

The impatient ADVOCATE

Bob Klein founded the California Institute for Regenerative Medicine, the biggest state-run research project in US history. What legacy will he leave behind?

BY ELIE DOLGIN

James Harrison had just stepped out to grab a sandwich when his mobile phone rang. Bob Klein, chairman of the California Institute for Regenerative Medicine (CIRM), was on the line telling Harrison, the agency's legal counsel, to skip lunch and come back to the office right away. It was 23 August, and a district court judge in Washington DC had just issued an injunction barring the use of federal grant money for human embryonic stem-cell research. At that instant, CIRM became the world's largest funder of such research, and needed to issue a public statement.

At CIRM headquarters in San Francisco's Mission Bay neighbourhood, executives from legal and communications branches soon gathered around the long, white board table in Klein's corner office. Klein sat at the head. The mood in the room was bittersweet, he says — a mixture of concern about the setbacks to stem-cell science and to CIRM-funded researchers who also received federal money, and vindication that at least Californian research dollars would continue to flow. The injunction — coming six years after Klein first convinced voters in California to fund embryonic stem-cell research despite major political and religious opposition — “became a huge reinforcer of the conclusion that [CIRM] is a critical safeguard for science”, Klein says.

As always, Klein took charge. He listened attentively to the advice of his colleagues and then delegated tasks. He asked the legal team to draw up an analysis of the decision's impact on CIRM grant recipients while he worked with the agency's press officer to issue a public statement that captured the nuanced emotion in the room. The agency “deplores the decision”, the statement read, although the injunction “points to the importance of CIRM's California model of sustained funding”.

“It illustrated to me what Bob does best,” recalls Harrison, “which is to bring people together and respond to crisis in a very thoughtful and intelligent way.”

On 17 December, however, Klein is stepping down as chairman of

the board — a position he has held since CIRM's inception. He leaves behind an agency with a long list of accomplishments, including more than US\$1.15 billion in grants, six new facilities dotted across the state and close to 700 scientific papers (see “Top earners”).

Yet many critics say that Klein and CIRM have failed to fully deliver. Despite promises that money borrowed from the state — at least \$6 billion over ten years, when interest is factored in — would be returned through commercial spin-offs and savings to health care, the first marketable therapies have yet to materialize. Only two CIRM-funded projects have made it to early-stage clinical trials, and neither of these involves embryonic stem cells — the main impetus for launching the agency in the first place. The embryonic stem-cell clinical trials that have recently been approved in the United States are the product of privately funded research.

Klein's critics say his promotion of stem cells' therapeutic promise was zealous and oversimplified. He “left voters with the impression that people will be jumping out of their wheelchairs and not being diabetic within a year”, says John Simpson, a long-time observer and critic of the agency's governance, who is at the consumer-advocacy group Consumer Watchdog based in Santa Monica, California. “There's been this constant compulsion for [Klein] to say, ‘See, we're delivering, we're delivering’, and that's something that's haunted him throughout the whole thing.”

Throughout CIRM's existence, Klein has pulled the strings, maintaining control over nearly every aspect of its structure and science, often to the chagrin of its other leaders. Still, many observers say that no one else could have weathered CIRM's early storms. “With Bob, there's always this indefatigableness,” says Douglas Wick, a movie producer and diabetes advocate who worked with Klein to get CIRM funded.

Bob Klein in front of the recently dedicated Lorry I. Lokey Stem Cell Research Building at the Stanford University School of Medicine in California.

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“His personal energy and charisma are so strong, and he has this ability to get punched, stand up and go at it again.”

Klein was a Stanford-educated lawyer who had made millions in real-estate development when, in September 2001, a week after the terrorist attacks on the Twin Towers and the Pentagon, his youngest son Jordan was diagnosed with type 1, or juvenile-onset, diabetes. Klein was devastated. “It’s a life-changing shock when you know your child’s life is in danger,” he says.

THE THREE FAMILIES

Klein wanted to speed the search for cures. “I thought, ‘we’ve got to get some broader-based research funding.’” He soon approached the Juvenile Diabetes Research Foundation International (JDRF) in New York to ask how he could help. Klein had some political experience from working with the state and with the national Democratic Party on housing issues. And in 2002, he put it to use, leading the JDRF’s efforts in lobbying Congress to pass a \$1.5-billion federal funding measure to support diabetes research. The experience of getting that bill approved, Klein says, “demonstrated to me that dedicated, well-informed, focused patient advocacy could be very effective.”

