SPECIAL REPORT

Seed money to bring in pioneers

California's stem-cell initiative has finally handed out its first research grants. But will all the money actually move the field forward? **Erika Check** reports.

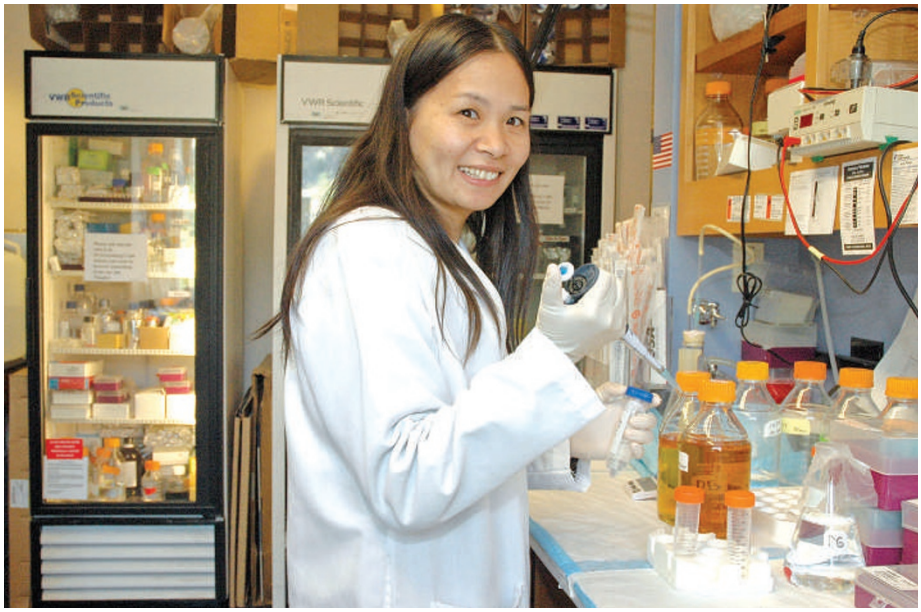
Gregory Kovacs has had no shortage of stimulating work. An engineer at Stanford University who makes biosensors, Kovacs serves as a regular adviser to the US Defense Advanced Research Projects Agency. He helped investigate the 2003 *Columbia* space-shuttle accident. And he climbed the 6,000-metre Licancabur volcano in Chile in the name of medical research — twice.

One thing Kovacs hasn't tried is stem-cell research. But that's about to change. Last month, Kovacs became one of 72 researchers from other fields who have been enticed to work on human embryonic stem cells. All were lured by grants from the California Institute for Regenerative Medicine (CIRM), the state initiative approved by voters in 2004 to overcome federal restrictions on such research. Kovacs, for his part, intends to use his $634,000 grant to study the electrical development of heart stem cells. And he doesn't seem fazed at entering one of the most controversial fields of science, and one in which he has little experience: "At Stanford, you're parking your car next to some Nobel laureate who knows how to work with stem cells," he says. "We can get help."

Kovacs will have even more company on 16 March, when the CIRM hands out further grants worth up to $80 million, this time to established scientists who are already experts in stem-cell research. But it is perhaps more intriguing to look at the initial round of money given to new investigators, the SEED (Scientific Excellence through Exploration and Development) grants. They constitute a rare experiment: to discover whether $45 million and a fresh cast of researchers can affect the future of one of science's hottest fields.

The answer begins with the SEED awardees themselves, who span the gamut from wet-behind-the-ears assistant professors to established scientists with sterling reputations. Twenty-seven of the SEED grants went to scientists who have been working independently for six years or less. Other grants went to highly experienced investigators — even institute directors (see 'Staking it all on stem cells').

The researchers approached the CIRM for a variety of reasons, including the exhilaration of entering a cutting-edge discipline and the opportunity to extend their work into a new system.



R. VENTE

Xianmin Zeng left the National Institutes of Health for stem-cell research at the private Buck Institute.

