus discovery (Bonetta 2009). In concurrence with the filing of their patents in the United States, Thomson and WARF filed a patent with the European Patent Office (EPO), which rejected the patent on moral grounds. WARF appealed the ruling, but the EPO's Enlarged Board of Appeal (EBA) decided that any patent applications involving the destruction of a human embryo would be rejected. This ruling meant that hESCs derived from existing lines or inventions relating to human stem cells could, in theory, still be patented (Fitt 2009). The United Kingdom Intellectual Property Office (UKIPO) currently interprets the directive and the EBA ruling to prohibit the patenting of methods to obtain hESCs and other stem cells. At this time, the UKIPO permits the patenting of inventions involving hESCs as long as the inventions can be obtained "by means other than the destruction of human embryos" (Dennehey 2009). This could include new techniques, which remove one cell from a growing embryo without destroying it. However, the ability to patent these types of technologies in Europe was recently challenged in the European Court's Grand Chamber. A comparison of U.S., EU, and U.K. patent regulations that impact stem cell products is found in Table 1.

In a German patent court in 2004, the environmental group Greenpeace challenged another patent involving the use of hESCs. In 1999, Oliver Brüstle obtained a patent for generating nerve cells from existing hESC lines. Greenpeace argued that "the patent offended public morality, threatened public order and contravened legislation that prohibits the industrial use of human embryos" (Abbott 2009). After the German

**TABLE 1: PATENTABLE AND NONPATENTABLE INVENTIONS IN THE UNITED STATES AND EUROPE**

	<b>Nonpatentable</b>	<b>Patentable</b>
<b>United States</b>	<ul style="list-style-type: none"> <li>• Human–nonhuman chimeras</li> </ul>	<ul style="list-style-type: none"> <li>• Isolated/purified hESCs</li> <li>• Methods of deriving hESCs</li> <li>• Culture conditions for hESCs</li> <li>• Processes for differentiating hESCs</li> <li>• Genetic transformation and nuclear transfer for altering hESCs</li> </ul>
<b>Europe</b>	<ul style="list-style-type: none"> <li>• Processes for extracting stem cells from human blastocysts</li> <li>• Direct destruction of human embryos</li> <li>• Available hESC lines and their use (if destruction of a human embryo was involved)</li> </ul>	<ul style="list-style-type: none"> <li>• Adult human stem cells and their use</li> <li>• Stem cells derived from nonhuman animal embryos and their use</li> </ul>
<b>United Kingdom</b>	<ul style="list-style-type: none"> <li>• Processes for obtaining stem cells from human embryos</li> <li>• hESC with the potential to become a human being</li> </ul>	<ul style="list-style-type: none"> <li>• The use of hESC lines in inventions (with the caveat that the inventions could be obtained by means other than the destruction of a human embryo)</li> </ul>

Source: L. Bonetta, 2009. “European Stem Cell Patents: Taking the Moral High Road?” *Cell* 132 (4): 514–516.

court ruled in favor of Greenpeace in 2006, Brüstle appealed to the European Court of Justice. In March 2011, Yves Bot, the case’s adjudicator, ruled in favor of Greenpeace, stating that, despite the fact embryos are not directly destroyed in the process, the patent still exploits human embryos for industrial or commercial purposes, which is prohibited in the EU Directive (Abbott 2011). This closed a loophole in the previous ruling that implied patents would only be rejected if they directly involved the destruction of an embryo (such as the WARF patent application for the technique deriving hESCs). In October 2011, the European Court’s Grand Chamber ruled again for Greenpeace (Callaway 2011a). They stated that procedures that involve hESCs cannot be patented. Some scientists believe that the decision in Greenpeace’s favor is “a disaster for Europe” that will lead some nations to establish restrictive stem cell policies (Abbott 2011). Others hope it will open up research by limiting patents on

• cells and methods of their differentiation, while  
 • still allowing companies to patent other aspects  
 • such as growth media, equipment, and chemicals  
 • (Callaway 2011b).

• Even though there are currently a limited  
 • number of FDA–approved stem cell therapies  
 • (adult and embryonic), the hype surrounding  
 • the potential of stem cells has resulted in the  
 • development of stem cell clinics around the world.  
 • These clinics advertise their stem cell treatments as  
 • cures for diseases ranging from autism to Parkinson  
 • disease. They play on the desperation and hope of  
 • patients in extreme circumstances, as few of these  
 • clinics have been validated by research or approved  
 • by the FDA or its equivalent. In fact, some of the  
 • clinics have done more harm than good and have  
 • the potential to jeopardize legitimate stem cell  
 • therapies and funding of stem cell research if  
 • treatments go wrong (Dobkin, Curt, and Guest  
 • 2006; Hyun 2010; Zarzeczny and Caulfield 2010). In  
 • 2009, one young boy received hESCs for paralysis

treatment and later developed tumors in his brain and spinal cord (Amariglio et al. 2009). As a result, ISSCR published a set of guidelines for clinics conducting unproven treatments to ensure patient safety and protect the reputation of responsible researchers and validated therapies, as well as a website for patients to assess the legitimacy of these centers (see box 1)(ISSCR 2008).

