

A patchwork quilt of funding

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A federal void fuels an expansion of state and private policies

In 2006, when Kevin Eggan and Doug Melton of the Harvard Stem Cell Institute in Boston, Massachusetts, wanted to collaborate with Rudy Leibel of Columbia University, New York, they were literally up against a solid wall. They wanted to make human embryonic stem cells (ES cells) using transplanted nuclei from cells from diabetes patients, but Columbia's administration blocked the research because it would have been carried out in a building whose construction was partially funded by the National Institutes of Health (NIH). It could therefore be prohibited by a reasonable interpretation of US government policy, which forbids federal support for research on ES cell lines derived after 2001. A private charity, the newly established New York Stem Cell Foundation (NYSCF), provided a safe haven in the form of a laboratory in Manhattan and has committed more than \$10 million in research funding since its founding in 2005. "This research simply wouldn't have happened if it weren't for this foundation," says Eggan.

To bypass federal restrictions, academic institutions have built new laboratories and purchased duplicate equipment with non-federal sources. Researchers wanting to work with newly derived human ES cells are turning to private funders and state initiatives to support their research (see Table 1).

But localized, specialized funding for stem-cell research requires scientists to negotiate legal and ethical regulations and interpretations that vary by funding source, state and institution. States are wrestling with regulatory and funding mechanisms they've never had to consider before; academic institutions must contend with shifting legal, ethical and accounting requirements of multiple stakeholders. The worry is that these smaller, overlapping systems mean less efficient and less powerful science.

"By no means is this a substitute for a great national policy," says Robert Goldstein, chief scientific officer of the Juvenile Diabetes Research Foundation (JDRF). The NIH has centralized funding, regulation and information dissemination in many scientific areas, and has built up significant scientific infrastructure, he says. Keeping track of what's happening in dozens of individual states and private foundations is complicated.

Whereas the NIH's charge is to "foster fundamental creative discoveries" and pursue scientific knowledge, state initiatives are more concerned with building economic opportunities. With US\$3 billion to spend over ten years, the California Institute of Regenerative Medicine (CIRM) is fostering basic science, but its primary goal must be to speed research to the clinic. Private foundations also have their own agendas. "We'd much prefer to spend our money to coax the people who are out there doing stem-cell research into paying more attention to creating insulin-secreting cells," says Goldstein.



Stem-cell scientists must juggle multiple sets of regulations and obligations.

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Donor	Amount	Recipient
William Bowes, founding partner of U.S. Venture Partners	\$3 million (announced Oct 2007)	University of California, Santa Barbara Center for Stem Cell, Biology and Engineering
Eli Broad, real estate entrepreneur	\$55 million (announced Sep 2007 and Feb 2006)	University of Southern California (\$25 million) University of California, Los Angeles (\$20 million)
Tom Ellison, the chairman of Savers Inc. of Bellevue	\$5 million (announced June 2007)	University of Washington
Bill Gross, founder of investment company PIMCO	\$10 million (announced July 2006)	University of California, Irvine
Ray Dolby, sound system businessman	\$16 million (announced May 2006)	Weill Medical College of Cornell, Memorial Sloan-Kettering and Rockefeller University
Stephen Weiner, founder of real estate firm	\$6 million (announced March 2005)	Beth Israel Deaconess Medical Center
Anonymous donor	\$25 million (announced March 2004)	University of Texas, Health Science Center at Houston

***Table 1.** Many funds cover both embryonic and nonembryonic work. Smaller, quieter donations also add up. As of June 2007, the Harvard Stem Cell Institute had raised some \$60 million from private sources. Notably, this table does not list political contributions for stem cell campaigns. Sources: CBS News; Forbes; Harvard Crimson; Puget Sound, Business Journal, Wall Street Journal, various universities.*

As states are starting to pay for stem-cell work, they are facing the challenge of setting up guidelines to govern that research. The stem-cell guidelines developed by the US National Academy of Sciences (NAS) provide a general framework, but individual states take their own approaches to particular legal and ethical concerns.

State laws on stem-cell research vary widely. Some states don't have specific regulations; others have various degrees of restriction. At one end of the spectrum, South Dakota bans all research on cells derived from a human embryo; on the other, California, Connecticut and several other states hope to provide long-term state funding for work on human ES cells.

But even permissive states have conflicting legal requirements. California's standards do not allow women to be paid for eggs apart from reimbursement for certain expenses, and do not allow research on stem-cell lines developed from embryos created with paid-for eggs. Connecticut's requirements are slightly different, and the differences mean that some cell lines created in Connecticut probably cannot currently be used in California. Regulators in Massachusetts recently changed wording of an executive rule that previously could have criminalized work on stem cell lines from embryos created for research purposes.

"There's clearly a need to try to calibrate those rules in such a way that researchers can both collaborate and exchange materials," says Geoff Lomax, senior officer for medical and ethical standards at the CIRM. There are already exchanges at the institutional level; Harvard and the University of California at San Francisco will send lines to researchers who request them. What's not clear, however, is what the recipients can and cannot do with the lines once they get them.

To help find a way through the thickets, a coalition of states supporting stem-cell research has organized the Interstate Alliance for Stem Cell Research, led by Warren Wollschlager, chief of the office of research and development in the Connecticut Department of Health. "We're looking right

now to try to line up the various state regulatory and statutory schemes [in regard to sharing cellular material]," says Wollschlager.

