

COMMENT

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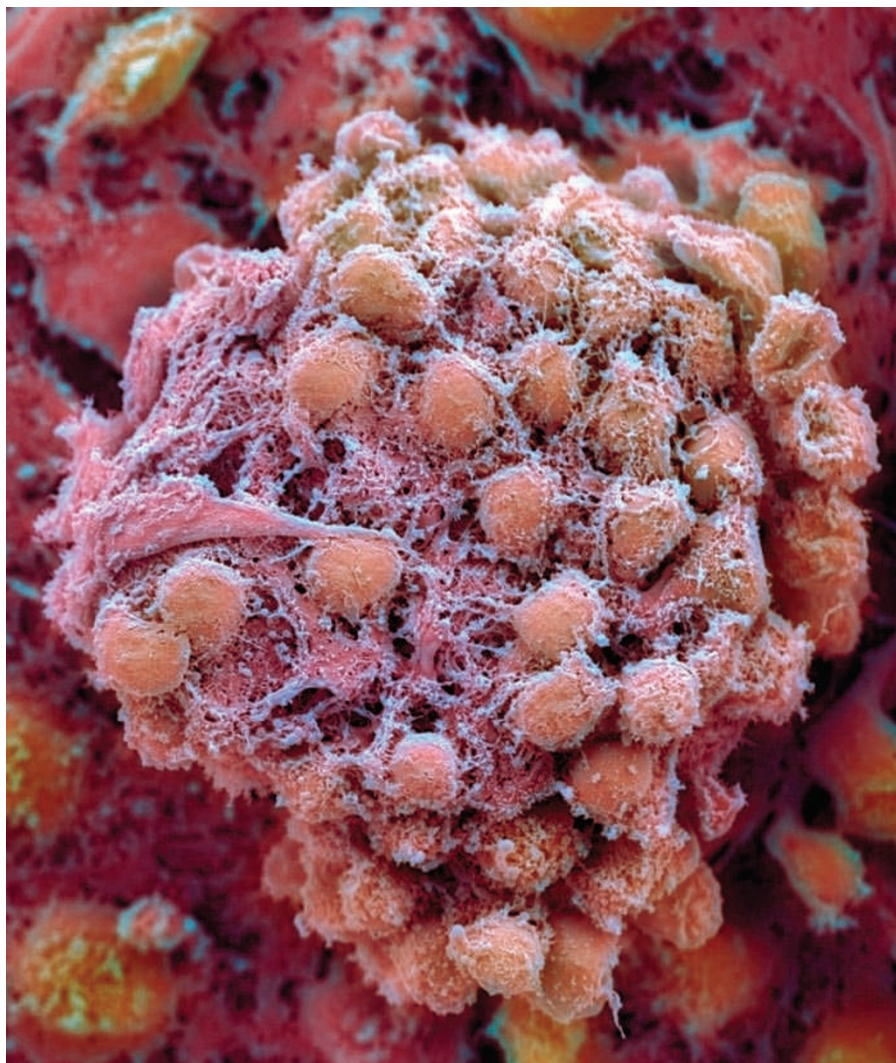


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Long shadow of the stem-cell ruling

Two months on from the court decision that briefly suspended US federal funding for human embryonic stem-cell research, uncertainty still stalks the field. Here an ethicist, a team of bankers and a lawyer warn of effects of this saga that could be felt for years to come.

THE ETHICIST

Vanguard of the new biopolitics

Jonathan D. Moreno is at the University of Pennsylvania in Philadelphia.

Whatever the outcome of the legal process that has called into question the future of US federally supported human embryonic stem-cell (hESC) research, there will be no turning back the clock to the day before such funding was temporarily banned by a district court judge. Quite rightly, life scientists are wondering whether this incident signals an extended series of controversies in the United States about experimental biology.

There is a narrative that suggests that it does. Seen in the light of other incidents, and cultural and political factors, the torturous tale of hESC research in the United States is but a more emphatic example of an emerging 'biopolitics'.