### U.S. hESC POLICY AND REGULATORY FRAMEWORK

The policy for human embryo research in the United States dates back to the 1970s and the birth of Louise Brown, the first child born using IVF (Matthews and Rowland 2011). As a result of IVF, President Jimmy Carter formed an Ethics Advisory Board (EAB) in 1978 to review and approve research projects using human embryos. The board, however, only met once, never approved any projects, and ultimately disbanded in the early 1980s during President Ronald Reagan’s administration (Matthews and Rowland 2011). The discussion regarding human embryo research funding was abandoned for several years until President Bill Clinton took office and rescinded the law that created the EAB.

President Clinton’s rescission prompted U.S. Representatives Jay Dickey (R-AK) and Roger Wicker (R-MS) to write an amendment in 1996 to the appropriations bill for the DHHS, which funds NIH. The Dickey-Wicker Amendment outlaws federal funding of any research “in which a human embryo is destroyed, discarded, or knowingly subjected to risk of injury or death” (see box 2). The amendment has been added, without substantial alteration, to the DHHS appropriations bill every year since its instatement (Omnibus Appropriations Act 2009).

Two years after the implementation of the Dickey-Wicker Amendment, the first hESCs were created (Thomson et al. 1998). In 1999, in order to determine the limitations placed by the Dickey-Wicker Amendment on hESC research, DHHS legal counsel Harriet S. Rabb was tasked with interpreting the amendment. Her memorandum,

#### BOX 1: SUMMARY OF KEY ISSCR GUIDELINES FOR THE TRANSLATION OF STEM CELL RESEARCH INTO THE CLINIC

- Investigators involved in preclinical or clinical research involving stem cells or their direct derivatives should act within the ISSCR guidelines and other relevant policies and regulations.
- Clinical research involving stem cells or their direct derivatives should be reviewed by human subject review committees supplemented with experts in stem cell science.
- Donors and patients need to give well-informed written consent, and they should demonstrate their understanding of the involved risks.
- Scientists and regulators should work to develop common reference standards.
- Appropriate quality standards and management systems for manufacturing cells need to be developed.
- Sufficient preclinical studies in relevant animal models need to be performed.
- Cells to be used in clinical trials must be extensively tested for potential toxicities, including tumorigenicity, *in vitro* and in animal studies.
- Patients should be monitored for long-term health effects and adverse events reported in a timely manner.

Source: I. Hyun, 2010. “The bioethics of stem cell research and therapy.” *The Journal of Clinical Investigation*, 120(1):71-75.

distinguishing the use of human embryos from hESC lines, set the NIH stem cell policy used in the past decade. Rabb wrote:

“Pluripotent [embryonic] stem cells are not organisms and do not have the capacity to develop into an organism that could perform all the life functions of a human being. They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin-producing cells ... Pluripotent stem cells do not have the capacity to develop into a human being, even if transferred to a uterus ... Based on an analysis of the relevant law and scientific facts, federally funded research that utilizes human pluripotent stem cells would

## BOX 2: THE 2009 DICKEY-WICKER AMENDMENT

The Dickey-Wicker Amendment first appeared as an appropriations rider in the 1996 Balanced Budget Downpayment Act (Pub. L. No. 104-99, §128, 110 Stat. 26, 34).

The amendment “prohibits the use of funds made available in the Act for: 1) the creation of a human embryo for research purposes or 2) research in which a human embryo is destroyed, discarded, or knowingly subjected to risk of injury or death...greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act.”

It defines “‘human embryo or embryos’ to include any organism ... that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.”

not be prohibited by the HHS appropriations law [Dickey-Wicker Amendment] prohibiting human embryo research, because such stem cells are not human embryos” (Rabb 1999).

This interpretation has allowed the federal government to fund research on hESC lines as long as it does not fund the derivation of the hESC lines.

Until the recent court case, the Rabb interpretation of hESC research had been consistently applied in U.S. policy. In 2001, President G.W. Bush issued an executive order limiting federal funding of hESC research to lines that had been created before August 9, 2001 (Bush 2007). He believed that the estimated 60 lines in existence would be sufficient for research purposes, although, in the end, the actual number of lines available was only 21 (Matthews 2009). Bush did not support the creation of new hESC lines, even if they were created from surplus IVF embryos, but instead advocated for embryo adoption programs (donating unused fertilized eggs to other couples). During his administration, the U.S. Congress twice passed bills that would have expanded hESC research funding to include new hESC lines created from surplus IVF embryos, but Bush vetoed both bills (Matthews and Rowland 2011). By allowing federal funding for hESC research, albeit placing limitations on the number of lines available to researchers, Bush implicitly accepted the Rabb interpretation of the Dickey-Wicker Amendment.

