The pendulum swung

President Barack Obama removes restrictions on stem-cell research, but are expectations now too high?

Since his inauguration on 20 January 2009, US President Barack Obama has been busy reversing and dismantling many of his predecessor's decisions and policies. Seven weeks into his presidency, he finally lifted the controversial restraints on embryonic-stem-cell research that had barred the National Institutes of Health (NIH; Bethesda, MD, USA) from funding projects beyond using the 60 extant cell lines—only 21 of which were viable. From the moment former President George W. Bush introduced this legislation in August 2001, embryonic-stem-cell researchers had to find other sources of funding to develop new lines.

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President Obama, who was delivering on a campaign promise, said: "At this moment, the full promise of stem-cell research remains unknown, and it should not be overstated. But scientists believe these tiny cells may have the potential to help us understand, and possibly cure, some of our most devastating diseases and conditions: to regenerate a severed spinal cord and lift someone from a wheelchair; to spur insulin production and spare a child from a lifetime of needles; to treat Parkinson's, cancer, heart disease and others that affect millions of Americans and the people who love them." The president also called on Congress to provide legislative backing and funding for the research, for which public support has grown in recent years. President Obama emphasized that his order did not open "the door to the use of cloning for human reproduction."

Even before President Obama announced his decision, two members of Congress—Democrat Diana DeGette, representing the First District of Colorado, and Republican Mike Castle, Representative for Delaware—had re-introduced legislation

to the House of Representatives on 4 February 2009 that would legally support federal funding for embryonic-stem-cell research; similar legislation was introduced on 26 February 2009 in the Senate by Senators Tom Harkin, an Iowa Democrat, and Arlen Specter, a Republican from Pennsylvania. Specter, who has fought a battle against Hodgkin disease, said legislation is needed to protect the policy, "so that it does not ping-pong back and forth with each successive president."

DeGette, whose daughter has juvenile diabetes—one of the diseases for which stem-cell research might provide a therapy or cure—said that it is crucial to pass legislation that will codify President Obama's executive order, to prevent the pendulum from potentially swinging back in the next administration. "By putting it in the statute, it gives permanency to allowing the research to continue," she said.

DeGette said that legislators would also need to remove the so-called Dickey-Wicker amendment that bans the use of federal funding for research that involves, "(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero*."

President Obama's policy shift and the legislation that DeGette and Castle have introduced should overturn almost a decade of restrictions on embryonic-stem-cell research; but such a step is not popular with everyone. As expected, the pro-life movement, which had kept a relatively low profile during the 2008 political season, attacked the president's policy; Roman Catholic leaders protested against President Obama's plans to speak at the May 17 commencement at Notre Dame University (South Bend, IN, USA) and prompted the local bishop to boycott the speech (Kusmer, 2009); and some states, including Mississippi and Georgia, acted quickly to block stem-cell research at the state level, in the light of the change to federal policy (Dewan, 2009).

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Within the bounds set by the Bush administration, the Republican Party had supported stem-cell research, but emphasized research on adult stem cells. Senate Minority Leader Mitch McConnell of Kentucky charged that President Obama's executive order represented a "troubling shift in US policy. With this announcement, the government is, for the first time, incentivizing the creation and destruction of human embryos at the expense of the US taxpayer." He said tax money would be better and more ethically spent on research on non-embryonic stem cells.

By contrast, the reversal of Bush's policy has been popular with the scientific community and has received wide support from advocates of stem-cell research, including former First Lady Nancy Reagan. John Kessler, Professor of Neurology and Director of the Feinberg Neuroscience Institute at Northwestern University (Chicago, IL, USA) said, "It's nice to see politics are no longer intervening in science, where they

never should have been in the first place. This is a good time, not just for stem-cell biologists, but [for] all scientists. This restores the integrity of the separation between politics and science."

