

# After the gold rush

California's voters have authorized the spending of \$3 billion over the next decade on stem-cell research.

But will this bonanza bring threats as well as opportunities? Peter Aldhous weighs the hopes and fears.

**B**ob Klein is a man in a hurry. This energetic 59-year-old entrepreneur rose to public prominence last year, spearheading the campaign that convinced California's voters to back an audacious plan to create a \$3-billion public fund to advance research on human stem cells. Interviewed by *Nature* in late February, he was determined to press ahead as soon as possible: "My goal would be to approve the first grants in May."

But today Klein and his supporters are wrestling with the practical realities of building their multibillion-dollar research agency, called the California Institute for Regenerative Medicine (CIRM), from scratch, while fending off political and legal attacks from both long-standing opponents and former allies. It's already clear that Klein's May deadline will be missed by several months.

Stem-cell biologists are looking forward to the injection of funds, whenever it finally

arrives. But some question whether the CIRM can spend the huge sums at its disposal without wasting money on second-rate research. Some also fear a public backlash against stem-cell research, as claims about 'cures' made during the ballot campaign may have left people with unrealistic expectations. Others worry that the initiative has set a dangerous precedent by moving the centre of gravity of an important area of biomedical research away from the federal government, and subjecting it to the shifting winds of state electoral politics. Indeed, with several other states following California's lead and providing budgets for stem-cell research (see map, opposite), an unprecedented shift in the balance of power is under way. And biologists are divided on its likely consequences.

The CIRM's legal and political difficulties centre on its governance, which is unusual for a state agency. The stem-cell ballot initia-

tive, known as Proposition 71, placed the agency under the control of a 29-person citizens' committee with little input from California's legislature. The committee, chaired by Klein, includes representatives of the biotech industry and academic institutions likely to receive CIRM funding.

## Under attack

Lawsuits have been filed denouncing the CIRM as unconstitutional. These have been denied a hearing in the California Supreme Court, but the battle will resume in lower courts, and could yet interfere with the institute's plans to begin distributing money. Meanwhile, state senators Deborah Ortiz, a Democrat, and George Runner, a Republican, have said that they will press for a new ballot initiative to "reform" the stem-cell programme. Ortiz backed Proposition 71, but has since criticized the initiative's procedures for accountability

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**Washington** A proposed law, which has passed one chamber of the state legislature and will be up before the other by mid-April, would ban cloning for reproduction but support it for research. Democratic governor Christine Gregoire — voted into office last autumn by the skin of her teeth — supported embryonic stem-cell research during her campaign.

**Wisconsin** It was here that biologist James Thomson did the pioneering work that made the field of human embryonic stem-cell research possible. Last November, Governor Jim Doyle proposed a massive spending boost for biotechnology, with a \$750-million package for work including stem-cell research. The proposal includes \$375 million for a Wisconsin Institute for Discovery at Thomson's home base, the University of Wisconsin at Madison.

**Illinois** State officials hope to create a \$1-billion Illinois Regenerative Medicine Institute this year, which would do stem-cell work and be financed by a tax on elective cosmetic surgery. The measure passed an initial hurdle in the state legislature on 17 March, but still has a long way to go.

**New York** Bills in favour of embryonic stem-cell research have died in the Republican-controlled Senate over the past few years. The Assembly has now proposed spending \$100 million in 2006 on the work. The measure faces an uphill battle which should play out by June.

**Massachusetts** With some of the most respected stem-cell researchers in the world, and a multimillion-dollar private stem-cell research foundation already set up, the Bay State looks set to pass a law explicitly supporting stem-cell research. In late March, the House passed a bill authorizing therapeutic cloning for medical research by a two-thirds majority — enough to override a veto expected from the state's Republican governor.

**Connecticut** The governor has proposed \$20 million over two years for stem-cell research. Scientists at Yale University and the University of Connecticut are lobbying for even more — up to \$100 million over ten years.

**New Jersey** Last year, New Jersey beat California to the punch to create the first state-funded, dedicated stem-cell research centre, the Stem Cell Institute of New Jersey. Building should begin this August. The state has already devoted \$11.5 million to the institute, and the governor is lobbying for an additional \$380 million for the next seven years.