When President Obama succeeded Bush, his administration continued to use the Rabb interpretation of the Dickey-Wicker Amendment. On March 9, 2009, Obama issued an executive

order revoking the Bush limitations to hESC research (Obama 2009). The order called upon NIH to introduce a new stem cell registry and guidelines for hESC research. These guidelines, which outline the conditions and review processes for researchers to register new and existing stem cell lines, remained consistent with the Rabb interpretation of the Dickey-Wicker Amendment. They were posted online for 30 days for public comment and were finalized in July 2009 (NIH 2011).

The NIH guidelines permit federal funding of research on hESC lines that are derived from surplus IVF embryos and obtained following informed consent procedures. In addition, IVF embryos must be donated freely, with a clear separation between the IVF procedure and the decision to donate (NIH 2011). An NIH ethical oversight committee reviews all hESC lines submitted to the national hESC registry for eligibility to ensure adherence to these procedures before they can be used in federally funded research. As of January 2012, the NIH hESC registry had approved 142 lines for federal funding and rejected 65 lines due to improper or undocumented informed consent procedures (NIH 2012).

Although U.S. stem cell policy specifies the research that NIH can fund, it does not oversee and has never regulated private or state-funded research. In theory, any type of research on human embryos or hESCs can be conducted with private or state funds, but many state laws limit or prevent such research. In addition, the lack of

a federal policy leaves gaps in controversial issues, such as reproductive cloning, which could result in unethical scientific practices. Without a clear policy in place, questions concerning the legality of embryonic research and the future of the policy abound. Some of these questions are currently being addressed in the courtroom.

**SHERLEY V. SEBELIUS**

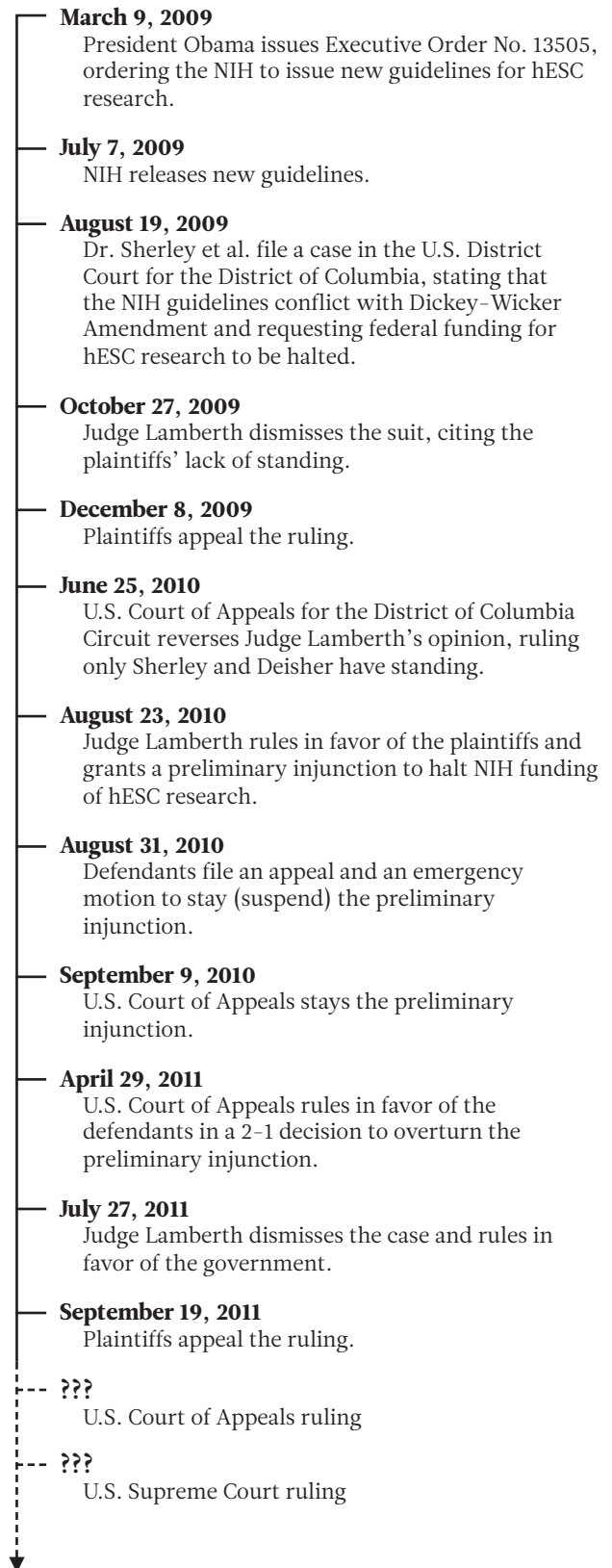
Soon after NIH released the new guidelines, James L. Sherley, M.D., Ph.D., and Theresa Deisher, Ph.D. (ASC researchers); Nightlight Christian Adoptions (an embryo adoption agency); “Embryos” (a reference to embryos donated for the creation of hESCs); Shayne and Tina Nelson and William and Patricia Flynn (both couples are clients of Nightlight); and the Christian Medical Association (CMA) brought forth a suit to prevent the guidelines from going into effect. The plaintiffs specifically sought to:

1. Declare the NIH guidelines unlawful and the creation of the guidelines a violation of procedures required by law, and;
2. Prevent the defendants from applying the guidelines and funding hESC research (Hungar 2010).