The first examples of the modern politics of biology, the recombinant-DNA debate and the first human birth by *in vitro* fertilization, took place during the 1970s in a less politically fevered environment than today. Memories of the public concerns and confusion in response to those events have faded. Like stem cells, both were direct technical challenges to what many regarded as the order of biological nature, and both reminded us, as stem cells do, that the human body, for all the advantages it gives us over other creatures, shares its fundamental systems of growth, organization and reproduction with other living things. Even while airy talk of post-modernism filled the philosophy seminar rooms, over in the science buildings it was hard to deny that something pretty basic was being learned as biologists began to manipulate the underlying mechanisms of life.

There was plenty of fodder for society's doubt about the implications of science and its concerns about the hubris of scientists. These are themes that reach back to the origins of the Enlightenment, from Francis Bacon's scientist-governed utopian *New Atlantis*, to Mary Shelley's *Frankenstein*, ▶

► H. G. Wells's *Island of Dr Moreau* and Aldous Huxley's dystopian *Brave New World* — all works in which the monster is not the creature, but the scientist.

But it is this stem-cell saga that has provided the fullest expression yet of the new politics of biology. Never before has a debate about a specialized laboratory practice been the occasion for passionate cultural division that surfaced in three presidential campaigns and many state elections, before completing its latest adventure in the judicial system.

Other biopolitical issues haven't achieved the status of stem cells but are based on the same competition for control. For example, a 2009 Louisiana law prohibits attempts to create, transfer or transport human-animal hybrids, and a similar bill is under consideration in Arizona; violators face prison and a seven-figure fine. Both bills were inspired by a congressional bill — drafted by the probable next governor of Kansas, Senator Sam Brownback — that seems to prohibit the use of cow eggs for somatic-cell nuclear transfer. The worry expressed by supporters of the law, that the mixing of human and animal cells tends to blur species lines and undermine human exceptionalism, is one that applies to much modern experimental biology. Britain had its own dust-up over 'cybrids' that played out in its parliament a couple of years ago.

The flashpoints of the US post-Enlightenment ambivalence about science — the abortion debate, end-of-life care, 'designer babies' and now stem cells are somewhat different from those of modern Western Europe. In the United States, genetically modified organisms are *persona non grata* on the menu. Yet the nation is the only country that was founded by a group of scientists under the explicit inspiration of the eighteenth century's valorization of reason and demonstration in the growth of knowledge. Their vision of a new nation that would be a magnet for inventors and invention was and remains embodied in the patent statute.

For much of the country's first century, anti-federalists disputed the constitutional reach of the central government in paying for 'internal improvements', including roads and bridges and innovations such as telegraphy. Although we can hardly imagine what US science and technology would look like in the twenty-first century without a robust federal role, it is remarkable that stem-cell funding is in essence tied up in a federal-state tension over internal improvements.

The United States faces a 20–30-year process of economic reconstruction that must include bio-based industries. Historically, Americans have reconciled themselves to change, however reluctantly and spasmodically, if it signified a brighter future. Without exaggerating the significance of a single policy decision, the nature of this choice foreshadows many more. Welcome to the new biopolitics.

THE BANKERS

US firms could be left behind

John M. Nolan, Emad U. Samad, Suy Anne R. Martins and Stephen G. Brozak are at WBB Securities in Clark, New Jersey.

The recent litigation in the District of Columbia Circuit attempting to suspend the public funding of hESC research in the United States also threatens privately funded research. It has created an atmosphere of grave uncertainty among Wall Street investors who now shy away from hESC products, alarmed by the increased risk that stems from protean federal policy and the ambiguous regulatory requirements (see graph).

The United States is at a crossroads. Never before has there been such a paucity of funding for the commercialization of a technology with such immense therapeutic potential. To date, we estimate that less than US\$250 million has been directly committed to meaningful commercial enterprises engaged in translating hESC research into viable therapeutic candidates for human disease.

Without the immediate adoption of a clear federal policy, backed by substantial funding for basic research and product development, we believe that the market for hESC technologies in the United States will be irreparably harmed. The country will lose its position as a leading developer of regenerative medical therapeutics despite the fact that as many as 60% of Americans now approve of the creation of hESC lines

for research and therapeutic use¹.

Researchers and companies are already turning to other nations to advance basic hESC science and product development². The United Kingdom, for example, has made hESC research a national priority, with funding commitments in excess of £350 million (\$556 million) and economic incentives that have already lured many top researchers to the country. Government-sponsored programmes, such as the UK Stem Cell Initiative, have encouraged collaborations between public and private institutions, in some instances mandating academia to seek out partners in industry for projects to qualify for government funding³.

