Cell Block

Bush's politicized stem-cell decision puts California on the verge of a "scientific secession."

BY CHRIS MOONEY

TWO YEARS AGO, EVAN SNYDER, A DEVELOPMENTAL AND child neurologist, was working at the Harvard Medical School, transplanting neural stem cells into the damaged brains and spinal cords of mice and other animals and watching them reconstitute tissue or recover function. "I had just moved to better lab space," Snyder recalled in June at the Argent Hotel in downtown San Francisco, where he'd gone to attend the Biotechnology Industry Organization's annual conference (BIO 2004). At the time, President Bush had recently announced strict limits on federal funding for embryonic-stem-cell research, and Snyder, like many scientists, sensed the federal government's troubled and hesitant relationship with a field he considered deeply promising.

Then, in September 2002, in an action that Snyder says "sent out a signal to scientists across the country," California passed a bill to explicitly endorse embryonic-stem-cell research, thumbing its nose at the White House in the process. Bush had limited federal funding to the study of currently existing stem-cell lines—research to which the National Institutes of Health (NIH) awarded $24.8 million in 2003—but the California legislation announced that the state would welcome much more expansive scientific inquiry. By early 2003, Snyder had left Harvard and relocated to the Burnham Institute in La Jolla, California, where he now heads the stem-cell-research program. Alliance for Aging Research Executive Director Daniel Perry, calls Snyder a "poster boy for scientists that are willing to pack up and move" over the issue of embryonic-stem-cell research.

Now California has embarked on phase two of its defiance. This November, Californians will vote on a stem-cell ballot initiative that could trigger a far bigger influx of scientific talent while simultaneously providing the closest thing to a popular referendum on the Bush policy. The initiative, Proposition 71, would license a stunning $3 billion public investment in stem-cell research over the next decade, shattering the Bush limit on available lines in the process. The initiative would support both embryonic-stem-cell research and the asexual creation of human embryos for research purposes (research cloning) while also establishing the California Institute for Regenerative Medicine, a kind of mini-NIH. If it passes, Proposition 71 would create a "brain drain within the United States to California," predicts Irving Weissman, a Stanford pathologist and cancer biologist and a leader in the study of "adult" stem cells.

Along with Weissman, other top California scientists, like Nobel laureates Paul Berg of Stanford and California Institute of Technology President David Baltimore, have lined up behind Proposition 71, which proponents promise will more than pay for itself in reduced health-care costs down the road. Also supportive or working on behalf of Proposition 71—supporters of which have already raised more than $7 million to promote the measure—are an array of Hollywood celebrities, disease activists, business groups, and state officials like Treasurer Phil Angiledes. When she spoke up in favor of embryonic-stem-cell research this May, Nancy Reagan found herself flanked by initiative supporters. And Proposition 71 can expect a boost from Kerry's strategists' decision to front embryonic-stem-cell research in the 2004 campaign, handing a prime-time slot during the Democratic national convention to Ronald Reagan's son Ron to promote the issue.

Granted, Governor Arnold Schwarzenegger remains officially agnostic on Proposition 71. And, given the state's money woes, even the initiative's clever funding scheme—using self-financing bonds for the first five years—might fail to appease voters. Yet regardless of its ultimate fate, California's movement toward what *The Wall Street Journal* memorably dubbed "scientific secession" underscores the dramatic failure of President Bush's restrictive policy on embryonic-stem-cell research. In 2001, the president claimed that he supported exploring "the promise and potential of stem-cell research"

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within moral limits. Yet scientists and disease activists have experienced such dramatic constraints under his policy that they've taken a radical step to circumvent it. What they're attempting is unprecedented: relieving the federal government of its responsibility for funding a major area of scientific research, and bestowing that duty on a state.

SCIENTISTS HAVE LONG KNOWN THAT THEIR FAVORITE LAB critters, mice, have both adult and embryonic stem cells. But in 1998, several research papers showed the medical promise of stem-cell research for human beings. Most prominently, biologist James Thompson of the University of Wisconsin published a paper in *Science* magazine revealing that he had isolated cells from the inner mass of human embryos, which had been donated for research from in vitro fertilization (IVF) clinics. The cells could divide indefinitely in culture (i.e., they were practically immortal) and had the potential to grow into every different cell type in the body—they were what scientists call "pluripotent." These attributes suggested that embryonic stem cells could generate a wide range of replacement tissues for human transplantation, potentially leading to cures for degenerative diseases like Parkinson's and diabetes while also fueling deep new insights into the processes of human development.

