Stem-cell battles

Stem-cell research in the USA is facing new legal and political challenges

Howard Wolinsky

Disputes over stem-cell research have been standard operating procedure since James Thompson and John Gearhart created the first human embryonic cell (hESC) lines. Their work triggered an intense and ongoing debate about the morality, legality and politics of using hESCs for biomedical research. "Stem-cell policy has caused craziness all over the world. It is a never-ending, irresolvable battle about the moral status [of embryos]," commented Timothy Caulfield, research director of the Health Law Institute at the University of Alberta in Edmonton, Canada. "We're getting to an interesting time in history where science is playing a bigger and bigger part in our lives, and it's becoming more controversial because it's becoming more powerful. We need to make some interesting choices about how we decide what kind of scientific inquiry can go forward and what can't go forward."

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The most contested battleground for stem-cell research has been the USA, since President George W. Bush banned federal funding for research that uses hESCs. His successor, Barack Obama, eventually reversed the ban, but a pending lawsuit and the November congressional elections have once again thrown the field into jeopardy.

Three days after the election, the deans of US medical schools, chiefs of US hospitals and heads of leading scientific organizations sent letters to both the House of Representatives and the Senate

urging them to pass the Stem Cell Research Advancement Act when they come back into session. The implication was to pass legislation now, while the Democrats were still the majority. Republicans, boosted in the election by the emerging fiscally conservative Tea Party movement, will be the majority in the House from January, changing the political climate. The Republicans also cut into the Democratic majority in the Senate.

Policies and laws to regulate stem-cell research vary between countries. Italy, for example, does not allow the destruction of an embryo to generate stem-cell lines, but it does allow research on such cells if they are imported. Nevertheless, the Italian government deliberately excluded funding for projects using hESCs from its 2009 call for proposals for stem-cell research. In the face of legislative vacuums, this October, Science Foundation Ireland and the Health Research Board in Ireland decided to not consider grant applications for projects involving hESC lines. The UK is at the other end of the scale; it has legalized both research with and the generation of stem-cell lines, albeit under the strict regulation by the independent Human Fertility and Embryology Authority. As Caulfield commented, the UK is "ironically viewed as one of the most permissive [on stem-cell policy], but is perceived as one of the most bureaucratic."

Somewhere in the middle is Germany, where scientists are allowed to use several approved cell lines, but any research that leads to the destruction of an embryo is illegal. Josephine Johnston, director of research operations at the Hastings Center in Garrison, NY, USA—a bioethics centre—said: "In Germany you can do research on embryonic stem-cells, but you can't take the cells out of the embryo. So, they import their cells from outside of Germany and to me, that's basically outsourcing the bit that you

find difficult as a nation. It doesn't make a lot of sense ethically."

Despite the public debates and lack of federal support, Johnson noted that the USA continues to lead the world in the field. "[Opposition] hasn't killed stem-cell research in the United States, but it definitely is a headache," she said. In October, physicians at the Shepherd Center, a spinal cord and brain injury rehabilitation hospital and clinical research centre in Atlanta, GA, USA, began to treat the first patient with hESCs. This is part of a clinical trial to test a stem-cell-based therapy for spinal cord injury, which was developed by the US biotechnology company Geron from surplus embryos from *in vitro* fertilization.

Nevertheless, the debate in the USA, where various branches of government—executive, legislative and legal—weigh in on the legal system, is becoming confusing. "We're never going to have consensus [on the moral status of fetuses] and any time that stem-cell research becomes tied to that debate, there's going to be policy uncertainty," Caulfield said. "That's what's happened again in the United States."

Johnson commented that what makes the USA different is the rules about federally funded and non-federally funded research. "It isn't much discussed within the United States, but it's a really dramatic difference to an outsider," she said. She pointed out that, by contrast, in other countries the rules for stem-cell research apply across the board.

The election of Barack Obama as US President triggered the latest bout of uncertainty. The science community welcomed him with open arms; after all, he supports doubling the budget of the National Institutes of Health (NIH) over the next ten years and dismantled the policies of

his predecessor that barred it from funding projects beyond the 60 extant hESC lines—only 21 of which were viable. Obama also called on Congress to provide legal backing and funding for the research.