This lawsuit initiated a cascade of legal actions that has kept stem cell researchers vigilant for the past two years (Figure 1).

Initially, the U.S. District Court in Washington, D.C., dismissed the suit and denied the plaintiffs’ request for a preliminary injunction, citing the plaintiffs’ lack of standing. Sherley and Deisher argued that they had competitive standing because the new NIH guidelines resulted in increased competition for limited federal funding and thus negatively affected their ability to compete for NIH funding (Hungar 2010). The district court rejected this argument by stating that research is not a strictly economic market where an increase in competition for funding necessarily harms all applicants (Lamberth 2009). It went further to point out that even if the regulations did not exist, the plaintiffs were not assured of receiving funding for ASC research. This decision was appealed

**FIGURE 1: TIMELINE OF SHERLEY V. SEBELIUS CASE**



and reversed by the U.S. Court of Appeals for the District of Columbia Circuit, which noted in its opinion that it could see “no reason a person competing for a government benefit should not be able to assert competitor standing when the government takes a step that benefits his rival and therefore injures him economically” (Ginsburg 2010). Because Nightlight Christian Adoptions, as well as the Embryos, Nelsons, Flynns, and CMA did not contest this standing decision, they were dropped as plaintiffs from the case when it was remanded to the district court for consideration.

### ***The Preliminary Injunction***

After the appeals court determined that Sherley and Deisher had standing, the plaintiffs sued for a preliminary injunction. A preliminary injunction is a measure that can be awarded to the plaintiffs by the court if the court sees that there is substantial likelihood of the plaintiff’s success in the case, and that the plaintiffs would suffer irreparable injury absent an injunction (Rehnquist 1987; *Cuomo v. U.S. Nuclear Regulatory Commission* 1985). In arguing for an injunction, the plaintiffs also have to prove that an injunction would not substantially injure the other parties involved in the suit, and that an injunction would further public interest. In this case, U.S. District Court Judge Royce Lamberth decided that these four factors, taken together, warranted an injunction (Lamberth 2010).

When evaluating the likelihood of success, the court considered the two arguments put forth by the plaintiffs. The first argument was that the NIH guidelines violate the language of the Dickey-Wicker Amendment, which forbids Congress from funding research that involves the destruction of human embryos. Once the court concluded that the language of the Dickey-Wicker Amendment unambiguously prohibits the destruction of human embryos, the debate shifted to the definition of “research” as utilized in the amendment. The defendants argued that research using hESC lines does not directly involve the destruction of human embryos. The use of human embryos only occurs in the initial creation of the hESC line, not in its use. But the court sided with the plaintiffs, who argued

that the Dickey-Wicker Amendment applies to all research connected to the destruction of an embryo, not just the research that involves the act of destroying an embryo. The Dickey-Wicker Amendment, as interpreted by the court, limits federal funding on the “piece of research” in which an embryo is destroyed, as well as all associated projects. Since conducting hESC research necessitates the destruction of an embryo in order to create a cell line, it is a violation of the Dickey-Wicker Amendment. Having established that the Dickey-Wicker Amendment prohibits the use of federal funding for the destruction of a human embryo and the use of the cells derived from such embryo, the plaintiffs then argued that the NIH guidelines violated the Dickey-Wicker Amendment.

The second argument was that, in setting forth the guidelines, the defendants violated the Administrative Procedure Act (APA) (Administrative Procedure Act 1946). Under this act, government agencies are required to keep the public informed of their procedures, rules, and organization. They are also required to provide time for public participation and feedback in the rulemaking process. Even though NIH provided a draft copy of the guidelines and solicited public advice regarding the guidelines from April 23, 2009, to June 26, 2009, collecting over 49,000 comments, many of which were addressed in the revisions, the plaintiffs felt that this did not provide the public adequate time to comment and thus violated the APA.

Having accepted that the plaintiffs had a likely chance of winning the case, the court then turned its attention to evaluating the plaintiffs’ irreparable injury claim. In order to meet this burden, the plaintiffs had to demonstrate that the irreparable injury was imminently present, and that the injury could not be remediated. As the plaintiffs are both researchers who work exclusively with ASCs, the court ruled that NIH funding is key to continuing their research. The new NIH guidelines for hESC research would increase the competition for NIH’s limited resources, thus jeopardizing the plaintiffs’ research. And such an injury has no remedy, as the court cannot compensate the plaintiffs for the lost opportunity to receive funds.

Additionally, the court did not see the injunction as a significant hardship for the defendants, as it would preserve the status quo and not prevent researchers from obtaining private funding. Based on these arguments, and reiterating that it is in public interest for courts to carry out the will of the Congress, the court issued the preliminary injunction on August 28, 2010.

