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A dangerous precedent

A legal challenge to US stem-cell policy poses a serious threat to the federal funding system.

The rift between opponents and supporters of research using human embryonic stem cells seems all but insurmountable, reaching to the core of individual notions of morality. That has meant that embryonic stem-cell research, in the United States and elsewhere, has in large part been delimited by governmental decree. Over the past decade, US scientists have pursued work on such stem cells — to a limited extent under former president George W. Bush and more freely under President Barack Obama — even while opponents have continued to challenge it.

One such recent challenge has overstepped the previous bounds of the battle, threatening not only embryonic stem-cell research, but also the very framework of federal funding for science. Both funders and the scientific community must speak out to ensure that the dangers it poses are clearly recognized.

Last August, several Christian groups joined forces with two scientists to file a lawsuit against the US Department of Health and Human Services and the National Institutes of Health (NIH). The lawsuit charged that the Obama administration's embryonic stem-cell policy violates the Dickey–Wicker Amendment, a law that prohibits federal funding of research on human embryos. The suit was dismissed on the grounds that the plaintiffs had no real standing in the case — that is, no tangible interest in its outcome.

But on 25 June, the Court of Appeals in Washington DC reversed the dismissal on the basis of an appeal made by the scientist plaintiffs: James Sherley, a researcher who works with stem cells derived from adult tissue at the Boston Biomedical Research Institute in Watertown, Massachusetts, and Theresa Deisher, research and development director of the firm AVM Biotechnology in Seattle, Washington. To justify their standing as plaintiffs, they argue that because federal funding is now going towards research on embryonic stem cells, there are fewer funding dollars — and therefore "increased competition" — for research using adult stem cells.

It is hard to say which is more disturbing — the argument made by the two scientists or the fact that it was accepted by the court. Both issues set a dangerous precedent by suggesting that researchers are legally entitled to a certain portion of the funding pie, and that changes in a federal agency's research priorities — which often occur as scientific disciplines evolve — open the agency up to lawsuits.

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Asked by *Nature* to respond to concerns about such a precedent, Sherley referred to the appeals court's decision to give him standing. "It should go without saying that I think the decision, and the reasoning therein, is correct," he wrote in an e-mail.

From a research perspective, stem cells, whether derived from embryonic or adult tissue, are simply a tool for studying biological systems and developing treatments for diseases — much like knockout mice or biochemical assays in a test tube. No single tool is inherently better than another, but each must be chosen for its use in addressing a specific research question.

For that reason, there is not and should not be a pot of money set aside for research on either embryonic or adult stem cells. Peer review should be enough to decide which projects merit funding. Adult and embryonic stem cells should not constitute competing areas of research — scientists who use these cells in their work should view their studies as complementary.

With Sherley and Deisher's appeal accepted, the original case will now go to court. The government agencies must decide on their next move: they could ask the Court of Appeals to reconsider its decision, or they could appeal to the Supreme Court. Alternatively, they could argue the case and hope to win. All federally funded researchers should watch the case closely; if the government loses, the implications will reach far beyond the stem-cell field. ■

Plagiarism pinioned

There are tools to detect non-originality in articles, but instilling ethical norms remains essential.

It is both encouraging and disheartening to hear that major science publishers intend to roll out the CrossCheck plagiarism-screening service across their journals (see page 167).

What is encouraging is that many publishers are not only tackling plagiarism in a systematic way, but have agreed to do so by sharing the full text of their articles in a common database. This last was not a given, considering the conservatism of some companies, yet it was a necessary step for the service to function — the iThenticate software used by CrossCheck works by comparing submitted articles against a database of existing articles. CrossCheck's 83 members have already made available the full text of more than 25 million articles.

What is disheartening is that plagiarism seems pervasive enough to make such precautions necessary. In one notable pilot of the system on three journals, their publisher had to reject 6%, 10% and 23% of accepted papers, respectively.

Granted, there are reasons to believe that such levels of plagiarism are exceptional. Previous studies of samples on the physics arXiv preprint server (see *Nature* **444,** 524–525; 2006) and of PubMed abstracts (see *Nature* doi:10.1038/news.2008.520; 2008) found much lower rates. But the reality is that data are sorely lacking on the true extent of plagiarism, whether its prevalence is growing substantially and what differences might exist between disciplines. The hope is that the roll-out of CrossCheck will eventually yield reliable data on such questions over wide swathes of

the literature — while also acting as a powerful deterrent to would be plagiarists.