The executive order had unforeseen consequences for researchers working with embryonic or adult stem cells. Sean Morrison, Director of the University of Michigan's Centre for Stem Cell Biology (Ann Arbor, MI, USA), said he thought that Obama's executive order had swung open the door on federal support forever. "Everybody had that impression," he said.

Leonard I. Zon, Director of the Stem Cell Program at Children's Hospital Boston (MA, USA), was so confident in Obama's political will that his laboratory stopped its practice of labelling liquid nitrogen containers as P (Presidential) and NP (non-Presidential) to avoid legal hassles. His lab also stopped purchasing and storing separate pipettes and culture dishes funded by the NIH and private sources such as the Howard Hughes Medical Institute (HHMI; Chevy Chase, MD, USA).

But some researchers who focused on adult cells felt that the NIH was now biased in favour of embryonic cells. Backed by pro-life and religious groups, two scientists—James Sherley of the Boston Biomedical Research Institute and Theresa Deisher of AVM Biotechnology (Seattle, WA)—questioned the legality of the new NIH rules and filed a lawsuit against the

Department of Health and Human Services (HHS) Secretary, Kathleen Sebelius. Deisher had founded her company to "[w]ork to provide safe, effective and affordable alternative vaccines and stem-cell therapies that are not tainted by embryonic or electively aborted fetal materials" (www.avmbiotech.com).

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Sherley argued in an Australian newspaper in October 2006 that the science behind embryonic stem-cell research is flawed and rejected arguments that the research will make available new cures for terrible diseases (Sherley, 2006). In court, the researchers also argued that they were irreparably disadvantaged in competing for government grants by their work on adult stem cells.

Judge Royce C. Lamberth of the District Court of the District of Columbia initially ruled that the plaintiffs had no grounds on which to sue. However, the US District Court of Appeals for the District of Columbia overturned his decision and found that "[b]ecause the Guidelines have intensified the competition for a share in a fixed amount" of NIH

funding. With the case back in his court, Lamberth reversed his decision on August 23 this year, granting a preliminary injunction to block the new NIH guidelines on embryonic stem-cell work. This injunction is detailed in the 1995 Dickey-Wicker Amendment, an appropriation bill rider, which prohibits the HHS from funding "research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death." By allowing the destruction of embryos, Lamberth argued, the NIH rules violate the law.

This triggered another wave of uncertainty as dozens of labs faced a freeze of federal funding. Morrison commented that an abrupt end to funding does not normally occur in biomedical research in the USA. "We normally have years of warning when grants are going to end so we can make a plan about how we can have smooth transitions from one funding source to another," he said. Morrison—whose team has been researching Hirschsprung disease, a congenital enlargement of the colon—said his lab potentially faced a loss of US\$250,000 overnight. "I e-mailed the people in my lab and said, 'We may have just lost this funding and if so, then the project is over'".

Morrison explained that the positions of two people in his lab were affected by the cut, along with a third person whose job was partly funded by the grant. "Even though it's

only somewhere between 10–15% of the funding in my lab, it's still a lot of money," he said. "It's not like we have hundreds of thousands of dollars of discretionary funds lying around in case a problem like that comes up." Zon noted that his lab, which experienced an increase in the pace of discovery since Obama had signed his order, reverted to its Bush-era practices.

On September 27 this year, a federal appeals court for the District of Columbia extended Lamberth's stay to enable the government to pursue its appeal. The NIH was allowed to distribute US\$78 million earmarked for 44 scientists during the appeal. The court said the matter should be expedited, but it could, over the years ahead, make its way to the US Supreme Court.

The White House welcomed the decision of the appeals court in favour of the NIH. "President Obama made expansion of stem-cell research and the pursuit of groundbreaking treatments and cures a top priority when he took office. We're heartened that the court will allow [the] NIH and their grantees to continue moving forward while the appeal is resolved," said White House press secretary Robert Gibbs. The White House might have been glad of some good news, while it wrestles with the worst economic downturn since the Great Depression and the rise of the Tea Party movement.