By that time, US President George W. Bush had imposed tough restrictions on federal funding for human embryonic stem-cell research. Convinced that such research offered the best hope for reversing his son’s disease, Klein turned his attention to an idea then percolating in California: that the state directly fund biomedical research that federal money couldn’t support. “Getting a Bush override was not feasible,” Klein recalls. “So the question then was: what can I do back home?”

Klein teamed up with several other affluent and politically savvy parents of diabetic children — including movie director Jerry Zucker and his wife Janet, and home developer Tom Coleman and his wife Polly — and the ‘three families’, as they called themselves, together with political consultants and lawyers, devised a ballot initiative that would ask California taxpayers to support stem-cell science to the tune of around \$300 million per year for ten years.

The measure — which became known as the California Stem Cell Research and Cures Bond Act of 2004, or simply Proposition 71 — did not require approval or regular appropriations from the legislature. Instead, the proposed initiative relied on long-term state-issued bonds, effectively shielding the endowment from the whims of lawmakers.

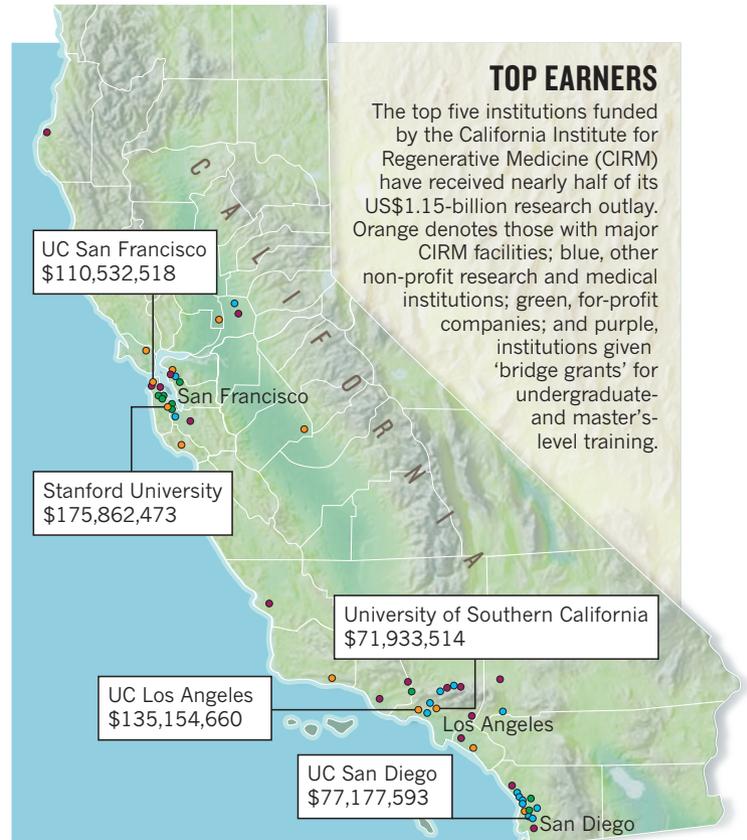
Klein had experience in bond financing for housing development and quickly took control of the campaign. He personally donated around \$1.2 million to get the initiative off the ground, later adding another \$3.1 million out of his pocket and raising \$30 million more in non-tax-deductible campaign contributions from others.

After a star-studded campaign endorsed by the likes of Brad Pitt, Christopher Reeve, Michael J. Fox and state governor Arnold Schwarzenegger, the campaigners gathered at the Millennium Biltmore hotel in Los Angeles on election night, in November 2004, to watch as the votes came in. The proposition passed with 59% approval. That night, says Wick, “I remember saying to the celebratory gathering that if our daughter is cured of her diabetes, the person who will be more responsible than any living human will be Bob Klein.”

But not all the early organizers of Proposition 71 remain enthusiastic about the way Klein led the charge. “It became Bob’s show almost entirely, and there was some friction about that,” recalls Peter Van Etten, former JDRF president and chief executive. Coleman has not spoken to Klein since the initiative passed, following disagreements over what Coleman viewed as Klein’s self-promotional approach. Zucker remains on better terms with Klein, but still feels some lingering resentment.

“If I had to do it over again I’d make the same call to Bob Klein because I don’t think the rest of us would have got it done without him,” Zucker

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says. But, he adds, “what I was most unhappy about was the realization after a while that [Klein] wrote the initiative for him to be the chairman. That was something I was too naive to realize. It’s shameless almost.”