But there was a catch. To extract the embryonic stem cells, Thompson had to destroy the IVF embryos. With his lab in possession of five embryonic-stem-cell lines derived from this process, a great controversy had officially begun. Soon after his disclosures in *Science*, the Clinton Department of Health and Human Services drafted a legal opinion concluding that the new research could receive federal funding from the NIH. True, for the previous two years the Republican Congress had blocked federal funding of research that destroys human embryos. But the new Clinton opinion identified a loophole in the law: As long as the NIH didn't fund the destruction of embryos, the administration argued, it could fund promising research on cells resulting from that destruction.

In 2001, President Bush publicly agonized over this policy. His constituents, meanwhile, were split: The religious right painted the federal funding of embryonic-stem-cell research as morally wrong because of the necessary destruction of human embryos, but some prominent Republicans, like Orrin Hatch, favored federal funding because of the research's medical and scientific promise. Ultimately Bush opted for a compromise: He would allow federal funding of research, but only on already derived cell lines. Thus, at least arguably, the federal government would not be complicit in the death of any embryos. From August 9, 2001, forward, Bush declared on national television, the NIH could only fund research on embryonic-stem-cell lines "where the life-and-death decision has already been made."

In the same speech, Bush pronounced that "more than 60" lines fit this criterion. Scientists were skeptical, and it soon became clear that the NIH–derived figure referred to stem-cell *derivations*—i.e., every known case in which scientists had removed the inner cell mass of a blastocyst before the Bush deadline. Derivations, however, may not always develop into cell *lines*, which must reliably grow and divide in culture so that scientists can study them in experiments and ship them to colleagues. Stanford professor emeritus of medicine Berg, a strong supporter of California's Proposition 71, vividly explains the problem with many of the so-called Bush lines: "At some point, somebody took a blastocyst from an IVF clinic and cracked it open and poured everything into a vial and stuck it into a liquid nitrogen tank—in which case we don't know if it's a line. And most of them died, and that's why there are so few now."

But the Bush White House, lacking a science adviser at the time, either didn't know or didn't care about the distinction between derivations and lines. "It is clear, in retrospect, that the White House sent Bush out on national television without having vetted (or even understood) the biological status of the cell lines he had embraced as the foundation of his compromise policy," journalist Stephen H. Hall notes in *Merchants of Immortality*, his book on the stem-cell debate. After considerable stonewalling, on September 5, 2001, Health and Human Services Secretary Tommy Thompson admitted to Congress that far fewer lines than promised were ready to be used. On the morning of September 11, *The New York Times* ran a telling front-page story headlined "Scientists Urge Bigger Supply of Stem Cells." A panel from the National Academy of Sciences, the paper reported, had concluded that for science to thrive, more lines would have to receive federal funding. Only the tragedy of 9-11 prevented a far earlier and broader recognition by most Americans of just how flawed the president's decision—and the process leading up to it—had actually been.

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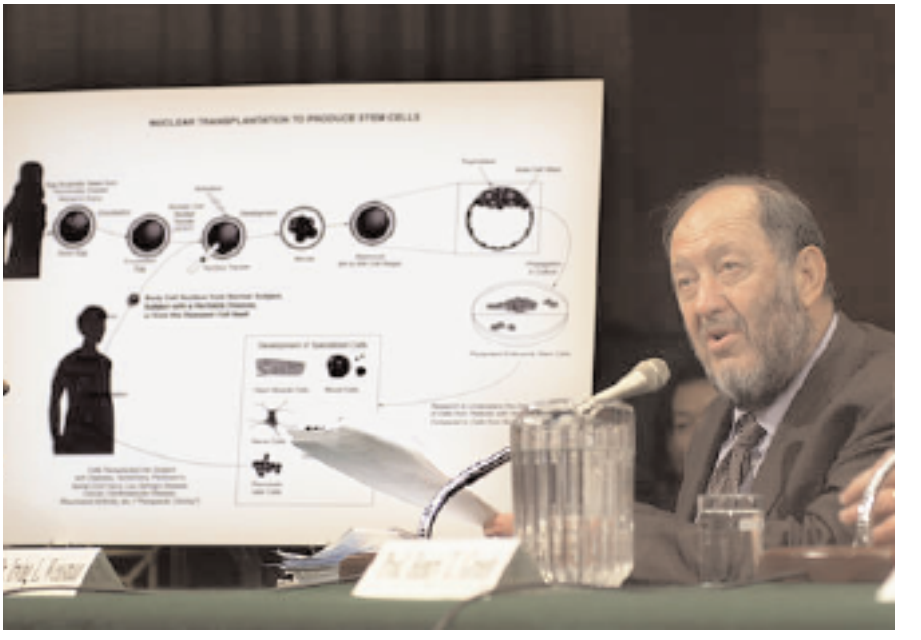
Instead, it took nearly three years, and growing dismay among scientists and politicians, before any government official finally owned up to the limitations the Bush policy placed on research. In March 2004, the NIH admitted that even under the "best-case scenario," only 23 lines would likely ever be available under the Bush policy. And on May 14, 2004, NIH Director Elias Zerhouni wrote in a letter to members of Congress that "from a purely scientific perspective, more cell lines may well speed some areas" of scientific study. As of this writing, scientists can only obtain 21 of the promised lines, and even that number exaggerates how many they work with regularly. "Realistically, it's probably only six or seven that people really use and feel comfortable with," says Snyder.