Kessler, who works with embryonic stem cells, and whose teenage daughter was paralyzed in a skiing accident, said President Obama was speaking for most Americans by loosening the rules and allowing this line of research to be explored. "The majority of Americans support stem-cell research, and the large majority of the great religions of the world also support this research. Imposing personal views out of step with the large part of the society is the ultimate abuse of political power," he said, adding that public support for embryonic-stem-cell research ranges in various surveys from about 60–75%. In a telephone survey of 1,005 adults in late 2008, the Virginia Commonwealth University (Richmond, VA, USA) Life Sciences Survey found that support for embryonic-stem-cell research is similar to past years: "57 percent

of adults favor embryonic stem-cell research, while 36 percent oppose" (VCU Life Sciences Survey, 2008).

But, it is not only the scientific community who are embracing the fact that the US government will again support stem-cell research; the business world is equally delighted. Robert Lanza, Chief Scientific Officer of Advanced Cell Technology (Los Angeles, CA, USA), said that the company, which had been on the verge of bankruptcy, was boosted by the election: "The day after Obama was elected, investors started to come out of the woodwork. I think this marks the end of a sad chapter in American scientific history [in which] actual laws were passed that criminalized scientific research and where President Bush had placed some serious restrictions on stem-cell research."

Lanza, whose company is seeking approval from the US Food and Drug Administration (FDA; Rockville, MD, USA) to test a stem-cell-based therapy to prevent blindness, added: "There's been a black cloud

hovering over stem-cell research for certainly the last eight years and that's been lifted. We've been operating for the last decade with one hand tied behind our back."

Indeed, the research climate might be about to change rather quickly: only a few days after Obama's inauguration—although officials maintain that the timing was coincidental—the FDA gave permission to Geron Corp. (Menlo Park, CA, USA) to conduct the first clinical trial of an embryonic-stem-cell-based therapy. Tom Okarma, President and Chief Executive Officer of Geron, whose company spent US\$200 million on seeking approval for permission to investigate this new drug application, said that he had expected a green light on the research no matter who was elected president. "However, there's no question that the path to approval was made much more difficult, torturous and prolonged by eight years under President Bush," he commented.

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Both the private sector and academic research institutions are eager to finally move on after almost eight years of political and legislative roadblocks to their research. Several universities said that they now expect to intensify their stem-cell research or to review their policies. Northwestern, for example, plans to apply for federal funding to study new human embryonic cell lines that had been developed with funding from the state of Illinois. Indeed, it was state funding that kept this research going; California is just one of several states that had been supporting its own embryonic-stem-cell research, including the creation of new cell lines, after Californians approved Proposition 71 in 2004 to spend US\$3 billion in bonds over the following decade.

The ban on federal funding for research that involves the destruction of a human embryo has had more far-reaching consequences over the past eight years than the simple fact that scientists could not submit grant applications to federal funding agencies. "Every

dean of medical schools in California was absolutely petrified that although their faculty wanted to work on embryonic stem cells, they couldn't do it in their own labs because even if the overhead in your lab is paid for by NIH, you risk losing your NIH grant if somehow that light bulb shone on your experiment with new embryonic stem cells. That's how crazy it was," Okarma said, recalling the repressive and confusing research atmosphere caused by the Bush executive order. As a consequence, many young postdoctoral researchers left the field because "[t]hey had been dying to get into it, but didn't know where to go," he added. "So that's why—about half of—the first tranche of Prop 71 funding went for bricks-and-mortar to build so-called safe harbour laboratories on the campuses of every major medical school in California."

Alan Trounson, President of the California Institute of Regenerative Medicine (CIRM; San Francisco, CA, USA)—which manages funding of stem-cell research by California institutions and has so far committed more than US\$693 million of the state's US\$3 billion budget for this research—commented that federal funding will mean reduced overheads and should remove the administrative headache of essentially having separate books and laboratories to keep federal funding separate. "What I think will change is a lot of things having to do with the federal money; for example, the need to duplicate records, to not use pieces of equipment that were funded by NIH, not use rooms and buildings that were funded by NIH," he said, adding that the combination of state and federal support will have an impact. "We'll be addressing problems together—as distinct from quite separately—so we won't have the duplication. We'll look towards where we can best mesh our appropriate funding to get the outcomes, the solutions, at both the federal and the state level. So, it changes a lot."