Under the terms of Proposition 71, the 29-member governing board must include appointees with experience in academia, research, disease advocacy and biotechnology. The chair of the board, meanwhile, must meet a laundry list of mandatory criteria. These include a history of patient advocacy, leadership experience with a government agency, legal experience passing medical legislation and a direct knowledge of bond financing. Scientific expertise is not a requirement.

Sound familiar? “Look at the qualifications. They don’t fit a lot of people,” notes board member David Serrano Sewell, a lawyer with the San Francisco city attorney’s office.

Klein defends the job qualifications that he wrote into the statute. “I wrote the job description based on what I thought would be the challenges. I’m trained as a lawyer, so I’m going to think that legal is an important criterion. I’m trained in finance, and I’m going to think that finance during the projected period of economic distress for the state is going to be very important. So I wrote those requirements in knowing that if no one else could qualify, I could meet those. But someone had to meet those criteria.”

Many people maintain that Klein was simply the best person for the job. “He lived and breathed the mission,” says Jeannie Fontana, executive director of patient advocacy at the Sanford-Burnham Medical Research Institute in La Jolla, California, who has often acted as a stand-in on the CIRM board. Bernard Siegel, director of the non-profit Genetics Policy Institute in Palm Beach Gardens, Florida, adds: “He was able to blend in his passion with his networking skills, which are formidable, with this knowledge of bonds. When you put all this together he was able to create a state agency with unprecedented resilience that has been extraordinary successful.”

That resilience would be tested almost immediately after Proposition 71 passed. Critics of embryonic stem-cell science mounted legal challenges against the agency; as a result, bond sales were frozen until the court cases were settled. Klein, thinking ahead, had written a workaround into the bylaws. He was able to take out loans from elsewhere on the basis

that the bonds would eventually be paid — a little-known instrument called a ‘bond anticipation note’. Buoyed by these and other loans from the state’s general fund, Klein managed to keep administrative operations going and fund the agency’s first training and research grants even before the lawsuits were eventually thrown out, in May 2007.

In the first two years of legal and financial setbacks, the board was struggling to find a president to lead the day-to-day operations of the agency. Zach Hall, then an associate dean at the University of Southern California School of Medicine in Los Angeles, was brought in as an interim president. He had the administrative chops, having previously directed the US National Institute of Neurological Disorders and Stroke. And as the lawsuits dragged on, Klein asked Hall to stay on full time.

Hall agreed. But it wasn’t long before he and Klein butted heads. One of the main points of contention revolved around the agency’s scientific strategic plan — a policy measure adopted in December 2006. Some maintained that the president’s office alone should set the agency’s scientific agenda, yet Klein made sure that he and several board members had a seat on the subcommittee that crafted the plan. As a result, many people felt that the original strategic plan, as well as last year’s update approved by Hall’s successor, the Australian assisted-reproduction pioneer Alan Trounson, focuses too heavily on clinical applications at the expense of more fundamental basic science. For example, the strategic plan allocates 16% of CIRM’s \$2.4 billion projected research budget to what it calls “innovation science”, exploratory open-ended research, and more than half is allocated to “mission-directed science”, which is focused on developing therapies.

Joel Adelson, a health-policy researcher at the University of California, San Francisco, who interviewed 17 of CIRM’s key stakeholders and co-wrote an independent review of the agency earlier this year¹, says that Klein’s disagreements with Hall, and to a lesser extent with Trounson, stemmed from Klein’s insistence on being involved in every aspect of CIRM’s operations, including the scientific decisions.

“Klein has in effect acted like the chief operating officer beside Trounson and beside Hall, and I can only say that this looks like it must have been very uncomfortable for these guys,” Adelson says. “It’s an unusual situation,” says Trounson. “And if you ask me what I prefer, I prefer the simple situation where the president is in charge of all management and reporting to a board on policies. But it’s bifurcated, and it was set up that way, so you don’t have a choice.” (Hall declined to comment for this story.)

STICK TO THE VISION

Klein defends his march to the clinic as adhering to the vision he presented to voters on the campaign trail. And although some basic scientists take issue with CIRM’s funding allocations, most have come to embrace the translational emphasis. For example, Jeanne Loring, a CIRM-funded stem-cell researcher at the Scripps Research Institute in La Jolla, says that Klein “has taken purely academic scientists who didn’t give a damn about the clinical applications of their work, and turned them into scientists who will now talk, without a trace of embarrassment, about the benefit of their research to patients”.