The preliminary injunction had a wider impact than even the plaintiffs predicted. It did not, as believed by Judge Lamberth and the plaintiffs, preserve the status quo but impacted all hESC research funded at NIH, including what was permitted under the Bush administration. The preliminary injunction prevented the NIH from:

1. Awarding any additional funds for extramural researchers (researchers outside of NIH) who work with hESCs, including any new or previously funded grants (such as year three of a five-year grant);
2. Funding intramural research, which, while not in direct competition with the plaintiffs for funding, is regulated under the NIH guidelines for hESC research;
3. Reviewing any new hESC proposals;
4. Maintaining the Human Embryonic Stem Cell Registry; and
5. Supporting administrative and regulatory activities (Sebelius 2010).

Furthermore, many scientists feared having to return funding that was already dispersed for the year, but spent after September.

These restrictions had detrimental impacts on both NIH intramural and extramural hESC research, which totaled approximately \$143 million in 2009, as well as NIH's administrative and regulatory activities. While the plaintiffs did not compete for the same funds as intramural researchers, the injunction still applied to these projects, including the eight intramural hESC research projects staffed by 45 scientists and personnel in 2009 alone (Collins 2010). These projects have a combined total of \$9.5 million in funding and covered research areas spanning cancer; human development; and eye, neurological, and cardiovascular diseases (Collins 2010). Any pause on this research can

jeopardize the unique biological materials that often have taken years to acquire and that require ongoing maintenance.

The injunction also applied to any NIH-funded extramural research utilizing hESCs, including those that are currently underway. There were 24 already-funded hESC projects that, under the injunction, would have been unable to receive their yearly funds as scheduled to be dispersed in September 2010 (West, Machen, and Lieber 2010). As with NIH's intramural research, the suspension of funds was likely to result in the loss of valuable research knowledge. The termination of these research projects was estimated to waste \$64 million in NIH funds. In fact, any hESC research receiving federal funding since 2001 was affected by the injunction, even though the lawsuit was focused on the NIH guidelines issued in July 2009 in response to President Obama's executive order to remove barriers to NIH funding of hESC research. Since 2001, the NIH has invested millions of dollars in hESC projects, many of which are still eligible for funding renewals. The injunction thus would have potentially undermined a decade's worth of knowledge.

Some of this research has already resulted in a number of potential therapies, the continual development of which would be at risk under the injunction. To date, drugs involving cells derived from hESCs are under development for diseases such as Lou Gehrig disease (ALS). Moreover, the FDA has approved clinical trials of hESC-derived therapies for spinal cord injuries and macular degeneration. Thus, the injunction not only compromised NIH's ability to support research, but also prevented the translation of the research, in which the government has already invested heavily, into therapies.

Furthermore, the injunction impeded NIH's ability to perform administrative and regulatory activities related to hESC research. Many of these activities, once stopped, were not easily resumed when the injunction was lifted. For instance, after the injunction was instated, NIH ceased all peer review of hESC project applications. It was estimated that the process would take six

to eight months to resume if the injunction was implemented for the remaining duration of the case and an appeal. Moreover, the process of determining which lines were eligible for hESC research was halted under the court’s order.

### ***Appeal of the Preliminary Injunction***

On September 9, 2010, addressing an appeal of the injunction filed by the Department of Justice (DOJ), the U.S. Court of Appeals for the District of Columbia stayed (suspended) the preliminary injunction issued two weeks earlier by Judge Lamberth. The court stated, “The purpose of the stay is to give the court sufficient opportunity to consider the merits of the emergency motion for stay and should not be construed in any way as a ruling on the merits of the motion” (Langer 2010). While the Court of Appeals considered the preliminary injunction, hESC research was allowed to continue under the 2009 NIH guidelines.

Nearly eight months later, on April 29, the panel of judges on the U.S. Court of Appeals for the District of Columbia issued a 2-1 decision overturning the injunction and, therefore, the ban on federal funding of hESC research (Ginsburg 2011). In making its decision, the court considered both the likelihood that the plaintiffs would succeed in the case and the balance of equities and hardships that both parties would face in the presence or absence of a preliminary injunction.

The majority decision, by Judge Douglas H. Ginsburg and Judge Thomas B. Griffith, agreed with the defendants and identified the Dickey-Wicker Amendment as ambiguous. They interpreted it to ban federal funding of the destruction and thus derivation of a hESC line, but not research utilizing hESCs. The judges noted that, in 1996, when the Dickey-Wicker Amendment was passed, scientists were able to isolate but not stabilize hESCs for research in the laboratory. The amendment, thus, was passed to preclude federal funding of research using embryos that were created for IVF, not federal funding of the derived cell lines. Additionally, they noted that the DHHS has consistently interpreted the amendment as not applicable

to research utilizing hESCs because hESCs are not considered embryos as defined under the amendment. Congress, in reenacting the amendment with the full knowledge that the DHHS has funded hESC research since 2001, has thus recognized and accepted the distinction that the DHHS made between the derivation of stem cells from an embryo and utilizing the hESCs for research.