CIRM is still committed to provide funding—the current financial crisis and California's budget problems notwithstanding—according to Don Gibbons, Chief Communications Officer at the Institute. "[W]e are very confident that we will be able to place California General Obligation bonds 'privately' in time to continue all our programmes," he said. "Large foundations have to invest their endowment and [...] a state fund paying four to five percent could be very appealing and for many foundations it could be

considered a 'programmatic' investment that fits in with the foundation's mission."

Lanza pointed out that, although support from states and philanthropic organizations—such as those founded by the late actor and spinal-cord-injury patient Christopher Reeves, and actor and Parkinson disease patient Michael J. Fox—is important to this type of pioneering research, federal funding is nonetheless crucial to sustaining it. "Traditionally, it's only been the federal government that has had shoes big enough to fill the role of getting basic research to the point of translation into the clinic. You've got to remember a lot of this is early-stage research that requires federal funding," he said.

Despite the general buzz and excitement about the fact that the US federal government will again support and fund research using human embryonic stem cells, the current financial and economic crisis—the largest since the Great Depression of the 1930s—will have a serious impact on the availability of both public and private funding, not only for stem cells but also for medical research in general. "There is an expectation that the floodgates are going to open in the US, and clearly that's not happening at the moment," commented Steve Minger, Senior Lecturer in stem-cell biology at King's College London (UK), and a US citizen. "The economy in the United States, Europe and worldwide is so terrible that companies are folding left, right and center, and the companies that are still afloat are retrenching massively. One of the major stem-cell companies here in the UK just announced that they're going to lay off half their staff."

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Moreover, Minger said that major US investors have told him that support will not be available from venture capitalists for another 18 months, and that investors he has spoken to now advise: "You better figure out how you're going to stay alive because there is not going to be any new investment whatsoever"; and these are guys

who normally would invest several hundred million dollars a year in new regenerative medicine-related spin-outs. It's a very sober environment at the moment."

As such, and even with the new possibility of federal support, Minger does not necessarily expect the first clinical applications of embryonic stem cells to roll out in the near future. "I think it's a big shot in the arm for somebody like Geron to be able to weather all of this and actually get into the clinic," he said. "But it's a very long time frame—a long road from when you first have something you think works in the lab to actually getting it into the clinic. You have to be in it for the long haul."

Scientists are therefore concerned both about a possible decline in clinical development by the private sector and about the increased expectations of the public—especially those whose loved ones are affected by diseases that stem-cell research might address. After all, the ongoing criticism of the federal ban on this research during the Bush years, and President Obama's quick decision to reverse it, have both attracted considerable media attention and have raised hopes. "One hundred and ten million Americans and their families are affected by diseases that could be helped by this research. And it's easy to get carried away with the prospects, especially when there's a breakthrough," DeGette said. "What we have to realize is, we're just allowing this basic research to occur and cures could be years away, but if we don't get started, then we delay the cures even that much longer."

"Public expectations in [the US] are an issue because scientific education and true medical awareness [are] so thin that people do jump to extremes when there's a breakthrough," Okarma commented. "We have tried to meter our enthusiasm, not getting people with spinal cord injury too excited about this right away." In spite of this, he said, "we had so many calls from existing spinal cord injury patients the Friday of the announcement [of the FDA's clearance] that it broke down our voicemail system."

President Obama is also apparently well aware of the problem of too high expectations. In an attempt to dampen false hopes and address over-enthusiasm for the potential of stem-cell research, he said at the signing ceremony in which he undid Bush's former policy: "Ultimately, I cannot guarantee that we will find the treatments and cures we seek. No President can promise that.

But I can promise that we will seek them—actively, responsibly, and with the urgency required to make up for lost ground. Not just by opening up this new front of research today, but by supporting promising research of all kinds, including groundbreaking work to convert ordinary human cells into ones that resemble embryonic stem cells" (Obama, 2009).

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