Patient advocates praise Klein as well. “He’s an historic figure with real genius in terms of moving biomedicine forward,” says Jeff Sheehy, a CIRM board member and director for communications at the University of California, San Francisco’s AIDS Research Institute. “He’s as good as they get if not better.”

Developments in both science and politics have challenged CIRM’s original rationale. In November 2007, researchers in Japan and Wisconsin reported that human skin cells could be coaxed in the laboratory to form embryonic-like pluripotent stem cells^{2,3}. This discovery provided a new path to patient-specific stem cells without the need for embryos. Then, a year and a half later, US President Barack Obama issued an executive order widening the scope of federal funding for embryonic stem-cell research, easing the need for state and private initiatives.

But Klein says CIRM’s mission goes beyond simply serving as a stop-gap for embryonic stem-cell research during Bush-era restrictions, stressing that its focus on translational medicine distinguishes the California agency from the National Institutes of Health (NIH). For instance, he points to the disease team grants, launched last year, that require recipients to have a strategy for landing an investigational new drug application within four years.

“The purpose of CIRM is not science for science’s sake,” Klein says. “The purpose of CIRM is medical science with a plan to drive that science all the way through to therapies.”

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Marie Csete, a former chief scientific officer at CIRM, says that Klein embraced the new ‘induced pluripotent’ stem cells. “There was a transient moment where hanging on to embryonic stem cells was important, but he very quickly grasped that they were only one tool in the toolbox of regenerative medicine,” she says.

After dedicating nine years and millions of dollars to the agency, Klein says

it’s time to step aside and focus on family issues — his son is still battling diabetes, he lost his mother to Alzheimer’s disease last year and his wife is currently undergoing chemotherapy for breast cancer. Agency insiders are sad to see him go. “The joke is to clone Bob Klein,” says Lynn Harwell, CIRM’s deputy to the chair for finance, policy and outreach. She pauses before quickly adding: “Although of course we don’t condone cloning.”

Geoffrey Lomax, CIRM’s senior officer for medical and ethical standards, commends Klein’s many accomplishments, but thinks that fresh leadership might help to clarify boundaries between the board and the staff. “As Mr Prop 71, Bob’s relationship to the organization is unique,” Lomax says. “I would suspect that there might be cleaner lines with someone coming in who doesn’t bring that intimacy with the proposition.”

Depending on who replaces him — nominations were made earlier this week by state officials including Schwarzenegger, and the new chair will be elected by the board on 15 December — Klein’s departure might also trigger the president to leave, thereby causing a complete overhaul of CIRM’s leadership. Trounson says he told Schwarzenegger that he would like that next chairperson to be “somebody who’s in the delivery end of the spectrum — that is, somebody who has worked with the biotech or pharmaceutical industry”.

But as this issue was going to press, the leading internal candidate to replace Klein, many say, is vice-chair Art Torres, a former state senator and chairman of the California Democratic Party. Torres and Trounson reportedly cannot stand each other. Trounson notes that Torres is “a politician, so he’s in that end of the spectrum”. Torres, for his part, declined to comment on his relationship with the president.

Whoever takes the reins will continue to deal with the fallout from the federal injunction. But Klein leaves the agency in strong legal and scientific positions, with several projects — including a few that rely on embryonic stem cells — likely to enter early clinical development in the next few years.

Gerald Levey, an ex-board member and former dean of the David Geffen School of Medicine at the University of California, Los Angeles, says that Klein’s record at CIRM stands for itself. “If he did nothing else with his life, he did a wonderful thing.”

But Klein vows to return to the agency’s service in 2014 to help CIRM secure another \$3 billion commitment from California’s taxpayers. “I have four years to put my life back into a position where I can commit myself to another campaign,” says Klein. He has no plans to retire or stop the search for a cure for his son’s diabetes: “You’re either learning and growing or you’re dying, and I want to continue to learn and grow.” ■

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1. Adelson, J. W. & Weinberg, J. K. *Am. J. Public Health* **100**, 446–451 (2010).
2. Takahashi, K. *et al. Cell* **131**, 861–872 (2007).
3. Yu, J. *et al. Science* **318**, 1917–1920 (2007).

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For an interactive graphic of CIRM grant recipients see: go.nature.com/38ew9w