Representatives from California, Illinois, New York, Massachusetts, New Jersey, Maryland, Rhode Island, Wisconsin and Connecticut meet quarterly with the NAS and representatives from the United Kingdom and Canada. "We're really not trying to come up with a model that would suit each state specifically," Wollschlager says. Instead, the alliance provides a forum for states to discuss common issues and facilitate collaboration. For example, documentation systems that track information such as informed consent, egg donation and the provenance of the cell line will be critical to sharing lines.

Even if states get to the point where they can exchange materials, collaboration and information sharing will be far more complicated under the fractured state system. The centralized NIH system provides well-established mechanisms for funding collaborators. "Anyone could be a subcontractor on anyone else's [NIH] grant and get a portion of those dollars for the collaboration," Eggan says. Grants from the states are restricted by location. "It will only encourage people to be more isolated," he says.

JDRF's Goldstein agrees that the patchwork slows down science. Researchers have first to worry about complying with their own state rules and then have to consider rules applying to out-of-state collaborators. "And then you have to be careful that you don't offend the feds," says Goldstein.

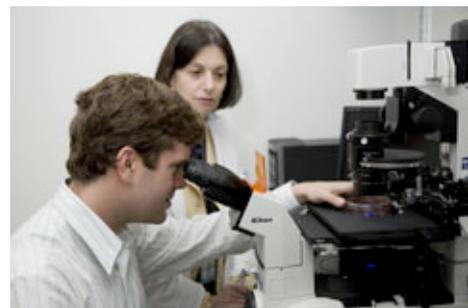
Creating a well-oiled bureaucracy takes time. Paperwork to verify that grant recipients were full-time employees of their institute stalled CIRM grants, and although the Maryland Stem Cell Commission awarded its first stem-cell grants in May, as of October it had yet to disburse the funds.

The fractured American system also complicates research collaborations on a global scale. The International Stem Cell Forum (ISCF) has sponsored collaborative work assaying various human ES cell lines under various culture conditions. Other countries have a single national representative to coordinate funding and research, says Robin Buckle of the UK Medical Research Council and secretary of the ISCF, but the United States has three: the NIH, the CIRM and the JDRF, all of which have their own agendas and limitations. "Anything that's above a bilateral arrangement becomes logarithmically more complicated," Buckle says.

Reinventing wheels

Each state that plans to fund ES cell research must create a system to assess and regulate grants. The NAS guidelines recommend having additional review panels specifically for stem cells, called embryonic stem-cell research oversight committees (ESCROs or SCROs), but they are not required. Some states, such as California, require SCROs, which are run at the institutional level, and so could create another layer in the regulatory system.

Hank Greely, professor of bioethics at Stanford University, California, compares the SCRO approval process with that of internal review boards for large multi-center clinical trials. "It will have some slowing effect compared to not having oversight, but I'm comfortable and confident that the slowing will be small and reasonable," says Greely, who chairs California's advisory committee on human stem-cell research and is the vice-chair of Stanford's SCRO committee. "For that oversight one buys public support — both financial support and political support — and reassurance for the public that things are being done in an ethically



Safe harbor: Kevin Eggan and Robin Goland at the New York Stem Cell Foundation lab in Manhattan

New York Stem Cell Foundation

appropriate manner." Many major research journals currently require review of the research through SCROs, Greely adds.

So far, most states are following the established practice of soliciting grant proposals and evaluating them through peer review. Inevitably, the same experts are contacted by multiple municipalities, leading to review fatigue and confusion.

Although the NIH and some other funding bodies reimburse researchers for their time in reviewing grant proposals, Connecticut cannot, says Wollschlager. Lomax says that organizing peer review has been a challenge, even though his institute, CIRM, does pay reviewers. "You are dealing with a limited pool of expertise and competition for that pool," he says. The hope is that if state funds lure more people into the field, the number of experts will increase.

Working together for the long term

Even though researchers, foundations and other funders are hopeful that a new president in the White House will loosen NIH restrictions in the next two years, such changes are not likely to heal the fractured funding climate. States such as California and Connecticut are already invested in the research for a 10-year period. On November 6, voters in New Jersey are scheduled to decide whether to sell \$450 million in bonds to support both adult and embryonic stem cell research. Similar legislation has been proposed in New York. By the time the NIH comes to the table, says Wollschlager, the states will be established funding sources.

With flat or declining funding for the NIH overall, many stakeholders doubt that it could take a leading role even if the Bush restrictions are eased — the NIH budgeted \$37 million for human ES cell research for financial year 2007, about 0.1% of its budget. In addition, the Dickey–Wicker amendment attached to government appropriations bills since 1996 prohibits federal funding to be used on any experiment that creates or destroys a human embryo, meaning that creating new ES cell lines with federal funding will still be forbidden. "Even if NIH is able to expand support for stem-cell research, it will only be one payer among many, and not even the largest one," wrote James Fossett of the Rockefeller College of Public Affairs and Policy, New York, in a 9 August Rockefeller Institute Policy Brief. So, efficient or not, a patchwork structure for human ES cell research is likely here to stay.