GIVEN THIS HISTORY, WE SHOULD HARDLY BE SURPRISED at the shortcomings of a policy that claims to support scientific inquiry. One problem, as Evan Snyder explained to me over coffee in the Argent Hotel's jazz bar, is what we might

call the "laptop analogy." As I struggled to type down everything Snyder had to say, he paused and gestured toward my computer. "Can you promise me that when we meet three years from now you're going to be using the same laptop?" Snyder asked. Of course not, he continued. Bush's policy precluded the funding of lines derived in later years through more advanced culturing and derivation techniques, or with different genetic makeups. It froze science in time.

What's more, because all of the Bush-approved lines come from IVF clinics, they hardly represent the genetic diversity of America. Rather, they contain the genes of affluent, mostly white Americans with fertility problems. Without a wide array of genetically distinct embryonic-stem-cell lines, scientists could find themselves inclined to wrongly infer that the quirky behavior of a few individual lines reflects the nature of embryonic stem cells in general. Moreover, because the lines come from embryos left over from IVF treatment—i.e., they were not chosen for implantation—scientists suspect they may have been flawed or undesirable to begin with. "They're not perfect in a family that already has a medical problem," says Snyder.

And perhaps most devastatingly, if embryonic-stem-cell research truly aims at curing disease, the existing lines probably cannot support that goal. All of the currently available 21 lines grew on a layer of "mouse feeder cells," raising concerns about potential viral contamination that makes the developed cells potentially unsuitable for transplantation into patients. Scientists have begun to develop culturing techniques that don't rely on mouse-feeder layers. Lines produced in this manner, however, won't qualify for federal funding in the United States.



Charting New Territory: Irving Weissman testifies before the Senate, February 2002.

AP/WIDE WORLD PHOTO

From the standpoint of understanding and ultimately curing diseases, the existing lines have yet another deficiency, as Irving Weissman explained to me last June when we met in his office at the Stanford University School of Medicine's Beckman Center. Ideally, Weissman said, scientists would like to have pluripotent stem-cell lines containing the genes of a diabetic, an Alzheimer's patient, someone with cystic fibrosis, and individuals suffering from various types of cancer—basically, a stem-cell line for virtually every disease. Then, by injecting the human cells into living mice and watching them grow, scientists could observe the step-by-step evolution of the disease over the short life span of a mouse rather than the long life span of a human. "You might be able to start to understand, especially with complex genetic diseases like Lou Gehrig's, which gene goes wrong in which order to cause that disease," says Weissman.

The problem is, these disease-specific cell lines can't come from embryos derived from fertility clinics, as the federally approved lines do. Instead, they would have to be obtained through the process of somatic-cell nuclear transfer, sometimes called "therapeutic cloning." It's simple: Find someone suffering from a given disease, extract the nucleus from one of their body cells, implant it in an unfertilized egg, get the egg to start dividing, and then extract pluripotent stem cells from it to start a line. Weissman says this technology could dramatically contribute to our understanding of diseases. Proposition 71 would support it. By contrast, Bush and his conservative allies want to criminalize the process out of the questionable fear that it could lead to reproductive cloning (which the Food and Drug Administration and many states have already banned anyway). "Whoever of you acts to ban this research is responsible for the lives it could save," Weissman warned legislators at a recent Senate hearing.

Meanwhile, the rest of the world is making strides. In February, South Korean researchers published a paper showing that they had derived human-research embryos through cloning and extracted stem cells from one of them. Great Britain, one of the most advanced nations in embryonic-stem-cell research, recently opened a new U.K. Stem Cell Bank. Other countries, from Australia to the Czech Republic, have also invested significantly in the science. In May, *The Boston Globe* conducted a survey and found 51 lines worldwide (though the article did not specify their states of development). In fact, the *Globe* predicted the possibility of "more than 100" global lines by the end of 2004. One of the lines, the *Globe* reported, has the genetic mutation causing cystic fibrosis, the first of potentially many such disease-specific lines. But no research on those lines will be able to be funded in the United States.

DESPITE THE OBVIOUS FLAWS OF THE BUSH POLICY, conservatives claim that the Bush lines suffice for research, that the promise of embryonic-stem-cell research isn't all it's cracked up to be anyway, and that adult stem cells can substitute for embryonic ones for research purposes. To prove their case, they rely on fringe scientists (or nonscientists),

ignoring the views of leaders in the field. Consider, for example, a lengthy article published recently in the *National Review Online* by Eric Cohen, a consultant to the President's Council on Bioethics. Cohen argued that "at least for now, the number [of lines available under Bush's policy] continues steadily to increase." He also argues that embryonic-stem-cell research has been hyped: "The promise of embryonic-stem-cell research is very real but wholly speculative. No human therapies of any kind have yet been developed or tested, and none are on the horizon."