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Timothy Kamp, whose lab at the University of Wisconsin (Madison, WI, USA) researches embryonic stem-cell-derived cardiomyocytes, said that he finds the Tea Party movement confusing. "It's hard for me to know what a uniform platform is for the Tea Party. I've heard a few comments from folks in the Tea Party who have opposed stem-cell research," he said.

However, the position of the Tea Party on the topic of stem-cell research could prove to be of vital importance. The Tea Party took its name from the Boston Tea Party—a famous protest in 1773 in which American colonists protested against the passing of the British Tea Act, for its attempt to extract yet more taxes from the new colony. Protesters dressed up as Native Americans and threw

tea into the Boston harbour. Contemporary Tea Party members tend to have a longer list of complaints, but generally want to reduce the size of government and cut taxes. Their increasing popularity in the USA and the success of many Tea Party-backed Republican candidates for the upcoming congressional election could jeopardize Obama's plans to pass new laws to regulate federal funding for stem-cell research.

Even without a formal position on the matter, the Tea Party has had an impact on stem-cell research through its electoral victories. Perhaps their most high-profile candidate was the telegenic Christine O'Donnell, a Republican Senatorial candidate from Delaware. The Susan B. Anthony List, a pro-life women's group, has described O'Donnell as one of "the brightest new stars" opposing abortion (www.lifenews.com/state5255.html). Although O'Donnell was eventually defeated in the 2 November congressional election, by winning the Republican primary in August, she knocked out nine-term Congressman and former Delaware governor Mike Castle, a moderate Republican known for his willingness to work with Democrats to pass legislation to protect stem-cell research.

In the past, Castle and Diane DeGette, a Democratic representative from Colorado, co-sponsored the Stem Cell Research Advancement Act to expand federal funding of embryonic stem-cell research. They aimed to support Obama's executive order and "ensure a lasting ethical framework overseeing stem cell research at the National Institutes of Health".

Morrison described Castle as "one of the great public servants in this country—no matter what political affiliation you have. For him to lose to somebody with such a chequered background and such shaky positions on things like evolution and other issues is a tragedy for the country." Another stem-cell research advocate, Pennsylvania Senator Arlen Specter, a Republican-turned-Democrat, was also defeated in the primary. He had introduced legislation in September to codify Obama's order. Specter, a cancer survivor, said his legislation is aimed at removing the "great uncertainty in the research community".

According to Sarah Binder, a political scientist at George Washington University in Washington, DC, the chances of passing legislation to codify the

Obama executive order are decreasing: "As the Republican Party becomes more conservative and as moderates can't get nominated in that party, it does lead you to wonder whether it's possible to make anything happen [with the new Congress] in January."

There are a variety of opinions about how the outcome of the November elections will influence stem-cell policies. Binder said that a number of prominent Republicans have strongly promoted stem-cell research, including the Reagan family. "This hasn't been a purely Democratic initiative," she said. "The question is whether the Republican party has moved sufficiently to the right to preclude action on stem cells." Historically there was "massive" Republican support for funding bills in 2006 and 2007 that were ultimately vetoed by Bush, she noted.

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"Rightward shifts in the House and Senate do not bode well for legislative efforts to entrench federal support for stem-cell research," Binder said. "First, if a large number of Republicans continue to oppose such funding, a conservative House majority is unlikely to pursue the issue. Second, Republican campaign commitments to reduce federal spending could hit the NIH and its support for stem-cell research hard."

Binder added that "a lingering unknown" is how the topic will be framed: "If it gets framed as a pro-choice versus pro-life initiative, that's quite difficult for Congress to overcome in a bipartisan way. If it is framed as a question of medical research and medical breakthroughs and scientific advancement, it won't fall purely on partisan lines. If members of Congress talk about their personal experiences, such as having a parent affected by Parkinson's, then you could see even pro-life members voting in favour of a more expansive interpretation of stem-cell funding."

Johnson said that Congress could alter the wording of the Dickey-Wicker Amendment when passing the NIH budget for 2011 to remove the conflict. "You don't have to get rid of the amendment completely, but you could rephrase it," she said. She also commented that the public essentially supports

embryonic stem-cell research. "The polls and surveys show the American public is morally behind there being some limited form of embryonic stem-cell research funded by federal money. They don't favour cloning. There is not a huge amount of support for creating embryos from scratch for research. But there seems to be pretty wide support among the general public for the kind of embryonic stem-cell research that the NIH is currently funding."

