HOPE ON THE LINE

A decade ago, voters in California changed the biomedical research landscape by directly funding embryonic stem-cell research. Now the organization they created needs a hit to survive.

BY ERIKA CHECK HAYDEN

On a brilliant day in April, tens of thousands of baseball fans stream past Jonathan Thomas's office towards AT&T Park for the first home game of the San Francisco Giants 2014 season. Thomas's standing desk faces away from the window, but the cheering throngs are never far from his mind.

Thomas chairs the board of the California Institute for Regenerative Medicine (CIRM), the US\$3-billion agency hailed by scientists around the world for setting a benchmark for stem-cell research funding. But scientists will not be the ones who decide what becomes of CIRM when the cash runs out in 2017. Instead, it will be the orange-and-black-clad masses walking past Thomas's window. And to win their support, Thomas knows that the agency needs to prove that their collective investment has been worthwhile. "We need to drive as many projects to the patient as soon as possible," he says.

Californians voted CIRM into existence in 2004, making it the largest funder of stem-cell work in the world. The money — the proceeds of bond sales that must be repaid with \$3 billion in interest by taxpayers

— helped to bring 130 scientists to the state, and created several thousand jobs there. It has funded research that led to the publication of more than 1,700 papers, and it has contributed to five early clinical trials.

The institute has navigated a difficult path, however. CIRM had to revamp its structure and practices in response to complaints about inefficiency and potential conflicts of interest. It has also had to adapt its mission to seismic shifts in stem-cell science.

Now, ten years after taking off, the agency is fighting for its future. It has a new president, businessman Randal Mills, who replaces biologist Alan Trounson. Its backers have begun to chart a course for once again reaching out to voters, this time for \$5 billion (with another \$5 billion in interest) in 2016. And it is under intense pressure to produce results that truly matter to the public.

Whether or not CIRM succeeds, it will serve ►

Patient advocates and parents at a 2012 meeting in which US\$100 million in CIRM grants were approved.

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STATE OF FUNDING

Since its birth in 2004, the California Institute for Regenerative Medicine (CIRM) has developed a unique mechanism to support research on stem cells.

as a test bed for innovative approaches to funding. It could be a model for moving technologies to patients when conventional funding sources are not interested.

Much of what is celebrated and lamented about CIRM can be traced back to the Palo Alto real-estate developer who conceived of it: Robert Klein. Although officially retired from CIRM — he chaired the board from 2004 to 2011 (see ‘State of funding’) — Klein’s office is adorned with mementos of the agency: a commemorative shovel from the groundbreaking of a CIRM-funded stem-cell research centre, and a photo of him with former governor Arnold Schwarzenegger at the ribbon-cutting ceremony.

It was Klein’s idea to ask voters to support stem-cell research in 2004, through a ballot measure called Proposition 71. When he succeeded, CIRM instilled a kind of euphoria in stem-cell scientists, who were at the time still reeling from a 2001 decree by then-President George W. Bush that severely limited federal funding for embryonic-stem-cell research. California’s commitment removed this roadblock and revealed that many in the state and the country supported the research.

“Before CIRM, the conversation was about where to draw restrictions on embryonic stem-cell research,” says Sean Morrison, a stem-cell and cancer biologist at the University of Texas Southwestern in Dallas. “Once the California voters supported CIRM, the conversation shifted to how the rest of the country could keep up.” Indeed, five other states went on to set up stem-cell-research agencies.

PLANNING THE SEQUEL

One afternoon, Klein doodles on a legal pad as he lays out the case for ‘CIRM 2’. He writes the word ‘scientists’, then draws a box around it. Science, he says, is more under attack than ever before. President Barack Obama might have loosened the restrictions on federal funding for embryonic-stem-cell research in 2009, but some presidential hopefuls — one of whom could be elected in 2016 — support reinstating the Bush-era restrictions or even an outright ban on funding the work. Klein points out that 26 states are led by legislatures that oppose the research.

Moreover, funding for the National Institutes of Health (NIH) has taken a hit and the agency closed its Center for Regenerative Medicine in April (see *Nature* 508, 157; 2014). This is the case that Klein plans to lay before the voters. “We have to protect science’s access to the full range of cellular types now,” he says. “And in doing that, we will protect the freedom of science to ethically pursue knowledge in this country outside of religious ideology.”