Another oft-cited factor is the tight budgets at the National Institutes of Health (NIH), the major public funder of US biology research. "In these times of greatly diminished NIH funding, it is fantastic to have a forward-thinking programme such as the CIRM that has stepped up to fill the void," says Warner Greene, a veteran HIV researcher who directs the Gladstone Institute of Virology and Immunology at the University of California, San Francisco.

> "Without CIRM funding, I wouldn't have gotten into this, given the barriers involved."

This year, the NIH will fund $37 million in human embryonic stem-cell research, but California researchers such as Greene see their future with the CIRM. Greene received a SEED grant for $778,000 to study how proteins that protect cells against HIV might also help human embryonic stem cells maintain stable genomes.

The typical SEED grant handed out is between $300,000 and $800,000 for two years — roughly comparable to the NIH R01, the typical biologist's bread-and-butter grant. The money from the CIRM is not enough to redirect the entire focus of a laboratory. But it does seem to have been enough to encourage scientists to overcome reservations about a field that is notorious for the difficulties involved, including restrictions on federal funding and the inherent challenges of working with cells that are extremely hard to deal with. "Without CIRM funding, I wouldn't have gotten into this, given the barriers involved," says Anirvan Ghosh of the University of California, San Diego, a leading developmental neurobiologist. Ghosh received $612,000 for work to try to make brain cells from human embryonic stem cells. "The CIRM lowered those barriers enough to give me the motivation to write up a proposal," Ghosh says.

Given the grantees' inexperience with stem cells, others may question how serious they are about staying in the field for the long term. But outgoing CIRM president Zach Hall says the agency's review process weeded out those who were only looking for quick cash. "We had 231 applications, and I'm sure among them there were those whose motivation was primarily to get some money to support their lab," he says. "But the quality of people that we funded is extraordinary."

Now the difficult work begins, as researchers confront the day-to-day realities of working with human embryonic stem cells.

NASA/JPL/SPACE SCI. INST.

LUNAR AND PLANETARY SCIENCE MEETING
Get all the news from the conference in Houston
http://blogs.nature.com/news

First, there's the challenge of just obtaining the cells. Researchers receiving federal funding must, by presidential directive, work only on particular stem-cell lines created before August 2001. Many researchers prefer to work on newer lines, which are seen as more reliable and better characterized, but to do so they must use private sources of funding. Many of the scientists who received SEED grants don't yet have labs funded by non-federal money, and so can work only on the 21 designated lines.

"The first thing we'll do is get the NIH-approved lines, and even that takes time," says David Feldheim, an assistant professor of biology at the University of California, Santa Cruz. Feldheim got $500,000 from the CIRM to study a family of signalling proteins that may affect the development of human embryonic stem cells.

But even those scientists lucky enough to be at a university with a privately funded lab still face issues working with CIRM funding. For instance, Ghosh intends to use his money to study cell lines not approved for NIH support. But it's still unclear whether he can perform part of the analysis using instruments at his university that were built with federal money, such as mass spectrometers. "There are still grey areas, and on the day-to-day issues there is still some hassle," he says.

And although there is plenty of excitement over the first round of SEED grants, others caution against hoping for too much. The patient advocates who helped convince voters to approve the CIRM believe that it will lead to life-saving cures. But veteran researchers have seen high hopes deflated in other fields many times before.

For instance, Stanford University biologist Mark Kay has seen hype lead to disillusionment in the controversial area of gene therapy. Kay received a $640,000 SEED grant to study ways to genetically modify human embryonic stem cells. But he worries that the stem-cell field is even more vulnerable to dashed hopes because of the astronomical expectations that have been set for it, and the way it has become a high-profile political and moral issue.

"Right now, we're in a honeymoon phase," Kay says, "but I'm really worried that this is going to be similar to what happened in gene therapy, where there was way too much hype, things don't come as quickly as people want, and there's a backlash."

For now, such concerns may seem premature. But soon the new grantees will have to start the hard work of actually spending the money. And all eyes will be on them to see whether they can deliver. ■

See also Editorial, page 232.