By comparison, only \$42 million of the National Institutes of Health's (NIH's) roughly \$30-billion budget in the 2007 financial year was allocated to hESC research. Even after President Barack Obama lifted the Bush-era cell-line restrictions, federal funding levels increased to a projected \$123 million in 2010, far less than the allocations for many areas such as nutritional education, alcoholism, substance abuse and gene therapy. Compared to the \$424.8 million allocated to the Human Genome Project in 2000 (\$335.9 million by the NIH and \$88.9 million by the Department of Energy) and the roughly \$2.6 billion that was allocated to the project throughout the 1990s, current funding levels for hESC research are simply not sufficient to bring a concept from inception to commercialization, nor have they been adequate to entice private industry into the market.

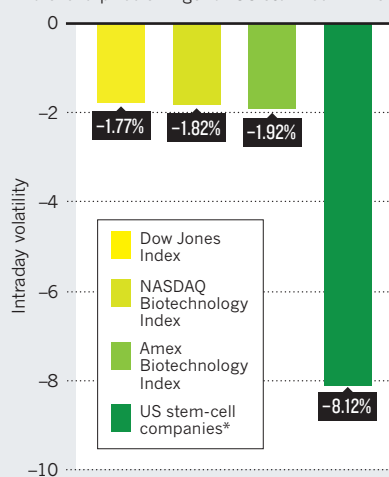
The United States must act now to rectify the missed opportunities of the past decade and to protect its future scientific, medical and commercial interests. It can begin by revising the 1996 Dickey-Wicker Amendment to permit future and continued use of embryonic cell lines.

We also recommend that the US government makes a financial commitment as large as that dedicated to the Human Genome Project and increase yearly NIH appropriations for hESC research to at least \$500 million. Otherwise, as research continues elsewhere, European pharmaceutical companies will continue to build a strong intellectual-property position that they will use to protect their investments and generate perpetual development and revenue cycles.

Some US companies have built substantial hESC intellectual-property portfolios. However, their science and commercialization pipelines are not maturing at the same pace as those of their European or Asian counterparts. Thanks to scant national coherence and significant regulatory risk, the US capital markets have failed to provide financing in sufficient sums to spur serious product development. As a result, hESC science and technology is now concentrated in the hands of a few undervalued US companies.

INDISCRIMINATE EFFECT

On 23 August, the suspension of funding for human embryonic stem-cell research caused wild share-price swings for US stem-cell firms.



*Average of ten adult- and embryonic-stem-cell companies

Over the past two years, growing numbers of pharmaceutical companies from emerging economies have vied for entry into Western pharmaceutical markets by manufacturing generic drugs. China, for example, is poised to become the world's third-largest pharmaceutical market next year and will contribute the same in annual sales in 2013 — more than \$40 billion — as the US market. Meanwhile, American and European pharmaceutical companies have become desperate to sustain eroding revenue as proprietary patents for blockbuster drugs expire, allowing more generic competition.

To corner the market that may hold the next medical revolution, an Asian pharmaceutical company could easily decide to acquire US companies that have advanced technologies but very low market valuations. If foreign pharmaceutical companies focused resources, they could proceed with product development at a pace that the US pharmaceutical industry would be unable to match. Such a move would signify a shift in the balance of power of the health-care market and set US stem-cell science back a generation.

1. Gallup stem cell research poll; available at go.nature.com/y5kxvi
2. Sipp, D. *Regen. Med.* **4**, 911–918 (2009).
3. UK Stem Cell Initiative (UKSCI) *UK Stem Cell Initiative: Report and Recommendations* (2005).

THE LAWYER

Why US science is stuck in the dock

Patrick L. Taylor is at the *Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School in Cambridge, Massachusetts.*

The judge forgot the potential for cures, writes one editorial. Appeal the decision, pass a new statute! But the impact of the court's methods will linger long after the dust has settled. The implication that no facts are certain in the United States means that no science is safe.