I read this passage to Paul Berg, who observed, "[I]t's a phony argument because it says, 'Show me, even though I told you you're not allowed to do the experiments.'" Berg added that while the human applications do not yet exist, scientists have differentiated mouse embryonic stem cells into insulin-producing beta-islet cells, and used those cells to cure diabetic mice. They have also differentiated them into dopamine-producing neurons, thereby relieving symptoms of Parkinson's in mice.

Some conservatives also argue that that uncontroversial adult stem cells can substitute for embryonic ones. At a recent hearing hosted by anti-abortion Senator Sam Brownback, the Kansas Republican promised the audience that "today's hearing is about miracles," and "today you will see answers to prayers." Human adult stem cells have certainly led to treatments, and will likely lead to more. Yet the argument that adult stem cells can replace embryonic ones for research purposes requires us to forget everything scientists know about human development—i.e., that once cells become specialized, they generally can't go back. No one has successfully shown that adult stem cells, located in the brain, bone marrow, and other organs, have the same potential to form all cell types that embryonic cells have—the very pluripotency that made these cells such a scientific holy grail in the first place.

But not everyone in the Republican Party has fallen in line with conservative pseudoscience. In late April, 206 members of the House of Representatives, including 36 Republicans, charged that Bush's rules were stifling research. Then Nancy Reagan spoke out passionately in support of allowing embryonic-stem-cell research to proceed without any more time lost. Soon a bipartisan group of 58 U.S. senators had joined the bandwagon.

Meanwhile, states and private-funding sources have sought to get around the Bush policy, or find a substitute for it. Like California, though on a smaller scale, New Jersey has signed a law encouraging embryonic-stem-cell research, and Governor James McGreevey has announced a $50 million plan over five years to support the work. At Harvard, based on research supported in part by the Juvenile Diabetes Research Foundation, stem-cell ace Douglas Melton announced in March the creation of 17 new embryonic-stem-cell lines, which he would share freely with scientists internationally and here in the United States. Scientists can work on these lines with private funding—if they can get it—but not with federal taxpayer dollars. (The Juvenile Diabetes Research Foundation, one of the biggest private donors, has committed $6.3 million for embryonic-stem-cell research for 2004. For their part, biotech and pharmaceutical firms are mostly avoiding stem-cell research, scared by the investment uncertainty that accompanies political controversy.)

Of all of these rebellious developments, the California initiative is, without doubt, the most dramatic in scope and possibility, as I quickly learned during my trip to San Francisco in June. There I spoke to initiative mastermind and disease advocate Robert Klein on the press balcony at BIO 2004, just above a noisy floor of exhibits where various biotechs hawked their wares to peers and potential investors. A Palo Alto real-estate developer who has sunk more than a million dollars into the initiative and whose son Jordan suffers from juvenile diabetes, Klein passionately explains why California is the only state massive enough to fill a science funding gap created by the federal government—and why he thinks support exists in the state to pass Proposition 71. "There are 12 million Californians who are members of patient-advocacy groups because they have a family member suffering from chronic disease or injury," he told me. In other words, in crafting a policy that appeased religious conservatives, President Bush may have underestimated an equally motivated constituency: disease activists, whose lives, or whose children's lives, are on the line.

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For Klein, the current stem-cell struggle has an important historical analogue. The year 1975 marked the advent of recombinant DNA technology, a.k.a genetic engineering. Religious groups and others, afraid of scientists "playing God" or creating horrific chimeras, quickly pushed for a ban. Congress held hearings, but thanks to lobbying from scientists and biotech entrepreneurs, did not restrict the research. Recombinant DNA went on to lay the groundwork for the Human Genome Project and the entire biotechnology industry, plus genetic screening and DNA evidence in courtrooms. "It was a platform technology that changed all of life sciences, caused the development of biotechnology, and hundreds of thousands of people's lives every year are saved from the use of that," says Weissman. (Berg won the Nobel Prize in chemistry in 1980 for his work in pioneering the discovery of recombinant DNA.)

Now scientists like Berg, Weissman, Snyder are saying, once again, that they found a line of research that will transform medicine. Politicians will have a hard time ignoring their advocacy. I asked Klein what he expected from Governor Schwarzenegger—previously a supporter of stem-cell research—when it came to the initiative. Klein's response: "a phone call" in support of the measure. If the recent behavior of other Republicans on the stem-cell issue provides any indication, he may be right. ■

CHRIS MOONEY *is a* Prospect *senior correspondent.*