His focus on a ‘full range’ of cells reflects the ways in which the stem-cell field has blossomed in the past decade, changing in ways that no one expected when Klein first proposed CIRM. And the biggest breakthroughs have come from outside California. A Japanese group, for example, discovered how to create induced pluripotent stem (iPS) cells (K. Takahashi & S. Yamanaka *Cell* 126, 663–676; 2006), which can be tailor-made from patients without the use of embryos. And scientists in Oregon managed to clone a human embryonic stem-cell line by nuclear transfer (M. Tachibana *et al.* *Cell* 153, 1228–1238; 2013).

Some treatments are progressing faster outside California, too. Japan, for instance, has raced ahead of the rest of the world in testing iPS cells as therapies for conditions such as age-related macular degeneration, which can cause blindness (see *Nature* 494, 413; 2013).

But in California, researchers are making nerve, heart, eye and skin cells from iPS cells and embryonic stem cells — a range of work rare for a single state — and they aim to test many of these in humans. They are developing drugs against cancer stem cells, which are thought to perpetuate the disease. And they are leading the world’s only two trials of treatments that combine gene editing and cell therapy to treat HIV. They are doing all this with an unmatched infrastructure, including a network of 12 new or newly renovated facilities, and a funding pipeline that acts as a beacon to young scientists.

“Almost every country would be jealous of what they’ve got in California,” says Christine Mummery of the Leiden University Medical Center in the Netherlands. Top-flight scientists such as Clive Svendsen, formerly at the University of Wisconsin–Madison, have flocked to the state, she says. But, she adds, “they haven’t cured a patient, which is the critique”.

That critique frequently bubbles to the surface. On 22 January, Thomas and CIRM’s senior vice-president of research and development, Ellen Feigal, faced uncomfortable questions from the state’s Citizens Financial Accountability and Oversight Committee at a meeting in Los Angeles. Committee member Jim Lott — a health-care executive and father of a 13-year-old daughter with a spinal-cord injury — grew frustrated as he listened to the pair run through PowerPoint slides full of numbers and abstract language touting the agency’s scientific accomplishments. None of the slides told him what CIRM had done that would get his daughter out of her wheelchair. He had asked the question before, and there was still no answer. “I’m telling you, pal,” Lott told Thomas, “I would have a hard time voting for it again.”

Lott says that he knows that CIRM is doing worthwhile science, but it is not doing a good job explaining how the science fulfils the promises of cures that were made in the Proposition 71 campaign.

“They think that people should understand that this is good work that they’re doing, and that should be compelling enough to continue it,” he later explained. “But that’s just not a realistic view.”

And it is not just parents who have raised concerns. A 2012 report from an Institute of Medicine panel, for instance, opined that CIRM’s ambitious translational goals were “unrealistic”. Only the year before, the California company Geron of Menlo Park had halted a CIRM-funded trial that was the first major test of human embryonic stem cells after deciding to focus on cancer treatments.

Klein says that the \$34-million campaign he organized to promote Proposition 71 never promised cures in ten years. But the proposition’s supporters frequently mentioned cures — for instance, in the state’s official voter information guide, where they said that “PROPOSITION 71 IS ABOUT CURING DISEASES AND SAVING LIVES”. CIRM is now working mightily to provide evidence to sway Lott and people like him.

A big part of CIRM’s translational aspirations has been wrapped into \$450 million in disease-team awards — funds that aim to mimic the

CIRM work of early-stage biotechnology companies by spurring groups of scientists to move discoveries into clinical trials. To give the scientists who spearhead the teams expertise and guidance, it created a panel of industry and regulatory experts that meets with each disease team at least once a year to help to nudge them along.

And CIRM has made a series of changes to focus more on its translational mission. In May, it awarded Asterias Biotherapeutics in Menlo Park \$14 million to continue testing the product Geron had abandoned. Realizing that it would need to boost the odds of success, CIRM adjusted its portfolio to free up more cash and prioritize the projects most likely to succeed. In 2013, for instance, it cut funding for shared lab spaces and basic research, and set aside \$200 million to accelerate work by existing disease teams.