In the process, editors and publishers must remember that plagiarism comes in many varieties and degrees of severity, and that responses should be proportionate. For example, past studies suggest that self-plagiarism, in which a researcher copies his or her own words from a published paper, is far more common than plagiarism of the work of others. Arguably, self-plagiarism can sometimes be justified, as when a researcher is bringing similar ideas before readers of journals in a different field. All plagiarism can also involve honest errors or mitigating circumstances, such as a scientist with a poor command of English paraphrasing some sentences of the introduction from similar work.

Such examples underscore that plagiarism-detection software is an aid to, not a substitute for, human judgement. One rule of thumb used by Nature journals and others in considering an article's degree of similarity to past articles — in particular, for small amounts of self-plagiarism in review articles — is whether the paper is otherwise of sufficient originality and interest.

Nature Publishing Group is a member of CrossCheck and has been testing the service on submissions to its own journals. It has noted only trace levels of plagiarism in research articles, which are spot-checked, and often in only the supplementary methods. Plagiarism has been more common in submitted reviews, all of which are tested. This is particularly true in clinical reviews, although the rates are still far below the 1% mark, and in most instances concerned some level of self-plagiarism.

Although the ability to detect plagiarism is a welcome advance, addressing the problem at its source remains the key issue. More and more learned societies, research institutions and journals have in recent years adopted comprehensive ethical guidelines on plagiarism, many of which carefully distinguish between different levels of severity. It is crucial that research organizations in all countries, and particularly the mentors of young researchers, instil in their scientists the accepted norms of the international scientific community when it comes to plagiarism and publication ethics. ■

The needs of the few

Developing drugs for rare diseases is a challenge that requires new regulatory flexibility.

On 29 June, Timothy Coté, head of the Office of Orphan Products Development at the US Food and Drug Administration (FDA), concisely summed up the agency's policies with respect to the approval of drugs and other medicinal products for rare diseases: "No policy at all."

The irony of this assessment is that the United States has long been a leader in stimulating the development of therapies for rare diseases. Congress passed the Orphan Drug Act in 1983 in an attempt to deal with the unique commercial and regulatory challenges posed by 'orphan' diseases, defined as those that affect fewer than 200,000 Americans. For industry, there is little appeal in pursuing a drug that will be required by only a small number of patients. For regulators accustomed to the clinical trials typically performed for common diseases, it can be difficult to ascertain the safety of a drug that, by necessity, can be tested in only a tiny cohort of patients.

The act aimed to incentivize orphan-drug development by rewarding drug-makers with a seven-year period of market exclusivity for such compounds. The FDA also created the Office of Orphan Products Development to shepherd companies through the approval process. Ten years later, Japan enacted similar legislation, and Europe followed suit in 2000.

In many ways the act was a success. In the decade before its passage, the FDA approved fewer than a dozen drugs for rare diseases; since then, the agency has approved 358. Nevertheless, the vast majority of the 7,000 known rare diseases remain without treatment. And, as Coté was explaining last week at the inaugural meeting of the FDA's new expert panel on orphan diseases, the agency still has no policy guiding how it evaluates possible treatments for a rare disease.

It is time for the FDA to develop one. The ranks of orphan diseases are growing. Better understanding of common ailments — for example, through genome sequencing — is shattering old classification schemes, fragmenting many 'common' diseases into smaller subtypes. The medical landscape will soon be crowded with 'orphans'.

This means that the FDA will be seeing more applications bearing data from small clinical trials, thrusting regulators into the uncomfortable position of ascertaining safety and efficacy with less than optimal data. Classical gold-standard, placebo-controlled studies force researchers to divide their already tiny experimental cohort in half — one half that receives the experimental drug, the other a placebo. And because these diseases are often fatal (of those afflicted with one of the 350 most common rare diseases, 27% will not see their first birthday), patients are understandably loath to spend much time receiving a placebo.

As a result, the FDA will need to allow more flexibility in clinical-trial design. In some cases this may mean a short placebo-controlled study that moves rapidly into an open-label trial, in which both researchers and patients know what is being administered. In other cases it may mean abandoning placebo controls altogether. Furthermore, post-marketing studies to monitor safety and efficacy of drugs after approval may have to be done with smaller sample sizes than are normally required. The FDA could also learn from Europe, which has carved out an 'exceptional circumstances' pathway to approval for therapies for which full, gold-standard clinical-trial data are not available.

All of these issues will be under consideration as the agency's new expert panel prepares an advisory report, due to be released in September. There are signs that it will fall on receptive ears: in remarks made before the Senate in March, FDA commissioner Margaret Hamburg expressed a commitment to finding new solutions to the problem of rare diseases. And two large pharmaceutical companies, GlaxoSmithKline and Pfizer, have recently announced new research divisions dedicated to orphan diseases. The present momentum should not be allowed to fail. ■