**Maryland** Lawmakers are considering a \$23-million spending bill for embryonic stem-cell research. As *Nature* went to press, the bill had passed the House but not the Senate.

**Virginia** The state's legislature has established a research fund in the name of actor and stem-cell research advocate Christopher Reeve. But it will not fund work on human embryonic stem cells.

**California** Proposition 71 has devoted \$3 billion over the next ten years to stem-cell research.



■ Legislation prohibits cloning for research purposes  
■ Legislation on cloned embryos for research unclear or absent  
■ Legislation supports therapeutic stem-cell research, including on cloned embryos

Source: National Conference of State Legislatures, March 2005

and avoiding conflicts of interest.

Assuaging these concerns will test Klein's powers of persuasion. But there's no doubting his personal commitment to the cause. Having made his fortune providing quality low-cost housing in the state, Klein ploughed \$3 million of his own money into the Proposition 71 campaign. And he makes no secret of his hope that stem-cell research will help his 14-year-old son, who has juvenile diabetes. Klein recalls a 2002 conversation with his son: "He said, 'Dad, don't worry about me. Everyone is dying. I'm just dying a little faster.' For a father, that's not something you can live with."

Klein's heart-on-sleeve demeanour and boundless energy were just what was needed in winning support for Proposition 71. But setting up a new research agency demands the skills of a consummate scientist-administrator, which he is not. Headhunters are still drawing up a shortlist of candidates for the key position of president of the CIRM. In the

interim, the post has been taken by Zach Hall, whose previous roles include directing the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

Hall has already begun to temper Klein's enthusiasm with a dose of caution, noting that the practical challenges of setting up a review process rule out the initial goal of approving some grants in May. "We still don't have our working groups appointed," says Hall. "In the fall we might be able to approve our first grants."

The CIRM's main goal is to support research that either can't be backed by the federal government, or is unlikely to receive "timely or sufficient" funding. Although the US Congress has recently considered the question of loosening federal rules<sup>1</sup>, the regulations currently limit federal dollars to work on the 78 human embryonic stem-cell lines created before August 2001. Many of the lines that seem most promising for

research were isolated after this date. Researchers also say they need new cell lines that haven't been grown on a layer of mouse cells, as this causes biochemical contamination that will rule out their eventual use in human therapies<sup>2</sup>.

So the CIRM's top priorities will include the creation of new embryonic stem-cell lines, mostly from embryos left over from *in vitro* fertilization procedures, but also from embryos created by cloning. In addition to investigating the feasibility of 'therapeutic cloning', in which a patient's own cells might be used to derive grafts to replace damaged tissues, cloning can be used to create embryonic cell lines from patients with genetic diseases — which could prove invaluable for understanding these conditions and testing potential treatments<sup>3,4</sup>.

Biologists also want to investigate the basics, such as how stem cells arise in the developing embryo, and which signals coax

them into developing into different tissue types. "I think everybody agrees that more fundamental work needs to be done," says Evan Snyder, a stem-cell biologist at the Burnham Institute in La Jolla. "This is an initiative to move the field forward in an unencumbered way."

Researchers will have to be careful to ensure that work involving non-approved cell lines is strictly separated from projects involving federal grants. In the long run, the CIRM may provide funding to build new labs to help this separation. But Klein wants to avoid delay, by leasing space lying empty in the San Francisco Bay Area and other cities. "There are lots of opportunities," he says.

Maybe so, but experts in the field point out that relatively few researchers currently have expertise in working with human embryonic stem cells. And this, some biologists argue, makes it unwise to pour hundreds of millions of dollars into this area any time soon. "A lot of money could be wasted on what is not the best work," warns Sean Morrison, a stem-cell biologist at the University of Michigan in Ann Arbor.

Institute officials say that maintaining quality will be their priority, adding that their efforts won't be entirely focused on embryonic stem cells. The CIRM will support work on adult stem cells, and fund research into other questions that must be addressed to bring stem-cell therapies to the clinic. The agency might also choose to back specific therapeutic strategies that have been neglected by the federal National Institutes of Health (NIH), Klein argues.