While the court recognized it was likely that the plaintiffs would have additional funding competition, the situation under the new guidelines is similar to the status quo that the plaintiffs have faced since 2001. The court also pointed out that simply removing the guidelines would not necessarily improve the plaintiffs’ ability to acquire NIH funding. The harms to the defendants, on the other hand, were substantial. The injunction not only prevented NIH from funding new hESC research that it has identified as meritorious, but also stopped the agency from supporting ongoing research, which could result in the loss of substantial NIH investment. And even if private funding were an option to sustain the current hESC projects, the court could not see why the plaintiffs would be precluded from such private funding.

In her dissent, Judge Karen LeCraft Henderson disagreed with the interpretation of “research” by her colleagues, stating that they had to “perform linguistic jujitsu” to arrive at their conclusion. The majority decision identified the definition of research as flexible enough to include discrete projects and extended processes. This flexibility, they claimed, reinforces that the text of the amendment is ambiguous. Judge Henderson, conversely, sided with the district court ruling that identified research as a “systematic inquiry or investigation”—one that encompasses the creation of any research materials. The creation of the hESC line, subsequently, cannot be separated from research that utilizes the lines. Because of this interpretation, the plain text of the Dickey-Wicker Amendment itself prohibits federal funding of hESC research. Judge Henderson went on to note that, in instances where the law is ambiguous,

congressional silence does not necessarily indicate its recognition and acceptance of an unlawful interpretation.

### ***Judge Lamberth's Decision***

The ruling sent the case back to Judge Lamberth at the federal district court who then, on July 27, 2011, dismissed the case and ruled in favor of the defendants. In his analysis, Judge Lamberth addressed the issues of standing, whether the NIH guidelines violate the Dickey-Wicker Amendment, and whether the NIH guidelines violate the APA (Lamberth 2011).

As the issue of standing was resolved by the court of appeals, Judge Lamberth reiterated the reasoning of the court in his decision and acknowledged that the plaintiffs had competitor's standing. Under the doctrine of competitor's standing, the plaintiffs not only had to demonstrate that they would suffer increased competition under the NIH guidelines but also had to establish that the imminent increase in competition would result in injury. Sherley and Deisher were found to have met both requirements, as the new NIH guidelines would increase the number of grant applications. And because there is a fixed amount of money for grants pertaining to stem cell research, the increased competition will force the plaintiffs to invest more time and money into crafting a successful grant.

Having established standing, Judge Lamberth turned to the issue of whether the NIH guidelines violate the Dickey-Wicker Amendment. The plaintiffs argued that federal funding of hESC research is prohibited because the Dickey-Wicker Amendment unambiguously prohibits research in which an embryo is knowingly subjected to injury or death. In determining the ambiguity of the Dickey-Wicker Amendment, Judge Lamberth deferred to the decision of the appeals court, which declared that the amendment, particularly the definition of research it utilizes, was ambiguous. The definition of research can either refer to the entirety of a project—involving the derivation of hESCs and their subsequent use in research—or it can refer to a specific piece of research. The NIH guidelines would violate the amendment if

the former, rather than the latter, definition was applied. And because of this ambiguity, Judge Lamberth also deferred the interpretation of the amendment to the appeals court, which found that the NIH had reasonably interpreted the amendment to allow for the funding of hESC research, but not the derivation of hESC lines.

In their original suit, the plaintiffs also argued that the NIH guidelines might create a demand for additional hESC lines, thus increasing the chances that embryos would be destroyed to meet these demands. This, they claimed, is also a violation of the Dickey-Wicker Amendment, particularly the clause that prohibits the government from funding research in which an embryo is subjected to injury or death. While the court of appeals did not directly address this argument, Judge Lamberth decided that the ambiguous definition of research in the amendment does not indicate whether embryonic stem cell research is research in “which an embryo or embryos are ... knowingly subject to risk” and, thus, deferred once again to the NIH interpretation of the amendment. He went even further to write that the plaintiffs' wide definition of research would “lead to such a far-reaching construction of the Dickey-Wicker Amendment that it would prohibit federal funding for research entirely unrelated to embryos or embryonic stem cell research if the research nevertheless posed some risk to embryos.” He provided the example of a tank of propane in an adjacent laboratory posing a risk to embryos. Under the plaintiffs' interpretation, the argument can be made that this research, regardless of its nature, poses a risk to embryos and thus is prohibited under the Dickey-Wicker Amendment.

Finally, Judge Lamberth addressed whether the guidelines were in violation of the APA. The plaintiffs argued that the government had violated the APA by failing to respond to relevant public comments and entering into the decision period with a closed mind. They specifically cited NIH's decision to ignore public comments objecting to the funding of hESC research. Judge Lamberth disagreed with the plaintiffs, noting that President Obama's executive order, “Removing Barriers to Responsible Scientific Research Involving Human

Stem Cells,” clearly set out the task of the NIH in establishing guidelines pertaining to hESCs. As the order did not ask the NIH to establish even more restrictive policies regarding hESC research, the NIH was found to have reasonably interpreted the executive order and thus had no legal obligation to consider comments objecting outright to the funding of hESC research.