The court had to interpret the Dickey-Wicker Amendment, a budget rider disallowing funding of research in which human embryos are “destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero”. Sound court orders depend on sound determination of two kinds of facts. The first is objective: will it cause harm to stop funding immediately? (No, said the court, without consulting other extramural researchers.) Whose harm will be greater? (Continued funding would seriously harm two plaintiff researchers claiming potential competitive

injury to their non-hESC research, said the court, whereas stopping all hESC funding will cause no harm, and preserve the status quo, because hESC researchers can go to industry.) The court said a stop-order was consistent with the “public interest”, but didn't say why — despite overwhelming public support for hESC funding.

The second kind of fact is interpretive: what did Congress mean, and what did it want? The ‘Chevron’ ruling, named after the Supreme Court case announcing it, requires courts to stick to legal text if it's unambiguous, as that best fulfils congressional intent. If a law is ambiguous, courts must defer to agencies charged by Congress to administer it.

US law is filled with useful heuristic rulings, establishing methods or reconciling new developments with old categories. But if misapplied or too crude, these rulings can supplant justice, prevailing over what basic factual inquiry would have required. Before slavery was abolished in the United States, courts were asked whether African people were property rather than persons. Yes, said the courts, so laws of sales and inheritance swung into place, paving the path from slavery to slums with falsehoods.

The district court's decision was an ingeniously literal use of Chevron. It capitalized upon the requirement to stick to law alone if the law is clear by determining that Dickey-Wicker is “unambiguous”. So the court could exclude evidence of congressional and presidential activity conclusively mandating hESC research funding, and could decide that all research using hESCs is of a piece. The differences between research that derives and research that uses hESC lines are well established. Congress is aware of them. Regulations, agency guidance and science practice would have shown that research protocols rarely encompass the creation of ingredients — cells, drugs and reagents are provided by third parties. A study that involves injecting hESCs to cure neonatal paralysis will raise important ethical and scientific questions. But it will not be research in which a human embryo is “destroyed”.

Such a broad reading of what it means for research to involve destroying embryos threatens important research. By the same logic, could federally funded research on HeLa cells now be construed as ‘research killing a patient’, because Henrietta Lacks died from the cancer that was the source of the original cells? Could research to correct fatal heart syndromes in fetuses, or all research into genetic diagnostic tests also be imperilled? More crucially, a judicial finding of “unambiguity” — which facts would have rebutted — now permits courts to ignore the NIH and other agencies, and scientists who engage with

Congress to influence legislation.

In a way, this was a legal accident waiting to happen. From the 1990s, political debate about stem cells has been excessively influenced by Dickey-Wicker's emphasis on what government would fund. Ethical rules linked to NIH funding — addressing issues such as the sharing of data or materials — did not apply to most stem-cell research because it was not federally funded. The result was complex funding rules, fear in the research community and patent monopolies.

Yet in this ethics vacuum, something spectacular occurred: people thought about the questions publicly, debated them closely and reached a reasonable, nuanced conclusion. They saw what other countries, such as the United Kingdom,

did. The media established an ongoing conversation across international borders. Scientists and others created, through national and global guidelines, a self-regulatory ethical framework that did what laws did not — such as requiring independent review to evaluate scientists' proposals, barring research on embryos once nervous-system development has begun, prohibiting coercion of egg donation and forbidding financial inducements for research eggs and embryos. Global discussion led to a shared US vision of ethically permissible funding. Subsequently, the NIH introduced rules that accurately reflected popular will and an interpretation of Dickey-Wicker that Congress had repeatedly confirmed.

The suspension saga has effectively annulled the marriage of law and ethics embodied by the final NIH rules. Public ethical consensus, votes conscientiously considered and norms for open science became irrelevant. Legal fictions replaced facts, and a heuristic legal ruling designed to respect congressional and public will was the very instrument of democracy's defeat.

Now the branches of government must work together not just to fix hESC funding but to stamp out the methods used to bring it so low — to head off future damage to novel science. Judicial appointments also need examining. They should not be principally based on divining candidates' personal politics, but more on the choice to set personal politics aside. How candidates discern fact, understand Congress and reconcile law with what is new, are key. Congress must also close the loopholes allowing courts to ignore authoritative evidence of congressional intent and textual ambiguity.

We need a new watchdog that tells us when law radically misaddresses science's rapid developments. For public ethics to become public law, we need to know when law fails, and why. And then we must act. ■

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