In the end, however, the debate about public funding for stem-cell research is only part of the picture, given the role of private business and states. Glenn McGee, a professor at the Center for Practical Bioethics in Kansas City, MO, USA, and editor of the *American Journal of Bioethics*, commented

that perhaps too much emphasis is being put on federal funding. He said that funding from states such as California and from industry—which are not restricted—has become a more important force than NIH funding. "We're a little bit delusional if we think that this is a moment where the country is making a big decision about what's going to happen with stem cells," he said. "I think that ship has sailed."

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Facing the credit crunch

Politics sends mixed messages for science in the wake of the global financial crisis

Philip Hunter

The overall state of biomedical research in the wake of the global financial crisis remains unclear amid growing concern that competition for science funding is compromising the pursuit of research. Such concerns pre-date the credit crunch, but there is a feeling that an increasing amount of time and energy is being wasted in the ongoing scramble for grants, in the face of mounting pressure from funding agencies demanding value for money. Another problem is balancing funding between different fields; while the biomedical sciences have generally fared well, they are increasingly dependent on basic research in physics and chemistry that are in greater jeopardy. This has led to calls for rebalancing funding, in order to ensure the long-term viability of all fields in an increasingly multidisciplinary and collaborative research world.

For countries that are cutting funding—such as Spain, Italy and the UK—the immediate priority is to preserve the fundamental research base and avoid a significant drain of expertise, either to rival countries or away from science altogether. This has highlighted the plight

of postdoctoral researchers who have traditionally been the first to suffer from funding cuts, partly because they have little immediate impact on a country's scientific competitiveness. Postdocs have been the first to go whenever budgets have been cut, according to Richard Frankel, a physicist at California Polytechnic State University in Saint Luis Obispo, who investigates magnetotaxis in bacteria. "In the short term there will be little effect but the long-term effects can be devastating," he said.

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According to Peter Stadler, head of a bioinformatics group at the University of Leipzig in Germany, such cuts tend to cause the long-term erosion of a country's science skills base. "Short-term cuts in science funding translate totally into a brain drain, since they predominantly affect young researchers

who are paid from the soft money that is drying up first," said Stadler. "They either leave science, an irreversible step, or move abroad but do not come back later, because the medium-term effect of cuts is a reduction in career opportunities and fiercer competition giving those already in the system a big advantage."

Even when young researchers are not directly affected, the prevailing culture of short-term funding—which requires ongoing grant applications—can be disruptive, according to Xavier Salvatella, principal investigator in the Laboratory of Molecular Biophysics at the Institute for Research in Biomedicine in Barcelona, Spain. "I do not think the situation is dramatic but too much time is indeed spent writing proposals," he commented. "Because success rates are decreasing, the time devoted to raise funds to run the lab necessarily needs to increase."

At the University of Adelaide in Australia, Andrew Somogyi, professor of pharmacology, thinks that the situation is serious: "[M]y postdocs would spend about half their time applying for grants." Somogyi pointed out that the success rate has been declining in Australia, as it has in some other countries. "For ARC [Australian Research Council] the success rate is now close to 20%, which means many excellent projects don't get funding because the assessment is now so fine cut," he said.

Similar developments have taken place in the USA at both the National Institutes of Health (NIH)—which provides US\$16 billion funding per year and the American Cancer Society (ACS), the country's largest private non-profit funder of cancer research, with a much smaller pot of US\$120 million per year. The NIH funded 21% of research proposals submitted to it in 2009, compared with 32% a decade earlier, while the ACS approves only 15% of grant applications, down several percentage points over the past few years.

While the NIH is prevented by federal law from allowing observers in to its grant review meetings, the ACS did allow a reporter from *Nature* to attend one of its sessions on the condition that the names of referees and the applications themselves were not revealed (Powell, 2010). The general finding was that while the review process works well when around 30% of proposals are successful, it tends to break down as the success rate drops, as more arbitrary decisions are made and the risk of strong