Having determined that the NIH guidelines did not violate the Dickey-Wicker Amendment or the APA, Judge Lamberth dismissed the case, allowing the federal funding of hESC research to continue for now.

### **Next Steps**

On September 19, 2011, the plaintiffs appealed Judge Lamberth’s decision to dismiss the case. As the appeals court is expected to rule in favor of the defendants, as it did in the decision regarding the preliminary injunction, the Supreme Court is likely the plaintiffs’ last hope. The Supreme Court, however, only hears about one percent of all the cases it is asked to review each year (Wadman 2011). The probability that the Supreme Court will hear the case is low, but if it does, it is unclear what the decision might be.

### **IMPACTS OF *SHERLEY V. SEBELIUS* AND RECOMMENDATIONS FOR THE FUTURE**

Many questions remain regarding the potential impacts of the case, not only on the intramural and extramural research funded by NIH, but also on science in general and America’s ability to collaborate—as well as compete—with international hESC research efforts. Essentially, Judge Lamberth, as well as the appeals court, sided with the Rabb interpretation of the Dickey-Wicker Amendment. The courts’ decisions allow NIH to continue funding hESC research under the guidelines issued in July 2009, which permit federal funding for hESC research but not the derivation of hESC lines. Interestingly, the U.S. interpretation differs markedly from how EU’s views on human embryo research as evident in their decisions regarding patents. As mentioned

previously, the European Court of Justice ruled that the destruction of human embryos prohibited the patenting of processes utilizing hESCs regardless of whether the application refers to their destruction.

Though Judge Lamberth ruled to dismiss the case, there has been much speculation as to whether the case will set a legal precedent with which researchers can sue the federal government over funding in the future. This is unlikely to happen because the plaintiffs were required to establish that they had competitor’s standing in the case. They also had to demonstrate how the current NIH policies on hESC research violated existing law.

In addition, there were negative consequences from the August 2010 preliminary injunction that temporarily halted federally funded hESC research for three weeks. The shutdown slowed the pace of research and forced many scientists to look to alternative research options. But the extent of the impacts on current research is unclear (Wadman 2011). Furthermore, Judge Lamberth’s decision has not assuaged the uncertainty surrounding the legality of hESC research or addressed the underlying ethical debate in the United States regarding the status of an embryo. Stem cell scientists (both adult and embryonic) say such policy uncertainties have negative impacts on research (Levine 2011). Several researchers have switched to more politically stable fields such as iPS cells, but the exact number of researchers who have abandoned hESC research is difficult to predict (“Safe, Not Secure” 2011). Even non-hESC scientists, whose research theoretically becomes more fundable under a policy framework in which federal funding of hESC research is precarious, have identified the policy uncertainty as having more negative impacts. These effects include hindered collaborations in, difficulty in recruiting students to, and blocked review of funding applications on all forms of stem cell research. Many of these scientists have avoided collaborations with individuals conducting hESC research, and some have cited the policy uncertainty as the reason why they have not transitioned to using hESCs, even when these cells might be more appropriate for their research. They

also attribute the difficulty in long-term planning to such policy uncertainty. Additionally, policy uncertainty is likely not only to limit collaborations between scientists, but also collaborations between academia and industry. Industry will be less likely to invest in hESCs if it appears regulation will limit research, clinical applications, and commercialization of hESC technologies in the United States (Harvey 2009). Indeed, in November 2011, Geron, one of the two companies conducting hESC clinical trials, announced it was halting all hESC research.

While the case largely manifested itself into a linguistic battle over the definition of research and the scope of the Dickey-Wicker Amendment, it also raises the ethical dilemma regarding the moral status of an embryo. The same individuals opposing hESC research in the *Sherley v. Sebelius* case are largely opposed to abortion and the landmark decision of *Roe v. Wade*. Unlike *Roe v. Wade*, this case did not rule on any ethical issues. The decision to dismiss the case without tackling these issues or addressing the Dickey-Wicker Amendment may indirectly affect future debates.

The initiation of this court case and the legal roller coaster that followed expose the flaws in U.S. federal stem cell policy. The uncertainties surrounding the current policy negatively impact all stem cell research, jeopardize potential lifesaving medical treatments, and render international collaboration and commercialization of stem cell technologies more difficult. Without a federal law in place that authorizes hESC research and clarifies or eliminates the Dickey-Wicker Amendment, there is likely to be a perpetual legal battle facing hESC research in the United States—one that may be waged again soon if *Sherley v. Sebelius* goes in front of the Supreme Court, the majority party in the U.S. Congress changes, or a new president is elected.

## **POLICY RECOMMENDATIONS**

It is vital for Congress to codify U.S. stem cell policy by passing legislation that explicitly states the U.S. policy toward hESC research. Several bills

have recently been penned with that goal. A bill introduced in the 112th House of Representatives in June 2011, the “Stem Cell Research Advancement Act of 2011,” would legalize the current NIH stem cell policy (Degette and Dent 2011). The bill would amend the Public Health Service Act to legalize hESC research in instances where the stem cells are derived from excess embryos donated from IVF clinics. It also would require the director of NIH to maintain guidelines regarding hESC research and update these guidelines at least once every three years to ensure that they are current with the latest scientific knowledge.