MATCHMAKER EXTRAORDINAIRE

Scientists who have benefited from these programmes say that CIRM's approach feels fresh. In 2008, for instance, it asked two groups — one led by immunologist Jeffrey Bluestone at University of California, San Francisco, the other led by the company ViaCyte in San Diego — to work together on a project to transplant insulin-producing cells derived from embryonic stem cells into people with diabetes. Bluestone worried that patients' immune systems might destroy or overreact to the cells, and had animal data showing that packaging the cells in some kind of container would prevent harmful immune reactions. So ViaCyte developed a porous membrane made from materials similar to those in medical

"I'M TELLING YOU, PAL, I WOULD HAVE A HARD TIME VOTING FOR IT AGAIN."

implants, into which it packed the cells. The company is now working with the US Food and Drug Administration to design a clinical trial.

"I don't think ViaCyte would be where it is today had there not been a partnership," Bluestone says. The NIH does not typically suggest that potential grant recipients — especially from academia and industry — pool their proposals in this way.

Irving Weissman, who heads the Institute of Stem Cell Biology and Regenerative Medicine at Stanford University in California, received a \$19-million CIRM disease-team award to work with colleagues in the United Kingdom and develop an antibody-based therapy for leukaemia. The team developed an antibody, tested it in animals, and in December received \$13 million more from CIRM for human safety trials.

Weissman says that CIRM funding has allowed science, rather than a focus on the bottom line, to drive the project. They were able to work on two potential approaches, for example, increasing the chance of a successful therapy. He says that this would be "unheard of" elsewhere. "In every biotech company, the money makes all the decisions — not the scientists."

Yet some have argued that CIRM puts too much power in the hands of scientists and others who have an inherent stake in its work. In its report, for instance, the Institute of Medicine said that CIRM's "built-in allocation of board seats to university leadership, patient advocates, and members of the biotechnology industry, for example, ensured that a high percentage of those seats would be permanently occupied by persons with almost unavoidable, conflicts of interest". In response, CIRM changed its rules so that board members whose institutions might receive money through CIRM programmes cannot vote on specific grants or funding issues.

The decision, made in March, came after years of complaints about potential conflicts on CIRM's 29-member oversight committee. This committee approves grant initiatives and awards, but one-third of it comprises administrators from academic institutes who receive the money (see *Nature* 453, 18–21; 2008). That kind of problem has plagued other efforts as well. The only other US state research funding initiative that rivals CIRM's size, the \$3-billion Cancer Prevention and Research Institute of Texas (CPRIT) has also been criticized over conflict issues, such as allegations that it awarded funds to preferred scientists without appropriate peer review (see *Nature* 486, 169–171; 2012).

Observers say that these seem to be common pitfalls of creating large state science initiatives. "Both CIRM and CPRIT have faced the reality that you can get into situations that create concerns about interest groups," says Aaron Levine, a member of the Institute of Medicine panel and a political scientist at Georgia Tech in Atlanta. On the whole, though, he adds, CIRM "has done a good job of awarding grants fairly".

Scientists who receive those grants argue that CIRM should continue to exist, but some are sanguine about the prospect of losing the funding. "In ten years more, we'll find out if CIRM's gamble pays off," Svendsen says. "But even if CIRM stops funding, we have enough preliminary data of some efficacy of stem cells that we'll continue getting funding from the NIH, wealthy donors and industry."

Thomas is trying to tap some of those sources to raise between \$1 billion and \$2 billion to help scientists to finish ongoing clinical trials if the agency closes and they run out of money. But if Klein can help it, that will not be a problem. He sees CIRM 2 as a way to tackle what he views as an ever-intensifying war on science. "If we don't take a position now," he says, "the next ten years may see a theocratic government at the state and federal level that restricts scientific research in this country for the next 50–100 years."

It is a shift in the message from 2004, designed to appeal to Californian pride and values. But clearly, it will resonate more if broadcast alongside ads of healthy, smiling patients who have been helped by CIRM. As one board member, former Hollywood executive Sherry Lansing, declared at a meeting in December, "We need a home run."

The point resonates back in Thomas's office as Giants fans head for the baseball stadium. They will cheer for a routine hit or a nice defensive play. But the only sure way to bring them screaming to their feet will be to slam the ball out of the park. ■

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