### Firm foundations

Klein adds that researchers have difficulty winning grants from the NIH in a young field such as stem-cell research, as it's difficult for them to gather enough preliminary data to make a case for serious study. "Some of the brightest minds cannot get access to funding," says Klein. So part of the CIRM's strategy will be to provide 'seed' money to allow researchers new to the field to gather sufficient results for a convincing full grant application. And the agency's first awards are expected to be for academic institutions across California to hire graduate students and postdocs. "What we're calling for here is a vast expansion of the intellectual and scientific workforce," says Hall.

Biologists welcome this emphasis on bringing young researchers into the field. But some are anxious about the CIRM's wider effects on the US funding landscape. With other states pitching in, the momentum in stem-cell research is shifting away from the federal government — and opinion is divided on whether that's a good or a bad thing.

"This represents a paradigm shift in how biomedical research gets funded in this country," says Snyder. "It could turn out to be a really wonderful opportunity." But other

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**Too much, too soon? Some scientists are worried that the election campaign for Proposition 71 oversold the state of stem-cell research.**

biologists see potential threats. For one thing, state activity is likely to provoke opponents of embryonic stem-cell research in the federal government into further action. 'Pro-life' conservatives in the US Congress will almost certainly resume legislative attempts to ban all human cloning procedures, whether for reproduction or research.

But the deeper concern is that the Bush administration and its congressional allies will let the states take the lead, and scale back funding for the NIH. The agency's budget is already under pressure, given Bush's programme of tax cuts and the cost of the Iraq war, and the biomedical research community knows that it can't expect many favours. "I am worried that the willingness of states to take up the slack is going to absolve the federal government of its responsibilities in this area," says George Daley, a stem-cell researcher at Harvard Medical School in Boston.

Many biologists are concerned about the implications of the NIH having a reduced role in stem-cell research. They respect the federal agency's procedures for backing scientific excellence and adhering to rigorous ethical standards. And although Hall says that the CIRM plans to import many NIH procedures, the institute and the other state funding mechanisms are still unknown enti-

ties. "The less the NIH is involved in something, the less assurance we have that good ethical guidelines are followed," observes Jon Retzlaff, director of legislative relations with the Federation of American Societies for Experimental Biology.

### Hope or hype?

Another worry about putting stem-cell research in state hands is that it may be more vulnerable to the ebb and flow of public opinion. And this, some researchers fear, may be set for a backlash. The use of the slogans "cures for California" and "save lives with stem cells" during the Proposition 71 campaign may have set public expectations too high, they say. Disappointment could result if treatments fail to emerge rapidly, or if patients suffer adverse events in clinical trials — as has happened in the field of gene therapy<sup>5</sup>.

"I think there was a concern about promising too much, even before Proposition 71," says Gordon Keller, a stem-cell biologist at the Mount Sinai School of Medicine in New York. "My fear is that there are people who will try to move forward quicker than they should, and that could backfire very badly."

The media are already alert to this possibility. A 23 February article in *The New York Times*, for instance, questioned whether a planned clinical trial to use human embryonic stem cells to treat spinal injury is going "too far, too soon into uncharted territory". The trial, which could begin next year, is based on the work of Hans Keirstead of the University of California, Irvine, who has shown that embryonic stem cells can be made to differentiate into cells that help to maintain and protect neurons<sup>6</sup>.

Keirstead took a prominent role in the Proposition 71 campaign, discussing unpublished experiments in which spinal-injured rats were made to walk again. "It has never been my intention to contribute to the hype," says Keirstead, who stresses that he doesn't expect to see similarly dramatic results in human patients. But such subtleties were lost in the frenzy of the campaign. Some Californian stem-cell researchers say that they are now planning outreach activities to help manage public expectations.

Indeed, some researchers who are gearing up to receive CIRM funding feel a heavy burden of responsibility. "A lot of people do feel accountable here in California," says Fred Gage, a stem-cell researcher at the Salk Institute for Biological Studies in La Jolla. "We want to make sure that it's done right, because we're under the microscope." ■

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