Unfortunately, it does not include any of the language or content of the Dickey-Wicker Amendment, nor does it attempt to interpret or explain the scope of the amendment in any way. Instead, it assumes that the amendment would continue to pass each year in its current form. Therefore, this bill could be made stronger by incorporating the main aspects of Dickey-Wicker and an explanation of how federal funding of hESC research—but not the derivation of hESC lines—is permitted under the amendment. This transparent and detailed description of the intent of the amendment would benefit researchers and would clarify the current language. One major issue in the *Sherley v. Sebelius* case was the ambiguity of Dickey-Wicker, specifically its definition of research. If Congress is unable to pass a comprehensive piece of legislation, as suggested above, we recommend, at the very least, removing Dickey-Wicker from future appropriations bills and replacing it with a clearer piece of legislation stating U.S. stem cell policy until a broader hESC research policy is instated.

A clarification of what is legal in regard to hESC research, as well as a stabilization of these rules through legislative action, is imperative to conducting such research. For the past 15 years, hESC policy has been based solely on the Dickey-Wicker Amendment and the executive orders of U.S. presidents. The constant flux in policy (or absence of a policy) is disruptive to research and makes it difficult for the field to progress. Congress can no longer passively permit the DOJ or the courts to

determine the interpretation of the amendment, but must specifically state that hESC research is allowed. NIH's adoption of a specific policy or set of guidelines does not have the same force of law as a congressional action. The statutes in this area are inadequate, leaving little for courts to interpret. Ultimately, Congress is the most appropriate body to address this issue of policy.

We recommend that the current bill, "The Stem Cell Research Advancement Act of 2011," be passed to legalize federal funding of hESC research with one alteration. The legislation should be amended to include language from the Dickey-Wicker Amendment so it can be codified, not just passed annually on an appropriations bill. The bill should also specifically permit privately funded research using hESC lines derived from embryos. This follows the Rabb interpretation of the Dickey-Wicker Amendment that has been accepted policy for over 15 years. It would also eliminate any ambiguity in the Dickey-Wicker Amendment. With the passage of a revised "Stem Cell Research Advancement Act of 2011," the Dickey-Wicker Amendment could then be completely removed from the appropriations bill.

It is important to keep in mind that advances in science and technology are vital to the success of the U.S. economy. A research environment that is permissive to new ideas and fields, while maintaining a set of ethical standards that provides a supportive framework to scientists and researchers, can attract talented individuals to the United States. The creation of a formal federal stem cell policy through legislation would allow the establishment of such an environment and enable advances in all fields of stem cell research. In doing so, the United States can remain on the forefront of cutting-edge medical research and technology and continue to give hope to people who suffer from diseases that currently have no cure.

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This report was written by:

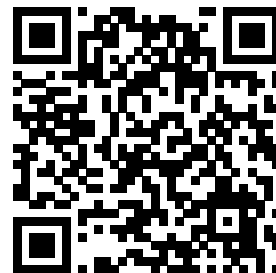
- Kirstin R.W. Matthews, Ph.D., fellow, Science and Technology Policy Program, James A. Baker III Institute for Public Policy, Rice University
- Maude Rowland, Ph.D., postdoctoral research associate, Science and Technology Policy Program, James A. Baker III Institute for Public Policy, Rice University
- Jingyuan Luo, graduate intern in the Science and Technology Policy Program, James A. Baker III Institute for Public Policy, Rice University; Marshall Scholar, The London School of Economics and Political Science and Imperial College London
- Monica Matsumoto, undergraduate intern, Science and Technology Policy Program, James A. Baker III Institute for Public Policy, Rice University

## ABOUT THE SCIENCE AND TECHNOLOGY POLICY PROGRAM AT THE BAKER INSTITUTE

Progress, innovation and the overall well-being of society depend on knowledge and inventions resulting from advances in science and technology. However, public policy plays a significant role in providing adequate funding of research, informing the public about science and related contemporary ethical debates, and ensuring that society benefits from the applications of scientific and technological innovation. The relationship between science and policy is important; yet, ever-expanding gaps between scientific knowledge, timely application and appropriate policy persist. It is becoming increasingly crucial to enhance communication between the scientific community, the public and policymakers.

The mission of the Science and Technology Policy Program is to engage policymakers and scientists in substantive dialogue with the hope that policy will more accurately reflect and be more consistent with current scientific knowledge. The program organizes workshops, lectures, research projects and conferences to bring attention to and help bridge the gap between science and public policy. Issues of interest include space, health and medicine, energy and the environment, national and domestic security, science education, and the public's understanding and trust of science.

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RICE UNIVERSITY - MS40  
JAMES A. BAKER III  
INSTITUTE FOR PUBLIC POLICY  
P.O. Box 1892  
HOUSTON, TEXAS 77251-1892

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