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Teetering on the brink

The US Congress must authorize federal funding of human embryonic stem cell research.

With his August 23 preliminary injunction banning federal funding of research on human embryonic stem cells (hESCs), US District Court Judge Royce Lamberth has singlehandedly upended one of the most promising fields of biomedical science. On September 9, in response to an appeal by the Department of Justice, the injunction was temporarily lifted by the US Court of Appeals in Washington, DC. Still to be decided are the plaintiffs' appeal of the appellate court's decision and the original lawsuit, *Sherley v. Sebelius*. The legal wrangling, which may reach the US Supreme Court, could drag on for some time. In the meantime, a cloud of uncertainty hangs over US hESC research, spreading confusion and anguish among US National Institutes of Health (NIH)-funded scientists and their collaborators, disrupting careers, damaging the prospects of companies working in the area of regenerative medicine and impeding the search for new therapies.

Lamberth's ruling rested on his interpretation of the ambiguous Dickey-Wicker amendment, a rider attached annually to the federal appropriations bill covering the NIH. Introduced in 1996, two years before hESCs were first derived, Dickey-Wicker prohibits the use of federal money for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death." Lamberth's reading of the amendment—that it excludes federal funding of hESC research—contradicts the interpretations of US Presidents Clinton, Bush and Obama; of Congress, which twice passed bills supporting federal funding of hESC research and has never acted to ban such funding; and of the NIH, responsible for administering grants in accordance with Dickey-Wicker. Their view that federally funded hESC research is permissible relied on a 1999 analysis by Harriet Rabb, then the general counsel of the Department of Health and Human Services, who noted that "human pluripotent stem cells [...] are not a human embryo within the statutory definition."

Although some US stem cell scientists and their supporters had worried about Dickey-Wicker for years, most were stunned by the latest turn of events. The field was thriving as never before. The NIH had funded hESC grants since 2002, Obama had removed Bush-era funding restrictions and offered an eloquent defense of hESC research, and support among the public and Congress was continuing to rise. To those familiar with *Sherley v. Sebelius*, the plaintiffs' case appeared weak. In hindsight, it is clear that many were lulled into a false sense of security and that Congress miscalculated in failing to codify Obama's March 2009 Stem Cell Executive Order when the political climate was more favorable. Now, only weeks before an election defined by an anti-incumbent mood that has politicians reluctant to take on controversial issues, the chances for Congressional action seem slim.

The chilling effect from Lamberth's ruling is likely to include an exodus of US scientists from the stem cell field, the departure of others to continue their studies abroad and loss of US leadership in a field with exceptional therapeutic promise. Although the ruling targets only federally funded scientists, it will surely affect regenerative medicine

companies as well, harming efforts to translate basic research on stem cells into therapies.

Research on hESCs has always been whipsawed by politics and inconsistent policy. If the US government abandons the field now, the consequences for tech transfer from federally funded universities and for industry partnerships with NIH-funded academics, as well as questions over the eligibility of hESC-based therapies for reimbursement, will make regenerative medicine even less attractive to investment. Investors, boards and industry scientists are already skeptical about how close hESCs are to therapies, and in a bad economic environment for biotech generally, a new round of uncertainty may prove to be the field's undoing. The bright spot in this sorry tale is California, where the California Institute for Regenerative Medicine has provided \$351 million for projects that include hESCs (not counting money spent on facilities and training grants). Although this and other smaller state initiatives have come under pressure from severe state budget crunches, such investments now seem prudent given that they have buffered the effects of fickle federal policy.

On scientific grounds, the argument for continued research on hESCs is irrefutable. Different hESC lines behave differently; understanding these differences and developing therapeutic strategies will require comparisons among a large number of lines. Although induced pluripotent stem cells have many advantages and may one day replace hESCs, in the foreseeable future the latter will remain an indispensable cell type for studying pluripotency and differentiation.

During the Bush administration, many US scientists and companies interested in working on hESCs concluded that the obstacles were simply too great. Obama's executive order placed the presidential imprimatur on this young, controversial science, granting it unprecedented legitimacy and encouraging those who had stayed on the sidelines to proceed. But as the Lamberth decision makes clear, Dickey-Wicker represents a sword of Damocles over the field.

It has often been pointed out that allowing excess *in vitro* fertilization (IVF) embryos to be discarded while outlawing federally funded research on these embryos is inconsistent. US prohibitions on embryo research reach back as far as 1974, when opponents of *Roe v. Wade* claimed that the ruling would bring about worst-case scenarios, including indiscriminate embryo experimentation. For 35 years, federal moratoria on embryo research have made investigation of infertility, early human development, reproductive medicine and pre-natal diagnosis off-limits to most US scientists and clinicians. The US needs laws that will protect free inquiry in these areas, and particularly in the field of hESCs, in accordance with ethical norms and the NIH's competitive, merit-based formula. On the day he signed his Stem Cell Executive Order, Obama also issued a memorandum requiring the development of "a strategy for restoring scientific integrity to government decision making." To ensure the scientific integrity of stem cell research—whatever the outcomes of the court cases—the best solution is swift legislative action. **EB**