Staking it all on stem cells

A $730,000 grant would be something of a pittance to one of the University of California schools, which have thousands of faculty and staff and billion-dollar endowments. But that same grant means a lot more to the typical independent research institute with an annual budget of tens of millions of dollars and perhaps as few as 15 faculty members.

That's part of the reason that the Buck Institute for Age Research, a seven-year-old, $30-million independent research institute in Novato, California, has staked its future on the California Institute for Regenerative Medicine (CIRM).

Less than a year after California's voters approved the CIRM, the Buck made two strategic recruitments. It hired stem-cell researcher Xianmin Zeng from the National Institutes of Health (NIH) and chief operating officer James Kovach from the stem-cell company Athersys, based in Cleveland, Ohio.

That expertise has so far helped the Buck win a training grant and a $734,000 SEED (Scientific Excellence through Exploration and Development) grant from the CIRM. The SEED grant will allow Dale Bredesen, the institute's chief executive, to study cell-death pathways in human embryonic stem cells.

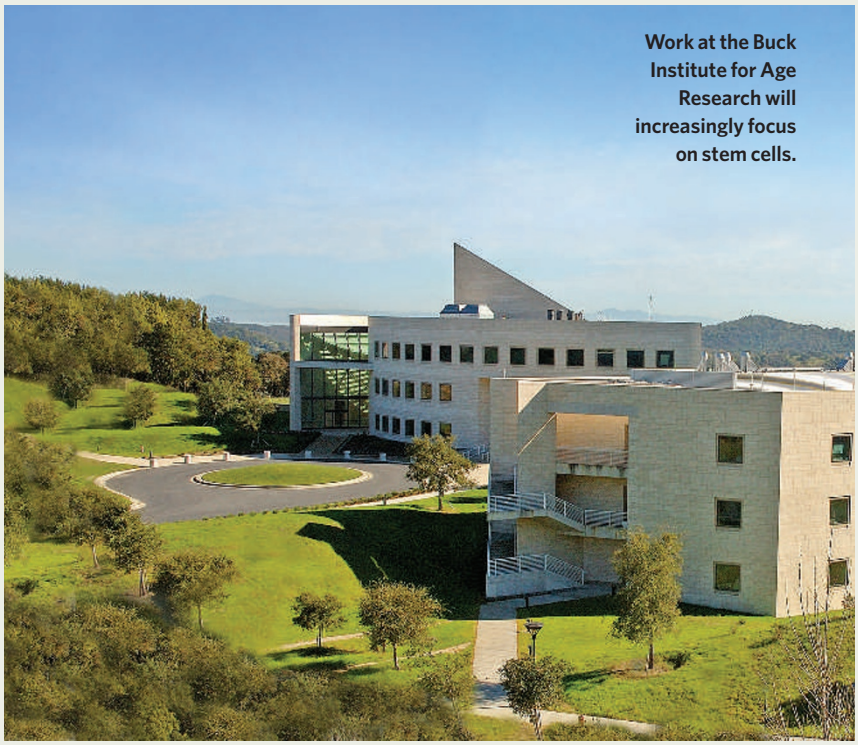
"Support from the CIRM will directly impact on our entire future."

The Buck is in the middle of an expansion, and Kovach says stem-cell research and the CIRM will play an increasingly important role in its plans for growth.

Last October, Kovach spoke to a CIRM working group, and he sums up his message this way: "I said, 'Your support will directly impact on our entire future,' " Kovach says. "Our goal is to partner with other California institutes to be among the first to have our human embryonic stem cells in clinical use."

That may not be an idle dream. Despite their small size, the Buck and California's other independent biomedical institutes have been disproportionately successful in winning CIRM funds so far. Typically, such institutes win 10% of NIH funds nationwide, but in California they have won 30% of the SEED money given out in February.

Kovach argues that the Buck and other institutes made up for their small size with high-quality, innovative CIRM applications. "We won't have as many bullets in the cartridge, but we will have directly interdisciplinary activities that other places don't have," he says. **E.C.**



R. VENTE

Work at the Buck Institute for Age Research will increasingly focus on stem cells.